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Case Report

Case Report: Infant with Citrullinemia Type I and Thrombosis

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Abstract

Citrullinemia type I (CTLN1) is a disorder that belongs to Urea Cycle Disorders (UCDs). Although thromboembolic complications have already been reported in others UCDs, mostly Ornithine transcarbamylase (OTC) deficiency, there are not yet reports for CTLN1. We describe a patient with CTLN1 treated in our Hospital who developed two episodes of catheter-related venous thrombosis. Amongst endogenous and exogenous prothrombotic risk factors, low plasma arginine (L-Arginine, L-Arg) levels were observed. L-Arg deficiency resulting in NO insufficiency may contribute as a key factor for thrombogenesis in these patients. The aim of this article is to discuss the existence of prothrombotic risk factors in patients with CTLN1 and raise awareness on other metabolic complications that accompanies hyperammonia, such as L-Arg deficiency that leads to vascular thrombosis, causing long-term hospitalization and high morbidity.

Keywords: *Citrullinemia; Thromboembolic; Thrombogenesis; Urea Cycle; NO*

Abbreviations

APS: Antiphospholipid Syndrome**;** ARG1: Arginase; ASL: Argininosuccinic Acid Lyase; ASS1: Argininosuccinic Acid Synthetase; AT: Antithrombin; CTLN1: Citrullinemia Type I; CPS1: Carbamoylphosphate Synthetase I; CLABSI: Central Line Blood Stream Infection; CVC: Central Line Catheter; DVT: Deep Venous Thrombosis; Factor VIII: Factor VIII; IEM: Inborn Error of Metabolism; L-Arg: L-Arginine; LMWH: Low Molecular Weight Heparin; MSSA: Methicillin Sensitive *Staphylococcus aureus*; NAGS: N-Acetylglutamate Synthase; NO: Nitric Oxide; ORNT1: Ornithine Translocase 1; OTC: Ornithine Transcarbamylase; UCDs: Urea Cycle Disorders; PC: Protein C; PE: Pulmonary Embolism; PS: Protein S; TE: Thromboembolism

Introduction

Citrullinemia type I (CTLN1), also known as argininosuccinate synthetase deficiency, argininosuccinic acid synthetase deficiency, ASS1 deficiency or classic citrullinemia is a rare autosomal recessive genetic disorder that belongs to a class of genetic diseases called Urea Cycle Disorders (UCDs), figure 1 [5,2]. The urea cycle plays a main role in humans in converting ammonia, a toxic waste product of protein metabolism, to urea. It also ensures the de novo synthesis of the non-essential amino acids, such as arginine, ornithine and citrulline [2,14]. UCDs result from inherited deficiencies in any one of the six enzymes or two transporters of the urea cycle pathway (CPS1, OTC, ASS1, ASL, ARG1, NAGS, ORNT1, or citrin; see figure 1), but severe symptoms including significant neurological sequelae, due to the accumulation of ammonia and other precursor metabolites during the first days of life, characterize partial deficiency or total absence of activity of any of the first four enzymes (CPS1, OTC, ASS1, and ASL) or the cofactor producer (NAGS).

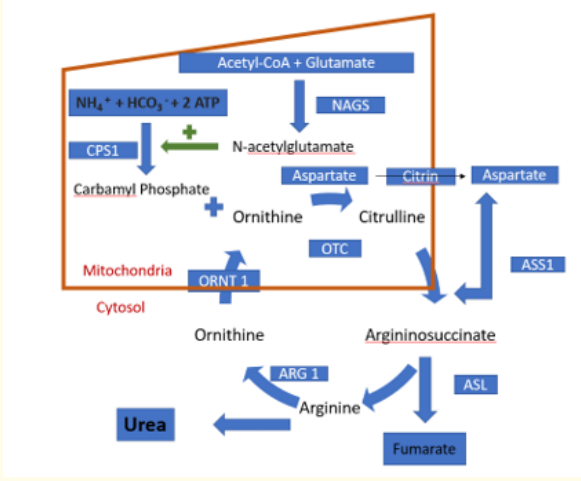

Figure 1: *Urea cycle.*

Carbamoylphosphate synthetase I (CPS1), Ornithine transcarbamylase (OTC),

Argininosuccinic acid synthetase (ASS1), Argininosuccinic acid lyase (ASL), Arginase (ARG1)

Two amino acid transporters: Ornithine translocase 1 (ORNT1), N-acetylglutamate synthase (NAGS).

