

## Ornithine transcarbamylase deficiency presenting with strokelike episodes

J. Christodoulou, MBBS, PhD, I. A. Qureshi, PhD, R. R. McInnes, MD, PhD, and J. T. R. Clarke, MD, PhD

From the Division of Clinical Genetics, Hospital for Sick Children, Toronto, Ontario, and the Pediatric Research Centre, Hôpital Sainte-Justine, Montreal, Quebec, Canada

**A girl with ornithine transcarbamylase deficiency had a history of recurrent strokelike episodes. The differential diagnosis of unexplained stroke should include primary urea cycle defects. (J PEDIATR 1993;122:423-5)**

Ornithine transcarbamylase (EC 2.1.3.3) deficiency, an X-linked inborn error of ammonia metabolism, is the most common urea cycle defect.<sup>1</sup> Affected hemizygous males usually have hyperammonemic encephalopathy in the newborn period that is often fatal.<sup>1</sup> Rarely, affected males are seen later with a range of symptoms including anorexia, poor growth, protein avoidance, behavior changes that can be mistaken for psychotic illness, and mental retardation.<sup>2</sup> The clinical phenotype in heterozygous females is broad, ranging from no symptoms to hyperammonemic episodes as severe as those seen in males.<sup>3,4</sup> We report here the novel observation of recurrent strokelike episodes in a heterozygous OTC-deficient girl.

### CASE REPORT

This girl was the first child of nonconsanguineous Chinese parents. The pregnancy, labor, and postpartum period were uncomplicated. The child was developmentally normal and had enjoyed good health until the age of 2 years 8 months, when she came to medical attention because of recurrent episodes of transient hemiparesis. One month before admission to the hospital, she had several transient episodes of right-sided weakness.

The girl's first admission to the hospital was because of the sudden onset of right-sided hemiplegia, with facial involvement and slurred speech. At that time her height (80 cm) was below the third percentile for age; her weight (13.2 kg) and head circumference (49 cm) were at the 50th percentile. She was alert and had no dysmorphic features, abnormal cardiorespiratory signs, or hepatosplenomegaly. She had patchy atopic dermatitis. Neurologic examination demonstrated right-sided upper motor neuron hemiplegia, with power being grade II/V in the upper extremity and grade IV/V in the lower. She had hyperreflexia on the right, and the plantar reflex was extensor on that side; power and reflexes were normal on the left.

The family history was unremarkable. In particular, there was

no history of unexplained neonatal or childhood deaths, mental retardation, or protein aversion in the maternal line.

Initial investigations showed normal values for hemoglobin, leukocyte count, erythrocyte sedimentation rate, coagulation, venous blood gases, electrolytes, glucose, creatinine, thyroxine, and thyrotropin. The plasma level of ammonium at admission was 339  $\mu\text{mol/L}$  (normal,  $<50$ ) but gradually fell to 167  $\mu\text{mol/L}$  with no specific treatment and during an unrestricted diet. The results of semiquantitative analyses of urinary amino and organic acids, acylglycines, and acylcarnitines were normal. Plasma levels of protein S, protein C, fibrinogen, D-dimer, heparin cofactor 2, antithrombin III, and plasminogen were normal. Mixed leukocyte  $\alpha$ -galactosidase activity was also normal. The results of other relevant tests are summarized in the Table.

OTC Ornithine transcarbamylase
--------------------------------

An electroencephalogram showed a slow-wave abnormality over the left hemisphere. A computed tomography scan of the head demonstrated a marked hypodensity in the left frontoparietal region, loss of gray-white matter differentiation, a hypodensity in the right frontal region, and a mass effect with midline shift (Figure). These findings were consistent with left frontoparietal and right frontal infarction. A single-photon emission computed tomography cerebral perfusion scan showed a marked reduction of perfusion in the left hemisphere, especially in the frontal lobe. A muscle biopsy specimen showed no histologic, histochemical, or electron microscopic abnormalities.

