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Case 7-2018: A 25-Year-Old Man with New-Onset Seizures

Erica C. Camargo, M.D., Susie Y. Huang, M.D., Ph.D., Amel Karaa, M.D., and Matthew W. Rosenbaum, M.D.

PRESENTATION OF CASE

Dr. Ethan I. Meltzer (Neurology): A 25-year-old man was admitted to this hospital because of new-onset seizures.

The patient had been in his usual state of health until 2 days before admission, when episodes of twitching of the head and neck occurred. The first episode occurred after he awoke in the morning, and the second occurred 2 hours later; each of these episodes lasted approximately 1 minute. A third episode occurred 4 hours after he awoke, lasted 2 minutes, and was accompanied by stiffness of the left arm and left leg; the patient was aware of the twitching and stiffness but did not recall the subsequent events. Observers report that the patient's full body shook and that he lost consciousness and fell, striking his face. He stopped shaking after a few minutes and regained consciousness, but he was confused and was taken by emergency medical services to another hospital for evaluation. At the other hospital, another self-limited episode with full-body shaking and loss of consciousness reportedly occurred, and levetiracetam was administered. Imaging studies were obtained.

Dr. Susie Y. Huang: Computed tomography (CT) of the head, face, and cervical spine, performed without the administration of intravenous contrast material, revealed minimally displaced fractures of the nasal bones bilaterally (Fig. 1A) but no acute intracranial process or fractures of the cervical spine. Magnetic resonance imaging (MRI) of the head, performed without the administration of intravenous contrast material, revealed restricted diffusion in the cortex of the right superior frontal gyrus (Fig. 1B and 1C). T₂-weighted and fluid-attenuated inversion recovery images showed marked hyperintensity in the cortex and white matter of the adjacent right frontal lobe (Fig. 1D), a finding consistent with vasogenic edema. Two-dimensional time-of-flight magnetic resonance venography of the head revealed evidence of thrombosis or slow flow in the anterior aspect of the superior sagittal sinus (Fig. 1E). Susceptibility-weighted images of the head showed prominent linear hypointensity and evidence of cortical-vein thrombosis (Fig. 1F).

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N Engl J Med 2018;378:941-8.

DOI: 10.1056/NEJMcp1712226

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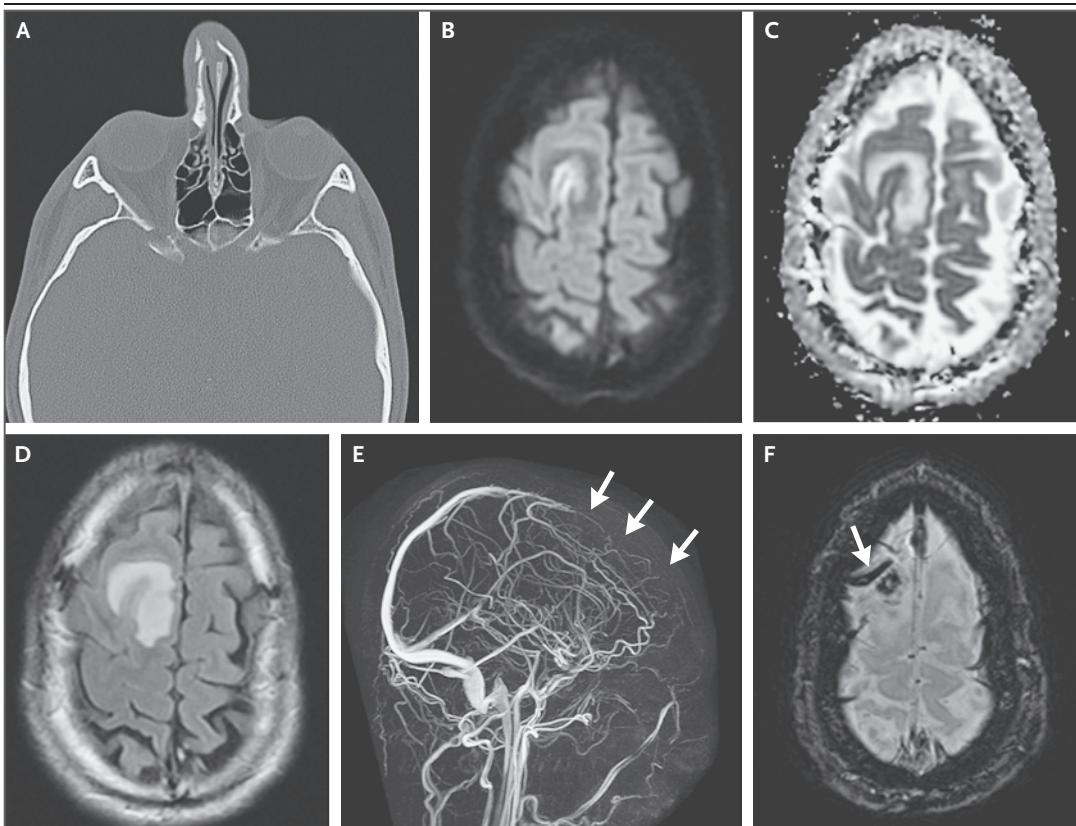


