

## Homocystinuria With Transverse Sinus Thrombosis

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## Homocystinuria With Transverse Sinus Thrombosis

### ABSTRACT

A case of cerebral venous thrombosis caused by undiagnosed homocystinuria is reported. The pitfalls regarding the diagnosis of a potentially medically treatable condition are discussed. Cerebral venous thrombosis in children has a variable type of onset and a multiplicity of causes. This type of pathology, although not frequent, is more common than previously thought. Among the different etiologies, undiagnosed homocystinuria is not routinely considered. We report a case of venous thrombosis of the left transverse cerebral sinus in a girl with drug-resistant partial epilepsy and homocystinuria. This diagnosis was considered and confirmed after the appearance of acute cerebral symptoms caused by venous thrombosis. (*J Child Neurol* 2001;16:688-690).

### Case Report

This 7-year-old girl was first evaluated when she was 6 years old at the Institute of Clinical Pediatrics of the University of Siena. She suffered a partial seizure with clonic jerks of the right arm accompanied by twitching of the right corner of the mouth, hypotonia, and loss of consciousness. Following this episode, which lasted about 1 hour, she was admitted to a local hospital. An electroencephalogram (EEG) showed paroxysmal activity in the left frontocentral region. A computed tomography (CT) cerebral scan was normal. She was placed on magnesium valproate 400 mg/day, but after 4 months, she suffered another brief partial seizure with clonus of the right arm, again followed by transient right arm paresis. She was then admitted to the Institute of Clinical Paediatrics for additional tests.

The neurologic examination was normal. An EEG showed bilateral spike discharges over the central regions. Other examinations including magnetic resonance imaging (MRI), serum aminoacidogram, funduscopy, cytogenetics, routine blood chemistry, and urinalysis were normal. Psychometric evaluation (March 1998) indicated a borderline intelligence, with an IQ of 78 according to the Wechsler Intelligence Scale for Children-Revised. Difficulties in visuomotor and spatial orientation performance were noted. The patient was placed on a therapy of magnesium valproate 550 mg/day and discharged.

On October 3, 1999, the patient exhibited eyelid myoclonias and chewing automatism followed by a generalized tonic-clonic convulsion. The seizure lasted about 2 minutes and left her agitated, confused, and with the headache she had complained of prior to the seizure. She was admitted to another hospital. Fundoscopic examination was normal. A cerebral CT scan showed a slowing of blood flow within the left transverse sinus. An MRI taken on October 4, 1999, showed an extensive venous infarction on the left mid and posterior temporal region owing to thrombotic occlusion on the transverse omolateral sinus (Figure 1A). Magnetic resonance angiography confirmed the absence of signal of the transverse left sinus and of Labbé's veins (Figure 1B).

The patient was admitted to the Neurosurgical Institute of the University of Siena on October 1999. She was confused and markedly agitated and could not answer simple questions. She could not walk and complained of headaches. Coagulation studies including fibrinogen, partial thromboplastin time, prothrombin time, protein S and C, factor V Leiden, and thrombocyte counts were normal. An EEG showed runs of slow waves in the left centro-occipital region and isolated spike and waves in the left central region. A serum aminoacidogram was again performed. Homocysteine was 388.50  $\mu\text{mol/L}$  and L-methionine was 70.72  $\mu\text{mol/L}$ . Folic acid and vitamin B<sub>12</sub> were within normal limits. A urine test with nitroprusside was positive. A diagnosis of homocystinuria was reached, and the patient was given 300 mg of pyridoxine intramuscularly and thereafter by mouth. An anticoagulant treatment was also administered with continuous intravenous infusion of sodium heparin, followed by warfarin 8 mg/day. Serum aminoacidogram was again checked after 3 days of pyridoxine treatment. Levels of homocysteine and methionine were 62.90  $\mu\text{mol/L}$  and 43.49  $\mu\text{mol/L}$ , respectively.

