

Coagulopathy Unmasking Hepatic Failure in a Child with Ornithine Transcarbamylase Deficiency

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Ornithine transcarbamylase deficiency is the most common of the urea cycle defects, with an incidence of around 1/70,000 births in the European population. Following an X-linked inheritance, phenotypic variability ranges from neonatal-onset hyperammonemic coma to moderate, mild and even asymptomatic states. Severely affected males, presenting with acute encephalopathy and metabolic crisis, are usually diagnosed during the neonatal period or early infancy, while males with a milder phenotype suffer recurrent but treatable episodes of hyperammonemia [1]. Females or males with subclinical or mild symptoms may be diagnosed in adulthood or miss diagnosis altogether [2]. Liver failure, which may in some cases necessitate transplantation, has been previously documented and is considered a rare manifestation of OTCD [3].

Pediatric acute liver failure is a relatively rare condition and a significant portion of cases remain with undetermined etiologies. This entity differs from its adult form, most notably with respect to encephalopathy which rarely presents in pediatric patients, especially infants. In this age group encephalopathy is also more difficult to assess. The other features

of liver failure such as coagulopathy, hyperbilirubinemia, liver enzyme elevation indicative of cellular damage, and ascites are more commonly present [4,5].

We present a case of acute liver failure in an infant with OTCD, unmasked and dominated by coagulopathy which was a single sentinel clinical finding. Increased awareness of this rare complication allowed for timely treatment and avoidance of urgent liver transplantation.

PATIENT DESCRIPTION

The patient was born to an asymptomatic mother carrying the c.806G>A G269E mutation in the *OTC* gene. Two of the patient's uncles (brothers of the mother) succumbed to OTCD during early infancy due to recurrent episodes of hyperammonemic encephalopathy. Genetic testing revealed a homozygous state for the c.806G>A (p.G269E) mutation. Following the positive genetic testing result and in the absence of any symptoms, the patient was treated with a regimen including a protein-restricted diet with supplementation of essential amino acids, L-citrulline and sodium benzoate. The patient remained asymptomatic until age 6 months when he began to experience frequent episodes of hyperammonemic encephalopathy, partially attributed to parental non-compliance. He responded well to the therapeutic regimen described above.

At age 2.5 years he presented with abnormal bleeding from a minor laceration. No change in behavior or vomiting was reported and on admission the infant seemed cheerful without evidence

of encephalopathy or metabolic crisis. However, coagulation indices were disturbed with an international normalized ratio of 2.9. Aspartate aminotransferase was elevated to 532 U/L. Blood counts, bilirubin levels as well as electrolytes and renal function were all within the normal range. Interestingly, ammonia was only mildly elevated at 136 mmol/L (normal < 53 mmol/L).

The patient was initially treated with repeated doses of intravenous vitamin K, but there was no improvement in the INR which continued to rise, peaking at 5.6. Repeated infusions of fresh frozen plasma showed only a modest and transient effect. Aspartate and alanine aminotransferase values correlated with the derangement of INR, peaking at 1656 and 1897 U/L respectively. Alkaline phosphatase and gamma-glutamyl transpeptidase showed minor elevations to 490 and 82 U/L respectively. Bilirubin was consistently normal and albumin levels were well maintained. Serum lactate levels were elevated from 3.1 to 7.4 mmol/L (normal < 1.8 mmol/L). Of note, throughout the hospital course the patient's ammonia levels were normal or only mildly elevated with a single transient peak of 296 mmol/L.

Clotting assays measuring active amounts of clotting factors and chromogenic thrombophilia tests were performed. The assays showed markedly reduced levels of factors V, VII, IX and protein C activity, with moderately reduced levels of factors II (prothrombin), X and XI, and a slight reduction in antithrombin III activity. Factor VIII

OTCD = ornithine transcarbamylase deficiency

INR = international normalized ratio

Results of the patient's clotting factors essays showing coagulopathy due to liver failure

Assay	Result	Normal range
Prothrombin time (sec)	31.7	8.5–12.5
INR	3.10	0.75–0.3
partial thromboplastin time (sec)	49.1	22.0–32.0
Clotting factor VIII (%)	131	55–170
Clotting factor IX (%)	7	60–130
Clotting factor II (prothrombin) (%)	37	60–130
Clotting factor XI (%)	56	60–130
Clotting factor V (%)	16.4	60–140
Clotting factor VII (%)	3.1	60–140
Clotting factor X (%)	30	60–130
Protein C activity (%)	6	70–130
Protein S antigen, free (%)	84.1	70–130
Antithrombin III activity (%)	63	70–130

activity, antigen levels of free protein S and fibrinogen levels were normal [Table].

A review of the patient's medical history revealed numerous hospital admissions due to acute episodes of "classic" metabolic crises that included encephalopathy, lethargy, vomiting and hyperammonemia, and only minimal-to-mild coagulopathy and hypertransaminemia. These episodes occurred at a frequency ranging from 2 to 8 weeks. However, during many of these admissions coagulation indices were not ordered, and in some neither were liver function tests. Laboratory evaluation of liver function and coagulation profile during 'well visits' to the clinic was scant, mainly due to the lack of parental compliance and the objective constraints of frequent acute admissions.

A search for other causes of the patient's liver malfunction, including serologic testing for hepatitis viridae A, B and C, herpes viridae 1, 6 and varicella, as well as Ebstein-Barr and cytomegaloviridae and adenoviridae, was negative for recent infection. Markers of autoimmune hepatitis, antinuclear antibody, anti-smooth muscle and anti-mitochondrial antibodies were all negative.

A strict therapeutic regimen with protein-restricted diet, supplementation of essential amino acids, L-citrulline and sodium benzoate led to gradual improvement of coagula-

tion indices and liver function to near-normal values within 3 weeks. Encephalopathy was completely absent throughout the hospital stay. Following the above improvement, the patient was discharged home.

