In conclusion, the 1040T/C SNP located in the coding region of the TAFI gene and resulting in the Thr325Ile substitution is associated with TAFI plasma levels, just like other SNPs in and around this gene. Presently, it is not known which SNP is/are responsible for this effect on TAFI levels. On the other hand, studies using recombinant proteins have demonstrated a functional effect of the Thr325Ile substitution on the stability of activated TAFI resulting in altered antifibrinolytic activity. The possibility that the same TAFI haplotype will affect levels and antifibrinolytic activity in opposite directions will hamper the interpretation of genetic association studies using this SNP.

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References

To the editor:

Increased Lipoprotein(a) levels are not a steady prothrombotic defect

We have read the paper by Nowak-Goëttl and coworkers on the meaning of combined prothrombotic defects for recurrence of venous thrombosis in childhood with great interest and congratulate the authors for their work. However, we would like to comment on their findings with regard to Lipoprotein(a) (Lp(a)). In their paper, the authors describe Lp(a) as the second most prevalent “prothrombotic defect” for recurrent and nonrecurrent venous thromboembolism (VTE) in childhood, using a cut-off of 300 mg/L (30 mg/dL).

We had the chance to examine Lp(a) concentrations in a small group of pediatric patients (n = 7) treated for acute lymphoblastic leukemia (ALL) or lymphoma on the ALL- or NHL-BFM (non-Hodgkin lymphoma–Berlin-Frankfurt-Muenster) trial 95, respectively. These 2 trials were used by Nowak-Goëttl et al to study the incidence of increased Lp(a) and its possible relationship to the incidence of venous thrombosis in this setting. We found that Lp(a) was significantly decreased during therapy on the BFM trial 95 (Figure 1), with every patient showing reduction of Lp(a) concentration. A patient with an increased Lp(a) of 325 mg/L displayed a decrease to a nadir of 58 mg/L, only to end the first block of therapy with a level of 111 mg/L. Mean Lp(a) fell by 75% from 116.1 mg/L on day 8, to 28.9 mg/L on day 16 (P = 0.049, Figure 1). It is very likely that these changes in Lp(a) concentrations were due to the use of L-asparaginase, as described by other investigators in a different setting. Variation of Lp(a) levels with albumin concentrations has been described as well as with the state of thyroid function. Also, Lp(a) levels have repeatedly been linked to acute-phase responses. On the other hand, negative acute-phase characteristics and decreases in catabolic states have also been shown to occur. In vitro experiments show that Lp(a) messenger RNA (mRNA) expression can be positively regulated by interleukin-6 (IL-6), whereas it can be suppressed by transforming growth growth.
factor β1 (TGF-β1) and tumor necrosis factor-α (TNF-α), suggesting that in vivo Lp(a) levels may be dependent on the balance between stimulatory and inhibitory cytokines, which could help to explain the variation of Lp(a) levels with regard to different clinical settings.

In a case control study with patients and controls matched for age and sex, the authors also considered acute-phase responses to control for “falsely” increased Lp(a) concentrations; in this study, no increased risk for VTE with increased Lp(a) concentrations could be demonstrated.

Epidemiologically, there seems to be a relationship between increased Lp(a) concentrations and VTE. However, given the fact that a clearly defined pathophysiologic model on how increased Lp(a) concentrations can convey an increased prothrombotic risk is still missing, we suggest that increased Lp(a) levels should not be looked at as a “prothrombotic defect” but rather a “surrogate risk marker.” This view is important in light of the above data, showing that Lp(a) levels are (although largely genetically determined) not “fixed” to a certain concentration.

Therefore, disregarding circumstances (such as comorbidity or treatment effects) that might cause variation of Lp(a) levels could lead to false estimation of numbers of patients at risk for VTE in a given population. In addition, an increased Lp(a) concentration cannot be assumed to be a stable risk marker of VTE during chemotherapy with asparaginase-containing regimens, since asparaginase greatly reduces Lp(a) levels.

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Data on Lp(a) during the BFM 95 trials was reported in poster form at the Annual Meeting of the Gesellschaft für Thrombose-und Hämostaseforschung, in Freiburg, Germany, February 16-19, 2000.

References

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