in the setting of minimal residual disease, but this should probably only be carried out with special attention to the prevention of infection.

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Rituximab kindly provided free by Genetech, Inc.

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To the editor:

Thrombophilia as a common predisposing factor in pseudotumor cerebri

Pseudotumor cerebri (PTC), also known as idiopathic or benign intracranial hypertension, is related in a significant number of cases to cranial venous outflow obstruction, defined as abnormal venous flow on imaging or venography that may or may not have demonstrable cerebral venous thrombosis which represents an extreme end of the spectrum. Indeed, it has been argued that such a mechanism underlies all cases of PTC, although depending on how assiduously such abnormalities are sought, or on the limitations of imaging modalities, this may not be documented.1,2 Recently, we reviewed a large series of PTC patients, including a subgroup in whom the cranial venous outflow was investigated in detail, and found that 31% had evidence of venous outflow obstruction.2

Clearly, there is the possibility of an underlying thrombophilia in PTC patients with cranial venous outflow obstruction with or without demonstrable thrombosis. An association of PTC with systemic lupus erythematosus and an increased incidence of anticardiolipin antibodies have been described; however, the importance of other thrombophilias in PTC with cranial venous outflow obstruction has not been examined.3 Martineelli et al recently described the association of thrombophilia, particularly hyperhomocysteinemia, and overt cerebral vein thrombosis.4 The importance of Factor V Leiden (FVL) and the PT20210 mutation had previously been recognized in cerebral venous thrombosis.5,6

We had the opportunity to examine 25 consecutive patients with PTC who were admitted to the neurosurgical unit between 1998 and 2000 and who previously had been assessed for venous outflow obstruction. Only 4 patients had frank cerebral venous thrombosis. The average age was 30 years (range, 11-49 years) and the majority female (23 of 25). All patients had a normal platelet count and screening coagulation studies (activated partial thromboplastin time and prothrombin time). Protein C (PC), protein S (PS; functional), antithrombin levels (AT; STA, chromogenic, Diagnostica Stago, Asnieres-sur-Seine, France), and activated protein C resistance were measured (GradiLeiden V, Gradipore, Australia). Lupus anticoagulant (LA) was examined using the Dilute Russel Viper Venom Time (DRVVT) and Kaolin Clotting Time (KCT) with confirmation by addition of excess phospholipid. The anticardiolipin antibody (ACA) was measured using an immunoglobulin G enzyme-linked immunosorbent assay and defined as positive if the titer was moderate to high and persisted for more than 6 weeks. Fasting serum homocysteine levels were measured (normal range, < 23 μM) without oral methionine loading, and all patients confirmed to have normal B12 and folate levels. Mutations for FVL and PT20210 were sought (multiplex amplification refractory mutation system polymerase chain reaction [ARMS PCR]). Fisher exact test was used for statistical analysis.

Thrombophilic defects were detected in 68% (Table 1). There were 2 patients with low PS levels (41% and 43%; normal, 80%-130%), 4 patients with APCR and FVL, 2 with PT20210, 6 with positive ACA, 3 with positive LA (none of whom had positive ACA), and 2 with elevated fasting homocysteine. The rate of FVL and PT20210 is in keeping with rates seen in other thrombotic disorders such as deep vein thrombosis.7 We confirm the high frequency of positive LA and ACA as previously described in PTC.3 Again, this is in keeping with other thrombophilic groups.8 The possibility exists that ACA positivity is related to an infective cause, and 2 of 6 patients had probable infected shunts at time of testing.

Only one patient had a personal history of deep venous thrombosis (no thrombophilia detected), whereas 3 patients had a family history of venous thromboembolism (all with thrombophilia). There was no history of autoimmune disease and all patients had anuclear antibody less than a titer of 1:80. No patient was receiving estrogen preparations but, given the striking female predominance, one must speculate on the relationship between endogenous estrogen and underlying thrombophilia. The association between users of oral contraceptives and cerebral venous thrombosis has been described.4,6

A slight predominance of thrombophilic defects was seen in patients with documented venous outflow obstruction: 77% (7 of 9) versus 62% (10 of 16) (P = .048). As mentioned, such a diagnosis may be difficult due to the limitations of imaging. It is, therefore, possible that some patients with thrombophilia did, in fact, have undetectable cranial venous outflow obstruction.

