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Pyridoxine-Unresponsive Homocystinuria With an Unusual Clinical Course

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Progressive premature atherosclerosis and associated thromboembolic complications are the main causes of morbidity and mortality in patients with homocystinuria. However, thrombosis is rarely the predominant or presenting manifestation leading to the diagnosis of homocystinuria. We report on an otherwise asymptomatic teenage boy of normal intelligence who had a superior sagittal sinus thrombosis documented by CT and MRI scans. He presented with pneumothoraces, papilledema, and transient right hemiparesis. He subsequently developed empyema and necrotizing pneumonia as well as deep venous thromboses. The diagnosis of pyridoxine-unresponsive homocystinuria was made on the basis of clinical chemistry analyses, enzyme assay, and clinical trial. He has remained symptom-free under treatment with betaine and methionine restriction. We suggest that there exists a subset of patients with pyridoxine-unresponsive homocystinuria who are at risk for thromboembolism, but who may remain undiagnosed because of an otherwise mild clinical course.

KEY WORDS: **homocystinuria, thrombosis, premature atherosclerosis, asthma, pyridoxine, betaine**

INTRODUCTION

Of the 3 autosomal recessive enzymopathies known to cause homocystinuria, cystathionine beta-synthase deficiency is the most common form [Mudd and Levy, 1983]. The stereotypic phenotype includes a Marfanoid habitus, developmental delay with mild-to-moderate mental retardation, osteoporosis with skeletal deformities, and ectopia lentis [Mudd and Levy, 1983]. A milder clinical course—including relatively higher intelligence and the development of ectopia lentis at a later age—is generally correlated with pyridoxine-responsiveness [Mudd and Levy, 1983; Mudd et al., 1985]. Thrombosis is rarely the presenting manifestation leading to investigation for homocystinuria [Mudd et al., 1985; Wong et al., 1977; Rodgers and Shuman, 1986]. Here we report on an intelligent teenage boy with pyridoxine-unresponsive homocystinuria, in whom sagittal sinus thrombosis was the presenting clinical event.

MATERIALS AND METHODS

Amino acid concentrations were determined by standard methods using an LKB Alpha Amino Acid Analyzer with plasma samples that were deproteinized immediately after they were obtained. Cultured skin fibroblasts were grown from a skin biopsy obtained from the propositus with informed consent. Cells were propagated according to standard procedures [Packman et al., 1987], with minor modifications (20% fetal calf serum, 5% CO_2, added gentamicin [50 μg/ml], and glutamine [1%]). Cystathionine beta-synthase assays were performed in homogenates of cultured skin fibroblasts according to published procedures [Fowler et al., 1978].

CLINICAL REPORT

The propositus is the only child of non-consanguineous parents. The diagnosis of asthma was made in infancy with a history of frequent exacerbations and hospitalizations since age 8 years. He maintained an "A" average in school and participated in the school band, despite frequent absences for asthma treatment. At age 14 years he was hospitalized because of recurrent left pneumothoraces requiring chest tubes. Soon thereafter he developed a right pneumothorax and staphylococcal pneumonia, and presented with headache, nausea, vomiting, syncope, diplopia, and dizziness. CT scan (head) showed diffuse white matter edema consistent with pseudotumor cerebri. He was transferred to the University of California-San Francisco because of increasing intracranial pressure and bradycardia. At the time of transfer he was being treated with theophylline, prednisone, micronase, phenobarbital, eryth-

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romycin, vancomycin, bronksol, meperidine, hydroxyzine, and metaproterenol nebulizer.

His height, weight, and head circumference were at the 70–80th centiles, with an upper/lower segment ratio of 0.98 (normal mean = 0.97 [Wilkins et al., 1965]) and an arm span/height ratio of 1.05 (normal mean = 1.02 [Wilkins et al., 1965]). The right anterior thorax was mildly tender to palpation, and there were multiple tube scars with right chest tube and subclavian line in place. Neurological examination was normal except for 2–3 beats of clonus bilaterally and right extensor plantar response (which later became flexor). There was mild papilledema without hemorrhage or vessel abnormality. Visual acuity was 20/20 uncorrected, O.U., and visual fields were full with normal color vision. On lumbar puncture the opening pressure was 225 mm H_2O, and closing pressure was 85 mm H_2O. Results of cerebrospinal fluid (CSF) studies were normal, and all CSF and blood cultures were sterile. Hypercoagulability work-up showed no abnormality.

Subsequently he developed empyema, necrotizing pneumonia, deep venous thromboses, and hypertension treated with antibiotics, heparin, and anti-hypertensive medications, respectively. His symptoms of increased intracranial pressure responded to acetazolamide. He was discharged to his referring hospital, and metabolic studies were continued as an out-patient.

RESULTS

The diagnosis of homocystinuria was made on the basis of a urine cyanide nitroprusside reaction and elevated plasma homocystine and methionine concentrations (Table I). Cystathionine beta-synthase activity in cultured skin fibroblasts was 0.3% of control activity and was not altered by the addition of pyridoxal phosphate (Table II).

CT scan of the head showed decreased density of the white matter diffusely, with normal-appearing gray matter. The ventricles and sulci were normal in size, shape, and position, with no extra-axial fluid collections. On intermediate windows, a small focus of low density was noted in the expected course of the superior sagittal sinus. MRI scan of the head confirmed the clinical suspicion of sagittal sinus thrombosis. The delta sign [Schwab et al., 1987; Zimmerman et al., 1987], indicative of superior sagittal sinus thrombosis, was absent on repeat head CT scan 24 days later.

