Case report

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Fulminant hepatic failure in a neonate with systemic echovirus infection

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We report the fatal case of neonatal fulminant hepatic failure due to Echovirus infection mimicking an acute metabolic decompensation. After exclusion of several metabolic disorders, the diagnosis of the infectious etiology was confirmed by Polymerase Chain Reaction of Echovirus in liver and spleen tissue. Establishment of etiological diagnosis and exclusion of inherited metabolic disease helped the family counseling regarding risk for future pregnancies. Fulminant hepatic failure in the neonate is a diagnostic and therapeutic challenge that requires a multidisciplinary management. Our case illustrates the broad differential diagnosis, the common final pathway leading to severe liver injury, and the multidisciplinary approach to diagnosis and treatment.

Key words: Hepatic Failure, Neonate, Echovirus.

Abbreviations: ECHO: entero-cytopathic human orphan

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Introduction

The diagnosis and management of fulminant hepatic failure requires a multidisciplinary approach for the evaluation of congenital, inflammatory, metabolic, infectious, and systemic conditions that may present with primary or secondary liver failure (1). Certain conditions, such as neonatal iron storage disease, affect the liver in utero since the placental feto-maternal unit does not protect the infant from a prenatal insult (2, 3), while other conditions manifest after birth as a result of toxic, metabolic, or infectious injury.

Careful attention to the perinatal history and physical examination in combination with biochemical parameters can help direct diagnostic and therapeutic interventions in a critically ill baby. Combinations of clinical and biochemical parameters and the timing of the presentation can fit into one of several patterns of liver injury

and help in the rapid determination of the cause. This allows for the timely initiation of therapy. Determination of the exact cause of the liver injury can be immensely helpful to the family in coping with the infant's illness and determine the risk to siblings and future offspring. However, establishing the diagnosis may be a challenge and despite extensive diagnostic investigations, the etiology of hepatic failure in neonates often remains unknown.

We report the case of fatal neonatal fulminant hepatic failure due to Echovirus infection presenting initially with hyperammonemia, and as such, mimicking a metabolic decompensation.

Case report

A seven-day old girl presented with acute onset of lethargy, hypotonia and hypothermia (which is a typical onset of urea cycle disorders). She was the product of a full-term pregnancy complicated by mild abdominal pain in the third trimester, born as a second child to a 27-year-old female without risk factors. The birth weight was 2630 gr, the length was 48 cm and head circumference was 33 cm. Apgar scores were 8 and 9 after the first and fifth minute, respectively. The child was dismissed from the hospital in good condition, on the third day of life, being breast-fed. Three days later she was noted to be uninterested in eating. Within a few hours she became cold to the touch and lethargic. She was admitted to the newborn intensive care unit.

At admission, the child was unresponsive, with core temperature of 32 Celsius and heart rate of 50/beats per minute. Her resuscitation was immediate and included intubation with positive pressure ventilation, chest compressions, and central lines placement with both umbilical venous and arterial catheter. The bradycardia resolved rapidly, but the infant remained lethargic. The examination was otherwise unremarkable, the child was nondysmorphic, normocephalic and well nourished. The skin had no bruises or birth marks, there was no rash. The neck was supple, without nodules. The chest was normal and the cardiac sounds were normal. There were no murmurs, clicks, or rubs. The lungs were clear. There was no organomegaly, jaundice, ascites, edema, and the baby had normal female genitalia.

Laboratory tests showed profound metabolic acidosis (with mild elevation of anion gap), which was corrected with bicarbonate administration. The patient had initial blood ammonia of 466 ug/dl, which rose to 852 within the next 12 hours of hospitalization. She had marked hyperkalemia and mild hyponatremia. Electrolyte imbalance raised the possibility of congenital adrenal hyperplasia, and appropriate evaluation was performed before the administration of dexamethasone. Her 17-hydroxyprogesterone and cortisol blood levels were normal. Blood glucose level was normal. Additional laboratory investigations performed at that time are summarized in Table 1. It became clear that the baby had evidence of liver disease with severe hepatocyte lysis and coagulopathy as well as disseminated intravascular coagulation (DIC).

