Case Reports

Cerebral Thrombosis in \(\beta\)-Thalassemia/Hemoglobin E Disease

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We describe two Chinese patients with \(\beta\)-thalassemia/hemoglobin E disease who developed cerebral infarction due to occlusion or stenosis of their extracranial carotid arteries. The roles of platelet abnormalities and other factors in this condition are discussed. (Stroke 1990;21:812–816)

Thalassemia is a congenital hemolytic anemia prevalent in Asian and Mediterranean races. The homozygous state results in thalassemia major or Cooley's anemia, and such patients are transfusion-dependent. A less severe syndrome, thalassemia intermedia, may be due to compound heterozygosity for \(\beta\)-thalassemia and \(\beta\) variant (e.g., hemoglobin E [HbE]) genes and is characterized by anemia, jaundice, hepatosplenomegaly, and delayed puberty. Patients with thalassemia intermedia require only occasional blood transfusions but often need splenectomy later in life because of progressive splenomegaly. Acute cerebrovascular insults are rarely reported in thalassemic patients. We describe two Chinese patients with \(\beta\)-thalassemia/hemoglobin E (\(\beta\)-thal/HbE) disease who developed cerebral infarction due to extracranial artery disease.

Case Reports

Case 1

This 10-year-old Chinese girl presented at age 9 months with anemia and hepatosplenomegaly and a hemoglobin pattern typical of \(\beta\)-thal/HbE disease. Her hemoglobin level was approximately 5–9 g/dl, and her platelet counts ranged from 381 to 997 \(\times\) 10^7/1. At 5 years of age, she underwent splenectomy. She did not require blood transfusion and was maintained on aspirin alone. She was first admitted to our hospital in October 1988 for generalized weakness, retrosternal pain, and pain in her left elbow and right metatarsal heads. Examination showed a child small for her age, with typical Cooley's facies, pallor, a tinge of jaundice, hepatomegaly, sinus tachycardia (104/min), and a displaced apex beat. She was observed for a few days and discharged. Four weeks later she developed severe left parietal headache, weakness, and focal seizures in her right limbs and face. Examination revealed a conscious, afibrile but very irritable child with right hemiplegia and facial paresis. There were no carotid or cranial bruits.

Initially, the results of computed tomography (CT) were consistent with mild cerebral edema in the left hemisphere, but subsequent CT showed a large hypodense area in the left frontal and temporal regions compatible with infarction in the middle cerebral artery territory (Figure 1). Arch aortography and bilateral carotid angiography (Figure 2) showed complete occlusion of the left internal carotid artery 0.5 cm above its origin, with no visualization of the left middle cerebral artery circulation via the circle of Willis. Results of other investigations are presented in Table 1. Case 1 made a gradual recovery, but during the second month of convalescence she developed a recurrence of the left hemisphere stroke. She was started on low-dose aspirin (10 mg/kg/day) and 125 mg ticlopidine daily. Assessment 2 months later revealed a residual memory deficit, moderate right-sided hemiparesis, hemianopsia, and cortical sensory loss.

Case 2

This 34-year-old Chinese man had \(\beta\)-thal/HbE disease diagnosed at age 10 years (in 1965). His hemoglobin pattern comprised 27.3% HbF, 44.4% HbE, and 28.3% HbA. He was given infrequent blood transfusions to maintain his hemoglobin level at 6–10 g/dl. He subsequently underwent splenectomy and was maintained on prophylactic penicillin, vitamin C, folic acid, and subcutaneous deferoxamine injections. One year before the present admission, he developed brief attacks of occipital headache and clumsiness and numbness of his right hand. The results of neurologic examination and brain CT were normal. Six months later, he complained of dizziness, palpitation, sweating, nausea, and vomiting. Examination and Holter electrocardiographic recording and electrophysiologic study revealed no cardiovas-
cular abnormality. In 1988 he was admitted to our hospital because of subacute weakness and paresthesia of his right arm. Examination revealed pallor, jaundice, hepatomegaly, a left carotid bruit, and right upper limb monoplegia (grade 3/5). Four weeks later, he suddenly developed expressive dysphasia.

A small left frontal hypodensity was obvious on nonenhanced CT after the onset of dysphasia (Figure 3). Arch aortography and bilateral carotid angiography demonstrated a long atheromatous plaque approximately 3 cm long at the anterolateral aspect of the upper left common carotid artery extending to the bifurcation; this plaque narrowed the lumen by approximately 30% (Figure 4). There was also a marked stenosis at the origin of the left external carotid artery. No other vascular lesion was detected. Doppler ultrasonography showed similar narrowing of the two arteries. The results of other investigations are shown in Table 1.

Case 2 recovered partially, but his mild dysphasia and monoparesis persisted. Carotid endarterectomy was not considered advisable, and ticlopidine was prescribed.

Figure 1. Brain computed tomograms of case 1 show massive infarct in left middle cerebral artery territory.