Figure 1. Imaging Studies of the Head.

CT and MRI were performed at the other hospital. An axial CT image (Panel A) shows minimally displaced fractures of the nasal bones bilaterally. An axial diffusion-weighted image (Panel B) and the corresponding apparent-diffusion-coefficient map (Panel C) show restricted diffusion in the right superior frontal gyrus. An axial T₂-weighted and fluid-attenuated inversion recovery image (Panel D) shows marked hyperintensity in the adjacent cortex and subcortical white matter, a finding consistent with vasogenic edema. A sagittal maximum-intensity-projection image from a two-dimensional time-of-flight magnetic resonance venogram (Panel E) shows no flow-related signal in the anterior third of the superior sagittal sinus (arrows), a finding consistent with slow flow or thrombosis. An axial susceptibility-weighted image (Panel F) shows linear hypointensity and susceptibility artifact in a superficial cortical vein along the right frontal convexity (arrow), a finding consistent with cortical-vein thrombosis.

Dr. Meltzer: Intravenous unfractionated heparin was administered. The patient was transferred to the neurology inpatient service of this hospital.

On arrival at this hospital, the patient reported no headache, blurred vision, nausea, vomiting, or dizziness. He had no history of bleeding or clotting disorders. Three years before admission, he had been involved in a motor vehicle accident related to falling asleep while driving. A CT scan of the head obtained at that time was reportedly normal, and antiepileptic medications were not prescribed. The patient had a tall stature and long arms; 10 years before admission, he had undergone cardiac evaluation after a family member in the health care field suggested the

possibility that he had Marfan's syndrome. Trans-thoracic echocardiography performed at that time reportedly showed normal size and function of the right and left ventricles, no clinically significant valvular disease, and a normal aortic root and ascending aorta.

The patient had a history of myopia and had used corrective lenses since he was 15 years of age. Three years before admission, during an ophthalmologic evaluation for laser-assisted refractive surgery, he had received a diagnosis of ectopia lentis with downward lens dislocation in both eyes. The ophthalmologist recommended repeat cardiac evaluation for Marfan's syndrome, and a transthoracic echocardiogram obtained at that

time was again normal. Four years before admission, the patient had undergone cholecystectomy. He had a history of attention deficit-hyperactivity disorder; his mother reported that he had had delays in reaching developmental milestones as a child and had followed an individualized educational plan for a learning disorder. He took no medications. His mother had hypercholesterolemia, his maternal grandmother had dementia and seizures, and his paternal grandfather had died after a stroke when he was 70 years of age. There was no family history of clotting disorders, congenital heart disease, or sudden cardiac death. The patient was a college student, and he did not smoke tobacco or use illicit drugs.

On examination, the temperature was 36.9°C, the blood pressure 112/80 mm Hg, the pulse 55 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 98% while the patient was breathing ambient air. The height was 189 cm, the weight 76 kg, the body-mass index (the weight in kilograms divided by the square of the height in meters) 21, and the arm span 192.5 cm. The distance from the top of the pubic symphysis to the floor was 105 cm while he was in the standing position.

