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## Acute Confusion and Mutism as a Presentation of Thalamic Strokes Secondary to Deep Cerebral Venous Thrombosis

Acute alteration of mental status in children is frequently associated with drug ingestion, hyperpyrexia, viral encephalitis including herpes simplex infection,<sup>1,2</sup> nonconvulsive status epilepticus,<sup>3</sup> and postictal confusion. Gascon and Barlow described acute confusion lasting 4 to 24 hours in four adolescents who later developed typical migraine, and described clinical features that differentiate this "acute confusional migraine" from toxic-metabolic encephalopathy and psychiatric disorders.<sup>4</sup> Sheth et al observed in six children similar clinical manifestations to those in adults with transient global amnesia.<sup>5</sup> Garg and DeMyer described six children with ischemic infarcts of the thalamus of arterial origin, three of whom presented with altered mental status and one with mutism.<sup>6</sup> We report a teenager who developed acute confusion and mutism due to bithalamic infarcts secondary to thrombosis of the internal cerebral vein, the basal vein of Rosenthal, the vein of Galen, and the straight sinus. Our case illustrates that deep cerebral venous sinus thrombosis may be an unusual cause of acute confusion and mutism.

## Case Report

A 17-year-old, previously healthy white adolescent girl presented to the emergency room with a 4-day history of headache, fatigue, nausea and vomiting, and a 4-hour history of confusion and difficulty walking. There was no history of loss of consciousness, fever, seizures, use of alcohol, smoking, or illicit drugs. Past medical history was significant for use of oral contraceptives for polycystic ovary disease. Family, birth history, and developmental milestones were unremarkable. On examination, she was afebrile, with a heart rate of 84 beats per minute and regular, and a blood pressure of 130/80 mm Hg. Signs of external injury or skin rash were absent. Neurologic evaluation showed her to be awake, appearing confused, and being completely mute. She was inattentive, though sometimes she could follow one-step commands (eg, show two fingers). She had a persistent right gaze preference, normal fundoscopy, and a mild left hemiparesis and facial weakness with brisk deep tendon reflexes and a left-sided Babinski reflex.

Her initial laboratory evaluation showed a white blood count (WBC) of 9600/ $\mu$ L with 59% neutrophils, 39% lymphocytes, and 2% monocytes; a normal hemoglobin concentration, hematocrit, and platelet count, normal blood urea nitrogen and electrolyte concentrations. The cerebrospinal fluid showed a normal opening pressure, a protein concentration of 286 mg/dL, a glucose concentration of 63 mg/dL, 5 white blood cells per  $\mu$ L with 61% neutrophils and 59% lymphocytes, 139 red blood cells/ $\mu$ L, and no xanthochromia. Blood toxicology screen was normal.

A computed tomography (CT) scan in the emergency room demonstrated bithalamic hypodensities and hyperdensity in the internal cerebral veins, the basal vein of Rosenthal, the vein of Galen, and the straight sinus (Figure 1). A magnetic resonance image (MRI) scan obtained 2 hours later demonstrated  $T_2$  hyperintensity consistent with infarction and/or edema in the thalami bilaterally, in the posterior right putamen, and the head of the caudate nuclei bilaterally (Figure 2). Magnetic resonance venography showed no flow-related enhancement in the internal cerebral vein, vein of Galen, and straight sinus, confirming the diagnosis of venous sinus thrombosis. Adequate flow-related enhancement was seen in the torcular, superior sagittal sinus and both transverse sinuses (Figure 3).

The patient was treated with heparin and admitted to the intensive care unit. Results of her coagulation panel included a normal prothrombin time, partial thromboplastin time, and fibrinogen concentration. Assays for the lupus anticoagulant and anticardiolipin antibodies were negative. Levels of antithrombin III, protein C, and protein S antigens were normal, although the level of functional protein S was low (39%; normal > 70%) in the setting of an elevated level of factor VIII (203%; normal < 200%). A screening test for activated protein C resistance revealed a suspiciously low ratio of 1.9% (normal > 2.5%). There was no evidence of the factor V Leiden mutation by polymerase chain reaction (PCR)-based analysis. A serologic assay of Epstein-Barr virus was positive [antiVCA IgG > 1280, IgM 40 (high), early antigen > 80, antinuclear antibody > 5], consistent with recent infection.

Over the following week, the patient's right gaze preference and left hemiparesis gradually improved, and her speech returned to being sensible and fluent. However, her neuropsychologic evaluation at discharge showed her to have problems with memory retrieval (with frank confabulations), sustained attention, and shifting sets. A CT scan performed 3 days after admission and while being treated with heparin showed mild petechial hemorrhage in the infarcts, but no frank hemorrhage. After 1 week's stay in the hospital on heparin, she was discharged on oral coumadin.