Over the next few months the child was admitted frequently for recurrent episodes of vomiting, hyperammonemic encephalopathy, and fluctuations in coagulation studies. Recently, the patient underwent successful liver transplantation – the only therapeutic modality that could prevent chronic progressive neurologic decline, as well as the risks of sudden non-reversible brain damage and progressive liver failure.

COMMENT

In this case, abnormal bleeding unmasked an acute episode of liver failure in an infant with known OTCD. Encephalopathy and the hallmarks of a hyperammonemic crisis were absent and other features of liver failure were present only to a moderate degree. Synthetic failure led to significantly lower plasma levels of clotting factors and derangement of coagulation indices. Vitamin K-dependent factor VII, having the shortest half-life, was the most severely affected factor. In contrast, the level of factor VIII, synthesized in vascular endothelium and usually elevated in acute

liver failure, was normal. The level of factor V, a sensitive indicator of liver failure, was also markedly decreased. Response to vitamin K was also poor, suggesting minimal hepatic reserve and a guarded prognosis.

Coagulopathy was thus the predominant feature and therapeutic challenge. The patient improved remarkably under dietary modification and a conservative therapeutic regimen of his basic condition despite these poor prognostic factors.

Acute liver failure is considered a rare, yet well-documented manifestation of OTCD [2,3]. However, isolated coagulopathy, encountered occasionally by several physicians treating these patients as evident from personal communications in this case, has received little emphasis. Its underlying pathophysiology remains speculative. Elevated plasma lactate level, considered a marker of mitochondrial dysfunction, may serve as an etiologic clue that accumulation of urea cycle intermediates is toxic to hepatocyte mitochondria and is a previously suggested theory for liver failure.

In some cases OTCD may evade diagnosis for many years and may present as a catastrophic event [2,3]. Liver involvement and coagulopathy may serve as the presenting signs, especially in older patients where targeted tests for metabolic disease are not routinely ordered due to a low index of suspicion or availability.

Pediatric acute liver failure is a rare entity with unique features, many of which are due to undetermined cause [4,5]. There is also a high variability in the diagnostic workup performed. Metabolic disorders account for 10–20% of cases and may also account for many cases of undetermined cause.

A diagnosis of OTCD and other metabolic conditions should be actively sought in any child presenting with previously undiagnosed coagulopathy and/or liver failure. Metabolic studies, which are not routinely ordered, should be performed.

In known OTCD patients, and in patients with other urea cycle defects, assessment of liver function and coagula-

tion studies should be undertaken during every acute event and periodically during times of relative health. A timely diagnosis allows targeted treatment and may obviate emergency liver transplantation with its inherent morbidity and costs. Counseling of family members regarding treatment options, prognosis and family planning may also be offered. The mechanisms of coagulopathy and liver disease are yet to be determined.

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Capsule

Genetic variation near IRF8 is associated with serologic and cytokine profiles in systemic lupus erythematosus and multiple sclerosis

Alleles of interferon (IFN) regulatory factor 8 (IRF8) are associated with susceptibility to both systemic lupus erythematosus (SLE) and multiple sclerosis (MS). Although high-type I IFN is thought to be causal in SLE, type I IFN is used as a therapy in MS. Chrobot and team investigated whether IRF8 alleles were associated with type I IFN levels or serologic profiles in SLE and MS. Alleles that have been previously associated with SLE or MS were genotyped in SLE and MS patients. The MS-associated rs17445836G allele was associated with anti-double-stranded DNA (dsDNA) autoantibodies in SLE patients (meta-analysis odds ratio 1.92). The same allele was associated with decreased serum IFN activity in SLE patients with anti-dsDNA antibodies, and with

decreased type I IFN-induced gene expression in peripheral blood mononuclear cell from anti-dsDNA-negative SLE patients. In secondary progressive MS patients, rs17445836G was associated with decreased serum type I IFN. Rs17445836G was associated with increased IRF8 expression in SLE patient B cells. In summary, IRF8 rs17445836G is associated with human autoimmune disease characterized by low-type I IFN levels, and this may have pharmacogenetic relevance as type I IFN is modulated in SLE and MS. The association with autoantibodies and increased IRF8 expression in B cells supports a role for rs17445836G in humoral tolerance.

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Capsule

Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys

Human immunodeficiency virus type 1 (HIV-1)-specific monoclonal antibodies with extraordinary potency and breadth have recently been described. In humanized mice, combinations of monoclonal antibodies have been shown to suppress viremia, but the therapeutic potential of these monoclonal antibodies has not yet been evaluated in primates with an intact immune system. Barouch and colleagues show that administration of a cocktail of HIV-1-specific monoclonal antibodies, as well as the single glycan-dependent monoclonal antibody PGT121, resulted in a rapid and precipitous decline of plasma viremia to undetectable levels in rhesus monkeys chronically infected with the pathogenic simian-human immunodeficiency virus SHIV-SF162P3. A single monoclonal antibody infusion afforded up to a 3.1 log decline of plasma viral RNA in 7 days and also reduced proviral DNA in peripheral blood, gastrointestinal

mucosa and lymph nodes without the development of viral resistance. Moreover, after monoclonal antibody administration, host Gag-specific T lymphocyte responses showed improved functionality. Virus rebounded in most animals after a median of 56 days when serum monoclonal antibody titers had declined to undetectable levels, although, notably, a subset of animals maintained long-term virological control in the absence of further monoclonal antibody infusions. These data demonstrate a profound therapeutic effect of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys as well as an impact on host immune responses. These findings strongly encourage the investigation of monoclonal antibody therapy for HIV-1 in humans.

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