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Ornithine Transcarbamylase Deficiency: A Possible Risk Factor for Thrombosis

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Abstract

Ornithine transcarbamylase (OTC) deficiency is the most common urea cycle defect. Thromboembolic complications have not heretofore been linked with this diagnosis. We describe four patients with neonatal-onset OTC deficiency who developed vascular thromboses. One patient had arterial thrombosis; the rest developed venous thromboses. Multiple pro-thrombotic risk factors were identified. Low plasma arginine levels were observed in all patients at the time of thrombosis. Arginine deficiency and the resultant nitric oxide insufficiency may contribute to thrombotic risk. Careful normalization of plasma arginine and citrulline levels and increased surveillance for thrombotic complications should be considered in patients with OTC deficiency.

Keywords

ornithine transcarbamylase; thrombosis; urea cycle

INTRODUCTION

The urea cycle (Fig. 1) plays a key role in humans in converting ammonia, a toxic waste product of protein metabolism, to urea [1]. Ornithine transcarbamylase (OTC) deficiency, the most common urea cycle defect is an X linked disorder, with an estimated incidence of 1:14,000 [2]. In the severe form, the male neonate develops a rapidly progressive metabolic encephalopathy, presenting with poor feeding, irritability, lethargy, progressing to seizures, respiratory failure, and coma. Hyperammonemia requires early, aggressive management

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including hemodialysis, the use of intravenous nitrogen scavengers and arginine in the acute period, sodium phenylbutyrate, L-citrulline supplementation and protein restricted diet in the chronic phase, and liver transplantation when feasible [3] for long term correction. The urea cycle is also an important source of de novo synthesis of the non-essential amino acid arginine, which becomes essential in patients with OTC deficiency. Arginine plays a crucial role in nitric oxide (NO) homeostasis [4] and NO deficiency can promote thrombogenesis by causing endothelial dysfunction and platelet hyperaggregability [5–7]. To date, thromboembolic complications have not been linked with this disorder.

We describe four infants with OTC deficiency treated at our institution, who developed arterial or venous thrombosis prior to undergoing liver transplantation. We analyzed their potential pro-thrombotic risk factors, and hypothesize that the presence of arginine and NO insufficiency may play a contributory role in thrombogenesis in these infants.

METHODS AND RESULTS

Four infants with OTC deficiency treated at our institution developed vascular thrombosis. This prompted a retrospective chart review of children with urea cycle disorders, evaluated at our institution between 1998 and 2008. Fourteen cases were reviewed, including 12 patients with OTC deficiency, and two with carbamoyl phosphate synthetase I (CPS I) deficiency. No additional cases with vascular thrombosis were identified. Data abstracted from the medical records of these patients included patient demographics, details about the thrombus, its management, associated pro-thrombotic risk factors and metabolic abnormalities.

Of these four infants, three developed venous thrombosis and one had arterial thrombus. All thrombotic episodes occurred prior to liver transplantation. All patients presented with symptoms of OTC deficiency within the first week of life, which included poor feeding, cyanosis, tachypnea, apnea, hypotonia, and seizure-like activity. Hyperammonemia was present consistently in all patients at diagnosis, requiring central line placement for hemodialysis. Initial management of acute metabolic crisis and subsequent amino acid supplementation and low protein diet were promptly instituted pending definitive therapy via liver transplantation. Plasma amino acid levels showed intermittently low arginine levels in all the patients, especially at the time of thrombosis despite intravenous supplementation.

Case 1

A 1-month-old male diagnosed with OTC deficiency on the second day of life was incidentally found to have portal vein thrombosis on abdominal ultrasound. Postnatally, the patient had umbilical venous and arterial lines placed. Preceding the diagnosis of thrombosis, he had multiple instances of low plasma arginine levels despite arginine and L-citrulline supplementation. While on therapeutic enoxaparin, during an episode of hyperammonemia requiring hemodialysis, he developed external iliac vein thrombus at the site of the hemodialysis catheter. Arginine deficiency was present during this period as well (Table I). The catheter was removed, and the enoxaparin dose was increased to target higher levels. With further anticoagulant therapy, the patient had complete resolution of extremity thrombus but persistence of calcified clot in the portal vein.

Case 2

A 6-month-old male diagnosed with OTC deficiency in the first week of life developed multiple venous thrombi during his clinical course. Initially he developed deep venous thrombus of upper extremity during his care at an outside hospital; subsequently at our institution, he developed thrombosis of hepatic, external iliac, bilateral common and superficial femoral veins. All thrombi occurred at or proximal to the site of central venous catheters. Low plasma arginine levels were present at the time of diagnosis of thrombosis at our institution. Information about plasma arginine levels at the outside institution was not available. He received therapeutic enoxaparin for 2 months and was subsequently placed on prophylactic doses for maintenance of central venous line patency. The patient had only partial resolution of the multiple thrombi.

Case 3

A 7-day-old male with OTC deficiency diagnosed at 5 days of life, developed external iliac, common and superficial femoral arterial thrombosis after femoral arterial line was attempted. Thrombolytic therapy was promptly initiated, followed by un-fractionated heparin and antithrombin supplementation for low antithrombin levels; despite these measures, the patient developed compartment syndrome requiring surgical intervention. Subsequently, enoxaparin was administered for a total duration of 4 weeks. Complete clot resolution was achieved at the end of therapy. Low plasma arginine levels were present at the time of thrombosis despite intravenous supplementation. Significant reduction in length and circumference of the affected limb was noted 3 months after the thrombosis.

