Renal Failure and Posterior Reversible Encephalopathy Syndrome in Patients With Thrombotic Thrombocytopenic Purpura

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Background: Little is known of the nature of the neurologic manifestations in thrombotic thrombocytopenic purpura (TTP). We have recently reported posterior reversible encephalopathy syndrome (PRES) as the predominant brain abnormality in patients with TTP. Posterior reversible encephalopathy syndrome has been associated with a variety of medications and pathologic states including increased arterial blood pressure and renal failure. The factors that predispose patients with TTP to PRES are not known.

Objectives: To ascertain whether the presence and degree of hypertension and typical laboratory abnormalities seen in hospitalized patients with TTP are predictors of PRES.

Design, Setting, and Patients: We performed a retrospective analysis of brain imaging in 46 hospitalized patients with acute TTP seen at St Mary’s and Rochester Methodist hospitals in Rochester, Minnesota, from January 1997 to June 2007. Head computed tomographic scans and brain magnetic resonance images were evaluated independently by 2 investigators. We then performed statistical analysis to determine whether the presence of PRES was associated with the presence of hypertension or abnormal laboratory data, including renal function.

Results: Forty-seven incidences of patients having TTP and neuroimaging were evaluated over a 10-year period. Thirty-three patients (70%) had brain magnetic resonance imaging performed. Of the patients who had acute abnormalities on brain magnetic resonance imaging, 13 (48%) were found to have PRES. Degree of hypertension was not associated with PRES on brain magnetic resonance imaging (P = .55). There was no association between hematocrit or platelet nadir, maximum blood urea nitrogen, D dimer, fibrinogen, lactate dehydrogenase, or total bilirubin levels and occurrence of PRES. The only variable highly associated with PRES on neuroimaging was the glomerular filtration rate (P = .02).

Conclusion: The occurrence of PRES in patients with acute TTP is associated with worse renal function.

Arch Neurol. 2010;67(7):831-834.

PATIENTS WITH ACUTE THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) are seen by neurologists due to a common involvement of the central nervous system. Most patients have a decreased consciousness, but little is known of the nature of the neurologic manifestations. Earlier studies have explained these transient neurologic deficits by microthrombi causing ischemia, but we have recently reported posterior reversible encephalopathy syndrome (PRES) as the predominant brain neuroimaging abnormality in patients with TTP. What factor predisposes patients to PRES in TTP is not known.

Posterior reversible encephalopathy syndrome is a clinicoradiographic entity characterized by the presence of altered sensorium. It is often associated with visual disturbances and seizures. There is vasogenic edema on brain imaging, which typically has a predominant distribution in the posterior circulation territory. Many diseases have been associated with PRES, including acute hypertension, autoimmune disorders, immunosuppressants, and sepsis.

In this study, we sought to ascertain whether the presence and degree of hypertension and typical laboratory abnormalities seen in hospitalized patients with TTP are predictors of PRES and thus might provide further insight into the pathophysiology.

METHODS

PATIENTS

This retrospective analysis was approved by the Mayo Foundation Institutional Review Board. More than 200 patient records with a possible diagnosis of TTP were manually screened to determine eligibility for the study. Using the Mayo Clinic text search database, we identified 47 incidences (1 patient with recurrence) of patients older than 18 years with TTP and brain neuroimaging from January 1997 to June 2007.

The inclusion criteria consisted of adult hospitalized patients with a diagnosis of TTP (confirmed by a hematologist) in whom brain imaging...
had been obtained during the acute hospitalization. Children and patients with a diagnosis of hemolytic uremic syndrome were excluded.

Basic patient demographic information was obtained. Collected clinical data included the presence or absence of coma, focal neurologic findings, seizure occurrence and type, and need for endotracheal intubation. The patient’s maximum systolic blood pressures before neuroimaging and during the hospitalization were obtained as available. Hypertension was defined according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure seventh report guidelines as a systolic blood pressure greater than 140 mm Hg. The collected laboratory data consisted of hematocrit, platelet, and glomerular filtration rate nadir. Maximum blood urea nitrogen, D dimer, fibrinogen, lactate dehydrogenase, and total bilirubin levels were also assessed.

NEUROIMAGING

All brain magnetic resonance images (MRIs) and head computed tomographic scans were independently reviewed by 2 of us (T.M.B. and A.A.R.). One of the study physicians (A.A.R.) was blinded to the clinical data. Brain lesions were considered to be due to acute ischemia if they exhibited a high-intensity signal on diffusion-weighted imaging and a corresponding low diffusion coefficient on the apparent diffusion coefficient map. Cases were classified as PRES if they presented areas of vasogenic edema with proven clinical and/or radiological reversibility. In the rare case where the reviewers differed, the interpretation that agreed with the staff neuroradiologist report was used in our analysis.