The patient was fully alert and oriented. He had complete fluency, with no paraphasic errors or dysarthria. His concentration and attention were intact. His memory was limited, with intact registration but poor recall. The visual fields were full in response to confrontation. The pupils were equal and reactive to light. There was no ptosis, and extraocular movements were intact, with no nystagmus or saccadic pursuit. On the face, sensations to light touch and temperature were normal. There was no facial asymmetry. The tongue and palate were midline, and the hearing was normal in response to a finger rub.

The patient was able to shrug his shoulders and turn his head. His muscle bulk and tone were normal. He did not have cogwheel rigidity, bradykinesia, pronator drift, fasciculations, myoclonus, or tremor. Throughout the body, strength was full. Proprioception and sensations to light touch, temperature, pinprick, and vibration were intact. Deep-tendon reflexes were normal, and the toes were downgoing bilaterally. Results of finger-nose-finger and heel-to-shin tests were normal. Excoriations and ecchymoses were present on the nasal bridge and forehead. The patient had a high arched palate and slight pectus

Table 1. Laboratory Data.

Variable	Reference Range, Adults*	On Arrival at This Hospital
Hematocrit (%)	41–53	38.6
Hemoglobin (g/dl)	13.5–17.5	13.2
White-cell count (per mm ³)	4500–11,000	6720
Differential count (%)		
Neutrophils	40–70	40.9
Lymphocytes	22–44	46.6
Monocytes	4–11	10.3
Eosinophils	0–8	1.3
Basophils	0–3	0.6
Platelet count (per mm ³)	150,000–400,000	112,000
Red-cell count (per mm ³)	4,500,000–5,900,000	4,170,000
Mean corpuscular volume (fl)	80–100	92.6
Mean corpuscular hemoglobin (pg)	26–34	31.7
Mean corpuscular hemoglobin level (g/dl)	31–37	34.2
Red-cell distribution width (%)	11.5–14.5	13.8
Reticulocyte count (%)	0.5–2.5	2.1
Erythrocyte sedimentation rate (mm/hr)	0–13	36
Prothrombin time (sec)	11–14	17.6
Prothrombin-time international normalized ratio	0.9–1.1	1.4
Partial-thromboplastin time (sec)	22.0–35.0	40.9
D-dimer (ng/ml)	<500	441

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

excavatum, and striae were present on his back. When he wrapped a hand around the contralateral wrist, the top of the thumb covered the entire fingernail of the fifth finger. The remainder of the physical examination was normal.

Blood levels of electrolytes and glucose were normal, as were the results of a urinalysis, urine toxicology screen, and tests of renal and liver function. Other laboratory test results are shown in Table 1. Treatment with intravenous unfractionated heparin was continued.

Dr. Huang: CT angiography of the head was performed after the administration of intravenous contrast material. It revealed a nonocclusive filling defect in the anterior aspect of the

superior sagittal sinus, a filling defect in the cortical vein of the right frontal lobe, a punctate filling defect in the left internal jugular vein, and an area of mild hypodensity and swelling in the middle aspect of the right superior frontal gyrus, with no associated hemorrhage.

Dr. Meltzer: A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Erica C. Camargo: This 25-year-old man presented with new-onset focal motor seizures on the left side and generalized motor seizures. The seizures were complicated by a fall, which resulted in facial trauma. The seizures were most likely symptoms of a process of the central nervous system involving the right hemisphere.

CEREBRAL VENOUS SINUS THROMBOSIS

In this patient, the most notable findings on neuroimaging were ischemic injury and vaso- genic edema in the cortex of the right frontal lobe due to thrombosis of the cortical vein and superior sagittal sinus. Clots in the cerebral venous system usually develop insidiously, leading to progressive congestion and focal cerebral edema in the corresponding venous territory. Untreated cerebral venous sinus thrombosis can evolve into venous cerebral infarctions and hemorrhages, which were seen in this case. Cerebral venous sinus thrombosis is rare, accounting for 0.5 to 1% of all strokes,¹ and it most often affects women younger than 50 years of age who are taking oral contraceptives or have recently given birth.² The most common presenting symptom of cerebral venous sinus thrombosis is persistent headache. However, affected patients may present with seizures.^{1,2} Anticoagulation is the first-line treatment for cerebral venous sinus thrombosis; the duration of anticoagulation depends on the underlying cause of the thrombosis.