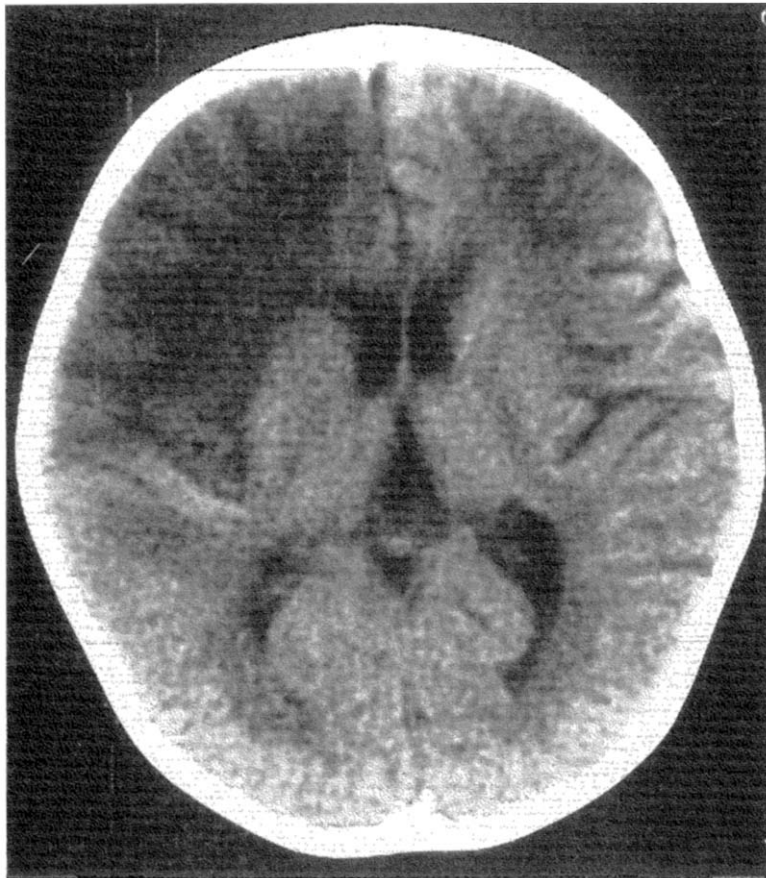
During the next few weeks, muscle strength progressively improved. She was readmitted to the hospital a few weeks later with a history of anorexia for 3 weeks, and increasing irritability, intermittent fever, and rhinorrhea for 3 days. Physical examination showed signs of an upper respiratory tract infection, an axillary temperature of 39.8° C, nonpurulent pharyngitis, and a clear nasal discharge. There was no evidence of encephalopathy. General physical examination findings were otherwise unremarkable. Muscle tone was slightly increased in the right arm, but the remainder of the neurologic findings were normal.

Relevant biochemical abnormalities at the second admission included elevated activity of plasma aspartate aminotransferase (84 U/L) and an elevated plasma ammonium level (131  $\mu\text{mol/L}$ ). The plasma glutamine level was elevated (1277  $\mu\text{mol/L}$ ), the arginine level was low (12  $\mu\text{mol/L}$ ; normal, 23 to 86), and the

Submitted for publication June 25, 1992; accepted Oct. 16, 1992.

Reprint requests: J. Christodoulou, MBBS, PhD, Department of Paediatrics and Child Health, Children's Hospital, Pyrmont Bridge Rd., Camperdown, New South Wales 2050, Australia.

Copyright © 1993 by Mosby-Year Book, Inc.  
0022-3476/93/\$1.00 + .10 9/22/43519



**Figure.** Computed tomography scan of the head taken during the first admission to the hospital. Left frontoparietal and right frontal infarcts are present, with mild midline shift to the right.

**Table.** Relevant investigations performed at first admission

	Value	Normal
Blood ( $\mu\text{mol/L}$ unless otherwise stated)		
Urea (mmol/L)	3.9	2.9-7.1
Aspartate aminotransferase (U/L)	117	<45
Lactate* (mmol/L)	2.99	<2.5
Ammonium	339	<50
Alanine	420	99-313
Glutamine	1223	<746
Lysine	200	45-144
Arginine	ND	23-86
Argininosuccinate	ND	ND
Citrulline	16	0.5-47
Carnitine		
Free	38	24-63
Total	73	35-84
Urine		
Orotic acid (mmol/mol creatinine)	41	6-12

ND, Not detected.

\*Five subsequent measurements were normal.

citrulline level was normal ( $5 \mu\text{mol/L}$ ). Urinary amino acid quantitation was normal; no argininosuccinate was detected. The urinary orotic acid concentration on this occasion was again elevated at  $29 \text{ mmol/mol creatinine}$ . The blood chromosome analysis was normal (46,XX), with no visible deletion or X-autosome translocation on routine G banding of a prophase preparation.

A provisional diagnosis of OTC deficiency was made and she was begun on a low protein diet (total protein intake of  $1 \text{ gm/kg per day}$ ) supplemented with product 80056 (Mead Johnson, Evansville, Ind.), Polycose (Ross Laboratories, Columbus, Ohio), and Pediasure (Ross Laboratories). In addition, oral therapy with carnitine,  $100 \text{ mg/kg per day}$ , and citrulline,  $240 \text{ mg/kg per day}$ , was prescribed.