A methionine-restricted diet was instituted, and the patient was begun on supplemental pyridoxine (up to 500 mg/day) and folate without change in plasma homocystine concentrations (Table I). The addition of betaine (3 g BID) to the regimen resulted in a substantial reduction in plasma homocystine levels during the initial 4 months of treatment (Table I). Subsequent variability in diet and compliance resulted again in elevations of plasma homocystine and methionine levels, and the effect of betaine is still being documented with re-institution of a controlled regimen. In addition the patient is receiving aspirin and dipyridamole and, except for minor symptoms of the post-phlebitic syndrome, is clinically well. Repeated slit lamp examinations have shown no lens dislocation.

TABLE I. Plasma Amino Acid Concentrations During Treatment*

	Homocystine (μmol/L)	Methionine (μmol/L)
Pyridoxine[a]	42 (27–62)	608 (446–819)
Betaine[b]	6.9 (0–32, 60% of values were 0)	745 (419–1158)
Normal range	0	1–120

*Values are means (ranges) of 5 (pre-betaine) or 15 (betaine) independent determinations over 10 and 4 months, respectively.
[a]During this period, patient was on pyridoxine (500 mg/day), folate supplementation (0.5 mg/day), and a methionine-restricted diet (10 mg/kg/day).
[b]During this period, patient was on betaine (6 g/day), and remained on pyridoxine (500 mg/day), folate (0.5 mg/day), and a methionine-restricted diet (10 mg/kg/day).

DISCUSSION

The paucity of manifestations in this patient is noteworthy in the face of pyridoxine-unresponsiveness by clinical trial (Table I) and enzyme assay (Table II). Pyridoxine-unresponsive patients generally have lower mental capabilities and show earlier manifestations than do pyridoxine-responsive patients [Mudd and Levy, 1983; Mudd et al., 1985]. In contrast, our patient is academically superior, without lens dislocation, Marfanoid habitus, or osteoporosis by routine radiographs (despite long term steroid treatment for asthma). While patients with sterotypic homocystinuria have had cerebral thromboses [Gibson et al., 1964; Zimmerman et al., 1987; Amram et al., 1986; Schwab et al., 1987], only one patient has been reported previously with multiple arterial occlusions without other signs of the disorder [Newman and Mitchell, 1984]. Further, it is rare for thromboembolism to be the presenting manifestation [Mudd et al., 1985; Newman and Mitchell, 1984].

Asthma is a major cause of morbidity in our patient and mortality in another (patient followed by J.K.). There are no published reports or postulated associations between reactive airway disease and homocystinuria. One study [Wilcken et al., 1983] noted severe asthma in 3 of 11 patients with pyridoxine-unresponsive homocystinuria. Two of the patients so described had "no additional attacks of asthma during treatment (with betaine)" [Wilcken et al., 1983]. Among 38 cases distributed in 20 families reviewed in detail by McKusick [1972], there was one patient with asthma and spontaneous pneumothoraces (case 25, family 14), a second with asthma alone (case 28, family 16), and a third patient with asthma requiring steroid treatment (case

TABLE II. Fibroblast Cystathione Beta Synthase Activity*

	−PLP[a]	+PLP
Patient	0.04	0.04
Control	11.77	19.93

*Values are specific activities, nmol cystathionine formed/#/h/mg protein, in patient and a simultaneous control fibroblast homogenate. The mean ± SD for 16 control fibroblast lines is 25.5 ± 12.
[a]PLP: 1 mM pyridoxal phosphate, added to the reaction mixture. The addition of 1 mM PLP to the assay stimulates cystathionine beta synthase activity in control fibroblasts by a factor of 1.4–1.7.

31 in family 18). We speculate that the interaction between homocystine and its metabolites and bronchial cells may play a role in the pathophysiology of reactive airway disease in such patients and may well be a subject for further investigation.

Opinion is divided as to whether the thrombotic tendency is due to homocystine-induced injury to the vascular endothelium [Natowicz and Kelley, 1987; Mudd and Levy, 1983; Harker et al., 1974, 1976], abnormal platelet turnover [Harker et al., 1974; Hill-Zobel et al., 1982; Schafer, 1985], or even of activation of factor V by a homocystine-induced vascular endothelial cell activator [Rodgers and Kane, 1986]. Recent studies have suggested the possibility of premature occlusive vascular disease in heterozygotes for homocystinuria [Boers et al., 1985; Brattstrom et al., 1984], although a different epidemiological study failed to demonstrate this [Mudd et al., 1981]. In the absence of a response to pyridoxine, our patient was treated with methionine restriction and betaine [Wilcken et al., 1983; Smolin et al., 1981] and has remained on dipyridamole and aspirin. Aspirin and dipyridamole may reverse decreased platelet survival time [Harker et al., 1974], although the evidence for this is conflicting [Hill-Zobel et al., 1982]. Further, it has been suggested that pyridoxine is an antithrombotic agent in its own right [Editorial, 1981]. Whatever the actual mechanisms in our patient, homocystinuria improved over the short term, and there have been no subsequent episodes of thromboembolism in 3 years.

While it has been suggested [Mudd et al., 1985] that thromboembolic disease in (homozygous) homocystinuria is infrequent before age 20 years, some young individuals with homocystinuria who have had thrombotic events without other "typical" clinical manifestations may be undiagnosed [Mudd et al., 1985; Schwab et al., 1987; Wilcken and Turner, 1978]. In the absence of appropriate testing, our patient might well have remained in the category of idiopathic thromboembolic disease. It is clear that sufficient evidence has accrued to dictate that homocystinuria should be considered in the differential diagnosis of venous or arterial thrombosis, even in the absence of other manifestations of the disease, and regardless of the age of the patient [Natowicz and Kelley, 1987; Mudd et al., 1985; Wong et al., 1977; Gibson et al., 1964; Zimmerman et al., 1987; Amram et al., 1986; Schwab et al., 1987].

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