Case 4

A 2-month-old male diagnosed with OTC deficiency on the second day of life at an outside institution was incidentally noted to have superior sagittal, bilateral transverse and sigmoid sinus thrombosis on magnetic resonance (MR) imaging. Review of his medical records revealed that placement of an internal jugular venous catheter was attempted but aborted due to misplacement of the guide-wire. In addition, low plasma arginine levels were present at the time of the diagnosis of venous sinus thrombosis. He completed a 6-month course of anticoagulation. Follow-up MR imaging of the brain showed only partial recanalization of the sinuses, hydrocephalus of lateral and third ventricles, and gliosis of the cerebral cortex.

DISCUSSION

Four of fourteen patients with urea cycle disorders reviewed in this study developed thrombotic complications. Various pro-thrombotic risk factors were present in our patients at the time of thrombus occurrence. The extreme severity of illness that accompanies neonatal-onset OTC deficiency [1], the need for aggressive metabolic support and hemodialysis necessitates the placement of large indwelling catheters. It is well recognized that vascular thrombosis in the pediatric population is most often associated with the presence of such a catheter [8], as its presence in the blood vessel and the altered integrity of the vascular conduit promote thrombogenesis. Furthermore, natural anti-coagulants such as anti-thrombin, protein C and protein S are physiologically low in early infancy, and do not reach adult values until 3 to 6 months of age [9]. Although spontaneous thrombosis is not a

consequence of these low levels in neonates, thrombogenesis may be accelerated in the presence of other contributing factors such as blood stream infections [8] and elevated acute phase reactants (e.g., factor VIII and fibrinogen), which were present in two of the affected patients. However, given the uncommon, yet shared underlying diagnosis of these four affected patients, we explored the possibility that some aspect of the metabolic derangement observed in patients with OTC deficiency itself may be prothrombotic.

Plasma citrulline levels are often undetectable in patients with OTC deficiency during the acute phase. This results in arginine deficiency, which becomes an essential amino acid. Despite arginine and citrulline replacement, plasma arginine levels were intermittently low, with consistently low levels in the peri-thrombotic period in each of our affected patients (Table I). Arginine, as a substrate for NO synthetase, leads to the production of NO [10,11]. Several studies have established the effect of NO on platelet function [6,7]. NO limits platelet activation, adhesion and aggregation, and restricts recruitment of platelets to the initial platelet plug. Recent studies have linked NO insufficiency to platelet hyperaggregability, endothelial dysfunction and vascular thrombosis [5–7]. Interestingly each of our patients had low plasma arginine levels during the peri-thrombotic period. Given the retrospective nature of this study, we were unable to evaluate platelet aggregation in these patients at the time of thrombosis. However, we postulate that the metabolic derangements in OTC deficient patients resulting in low plasma arginine levels and subsequent NO insufficiency can lead to endothelial dysfunction and increased platelet aggregation, thereby adding to the already thrombogenic vascular milieu imposed by intravascular catheters and other prothrombotic risk factors [8,11]. Though arginine and/or citrulline depletion is seen in other urea cycle disorders such as N-acetyl glutamate synthetase deficiency, CPS I deficiency, citrullinemia and arginosuccinic acidemia, vascular thrombosis has not been reported in these conditions, most likely due to their rarity when compared to OTC deficiency. We hope that our crucial observation will set a platform for future studies evaluating the link between arginine deficiency, NO insufficiency and thrombogenesis. Based on our observation, vigilant monitoring for vessel thrombosis seems warranted in this subset of sick neonates with OTC deficiency.

In summary, our observations suggest that patients with OTC deficiency appear to be at increased risk for developing vascular thrombotic complications. Although other risk factors likely contributed to thrombogenesis in our patients, we propose that metabolic derangements such as arginine and NO deficiencies further increased the risk of thrombosis. This warrants future studies in patients with OTC deficiency to elucidate the role of these derangements in thrombogenesis. In addition, careful review of patients with other urea cycle disorders with similar metabolic derangements needs to be undertaken to identify thrombotic complications. Finally, we suggest that patients diagnosed with OTC deficiency, especially those with a central vascular access device, should be kept under increased surveillance for thrombotic complications.

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Figures were produced using Servier Medical Art and Inkscape version 0.46.

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Fig. 1.

Urea cycle. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I

Patient Characteristics: Metabolic Abnormalities and Prothrombotic Risk Factors Present at the Time of Thrombosis

Risk factors	Patient 1	Patient 2	Patient 3	Patient 4
Indwelling catheter at the site of thrombus	Yes	Yes	Yes	Yes
Hyperammonemia (>94 $\mu\text{mol/L}$)	Yes	No	Yes	Yes
Low plasma arginine (<42 $\mu\text{mol/L}$)	Yes	Yes	Yes	Yes
Hypercoagulable risk factors	None	Elevated factor 8, fibrinogen	Elevated fibrinogen, low anti-thrombin	Dysfibrinogenemia
Infection (positive blood culture)	None	<i>C. albicans</i>	Coag neg Staph	None