Figure 2. Common carotid angiograms of case 1. Left: lateral projection of left common carotid angiogram; right: frontal projection of right common carotid angiogram. Total occlusion of left internal carotid artery is shown just beyond bifurcation. No cross-circulation to left middle cerebral artery is evident.
TABLE 1. Results of Relevant Laboratory Investigations in Two Patients With /3-Thalassemia/Hemoglobin E Disease

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Normal range</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin concentration (g/dl)</td>
<td>δ: 12.8–17.0, Ψ: 11.8–15.5</td>
<td>7.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Reticulocyte percentage (%)</td>
<td>&lt;1</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Leukocyte count (x10^9/l)</td>
<td>4.0–10.0</td>
<td>24.8</td>
<td>35.4</td>
</tr>
<tr>
<td>Platelet count (x10^9/l)</td>
<td>150–400</td>
<td>793</td>
<td>224–724</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/hr)</td>
<td>&lt;30</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Total bilirubin concentration (µmol/l)</td>
<td>4–23</td>
<td>40</td>
<td>61</td>
</tr>
<tr>
<td>Direct bilirubin (µmol/l)</td>
<td>0–4</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>SGOT, SGPT, and GGT (µmol/min/l)</td>
<td>11–35, 5–48, and 9–54</td>
<td>Normal</td>
<td>45, 71, and 44</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>In vitro platelet response to collagen, adrenaline, and ADP</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Protein C and protein S contents</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Antithrombin III content</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Lupus anticoagulant</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
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<tr>
<td>Antinuclear factor, rheumatoid factor</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Extractable nuclear antibody</td>
<td>ND</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Complement 3 and 4 levels</td>
<td>Normal</td>
<td>ND</td>
<td>Negative</td>
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<tr>
<td>Fasting blood glucose concentration</td>
<td>Normal</td>
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<tr>
<td>Fasting lipid profile</td>
<td>Normal</td>
<td>Normal</td>
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</tr>
<tr>
<td>VDRL</td>
<td>Negative</td>
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<td>Negative</td>
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<tr>
<td>Urine amino acid chromatography</td>
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<tr>
<td>Echocardiography</td>
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</table>

SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; GGT, γ-glutamyl transferase; ADP, adenosine diphosphate; ND, not done; VDRL, Veneral Disease Research Laboratory test.

Discussion

Cerebral thrombosis, while a frequent complication of sickle cell anemia, has rarely been reported in patients with thalassemia. Among 138 cases of β-thalassemia major from Greece, Logothetis et al briefly described two cases of “stroke syndromes.” One patient developed acute transient hemiparesis preceded by a convulsion 4 days after splenectomy.

Another patient presented with headache, visual blurring, behavioral changes, and right hemiparesis shortly after a blood transfusion, and the clinical picture was that of the posttransfusion syndrome. Paolino et al reported an Italian man with β-thalassemia major who had hypertension, increased intracranial pressure, convulsions, and right cerebellar ischemia 1 week after a blood transfusion. How-
ever, recurrent transient cerebral symptoms such as dizziness, visual blurring, and fainting were reported in 20% of the 138 patients in the series of Logothetis et al,2 and these symptoms were presumed to be ischemic in nature since they improved following transfusion.

Our two cases of cerebral infarction are interesting in several respects. Frequent blood transfusions, which have been associated with most reported cases of cerebrovascular syndromes,3-8 were not a feature in either patient. Moreover, extracranial carotid occlusion or stenosis causing stroke is reported for the first time in patients with β-thal/HbE disease. Exhaustive investigations in these two patients indicated that the only abnormalities were chronic anemia and thrombocytosis. The extracranial artery pathology was focal and probably thrombotic in origin. It has been recognized that prolonged thrombocytosis tends to occur following splenectomy in patients with persistent anemia and thrombocytosis. The extracranial artery pathology was focal and probably thrombotic in origin. It has been recognized that prolonged thrombocytosis tends to occur following splenectomy in patients with persistent anemia and thrombocytosis.9

Thrombocytosis (>400×10^9/l) was present in both of our patients, who underwent splenectomy years before the onset of stroke. Winichagoon et al10 studied 34 cases of β-thal/HbE (17 splenectomized) and found increased numbers of circulating platelet aggregates, impaired in vitro platelet function, and thrombocytosis in the splenectomized cases. The authors postulated that these abnormalities accounted for the high incidence of pulmonary artery thrombosis and hypoxemia observed in splenectomized thalassemic patients.11,12 Preston et al13 also reported neurologic dysfunction in 12 patients with thrombocytosis and deranged spontaneous and/or circulating platelet aggregation. The presumed mechanism was obstruction of the cerebral circulation. In our patients in vitro platelet functions were normal, but the numbers of circulating platelet aggregates were not assayed. In thalassemic patients with pulmonary artery thrombosis, antiplatelet agents have been recommended as they improve PaO2.11,12 In our patients, ticlopidine was used for secondary prophylaxis because of its proven efficacy as an antiplatelet agent and the relative absence of gastrointestinal side effects.14

In HbH disease, an α-thalassemia with a clinical picture similar to β-thal/HbE disease, Tso et al15 reported that two of nine splenectomized patients developed venous thrombosis and suggested that the hypercoagulable state in addition to thrombocytosis may be attributed to increased intravascular hemolysis similar to that in patients with paroxysmal nocturnal hemoglo-
Whether these factors operate in patients with \( \beta \)-thal/HbE disease remains to be determined.

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References


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