Hepatic OTC activity was measured as previously described<sup>5</sup> in a needle biopsy specimen. The sample was snap frozen in liquid nitrogen and stored for 2 weeks at  $-80^\circ \text{C}$  before assay. A frozen sample obtained post mortem from a known OTC-deficient patient was used as a negative control, along with a sample from a normal child as a positive control. The OTC activity for the normal control sample was  $28.8 \mu\text{mol/hr per milligram of protein}$  (previous normal values  $42.2 \pm 11.5$ ), and for the negative control sample

was 0  $\mu\text{mol/hr}$  per milligram. In our patient the OTC activity was 1.72  $\mu\text{mol/hr}$  per milligram, only 6% of the control value.

## DISCUSSION

Inherited metabolic diseases known to cause stroke include homocystinuria, Fabry disease, sulfite oxidase deficiency, Leigh disease, the MELAS (*mitochondrial myopathy, encephalopathy, lactic acidosis and strokelike episodes*) syndrome, and organic acidopathies including methylmalonic acidemia, propionic acidemia, isovaleric acidemia, and glutaric aciduria type I.<sup>6</sup> The pathogenesis of stroke in these disorders is not certain but may include such mechanisms as alterations in vascular endothelial wall integrity, platelet dysfunction, or alterations in cerebral perfusion or metabolism caused by the accumulation of toxic metabolites. In addition, defects of coagulation such as protein C or S deficiency may also cause stroke in childhood.<sup>7</sup> All these disorders were excluded in our patient on the basis of clinical, biochemical, or histologic studies.

Acute hyperammonemia in OTC-deficient heterozygotes may develop as a consequence of the catabolic stress of infection, or after excessive protein intake.<sup>1</sup> More recently, hyperammonemia has been reported in otherwise healthy OTC-deficient heterozygous females in the postpartum period,<sup>8</sup> and after valproate therapy for suspected epilepsy.<sup>9</sup> Such patients have symptoms and signs of an acute encephalopathic process. The caloric intake of our patient before the first admission had been poor; the second admission was precipitated by an apparent intercurrent viral illness. Our patient had no evidence of diffuse encephalopathy during either illness. To our knowledge, there are no previous reports of OTC deficiency with an initial or subsequent presentation of recurrent strokelike episodes, although there is one report of a child with carbamoyl-phosphate synthetase deficiency who had strokelike episodes.<sup>10</sup> The basis of this apparently rare complication in patients with urea cycle defects is unclear but could include several of the possibilities mentioned above. Alternatively, the strokelike episodes could be due to some other cause, although at present such a cause remains unknown.

The diagnosis of OTC deficiency in our patient was ini-

tially delayed because the clinical findings did not suggest a disorder of ammonia metabolism. However, the biochemical hallmarks of hyperammonemia, hyperglutaminemia, and orotic aciduria prompted us to assay OTC activity in the liver. In the light of our experience with this child, we recommend that the investigation of children with strokes or strokelike episodes, when there are no known predisposing factors, should include plasma and urinary amino acid quantitation, plasma lactate and ammonium measurements, and urinary organic acid analysis, including orotic acid quantitation.

## REFERENCES

1. Brusilow SW, Horwich AL. Urea cycle enzymes. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic basis of inherited disease. 6th ed. New York: McGraw-Hill Information Services, 1989:629-63.
2. Finkelstein JE, Hauser ER, Leonard CO, Brusilow SW. Late-onset ornithine transcarbamylase deficiency in male patients. *J PEDIATR* 1990;117:897-902.
3. Batshaw ML, Msall M, Beaudet AL, Trojak J. Risk of serious illness in heterozygotes for ornithine transcarbamylase deficiency. *J PEDIATR* 1986;108:236-41.
4. Nagata N, Matsuda I, Matsuura T, et al. Retrospective survey of urea cycle disorders. II. Neurological outcome in forty-nine Japanese patients with urea cycle enzymopathies. *Am J Med Genet* 1991;40:477-81.
5. Qureshi IA, Letarte J, Ouellet R. Study of enzyme defect in a case of ornithine transcarbamylase deficiency. *Diabetes Metab* 1978;4:239-41.
6. Natowicz M, Kelley RI. Mendelian etiologies of stroke. *Ann Neurol* 1987;22:175-92.
7. Israels SJ, Seshia SS. Childhood stroke associated with protein C or S deficiency. *J PEDIATR* 1987;111:562-4.
8. Hawks Arn P, Hauser ER, Thomas GH, Herman G, Hess D, Brusilow SW. Hyperammonemia in women with a mutation at the ornithine carbamoyltransferase locus. *N Engl J Med* 1990;322:1652-5.
9. Tokatli A, Coskun T, Cataltepe S, Ozalp I. Valproate-induced lethal hyperammonemic coma in a carrier of ornithine carbamoyltransferase deficiency. *J Inher Metab Dis* 1991; 14:836-7.
10. Batshaw M, Brusilow S, Walser M. Treatment of carbamoylphosphate synthetase deficiency with keto analogues of essential amino acids. *N Engl J Med* 1975;292:1085-90.