Identification of neonatal liver failure and perinatal hemochromatosis in Canada

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Severe liver disease in newborns is regarded as being relatively rare. However, the diagnosis and management of patients with the disease are often perplexing because little is known about the clinical spectrum of neonatal liver failure. Recognized causes include viral infection, hereditary metabolic diseases, neoplasia and vascular problems. Some of these conditions can be treated medically. Alternatively, liver transplantation may be life-saving. By understanding more about the different types and causes of neonatal liver failure, the authors hope to promote earlier diagnosis, and more prompt and effective treatment. This goal may be achieved by the extensive, nationwide epidemiological data collection which is performed through the Canadian Paediatric Surveillance Program.

Neonatal liver failure presents a unique clinical challenge. Liver failure in older children and adults is defined in terms of the duration of liver disease, coagulopathy and encephalopathy. Recognition of liver disease in a newborn is difficult because biochemical findings, such as hyperbilirubinemia and coagulopathy, may be due to various physiological and pathophysiological processes (1). Hepatic encephalopathy is difficult to identify in any infant and almost impossible to distinguish from other metabolic encephalopathies in an ill neonate, especially if the infant requires ventilation support (2). Because infants are so young, all neonatal liver failure tends to be labelled as 'acute', which is consistent with the adult definition of a duration of less than eight weeks. However, some infants clearly have liver failure from end-stage liver disease with cirrhosis due to liver damage that occurred during gestation.

We propose a more suitable definition of neonatal liver failure: severe hepatic dysfunction with coagulopathy,

TABLE 1: Established causes of acute and chronic pattern neonatal liver failure

	Acute pattern	Chronic pattern
Infection	Hepatitis B virus	Parvovirus B19
	Hepatitis C (rare)	
	Herpes simplex virus	
	Human herpesvirus 6 (rare)	
	Enteroviruses: echovirus, coxsackievirus type A and B, adenovirus	
	Cytomegalovirus	
Metabolic diseases	Hereditary tyrosinemia type 1	Hereditary tyrosinemia type 1
	Galactosemia	Galactosemia
		Hereditary fructosemia
		Niemann-Pick disease type C
	Reye-like syndromes/ mitochondrial disorders	Reye-like syndromes/ mitochondrial disorders
		Perinatal hemochromatosis
		Inborn error of bile acid synthesis:delta^4-3-oxoster oid 5beta-reductase
Neoplasia	Neuroblastoma	Erythrophagocytosis syndromes
	Congenital leukemia	
Vascular	Hepatic vein thrombosis	
	Shock	
Idiopathic		'Le foie vide' (hepatic nonregeneration syndrome)

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TABLE 2: Case definition and diagnostic strategy for neonatal liver failure

For neonatal liver disease occurring in an infant 60 days old or younger, consider either differential diagnosis number 1 or number 2

1. Neonatal liver failure (acute pattern) is characterized by one or more of the following:
   - serum aminotransferase (aspartate aminotransferase and alanine aminotransferase) levels extremely elevated (above 1000 U/L)
   - coagulopathy despite vitamin K supplementation
   - unexplained hypoglycemia
   - serum conjugated bilirubin levels elevated, but jaundice may not be prominent
2. Neonatal liver failure (chronic pattern) is characterized by one or more of the following:
   - serum albumin levels low, normal or subnormal
   - serum aminotransferase (aspartate aminotransferase and alanine aminotransferase) levels normal or mildly elevated
   - coagulopathy despite vitamin K supplementation
   - serum conjugated bilirubin levels elevated
   - unexplained hypoglycemia
   - abnormal liver on sonography (ultrasound)

Investigations relating to differential diagnoses

- serological studies for herpes simplex, cytomegalovirus, enteric viruses (echoviruses, coxsackieviruses) and parvovirus B19 (*relating to congenital infections)*
- serum gamma-glutamyltranspeptidase normal (*relating to inborn errors of bile acid synthesis and progressive familial intrahepatic cholestasis types 1 and 2*)
- serum amino acids profile (*relating to hereditary tyrosinemia type 1*)
- urinary succinylacetone (*relating to hereditary tyrosinemia type 1*)
- serum-alpha fetoprotein (*relating to hereditary tyrosinemia type 1*)
- magnetic resonance imaging of abdomen (consistent with increased iron in liver and pancreas but not in spleen) (*relating to perinatal hemochromatosis and other disorders causing iron overload*)
- serum ferritin level elevated, typically above 1000 µg/L (if above 20,000 µg/L, consider erythrophagocytic syndrome to be an alternative diagnosis) (relating to perinatal hemochromatosis)
- histopathology (salivary gland biopsy or liver biopsy are not obligatory if hazardous to obtain) shows an iron overload or other process (*relating to perinatal hemochromatosis and other etiologies*)
- serum lactate to pyruvate ratio and urinary organic acids (*relating to mitochondrial disorders)]*
- sweat chloride in older infants (*relating to cystic fibrosis*)
- length of time receiving total parenteral nutrition (*relating to total parenteral nutrition cholestasis*)

metabolic instability and signs of liver damage that present in the neonatal period (ie, the first 60 days of life). Many affected infants present in the first few days of life, but some are older (two to six weeks of age or older) at the time of presentation. Prematurity is encountered frequently. The established causes of neonatal liver failure are outlined in Table 1, and a working case definition with a diagnostic strategy is presented in Table 2. There are no data on the true incidence of neonatal liver failure because most information has come from case reports and series.