The patient's condition gradually improved. She regained the level of consciousness she had prior to the episode. She was able to walk, her speech became normal, and she was able to answer questions. An EEG showed runs of slow waves in the left centro-occipital regions that were less evident than in the previous EEG. She was discharged after 25 days with anticoagulant therapy (warfarin 8 mg/day), desamethasone (1 mg/day), pyridoxine 300 mg/day, diazepam 3.5 mg/day, ranitidine 150 mg twice daily, and carbamazepine 800 mg/day. A cyanide nitroprusside test on urine was negative. On November 9, 1999, an MRI showed a decrease in the size of the abnormal area in the left temporal region. On a magnetic resonance angiogram, occlusion of the left transverse sinus was still present. The EEG showed some slow waves in the left occipital region.

A psychometric evaluation in February 2000 with the Wechsler Intelligence Scale for Children-Revised showed a Full-Scale IQ of 70, with a significant variance between Verbal IQ (81) and Performance IQ (61), and the scores on the subtests of comprehension and visuomotor and spatial competence were significantly lower than those obtained in the previous examination in 1998.

In the mother's serum, homocysteine was 76.66  $\mu\text{mol/L}$  and methionine was 30.37  $\mu\text{mol/L}$ . In the father's serum, homocysteine was 27.27  $\mu\text{mol/L}$  and methionine was 35.16  $\mu\text{mol/L}$ .

### Discussion

This patient's history was consistent with a diagnosis of epilepsy with complex partial seizures and Todd's paralysis. The last seizure was characterized by a generalized convulsion followed by headache and an acute alteration of her mental state. This situation in children can be associated with viral encephalitis and, in particular,



Figure 1. A, T<sub>2</sub>-weighted axial image. Extensive hyperintensity area localized in the left medial and posterior temporal lobe. B, Magnetic resonance angiogram. Coronal section. Absence of circulation blood in the left transverse sinus.

herpes simplex infection,<sup>1</sup> nonconvulsive status epilepticus,<sup>2</sup> and drug ingestion or hyperthermia.<sup>3</sup> Cerebral ischemic infarcts of the thalamus of arterial origin can also lead to similar manifestations.<sup>4</sup>

Deep cerebral venous sinus thrombosis can also cause acute confusion.<sup>5</sup> However, this condition is rare in children.<sup>6</sup> MRI and magnetic resonance angiography can be very helpful in the diagnosis because they localize the thrombosis and the extent of the cerebral infarction. Sinus thromboses have multiple etiologies. Protein C, protein S, and antithrombin III deficiencies can be responsible for 5 to 10% of the cases of familial thromboses, and resistance to activated protein C can be the cause in another 50% of the cases.<sup>7</sup> The mechanism of this abnormality has only recently been clarified. Protein C is a vitamin K-dependent proteinase locally activated by the thrombin thrombomodulin complex at the site of a vascular endothelial lesion. Factors V and VII are inactivated enzymatically by an activated protein C. Fibrin formation and clot stabilization are thus blocked. Protein S is the cofactor that

enhances the proteolytic activity of protein C. Denominated factor V Leiden is a mutant form of factor V with an amino-acid substitution at the protein C cleavage site and accounts for most cases of protein C resistance. The mutation of the gene for factor V is a single base-pair substitution.<sup>8-10</sup> Prothrombin G 20210 gene mutation, heparin cofactor II defects, and primary thrombocytopenia are also to be considered among the causes of thrombotic manifestations.<sup>11</sup> Primary antiphospholipid syndrome is another recently described condition associated with superior sagittal sinus thrombosis.<sup>12</sup> Epstein-Barr virus infection has also been implicated in venous thrombosis in a patient with a heterozygous form of protein C deficiency.<sup>13,14</sup> Thrombocytopenia with a positive lupus anticoagulant test associated with sagittal sinus thrombosis has been reported in a 22-month-old female.<sup>15</sup> Neurobrucellosis,<sup>16</sup> sickle-cell disease, autoimmune disease, and idiopathic hypereosinophilic syndrome must also be included in the differential diagnosis of deep cerebral vein thrombosis.<sup>17,18</sup> Among the possible etiologies in the above-reported literature, homocystinuria is not considered. However, hyperhomocystinemia is emerging as a strong risk factor for atherosclerotic vascular disease and for arterial and venous thromboembolism. Hyperhomocystinemia can be related to common genetic and acquired factors including folate and vitamin B<sub>12</sub> deficiencies. Vitamin B<sub>12</sub> supplements, in particular with folic acid, can reduce this effect.

