Regional variations in hepatic vascular occlusion

Articles in this issue of the Journal highlight regional differences, according to both geography and venular territory, in vascular disorders of the liver. Hepatic venous outflow tract obstruction (HVOTO) predominantly caused by isolated inferior vena cava (IVC) obstruction or combined obstruction of IVC and hepatic veins is largely reported from Asia. In contrast, isolated hepatic vein obstruction is the predominant type of HVOTO seen in the West as well as in some series from India. Differences in genetic and/or acquired/environmental etiological factors may account for this geographical variation in the types of HVOTO.

Myeloproliferative disorders are the commonest underlying prothrombotic condition in HVOTO, with overt clinical features detectable in approximately 25% of HVOTO patients and their detection whilst still occult, by highly sensitive tests for spontaneous erythroid colony formation, in a further 25% of patients. The identification of somatic Janus kinase 2 (JAK2) mutation has lead to new approaches to diagnosis and classification of myeloproliferative disorders.

Resistance to activated protein C conferred by the factor V Leiden mutation is the most frequent cause of hereditary thrombophilia, with prevalence of approximately 5% in Caucasian populations. Varying incidence of factor V and II mutations in different populations has been documented. A prevalence of factor V mutations of 1% has been reported in the Indian population.

An increased incidence of factor V mutations in HVOTO patients was recognized a decade ago. In contrast, the study in this issue of the Journal reports lack of increased incidence of factor V mutations in HVOTO patients from northern India, mostly with IVC obstruction. Factor II mutations occur in 2% of the general population and in 5% of HVOTO patients in Europe. In contrast, factor II mutations have not yet been reported from India. Thus, evidence is accruing that inherited prothrombotic factors associated with HVOTO differ in different geographic areas and those associated with HVOTO due to IVC obstruction are different from those with associated HVOTO due to hepatic vein obstruction.

It has been suggested that IVC obstruction is associated with poor standard of living, implying that environmental factors could play a role in HVOTO caused by this. If this is correct, it is possible that with improved standards of living, the spectrum of HVOTO may change with the IVC obstruction type becoming less common.

Interestingly, the predisposing thrombophilic conditions associated with HVOTO are different from those associated with portal vein thrombosis, supporting the concept of specific risk factors for different thrombotic sites. Factor V mutation, a risk factor for HVOTO, is not a predisposing factor for portal vein thrombosis. A study of the two gain-of-function mutations of factor V and factor II genes showed increased risk for portal vein thrombosis with factor II mutation but not with factor V mutation, though a weak association between extrahepatic portal vein thrombosis and factor V mutation (odds ratio 2.7) was found in another study.

A study of patients with non-cirrhotic portal vein thrombosis in this issue of the Journal documents underlying thrombophilic conditions in a majority of the patients (19 of 26) studied. While molecular tests like factor V or II mutations are straightforward to interpret, functional assays of protein C, protein S and antithrombin activity are hampered by diagnostic difficulties in patients with portal vein thrombosis in whom deficiency of natural anticoagulant proteins may occur as a secondary phenomenon. In family studies, only a minority of patients had evidence of an inherited deficiency. Not only anticoagulant proteins but also procoagulant proteins may be reduced in portal vein thrombosis.

What are the issues regarding anticoagulating these patients? It appears reasonable to base the decision to anticoagulate patients with portal vein thrombosis on the risk of further thrombosis in the portal venous tree rather than on thrombophilic tests. Non-cirrhotic portal hypertension is caused by occlusion of intrahepatic portal vein radicles. High risk of subsequent thrombosis in the portal venous system has been reported in non-cirrhotic portal hypertension patients (13 of 28 patients studied). More studies are needed to address the risk of further thromboses in the portal venous system and the role of anticoagulation in patients with intrahepatic portal vein occlusion (causing non-cirrhotic portal hypertension) compared to those with extrahepatic portal vein occlusion.

In contrast to portal vein thrombosis, anticoagulation is currently routinely used to treat patients with HVOTO. However, it must be remembered that there are only two retrospective studies to support...
the use of warfarin in patients with HVOTO.\textsuperscript{16,17} The documentation of underlying thrombophilic conditions in the majority of patients is one of the justifications for anticoagulation in HVOTO. Hence, the study in this Journal issue\textsuperscript{1} suggesting factor V and factor II mutations have no role in HVOTO when mainly due to IVC obstruction has to be factored into the decision making.

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References