Diseases which cause neonatal liver failure can be categorized as 'acute hepatocellular necrosis' and 'chronic hepatic insufficiency' (Table 1). In the acute process, a previously normal liver is damaged by an acute insult, such as herpes simplex infection, resulting in marked increases in serum aminotransferase, jaundice and coagulopathy. In the chronic pattern of neonatal liver failure, there is significant liver damage. Cirrhosis may be present at birth, with near normal aminotransferase, coagulopathy, hypoalbuminemia and ascites (including fetal ascites). Neonatal liver failure is not uniformly fatal. Potentially treatable conditions for which the early initiation of therapy may greatly improve outcome are listed in Table 3. It is essential to note that some of the treatments listed are still experimental; concurrent, intensive supportive treatment is vital. Although some infants with chronic pattern neonatal liver failure can recover spontaneously, many require extensive supportive therapy leading to successful liver transplantation (3).

An important disease with the chronic pattern of neonatal liver failure is perinatal hemochromatosis (PH), which is also known as neonatal hemochromatosis or neonatal iron storage disease. PH is considered to be rare and typically presents early in the newborn period. Severe neonatal liver damage of intrauterine onset with extensive hepatic and extrahepatic iron-overload but sparing of the reticuloendothelial system is characteristic (4). PH is distinct from hereditary hemochromatosis for which a genetic basis which relates to (*HFE*) gene mutations has been discovered. The term 'perinatal' is used in preference to 'neonatal' hemochromatosis because the condition is extremely early in onset, often occuring in slightly preterm or low birth weight infants, and the severity of

TABLE 3: Causes of neonatal liver failure that are amenable to medical treatment

Disease	Treatment
Hepatitis B	Lamivudine*
Hepatitis C	Interferon-alpha plus ribavirin*
Herpes simplex	Acyclovir
Enteric virus infection	Intensive medical supportive care
Hereditary tyrosinemia type 1	NTBC, tyrosine-free diet
Galactosemia	Galactose-free diet
Hereditary fructose intolerance	Fructose-free diet
Perinatal hemochromatosis	'Antioxidant cocktail'
Congenital lack of delta^4-3-oxosteroid 5-beta-reductase	Cholic acid supplementation
Neuroblastoma	Appropriate chemotherapy
Congenital leukemia	Appropriate chemotherapy
Erythrophagocytosis syndromes	Appropriate chemotherapy

**Use not yet reported in neonates. NTBC 2-(2-nitro-4-trifluoromethyl-benzoyl)-1, 3-cyclohexanedione): inhibitor of 4-hydroxy-phenylpyruvate-dioxygenase*

liver fibrosis and siderosis at presentation clearly points to a process which begins in utero.

PH may be clinically heterogeneous. Although most patients with PH often die early from complications of neonatal liver failure, reports of favourable outcomes with only supportive treatment suggest diversity of pathogenesis (5,6). Some patients have survived with minimal evidence of liver damage once they recovered from the initial liver failure. The classic presentation of PH consists of profound coagulopathy, hyperbilirubinemia, ascites, and renal and liver failure, with only a mild increase in aminotransferase levels, features similar to those of other chronic forms of neonatal liver failure. The diagnosis of PH is not uncommonly delayed due to difficulty in recognizing how ill an infant is when liver enzymes are relatively normal. The diagnosis is established by the presence of an iron overload in serum, the liver and other organs, with sparing of the reticuloendothelial system, along with the classic clinical picture. Serum ferritin levels are often markedly elevated but not necessarily diagnostic. Liver or buccal mucosal biopsies show iron overload but may be technically difficult to obtain. The T2-weighted magnetic resonance imaging scan is often used as a noninvasive way to show iron accumulation in the liver and other organs (7). However, severe loss of hepatocytes may give a false impression of low iron levels on magnetic resonance imaging scans.

Recent evidence suggests that treatment using an 'antioxidant cocktail' (*N*-acetylcysteine, selenium, alpha-tocopherol, prostaglandin E^1 and desferroxamine) (8,9) may lead to recovery in some infants, while in others it may allow clinical stabilization until liver transplantation is possible (10). Recent reports of successful outcomes following neonatal liver transplantation for PH are encouraging. The pathogenesis of PH remains unclear. It may be the clinical phenotype of various diseases, which can cause neonatal liver failure, such as inborn errors of bile acid synthesis or congenital parvovirus B19 infection (11,12). In some infants, it may reflect an inherited metabolic disorder, but the inheritance pattern and nature of the metabolic defect remain unknown. In some cases, a mitochondrial disorder is postulated. Even the true incidence of PH is not clear, with approximately 100 cases reported in the literature since it was first described in 1980.

With the comprehensive surveillance method available through the Canadian Paediatric Surveillance Program, the authors aim to collect information on all cases of neonatal liver failure in Canada in a general and prospective manner. The authors anticipate finding acute pattern neonatal liver failure due to viral infections, acute and chronic pattern neonatal liver failure due to hereditary tyrosinemia type 1 and chronic-pattern neonatal liver failure due to various disorders, especially PH. These data will provide a unique epidemiological perspective on this important group of neonatal liver diseases. We anticipate developing improved diagnostic methods and more effective treatment for these potentially salvageable conditions.

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