The patient was taken off coumadin 6 months after her stroke, when repeat magnetic resonance venography demonstrated normal flow-related enhancement in her deep venous structures. Neuropsychological evaluation showed almost complete recovery of her memory and attention, although she continued to have difficulties with naming objects, reading, and with her vocabulary. One year after her stroke and 6 months after discontinuing coumadin, her magnetic resonance venogram remained normal. Repeat assays of factor VIII and a screening test for activated protein C while not taking any contraceptives were normal; however, functional assessment of protein S revealed a persistently depressed activity level of 56% (normal > 70%). Blood for hypercoagulation studies in both parents were normal.

## Discussion

Cerebral venous thrombosis is more common than previously thought, and is remarkable for its large spectrum of clinical presentation, its highly variable mode of onset, numerous causes, and unpredictable, but usually favorable, outcome.<sup>7</sup> Although cerebral venous sinus thrombosis is rare, there are reported cases in neonates and children,<sup>8,9</sup> but reports of deep cerebral venous sinus



Figure 1. Noncontrast-enhanced axial CT scan demonstrates hypodensity, consistent with infarction and/or edema, throughout the thalami bilaterally (arrow). Hyperdensity, consistent with thrombus, is seen in the deep venous structures (curved arrow).

thrombosis in children are extremely rare. Adults with dural venous sinus thrombosis present with headache, irritability, seizures, and papilledema.<sup>10</sup> In contrast, the cerebral manifestations of deep cerebral venous sinus thrombosis are typically characterized by altered consciousness, decerebrate posturing, changes in extrapyramidal tone, and variable neurologic sequelae.<sup>6,11</sup> Some patients may die in the acute phase. These clinical manifestations correlate with bilateral lesions of the thalamic and basal ganglia, along with involvement of the corticospinal tract at the level of the internal capsule or the cerebral peduncles. These areas are drained by the deep cerebral venous system, which may be obstructed by a thrombus in any of its branches.<sup>12</sup>

The presenting manifestations of confusion, mutism, and motor abnormalities in our patient led us to consider the list of causes of an acute encephalopathic presentation. We eliminated some of the important conditions, including drug intoxication, head trauma, and acute infectious processes. The presence of an abnormal hyperintensity along the course of the deep venous structures along with bithalamic hypodensities (Figure 1), seen on the initial CT scan in the emergency room, was highly suggestive of a deep cerebral venous sinus thrombosis.<sup>13</sup> Although the CT scan aided us in our diagnosis, MRI and magnetic resonance venography (Figures 2 and 3) provided further confirmation of the anatomic localization of the thrombosis, as illustrated by Medlock et al in 1992.<sup>14</sup>



Figure 2.  $T_2$ -weighted axial magnetic resonance image at the same level demonstrates hyperintensity throughout the thalami (arrow head), the posterior right putamen (open arrow), and the caudate heads, consistent with infarction and/or edema. The deep venous structures are hypo-intense (curved arrow), most likely representing thrombus containing intracellular methemoglobin, rather than flow

The etiology of deep venous sinus thrombosis in our case is uncertain. Potential contributors to the pathogenesis of cerebral venous sinus thrombosis include inherited quantitative or functional defects in naturally occurring anticoagulant proteins, infections, systemic lupus erythematosus, brain tumors, and estrogen-containing oral contraceptives. Deficiencies of protein C, protein S, and antithrombin III are collectively identified in 5% to 10% of all cases of recurrent or familial thrombosis.<sup>15</sup> In contrast, more than 50% of patients with thrombophilia are affected by resistance to activated protein C.<sup>15</sup> A recent case-controlled study demonstrated that activated protein C resistance is the coagulation defect most frequently identified in association with cerebral venous sinus thrombosis.<sup>16</sup>

Protein C, a vitamin K-dependent serine proteinase, is locally activated by the thrombin-thrombomodulin complex at sites of vascular endothelial injury. Activated protein C exerts its anticoagulant effect by enzymatically cleaving and inactivating factors V and VIII, thus impeding fibrin formation and clot stabilization. The proteolytic activity of protein C is greatly enhanced by its cofactor, protein S, a second vitamin K-dependent protein with no proteolytic activity of its own. A single base-pair substitution in the gene for factor V results in an amino acid substitution at the protein C cleavage site that renders this mutant form of factor V resis-



Figure 3. Two-dimensional phase-contrast magnetic resonance venogram demonstrates no definite flow-related enhancement in the deep venous structures (straight arrow). There is normal flow-related enhancement in the superior sagittal sinus (curved arrow).

tant to proteolytic degradation by activated protein C. This mutation, designated Factor V Leiden, accounts for 90% to 95% of all activated protein C resistance. A Factor V Leiden mutation occurs in 5% to 7% of the general population, an extraordinarily high prevalence that far exceeds the frequency of thromboembolic events (1 per 1000, annually) in the same population.<sup>16</sup> Clearly, other congenital or acquired risk factors must conspire with the genetically conferred activated protein C resistance to produce a thrombotic event.