STATISTICAL ANALYSIS

Data were summarized by descriptive statistics, including counts and percentages for categorical data and means and standard deviations for continuous parameters. Patient demographic characteristics, clinical characteristics, and laboratory parameters were tested for an association with the presence of PRES using univariate logistic regression. Odds ratios and 95% confidence intervals are reported to gauge the strength in association between the risk factor and the presence of PRES. To measure the prognostic ability of each clinical factor detected as significant, the c statistic was estimated and reported. The c statistic is identical to the area under the receiver operating characteristic curve; a value of 0.50 indicates random predictions and a value of 1.0 indicates perfect predictions. The desired c statistic is 0.70 or higher. P<.05 was considered statistically significant. Statistical analyses were carried out using JMP software version 7.0.1 (JMP, Cary, North Carolina).

RESULTS

Among 47 episodes of TTP, 15 of the patients (32%) developed coma, 17 (36%) had seizures, and 14 (30%) manifested with focal neurologic deficits. Thirty-three of these patients were examined with brain MRI. Table 1 displays their demographic and clinical characteristics. Acute changes on MRI were observed in 27 cases (82%), including 13 patients with PRES (39% of patients with TTP and brain MRI) and 48% of patients with acute changes on brain MRI. Among patients with PRES, coma occurred in 5 (38%), seizures in 8 (62%), and focal deficits in 6 (46%).

Focal signs ranged from subtle upper motor neuron facial weakness to hemiplegia. The brain MRIs for these patients reflected the neurologic findings (ie, patients with aphasia had left cortical lesions) (Table 2). The majority of patients with TTP had generalized tonic-clonic seizures (14 patients [82%]), 2 patients had focal seizures (11%), and 1 developed nonconvulsive status epilepticus. Electroencephalography was performed for 23 patients (49%). The most frequent electroencephalographic finding was delta slowing found in 13 patients (57%). The remaining electroencephalograms predominantly showed various degrees of generalized slowing. Seizures in patients with TTP and PRES were generalized tonic-clonic in 6 patients (75%), focal in 1 patient, and nonconvulsive status epilepticus in 1 patient. The most frequent electroencephalographic finding in this group was also diffuse slowing.

The maximum systolic blood pressures preceding neuroimaging and during hospitalization were obtained. Blood pressure measurements were not available for 2 patients (4%). The mean systolic blood pressures were 163 mm Hg prior to neuroimaging and 171 mm Hg for the complete hospitalization. Presence of systolic hypertension (blood pressure >140 mm Hg) was not significantly associated with radiological evidence of PRES on MRI only (P=.55). Patients with systolic blood pressure greater than 160 mm Hg also showed no statistically significant correlation with the presence of PRES (P=.41).

We then analyzed laboratory values deemed clinically relevant in hospitalized patients with TTP. We found that there was no significant association between the presence of PRES and the degree of leukocytosis, anemia, azo-

Table 1. Patient Demographic and Clinical Characteristics and Univariate Analysis of All Patients With Magnetic Resonance Imaging Findings Consistent With Posterior Reversible Encephalopathy Syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PRES (n = 13)</th>
<th>No PRES (n = 20)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation, mean (SD) [range], y</td>
<td>48.9 (18.2) [20.3-78.8]</td>
<td>57.3 (17.1) [20.6-81.9]</td>
<td>1.35 (0.84-2.33)</td>
<td>.24</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>19 (71)</td>
<td>23 (70)</td>
<td>0.61 (0.11-3.49)</td>
<td>.58</td>
</tr>
<tr>
<td>Coma, No. (%)</td>
<td>5 (58)</td>
<td>10 (50)</td>
<td>1.13 (0.23-5.52)</td>
<td>.88</td>
</tr>
<tr>
<td>Endotracheal intubation, No. (%)</td>
<td>6 (46)</td>
<td>14 (42)</td>
<td>1.00 (0.21-4.77)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Seizure, No. (%)</td>
<td>8 (62)</td>
<td>9 (45)</td>
<td>3.60 (0.74-20.10)</td>
<td>.11</td>
</tr>
<tr>
<td>Focal neurologic deficit, No. (%)</td>
<td>6 (46)</td>
<td>8 (40)</td>
<td>1.54 (0.33-7.54)</td>
<td>.58</td>
</tr>
<tr>
<td>Hospitalization, mean [SD] [range], d</td>
<td>22.4 (10.6) [3-39]</td>
<td>34.2 (42.6) [0-218]</td>
<td>2.35 (0.88-10.60)</td>
<td>.15</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; PRES, posterior reversible encephalopathy syndrome.