Homocystinuria is a genetic metabolic disorder owing to a defect of enzyme cystathionine β-synthase. Clinical manifestations include subluxation of ocular lenses, hypopigmentation, malar flush, and skeletal abnormalities. Mental retardation is common. Epilepsy is present in 20% of cases. Arterial and venous thromboses are frequent. Deep cerebral venous thrombosis is not reported. There are patients who are pyridoxine responsive and patients who are not.<sup>19</sup> The gene has been mapped in the subtelomeric area of chromosome 21q22.3 and cloned.

In the patient we described, we also considered a diagnosis of homocystinuria when she was first admitted to the Institute of Clinical Paediatrics, but the first aminoacidogram report was normal. This was possibly owing to a mishandling of the blood. There were no clinical findings that could indicate homocystinuria such as skeletal abnormalities, ocular lens subluxation, malar flush, or peculiar gait. Epilepsy and borderline intelligence were the only clinical abnormalities. A nitroprusside test was not performed because freshly voided urine is necessary. Because headache, seizures, mental confusion, and somnolence indicated the possibility of an acute cerebral episode, MRI with gadolinium and magnetic resonance angiography demonstrated a thrombosis of the left transverse and sigmoid sinus plus an extensive venous infarction of the left mid and posterior temporal lobe (see Figure 1). The diagnosis of homocystinuria was then considered along with the other possible causes of hypercoagulability states and confirmed through the high values of plasma homocystine and methionine. Since the patient was responsive to pharmacologic doses of pyridoxine, a dietary treatment was not instituted.

This case illustrates the necessity of considering the diagnosis of homocystinuria in any case with hypercoagulability syndrome and the usefulness of pyridoxine treatment if the diagnosis of homocystinuria is confirmed.

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## Optic Neuropathy in Primary Antiphospholipid Syndrome in Childhood

### ABSTRACT

Neurologic symptoms associated with antiphospholipid antibodies in children include thrombotic events, unilateral movement disorders, or migraine. We present a 7-year-old girl with bilateral optic neuropathy, cerebral white-matter lesions, and antiphospholipid IgM that responded to prednisone and tended to relapse when it was stopped. Remission was obtained under maintenance corticosteroid therapy, and the antiphospholipid antibodies disappeared. This case suggests a role for antiphospholipid antibodies in the pathogenesis of optic neuropathy in childhood. (*J Child Neurol* 2001;16:690-693).

Antiphospholipid antibodies are autoantibodies of the IgG or IgM type that affect in vitro coagulation tests.<sup>1</sup> They include anticardiolipin antibodies, Venereal Disease Research Laboratory (VDRL) test, and lupus anticoagulant. Antiphospholipid antibodies can be detected in infectious, drug-induced, malignant or collagen vascular disorders, or in the absence of such underlying conditions as the primary antiphospholipid syndrome.<sup>2</sup> Symptoms and signs associated with primary or secondary antiphospholipid antibodies have mostly been described in adults and include arterial or venous thrombotic events, thrombocytopenia, recurrent fetal loss, and a variety of neurologic symptoms. There are very few reports on primary antiphospholipid syndrome in children.<sup>1-4</sup> We present a child with primary antiphospholipid syndrome whose symptoms involved the optic nerve and central nervous system.

### Case Report

This 7-year-old girl started to complain of daily headache and abdominal pain in February 1998. Decreased vision in the right eye and total visual loss in the left eye were noticed 4 months later. Topical corticosteroids were prescribed by her local doctor, and vision improved in 2 months. She was symptom free until September 1998, when she experienced back pain, vomiting, decreased vision, and weight loss. Although she had no fever, she was treated for meningitis in another hospital for 2 weeks. The symptoms persisted, and she was referred to Hacettepe University Children's Hospital in November 1998.

Her past medical history included typhoid fever at the age of 1 year and measles at 2 years. Her parents were nonconsanguineous, and her nine siblings were healthy. There was no history of tuberculosis or brucellosis in the family. Two maternal uncles had died at 12 years of age from