The presence of hyperammonemia prompted further evaluation for metabolic disorders. Plasma amino-acid analysis showed markedly elevated proline, glycine, tyrosine, glutamine and alanine, normal citrulline and undetectable arginine. Argininosuccinic acid and orotic acid were normal in a urine sample. Urine organic acid showed massive amounts of lactate but no other abnormal metabolites. The urine sample was negative for succinylacetone, excluding tyrosinemia. The relatively low ferritin and the high elevation of the aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase

Table 1 Initial laboratory evaluation in infant

Analysis	Parameters	The patient's range	Normal range
Serum	Ammonia	466-852	<50 μg N/dl
	Lactic acid	14.5-16.7	<2.2 mmol/l
	Pyruvic acid	0.30	0.08-0.16 mmol/l
	Osmolality	330	275-295 mosm/kg
	Potassium	7.3-8.2	3.7-5.0 mEq/l
	Sodium	115-128	135-145 mEq/l
	AST	7896-11308	26-48 U/l
	ALT	828-1104	12-31 U/l
	pH	7.16	7.35-7.45
	Bicarbonate	7-17	21-25 mEq/l
	Base	(-20) – (17)	0-(-2) mEq/l
	D-dimer	>500	< 250 ng/ml DDU
	Fibrinogen	84-104	175-350 mg/dl
	Prothrombin time	32-19.7	8.4-12.0 sec
	APTT	96-225	21-33 sec
	Ferritin	581	25-200 ug/l
	Acylcarnitine	Normal profile	-
Urine	Generalized aminoaciduria	Massive	Negative
	Lactic acid	Massive amount	Negative
	4-hydroxy phenyllactic	Massive amount	Negative
	4-hydroxy phenylpyruvic	Massive amount	Negative
	Lactose	Large amount	Negative
	Galactose	211 mg/dl	<30 mg/dl
	Acylglycines	Normal profile	-
	Succinylacetone	Negative	Negative

(GGT) excluded the diagnosis of iron storage disease. Blood counts and bilirubin were normal. The exclusion of inborn error of bile acid synthesis was performed by Fast Atom Bombardment Spectroscopy on a urine sample. Mitochondrial beta-oxidation defects and carnitine deficiency were also excluded.

The patient remained unresponsive despite therapy that normalized her hyperammonemia, electrolyte abnormalities, and acidosis with continuous veno-venous hemofiltration. After samples for microbiologic studies were collected (blood, urine, rectal and pharyngeal swab), broad-spectrum antibiotic therapy was initiated. Fresh frozen plasma, packed red blood cells, maintenance fluid with appropriate glucose and electrolytes achieved normal homeostasis of the infant from a biochemical point of view but she continued to show evidence of severe liver failure with persistent bleeding from puncture sites. The patient developed an increased requirement for inotropic support with poor cardiac contractility. Persistent coagulopathy and poor perfusion resulted ultimately in her demise early on the third hospital day.

Immediately post mortem, tissue was obtained with the family's consent to determine the possibility of an inborn error of metabolism with particular emphasis on the possibility of a respiratory chain defect. An exhaustive metabolic evaluation was conducted on available tissues, and remained negative (Table 2). Reduced activity of CPSI,

Table 2 Postmortem evaluations

Analysis	Parameters	The patient	Normal range
Erythrocytes	Galactose-1-phosphate uridyl transferase	Normal	
Fibroblasts	Chromosomes	46, XX	N/A
	Electron microscopy	Normal	N/A
Skeletal muscle	Histology	Normal	N/A
	Respiratory chain enzyme activities[1]	All reduced, no abnormality detected	N/A
Spleen tissue	PCR for enteroviruses[2]	Positive	Negative
Liver tissue	CPS I activity[3]	0.6	5.6±0.3 mmol/g liver/min
	OTC activity[3]	8.3	70.1±9.7 mmol/g liver/min
	PCR for enteroviruses[2]	Positive	Negative
Urine	Succinylacetone	Negative	Negative
	Fast Atom Spectroscopy[4]	Normal Bile Acids	Normal Profile

N/A= not applicable; PCR= polymerase chain reaction
Measured activities of fumarase, citrate synthase, cytochrome oxidase, NADH cytochrome C reductase, NADH dehydrogenase, succinate cytochrome reductase and succinate dehydrogenase
[1] Performed in Clinical Genetics Laboratory, The Children's Hospital of Buffalo
[2] Performed at the Center for Disease Control in Atlanta
[3] Performed in Biochemical Genetics and Metabolism Laboratory, Children's National Medical Center, Washington DC
[4] Performed at the University of Cincinnati, The Children's Hospital Medical Center

OTC activity and respiratory chain analysis reflected the analysis performed on the sample collected postmortem. A limited autopsy disclosed bilateral adrenal hemorrhage and massive hepatic coagulative necrosis with little evidence of viable hepatocytes.

Blood, urine, nasopharyngeal, rectal, and CSF fluid were collected for bacterial, fungal and viral cultures. Viral cultures and serum titers for congenital infections were obtained. The culture from the spleen and the liver yielded echovirus. The typing of the virus was performed at the Center for Disease Control in Atlanta by polymerase chain reaction (PCR) and showed 90% homology to type 11, the most common type involved in neonatal fulminant hepatic failure.