Why did cerebral venous sinus thrombosis develop in this patient? Most patients with this condition have an identifiable cause, and 44% have multiple causes.²

TRAUMA

Cranial trauma is a possible cause of cerebral venous sinus thrombosis in this patient, since he fell and struck his head, which resulted in nasal-bone fractures. However, I would not expect nasal-bone fractures to be associated with an

injury to the superior sagittal sinus, nor would I expect venous thrombosis with infarction to develop immediately after minor cranial trauma.

HYPERCOAGULABLE STATE

This patient had cerebral venous sinus thrombosis that simultaneously involved different venous territories, including the territory of the left internal jugular vein, which raises the possibility of an underlying hypercoagulable disorder. The combination of thrombocytopenia and a prolonged partial-thromboplastin time could be consistent with the antiphospholipid antibody syndrome. However, when these laboratory test results were obtained, the patient had recently been treated with unfractionated intravenous heparin, and such treatment is the most likely explanation for these abnormalities in this case. To definitively rule out a hypercoagulable disorder, further testing is needed.

INFLAMMATION

Infections and systemic inflammatory diseases can cause cerebral venous sinus thrombosis. However, this patient did not have a fever, and there was no obvious source of infection on physical examination. The mildly elevated erythrocyte sedimentation rate of 36 mm per hour is not consistent with either of these entities.³ Furthermore, inflammation related to cerebral venous sinus thrombosis can lead to a mildly elevated erythrocyte sedimentation rate and thus may account for this abnormality in this case.

MARFAN'S SYNDROME

Marfanoid habitus is a distinctive feature in this patient. Marfan's syndrome is a hereditary systemic connective-tissue disorder that is often caused by mutations of the gene encoding fibrillin 1 (*FBN1*), on chromosome 15. Patients with Marfan's syndrome may have ocular, cardiovascular, skeletal, and pulmonary abnormalities, as well as changes of the skin and lumbosacral dura mater. Tall stature, dolichostenomelia, arachnodactyly with a positive Walker-Murdoch sign (overlap of the distal phalanges of the thumb and fifth finger when a hand is wrapped around the contralateral wrist), pectus excavatum, myopia, ectopia lentis in both eyes, a high arched palate, and striae atrophicae are all features of Marfan's syndrome that were seen in this patient. We do not know whether he had a mutation of

FBN1, but he did not have a family history of Marfan's syndrome or a diagnosis of aortic-root aneurysm, and the absence of these factors makes the diagnosis of Marfan's syndrome unlikely.^{4,5} In addition, patients with Marfan's syndrome usually have normal cognitive development, but this patient had had delays in reaching developmental milestones as a child and had followed an individualized learning plan in school. Finally, to my knowledge, Marfan's syndrome has not been associated with cerebral venous sinus thrombosis. Are there any conditions that can explain the marfanoid habitus, cognitive delay, and cerebral venous sinus thrombosis in this patient?

SYNDROMES SIMILAR TO MARFAN'S SYNDROME

There is a wide spectrum of disorders that have overlapping features with Marfan's syndrome. These disorders are mostly due to mutations of *FBN1* or of the genes encoding transforming growth factor β receptor types 1 and 2 (*TGFBR1* and *TGFBR2*).^{4,6,7} They can be associated with skeletal abnormalities and with involvement of the vascular system, mainly in the form of arterial tortuosity, arterial dissection, or aneurysm of the sinus of Valsalva, aorta, or intracranial arteries. Patients with the Loeys–Dietz syndrome and those with the Shprintzen–Goldberg syndrome may have developmental and cognitive delay, and patients with involvement of the mitral valve, aorta, skin, and skeleton (known as the MASS phenotype) and those with familial ectopia lentis may have prominent ocular abnormalities. However, the only syndrome similar to Marfan's syndrome that is associated with skeletal, developmental, and ocular manifestations and with vascular thrombosis is homocystinuria.⁴