Although our patient had no evidence of factor V Leiden on PCR assay, her initially abnormal screening test for activated protein C resistance suggests a possible acquired inhibitor of activated protein C function. Her use of estrogen-containing oral contraceptive pills may have contributed to this apparent interference with activated protein C activity. The association between estrogen and venous thrombosis was first proposed more than 35 years ago.<sup>17</sup> A recent study of healthy women on oral contraceptive pills demonstrated acquired resistance to activated protein C, suggesting a possible mechanism by which oral contraceptive pills may mediate an increased risk of stroke.<sup>18</sup> Interestingly, estrogens have been shown to increase the level of  $\alpha_2$ -macroglobulin, one of several naturally occurring inhibitors of activated protein C.<sup>19</sup>

In addition to the effect of estrogen on protein C function, estrogen-containing oral contraceptive pills have been shown to decrease the levels of total (protein-bound/inactive) and free (unbound/functional) protein S by approximately 20%. It has been suggested that a decrease of this magnitude would pose little risk to women with normal protein S levels before initiating estrogen therapy. The potential for thrombotic complications may become clinically significant, however, when secondarily diminished levels of protein S are superimposed on a pre-existing, but clinically silent quantitative or functional deficiency of this anticoagulant protein.<sup>20</sup> Our patient's functional protein S level was low at initial presentation (39%), although this assay may have been confounded by an elevated level of factor VIII (203%). Her subsequent functional

assays of protein S remained abnormally low, however, at 17 and 20 months after discontinuing oral contraceptive pill therapy which was discontinued at her initial presentation. These findings indicate that she has either a congenital or acquired, persistent defect in protein S function. Familial dysfunction involving protein S has been well documented.<sup>21</sup> Since our family studies revealed normal protein S function in both parents, this finding in our patient reflects either a rare, spontaneous mutation, or the presence of an acquired inhibitor of protein S activity.

Cerebral sinus thrombosis in a young woman with previously undiagnosed, genetically transmitted protein S deficiency and complicated by oral contraceptive therapy has been documented before.<sup>22</sup> There appears to be a strong likelihood that our patient's abnormally low protein S function and the use of oral contraceptive pills were significant contributors to the pathogenesis of her sinus vein thrombosis and thalamic infarcts.

The serological tests in our patient are consistent with acute Epstein-Barr virus infection. The role of Epstein-Barr virus in the evolution of the cerebral venous thrombosis in our patient is unclear. Review of the literature showed no clear relationship between the two. A single case report<sup>23</sup> described pelvic venous thrombosis following infectious mononucleosis in a 15-year-old girl, whose laboratory evaluation revealed a heterozygous form of protein C deficiency. Though a clear association between acute Epstein-Barr virus infection and thrombosis have not been established, procoagulant alterations in the vascular endothelium have been described in herpes virus infection leading to thrombotic complications.<sup>24</sup> Clearly, more studies need to be done to look for any relationship of infections to hypercoagulable states.

The role of anticoagulation in the treatment of cerebral venous thrombosis remains controversial in the pediatric and neonatal population; it has been advocated by some as a means for prevention and treatment of thrombosis.<sup>25</sup> The dangers of deep venous sinus thrombosis cannot be underestimated; they include serious neurologic sequelae and even death. Others stress the dangers of provoking major intracranial hemorrhage during anticoagulation therapy.<sup>8,9</sup> In our case we elected to treat our patient with heparin, to prevent extension of the thrombus from the straight sinus into the torcular, thus avoiding serious complications.25 Mild petechial hemorrhage into the thalamus was detected on CT scan done 3 days after admission. Although this finding raised concerns about the safety of continuing anticoagulation therapy, the minimal changes on CT scan were felt insufficient to warrant discontinuation of the heparin. Fortunately, there was no further radiographic or clinical evidence of postinfarct hemorrhage. Our patient subsequently made a remarkable recovery.

In conclusion, we would like to emphasize the awareness of deep cerebral venous thrombosis as a rare cause of acute confusion and mutism in children seen in the emergency room. Magnetic resonance venography may be useful in confirming the diagnosis in cases with conflicting data on CT or MRI scans of the head.<sup>14</sup> Timely anticoagulation may be warranted on an individual basis to prevent extension of thrombus and resultant morbidity and mortality. A thorough evaluation of an underlying hypercoagulable disorder (protein C, S, antithrombin III, activated protein C resistance, antiphospholipid antibodies) must be made in every case of cerebral venous sinus thrombosis. Evaluation of family members

may facilitate the distinction between acquired and inherited risk factors for a hypercoagulable state. Catheter-directed venous thrombolytic therapy may also be considered on an individual basis.<sup>26</sup> Magnetic resonance imaging and magnetic resonance venography play an important role in monitoring the effects of anticoagulation and dissolution of the thrombus.

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