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The exact pathophysiology of PRES remains speculative at this point. Some investigators postulate that dysfunction in the autoregulation of cerebral blood flow from hypertension causes endothelial injury with subsequent vasoconstriction resulting in hypoperfusion. Others hypothesize that there may be direct damage to the endothelial cell promoting leukocyte trafficking or vasoconstriction resulting in hypoperfusion. A recent study found no significant correlation with the distribution of PRES with underlying pathology or degree of blood pressure, and so the pathophysiology remains elusive.

In 1925, Eli Moschcowitz, MD, described a severe multisystem disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, renal failure, and fever. In fact, TTP was uniformly fatal until the advent of plasmapheresis. We recently described PRES as the predominant neuroimaging pattern in patients with acute TTP. Clinical reversibility occurred within 1 to 2 weeks, but time to repeated imaging varied. Historically, PRES has been associated with blood pressure fluctuations and hypertension. In our TTP cohort, neither the presence of hypertension nor the maximum degree of systolic blood pressure prior to neuroimaging or throughout the patient's hospitalization correlated with the occurrence of PRES. Unfortunately, we were limited in that we did not have patient baseline blood pressure measurements and therefore...
could not include the potential correlation of blood pressure fluctuations with the development of PRES. However, our finding is in agreement with previous reports of PRES in patients without elevated blood pressure.13 The lack of association between hypertension and PRES in our patients with TTP suggests that the pathophysiology of PRES in these patients might be related to other factors, such as endothelial dysfunction or an immune-mediated response. Horbinski et al10 recently described a case of a patient with PRES with histologic confirmation of endothelial activation and the presence of markers of cell-mediated immune response. Maganta et al11 also described PRES in patients with neuromyelitis optica and aquaporin 4 autoimmunity. Aquaporin 4, a component of the astrocytic foot process in the blood-brain barrier, is a well-known water conduit that, when altered, leads to vasogenic edema.

We did not find a significant correlation between anemia, azotemia, hyperbilirubinemia, elevated lactate dehydrogenase level, high D dimer level, or thrombocytopenia and having PRES in our patients. We did, however, find that kidney injury was associated with the presence of PRES in hospitalized patients with TTP. Recently, Mueller-Mang et al12 analyzed creatinine level in 30 consecutive patients with findings consistent with PRES. They did not appreciate any significant difference in the severity or pattern of neuroimaging in their patients depending on creatinine level. In that study, the mean (SD) creatinine concentration was 2.29 (2.36) mg/dL among patients with hypertension and 2.44 (2.06) mg/dL among those who were normotensive (to convert to micromoles per liter, multiply by 88.4).10 This study did not include any patients with TTP. Our retrospective study is limited because our cohort consisted of the most severe cases of TTP in that they were all hospitalized patients. Thus, one could consider that more severe TTP is associated with PRES and not worse renal function. However, analysis of other commonly abnormal laboratory values in patients with severe TTP did not reveal any associations with PRES. We did not adjust for multiple comparisons due to small sample size. A P value of .02 in the case of glomerular filtration rate nadir (Table 3) is well below the conventional cutoff value of significance (ie, .05) despite the small sample size. An α-level of .05 implies that 5 in 100 comparisons (or 1 in 20) will be significant by chance alone.

Our finding that worse renal function is associated with PRES in patients with TTP raises the question of whether there could be a common target in the brain and kidneys affected as part of the pathophysiology of the disease. The link could be nonspecific endothelial damage. There are transporter proteins in the blood-brain barrier that are also present in the kidneys. For instance, P-glycoprotein, an adenosine triphosphate export pump, is present on the luminal side of the brain capillary endothelium and could have a significant role not only as a drug excretory pump but also as a barrier component.15,16 This protein has also been found to be expressed in proximal renal tubules.17 It is tempting to hypothesize that the function of this protein could be altered in the brain and the kidneys of patients with TTP.

In this study of patients with acute TTP complicated with PRES, we found that kidney injury was a significant predictor of PRES. This association may provide further insight into the pathophysiology of PRES. Encephalopathy in patients with TTP and decreased glomerular filtration rate should raise suspicion of PRES.

Accepted for Publication: October 28, 2009.

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Author Contributions: Study concept and design: Burrus and Rabinstein. Acquisition of data: Burrus. Analysis and interpretation of data: Burrus, Mandrekar, Wijdicks, and Rabinstein. Drafting of the manuscript: Burrus. Critical revision of the manuscript for important intellectual content: Burrus, Mandrekar, Wijdicks, and Rabinstein. Statistical analysis: Burrus and Mandrekar. Administrative, technical, and material support: Burrus. Study supervision: Wijdicks and Rabinstein.

Financial Disclosure: None reported.

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