HYPERHOMOCYSTEINEMIA AND HOMOCYSTINURIA

Hyperhomocysteinemia is a pathologically elevated level of total serum or plasma homocysteine that can be due to one of several causes. Homocysteine is an amino acid that is produced through transmethylation of methionine. It is metabolized into cysteine by vitamin B_6 –dependent cystathionine β -synthase. Remethylation of homocysteine occurs in a pathway that is catalyzed by vitamin B_{12} –dependent methionine synthase and involves folate-dependent methylene-tetrahydrofolate reductase. Dysfunction of one of these enzymes or a deficiency of vitamin B_6 ,

folate, or vitamin B_{12} may result in hyperhomocysteinemia (Fig. 2).⁸ Hyperhomocysteinemia has been implicated in vascular injury in arterial and venous circulations, and it is strongly associated with venous thrombosis, including cerebral venous sinus thrombosis.^{8–10}

Homocystinuria is an inherited metabolic disorder in which a deficiency of cystathionine β -synthase leads to excess accumulation of homocysteine, methionine, or both in blood and urine.^{11–13} Classic homocystinuria is a rare autosomal recessive disease that is caused by mutations of the gene encoding cystathionine β -synthase (CBS), on chromosome 21.¹⁴ Affected patients may have marfanoid skeletal abnormalities and premature osteoporosis. Developmental delay is a common feature of homocystinuria that helps to distinguish it from Marfan's syndrome.¹⁵ Myopia often manifests in patients as young as 1 year of age, and ectopia lentis manifests between 3 years and 10 years of age. Downward lens dislocation occurs in 90% of patients with homocystinuria (as in this patient), whereas upward lens dislocation is common in patients with Marfan's syndrome. Thromboembolic disease develops in 25% of patients with homocystinuria, often when they are 8 to 12 years of age; systemic or cerebrovascular thromboembolism is the cause of death in 71% of patients with homocystinuria. Seizures occur in approximately 20% of patients.

This patient presented with cerebral venous sinus thrombosis and had several features suggestive of homocystinuria, including marfanoid habitus, developmental delay, early myopia, and downward lens dislocation. Are any other features of his presentation consistent with homocystinuria? He had premature gallbladder disease, which has been reported in both hyperhomocysteinemia and homocystinuria.^{16,17} In addition, hyperhomocysteinemia has been associated with the development of Alzheimer's disease and dementia.¹⁸ It is plausible that the patient's grandmother had been an asymptomatic carrier of a CBS mutation and had had subclinical hyperhomocysteinemia throughout her life, leading to dementia.

I suspect that anticoagulation was begun in this patient to prevent the progression of cerebral venous sinus thrombosis. I also suspect that the serum or plasma homocysteine and methionine levels were obtained and a sequence analysis