In conclusion, there is a high incidence of thrombophilic defects in PTC, particularly in patients with cranial venous outflow obstruction. Cranial venous outflow obstruction may exist in the absence of frank cerebral vein thrombosis and may

Table 1. Thrombophilias in pseudotumor cerebri patients

<table>
<thead>
<tr>
<th>Thrombophilic defect</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All defects</td>
<td>17 (68)</td>
</tr>
<tr>
<td>PT20210</td>
<td>2 (8)</td>
</tr>
<tr>
<td>FVL/APCR</td>
<td>4 (16)</td>
</tr>
<tr>
<td>LA</td>
<td>3 (12)</td>
</tr>
<tr>
<td>ACA</td>
<td>6 (24)</td>
</tr>
<tr>
<td>PS deficiency</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

References

underlie the pathophysiology of this condition. Further investigation is underway.

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References


To the editor:

IVIg-mediated amelioration of murine ITP via FcγRIIb is not necessarily independent of SHIP-1 and SHP-1 activity

Crow et al1 state that the protective effect of intravenous immunoglobulins (IVIgs) in murine idiopathic thrombocytopenia (ITP) requires FcγRIIb but not its signaling molecules Src homology 2 domain-containing inositol polyphosphate phosphatase-1 (SHIP-1), Src homology 2 domain-containing polyphosphate phosphatase-1 (SHP-1), or Bruton tyrosine kinase (Btk). However, SHP-1 and SHIP-1 can replace each other functionally. Thus, the study by Crow et al does not definitely rule out a role for these molecules in the effect of IVIg on murine ITP.

Treatment of ITP with IVIg is nowadays well established. The mechanism of action of IVIg in ITP is considered to be blockade of Fcy receptors (FcyRs). Indeed, in animal models there is evidence for such a mechanism.2 However, studies in knockout mice have revealed that the mechanism of action of IVIg’s in ITP may be more complicated, since mice deficient for the inhibiting Fc receptor, FcγRIIb, do not respond to IVIg’s when suffering from experimental ITP.3 This absolute requirement of FcγRIIb for the efficacy of IVIg’s in murine ITP was confirmed in a study published by Crow et al4 in the July 15, 2003, issue of Blood. In that interesting study the authors also report that mice with a single deficiency of molecules involved in signaling via FcγRIIb (ie, SHIP-1, SHP-1, and Btk), respond normally to IVIg’s when suffering from experimental ITP. The authors concluded that the beneficial effect of IVIg’s in this experimental ITP model is mediated via recruitment of as-yet-unknown signaling molecules by FcγRIIb. However, we would like to point to another possible explanation for the data of Crow et al. Huang et al5 have published evidence that both SHIP-1 and SHP-1 bind to phosphorylated immunoreceptor tyrosine-based inhibition motifs (ITIMs) in FcγRIIb. Furthermore, these authors also show that SHIP-1 and SHP-1 carry out similar functions; as indeed is well known in literature, as summarized by Erneux et al.6 In addition, SHP-1 and SHIP-1 share considerable homology, especially the N-terminal region, which harbors the SH2 domains. As a matter of fact, 24 of the first 107 amino acid residues are identical, yielding 22% identity. The homology of these domains, which have long been known to bind to phosphorylated tyrosine residues in so-called immunoreceptor tyrosine-based activation motifs (ITAMs) and ITIMs, is up to 56%. Thus, it is very well possible that signal transduction via FcγRIIb in the absence of SHIP-1 is mediated by SHP-1, and vice versa. Hence, the data in the report by Crow et al in our opinion do not definitely rule out a role of these signaling molecules in the FcγRIIb-dependent effects of IVIg’s in experimental ITP. In addition, the role of SHIP-2, which has been shown to have inducible expression on monocytes,6 is not taken into account in the study of Crow et al. Thus, it would be interesting to see whether IVIg’s are capable of inducing SHIP-2 in cells of the reticuloendothelial system and whether this has functional consequences for the protective mechanism of action of IVIg’s.

In conclusion, the experiments by Crow et al do not allow definite conclusions regarding involvement of SHIP-1, SHP-1, SHP-2, and Btk in the intracellular signaling pathways triggered by IVIg’s via FcγRIIb during ITP.

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References

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