Albeit ornithine transcarbamylase deficiency (OTCD), inherited as an X linked trait, is the most common disorder of ureagenesis with an estimated incidence of 1:14,000 [3], CTLN1 occurs in approximately 1/57,000 births [5]. More than one forms of citrullinemia have been described, caused by different mutations and having different signs and symptoms. CTLN1 caused by profound lack or total absence of the enzyme argininosuccinic acid synthetase (ASS 1) reflects the more severe type of citrullinemia, the classic form, which displays symptoms shortly after birth. Newborns with CTLN1 demonstrate symptoms within 24 - 72 hours after birth, usually following a protein feeding. Initially, the alarming symptoms include lack of appetite, vomiting, lethargy or irritability while the symptomatic newborns often experience respiratory distress and liver failure. If left untreated, because of the extremely high levels of ammonia in the cerebrospinal fluid (CSF), CTLN1 can progress to coma (hyperammonemic coma). Ammonia can cause brain damage through the proposed mechanisms of cerebral edema through increased levels of glutamine. It is mentioned that experience treating patients with CTLN1 are in hyperammonemic coma for more than three days end up with severe forms of developmental delay, intellectual disabilities and cerebral palsy while refractory seizures are also a common finding from early infancy [2,5]. Hyperammonemic crisis requires early, aggressive management including the use of intravenous nitrogen scavengers, sodium phenylbutyrate, sodium benzoate and arginine, in the acute period and protein restricted diet in the chronic phase. Hemodialysis is also an option during the acute phase. However, conservative medical treatments require close medical supervision to control the risk of severe hyperammonemic coma. Therefore, liver transplantation, when feasible, plays a key role in the treatment of CTLN1 as it does for all the UCDs, considering that the urea cycle pathway is conducted almost exclusively in the liver [3,13].

As mentioned earlier, the urea cycle contributes in the endogenous production of the non-essentials amino acids, like l-arginine (L-Arg) for instance, which becomes essential in patients with CTLN 1. L- Arg contributes significantly in the homeostasis of nitric oxide (NO). NO deficiency due to low arginine plasma levels, has already been linked to thrombo-embolic complications in children suffering from UCDs, mainly from OTC deficiency, but not yet with CTLN 1 [13]. Therefore, L- Arg supplementation in these patients is a necessary therapeutic tool not only for confronting hyperammonemia but also for achieving adequate arginine plasma levels that might prevent thrombotic episodes.

We describe a patient with CTLN1 treated in our Hospital who developed two episodes of venous thrombosis with the last one occurring while on anticoagulant therapy. The aim of this article is to discuss the existence of prothrombotic risk factors in patients with CTLN1 and notably the role of arginine insufficiency as a key factor for thrombogenesis in these patients.

Case Presentation

An 10-month-old infant with Citrullinemia type 1 (CTLN 1) has experienced two episodes of catheter-related venous thrombosis during his last two admissions for acute hyperammonemia.

He is the fourth child of consanguineous parents, born full-term by normal vaginal delivery with unremarkable antenatal history and needed no resuscitation at birth.

The diagnosis of CTLN1 was made on the second day of life due to the strong suspicion of the same condition that was diagnosed in the older sibling. Therefore, a metabolic screening profile for inborn error of metabolism (IEM) was planned immediately after birth and amino acid profile showed markedly increased plasma level of citrulline (1099 μmol/l), while serum results showed marked hyperammonemia (303 μg/dl). Since then, the patient was on the protein restriction diet and on systematic ammonia scavenging therapy with oral sodium benzoate and arginine with ammonia ranging from 75 - 95 μg/dl from birth to the age of 6 months. Arginine levels were always above 100 μmol/l.

After the introduction of solid food at the age of 7 months, three consecutive hospitalizations followed due to episodes of acute hyperammonemia. Due to the great need of constant monitoring of ammonia and liver function, a lot of efforts for central line placement had been performed. During his second hospitalization the attempt to place a central line catheter in the left femoral vein (Central Venous Catheter, CVC) had failed due to clotting in the catheter's lumen. Therefore, the insertion of the catheter was cancelled and it was advised by the Pediatric Hemophilia Centre of Athens to start on anticoagulant therapy with Low Molecular Weight Heparin (LMWH). While on LMWH for 3 months, a port-a-cath (CVC) had been placed in the right internal jugular vein but was also clotted and removed. Due to the two episodes of CVC thrombosis a thorough thrombophilia testing was performed and found normal except slightly elevated factor VIII and D-Dimers with fibrinogen approaching the upper normal limit. Interestingly, during both these circumstances, apart from the high levels of ammonia and the presence of CVC, arginine plasma levels were noticed low (See table 1 below).