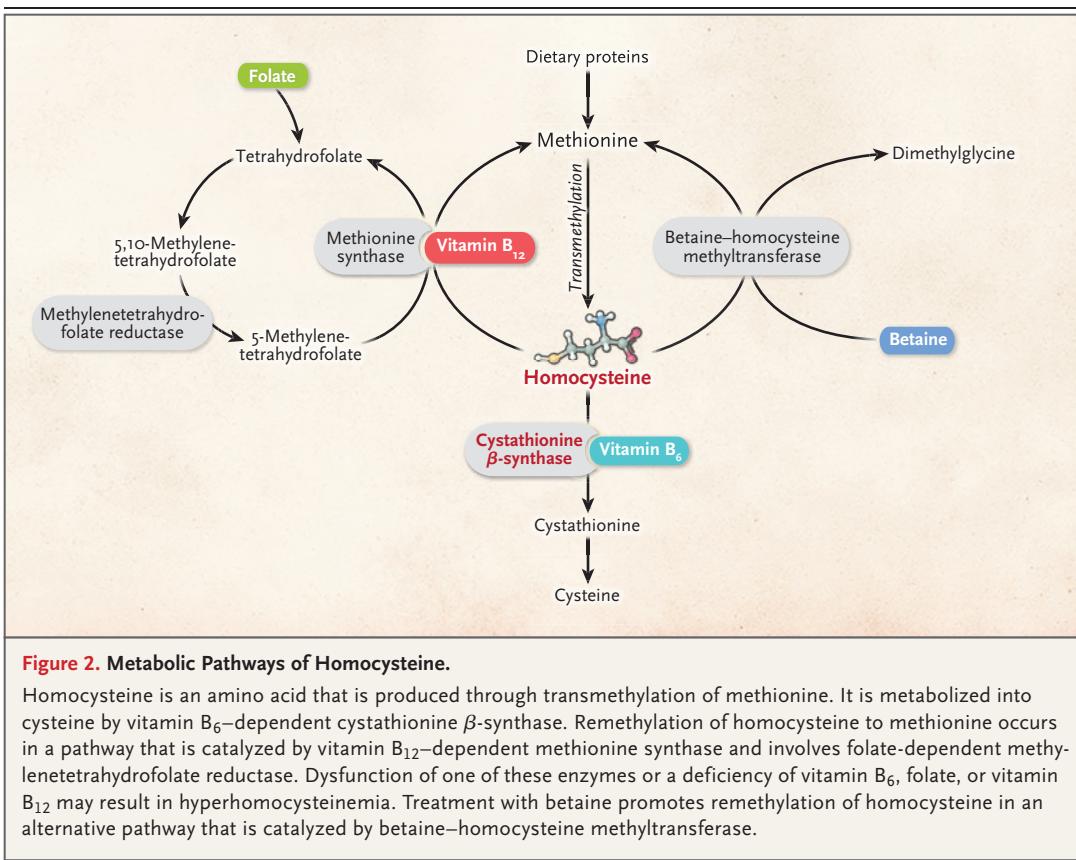


Figure 2. Metabolic Pathways of Homocysteine.

Homocysteine is an amino acid that is produced through transmethylation of methionine. It is metabolized into cysteine by vitamin B₆-dependent cystathione β -synthase. Remethylation of homocysteine to methionine occurs in a pathway that is catalyzed by vitamin B₁₂-dependent methionine synthase and involves folate-dependent methylenetetrahydrofolate reductase. Dysfunction of one of these enzymes or a deficiency of vitamin B₆, folate, or vitamin B₁₂ may result in hyperhomocysteinemia. Treatment with betaine promotes remethylation of homocysteine in an alternative pathway that is catalyzed by betaine–homocysteine methyltransferase.

of the CBS gene was performed to determine the cause of the homocystinuria.

Dr. Meridale Baggett (Medicine): Dr. Meltzer, what was your clinical impression when you evaluated this patient?

Dr. Meltzer: Given this young man's unusual presentation with cortical-vein thrombosis in the absence of any clear risk factors or inciting events for clot formation, we were concerned about an underlying hypercoagulable state caused by a genetic syndrome associated with stroke. Since the patient had marfanoid habitus and ectopia lentis with downward lens dislocation, we suspected homocystinuria as the cause of his hypercoagulable state.

PATHOLOGICAL DISCUSSION

Dr. Matthew W. Rosenbaum: The diagnostic test was a test of the plasma homocysteine level, which was markedly elevated at 365 μ mol per liter (reference range, 0 to 14). Causes of a mild-to-moderate elevation in the plasma homocysteine level include kidney disease and liver disease; use of a sample obtained when the patient had not fasted can also result in an elevated level.^{19,20} This patient presented with a normal creatinine level and normal results of liver-function tests, findings that make kidney and liver disease unlikely. Most nongenetic causes of an increased homocysteine level are associated with a deficiency of vitamin B₁₂ or folate. Although vitamin B₁₂ and folate levels were not initially measured in this patient, deficiencies of these vitamins were thought to be unlikely, because he did not have macrocytic anemia or other signs or symptoms of vitamin B₁₂ or folate deficiency. Drugs that interfere with vitamin B₁₂ and folate metabolism, such as antiepileptic medications and metho-

CLINICAL DIAGNOSIS

Homocystinuria.