Discussion

Fulminant hepatic failure in the neonatal period is rare and the presentation can be devastating with rapid decompensation by multiorgan failure (1-10). The classic definition of fulminant hepatic failure, i.e. the onset of encephalopathy within two weeks of jaundice, is problematic in the neonate due to the difficult assessment of encephalopathy in this age group. In addition, the neonatal period precludes the characterization of liver failure into acute and subacute forms, which carry prognostic implications in the adult.

Therefore the definition of fulminant hepatic failure in the neonate involves a combination of clinical and biochemical parameters that reflect severe primary liver injury. This may include lethargy, jaundice, petechiae, bruising, bleeding, as well as ascites and organomegaly. These clinical findings are of course not specific for primary liver disease and occasionally reflect severe circulatory compromise.

A biochemical profile of elevated transaminases, coagulopathy, hyperammonemia, and hypoglycemia are important in this diagnosis. The degree and pattern of biochemical abnormalities and time of onset of liver injury may help in the differential diagnosis of the liver failure (1, 3-12). For example, disproportionate prolongation of the pro-

thrombin time in relation to mild elevation of the transaminases is indicative of a toxic hepatopathy, as seen in tyrosinemia, or the association of liver disease and persistent diaper dermatitis as the original manifestation of Langerhans cell histiocytosis.

Recently, the recognition of several metabolic diseases affecting the liver in the early neonatal period has shifted the emphasis of the evaluation of an ill neonate with liver failure towards this group of disorders (4-9, 11, 12). Various inborn errors of bile acid metabolism, urea cycle defects, mitochondrial oxidation and respiratory chain defects can present with liver failure. Making a correct diagnosis often allows efficient therapy for the infant and can help family planning by predicting risk for recurrence in future children.

Enteroviruses are one genus of the Picornaviridae; they comprise coxsackieviruses, echoviruses, enteroviruses and polioviruses (13). The group of enteric cytopathic human orphan viruses or echoviruses comprises several viruses that were initially found to lack animal pathogenicity and hence were termed "orphan" viruses. Viral transmission of echovirus in the newborn period is either transplacental or perinatal. The factors that affect pathogenesis include viral load, virulence, and the subtype of the virus (10, 13-15). Over the last decade or so, fatal newborn infections have been reported with echovirus (11, 15-28). In the majority of cases, massive hepatic necrosis was present. Other findings included adrenal hemorrhage, renal tubular necrosis, and myositis. Massive hepatic necrosis was reported with types 3, 6, 9, 14, 19, 20 and 21. The range of severity of enteroviral illness is variable. Mild febrile illness occurs in about 10% of cases. Hepatitis occurs in about 2% of enteroviral infections. The newborn is particularly susceptible to overwhelming infection with multiorgan failure and death. The combination of hepatitis, disseminated intravascular coagulation, apnea, lethargy, poor feeding, and jaundice were described in several cases of neonatal echovirus infection.

This case represents another echovirus 11 infection resulting in liver failure and multiorgan dysfunction that mimicked an inborn error of metabolism. The identification of the virus in secretions may not be sufficient to establish a causal relationship to liver injury and may be an incidental finding (23, 24). Nursery outbreaks have been described without overt liver failure. However, knowing that the virus has been implicated in other liver failure cases prompted us to evaluate the presence of the virus in multiple tissues in this baby. The likelihood of the enterovirus being an innocent bystander was eliminated with the use of PCR tissue samples from the spleen and the liver. The exclusion of metabolic disorders, including disorders of bile acid metabolism, urea cycle defects, and mitochondrial oxidation and respiratory chain defect was performed as part of this evaluation.

It is important to consider a metabolic cause of liver disease, where therapeutic intervention might be available to prevent irreversible liver damage, neurologic damage and other complications. Another important aspect in the identification of a potential metabolic disease is genetic counseling and evaluation of the parents for carrier states, which has implications in counseling regarding risk for future pregnancies.

Conclusion

Increased awareness of a number of metabolic disorders and improved diagnostic capabilities for detection of rare inherited conditions may cause a bias toward neglecting other etiologies of neonatal liver failure. The possibility of perinatal infection as a cause of severe hyperammonemia and fulminant hepatic failure should be kept in mind when evaluating a sick neonate. The team ap-

proach in the evaluation and management of this complex entity is necessary. Establishment of the correct diagnosis is essential for appropriate management. Elimination of metabolic liver disease and the presence of multiorgan infectious process preclude liver transplantation. Correct diagnosis helps identification of other family members at risk and allows counseling for the family regarding disease recurrence in subsequent pregnancies.

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