Prothrombotic Risk Factors	1st thrombotic episode	2nd thrombotic episode
Catheter - related (CVC)	Yes	Yes
Ammonia levels (normal < 70 μg/dl)	290	200
Arginine levels (normal > 80 mmol/l)	40	50
Other hypercoagulable risk factors	Elevated VIII, D-Dimers	Elevated VIII, D-Dimers
Infections (positive blood culture)	No	No

Table 1: *Characteristics of each episode at the time of thrombosis.*

Regarding the extended thrombophilia testing other coagulation factors such as fibrinogen were normal. The genetic tests for the heterozygosity for the 20210A allele of the common FII polymorphism 20210G/A in the untranslated 3′ region of the Prothrombin (FII) gene and for the heterozygosity for the FV mutation Arg506 to Gln506 (FV Leiden) were negative. Inhibitors of hemostasis such as Protein S, Protein C, Antithrombin III were also within normal range. Furthermore, besides the normal homocysteine plasma levels, a genetic test for MTHFR (5, 10 Methyl-tetrahydrofolate-reductase) polymorphism was conducted and found normal, while there were no abnormal findings from the antiphospholipid syndrome (APS) antibody panel.

The last CVC has been preserved for two months without any other thrombotic episode reported, although a Central Line Blood Stream Infection (CLABSI) with S. aureus (Methicillin Sensitive Staphylococcus Aureus- MSSA) had occurred three weeks after the CVC placement. Notably, no derangements of plasma arginine levels were noticed throughout this period.

Discussion

The thrombotic events can be attributed to a lot of reasons and the presence of the CVC was the triggering one. Except for CVC's critical importance as medical and supportive tool for the management of various diseases, its presence has the disadvantage to alter the blood vessel conduit integrity promoting thrombogenesis. Therefore, it is well recognized that CVC associated DVT and systemic infections can lead to thrombotic occlusion, CVC-associated deep venous thrombosis (DVT) and systemic infections [11].

Taking into consideration the endogenous thrombophilic risk factors, genetic testing was negative for detecting hereditary prothrombotic factors, such as mutations in Prothrombin (FII 201210A), FV Leiden and MTHFR genes. Genetic defects causing dysfibrinogenemia were not detected. Inhibitors of hemostasis, Antithrombin (AT), Protein C (PC), Protein S (PS) that are mostly correlated with venous thrombosis like in our patient, were measured and found normal [11]. Only Factor VIII (FVIII), that seems to contribute to the risk of thromboembolism (TE) in children, was slightly elevated, but its significant role alone in thrombogenesis in this patient is questionable due to the moderate increase. D-dimers were increased as expected, albeit in a much lower lever as noticed in Deep Venous Thrombosis (DVT) or Pulmonary Embolism (PE). As indicators of the current activity of the fibrinolytic system, D-dimer is a result of lysis of cross-linked fibrin directed by plasmin, reflecting activation of both coagulation and fibrinolysis, which is expected in a patient with thrombosis [4,9].

Surprisingly enough, the last CVC had been preserved and kept free of any thrombotic occlusions for months since the increased supplementation with L-arginine, which points towards the critical role of this particular amino acid in thrombogenesis. As mentioned earlier, the urea cycle contributes in the endogenous production of the non-essentials amino acids, like arginine for instance, which becomes essential in patients with CTLN 1. It also includes enzymes that overlap with the nitric oxide (NO) production pathway (ASS1 and ASL), indicating that l-arginine (L-Arg) acts as a precursor of NO synthesis. In details, L-Arg plays a role as a substrate for NO synthetase, leading to the production of NO. Therefore L-Arg deficiency leads to low NO levels, which has gained ground over the last 15 years as a vascular mediator linked to auto regulatory functions in platelet adhesion and aggregation. Specifically, NO limits platelet activation, adhesion, and aggregation controlling platelet recruitment to the initial growing thrombus [7]. Consequently, as reported in many studies, NO deficiency is linked with platelet hyperaggregability, dysfunction of the endothelium and thrombogenesis [6,7,12]. As Venkateswaran., *et al.* described in their case reports, our patient also demonstrated low arginine plasma levels during these thrombotic episodes [13]. Although, we did not evaluate platelet aggregation at the time of thrombosis, we assume that extreme metabolic derangements in this patient with UCD, such as L-Arg insufficiency leading to NO deficiency, along with the presence of a CVC, can damage severely the endothelium. Thrombo-embolic complications have already been linked mainly with OTC deficiency, but not yet with CTLN 1 due to its rarity when compared to OTC [8,10,13]. The main consequence of hyperammonemic crisis in children with UCD is the permanent neurologic sequelae that can be caused irreversibly if hyperammonemia is not managed properly.

Conclusion

The aim of this article is to raise awareness on other metabolic complications that accompanies increased levels of ammonia, such as the lack of L-Arg resulting in vascular thrombosis, which can also lead to long-term hospitalization and high morbidity. Of course we need larger number of patients to evaluate the correlation between L-Arg insufficiency, NO deficiency and vascular thrombosis, but we hope that our significant observation in an extremely rare Urea Cycle Disorder, as it is reported for the first time for CTLN 1, will lead to vigilant monitoring for thrombotic complications in such patients especially those with a intravascular catheter present. On top, we would like to emphasize the potential benefit of L-Arg supplementation in these patients for preventing thrombotic occurrences.

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