DR. ERICA C. CAMARGO'S DIAGNOSIS

Homocystinuria.

trexate,¹⁹ may cause an elevation in the homocysteine level, but this patient was not known to be taking any such drugs.

The extreme elevation in the plasma homocysteine level that was seen in this patient (>25 times the upper limit of the normal range) is helpful in narrowing the differential diagnosis to the genetic causes of homocystinuria, including deficient cystathionine β -synthase, defective methylcobalamin synthesis, or abnormal methylenetetrahydrofolate reductase (Fig. 2). A homocysteine level of more than 100 μ mol per liter is typically considered to be specific for a genetic cause of homocystinuria.

DISCUSSION OF MANAGEMENT

Dr. Amel Karaa: This patient was referred to the genetics and metabolism department for further evaluation and treatment. Additional testing revealed normal plasma folate and vitamin B_{12} levels. Amino acid testing revealed a high plasma methionine level (570 nmol per milliliter; reference range, 4 to 44), a finding consistent with a diagnosis of homocystinuria due to a deficiency of cystathionine β -synthase.

In treating young adults with homocystinuria, the goal of therapy is to maintain the total homocysteine level at less than 120 μ mol per liter to prevent the thromboembolic events that are commonly seen in late-onset forms of homocystinuria. Vitamin B_6 is a cofactor for cystathionine β -synthase, and some patients with homocystinuria have decreases in the homocysteine level when they are treated with vitamin B_6 . Therefore, the initial step in this patient's treatment was to establish whether the homocysteine level was responsive to the administration of high doses of vitamin B_6 . The patient was also treated with vitamin B_{12} and folate to facilitate the conversion of homocysteine to methionine by methionine synthase. A low-methionine diet, which requires low intake of natural protein, was recommended.²¹ The patient's homocysteine level remained high, at 245 μ mol per liter, and the level did not decrease despite further increases in the daily intake of vitamin B_6 . We suspected that the persistent elevation in the homocysteine level was related, at least in part, to nonadherence to the low-methionine diet, which can be difficult for patients to follow.

We also performed a CBS sequence analysis, which revealed that the patient was compound heterozygous for two known disease-causing mutations: c.1152G→C (p.Lys384Asn) and c.919G→A (p.Gly307Ser). This finding genetically confirms the diagnosis of homocystinuria due to a deficiency of cystathionine β -synthase. The Gly307Ser mutation is known to cause homocystinuria that is nonresponsive to vitamin B_6 , which explains why the patient had no benefit from high doses of vitamin B_6 .²² Therefore, treatment with betaine was initiated to provide an alternative remethylation pathway to convert excess homocysteine to methionine (Fig. 2). Treatment with betaine is usually associated with an acceptable side-effect profile, but in rare cases, the increase in methionine production causes cerebral edema when an extreme level is reached (>1000 nmol per milliliter). In this patient, the plasma total homocysteine, methionine, vitamin B_{12} , and folate levels were closely monitored, and 4 weeks after the initiation of betaine therapy, the homocysteine level finally dropped to 129 μ mol per liter.

Once the desired total homocysteine level was reached, the daily intake of vitamin B_6 was decreased to avoid the development of peripheral neuropathy. The patient was instructed to have regular eye examinations because of the risk of lens dislocation, to undergo regular bone densitometry because of the risk of early osteoporosis, to seek nutritional intervention to maintain a low-methionine diet, and to have neuropsychiatric assessments as needed. An evaluation for other cardiovascular risk factors was performed to prevent further thromboembolic events. Finally, contingency planning for acute illnesses and surgeries was provided to avoid clotting complications that are caused by an elevation in the total homocysteine level during periods of stress. The patient continued to receive treatment with anticoagulation. He had a planned duration of therapy of at least 6 months, but his care was transferred to another facility during that time.

ANATOMICAL DIAGNOSIS

Homocystinuria due to genetic mutations of the gene encoding cystathionine β -synthase (CBS).

This case was presented at Neurology Grand Rounds.
No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Anand Dighe, M.D., for his assistance with the pathological discussion.

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