A 15-day-old infant with acute liver failure

มหาวิทยาลัยสงขลานครินทร์

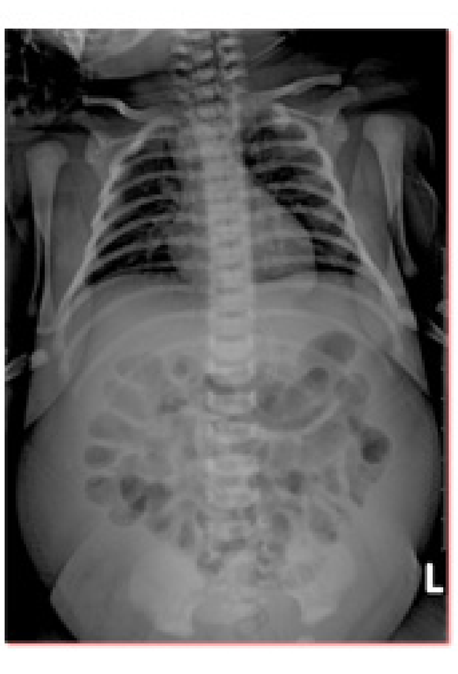
History:
ผู้ป่วยทารกหญิงอายุ 15 วัน ถูกส่งมา รพ.สงขลานครินทร์ เพราะสงสัย bowel gangrene

ประวัติปัจจุบัน: คลอดปกติ ครบกำหนด น้ำหนัก 2,800 กรัม APGAR Score 9, 10 กินนมมารดา อายุ 2 วัน มีอาการซึม กระตุก ตาเหลือก แพทย์วินิจฉัย sepsis รักษาด้วย Cefotaxime อายุ 12 วันเริ่มท้องอืด ขาบวม ไม่ซึม ไม่มีไข้ ถ่ายอุจจาระสีเหลืองวันละ 2-3 ครั้ง เนื่องจากท้องอืด แพทย์โรงพยาบาลใกล้บ้านสงสัย NEC จึงส่งต่อมารพ.สงขลานครินทร์

Past history: ประวัติการตั้งครรภ์ มารดา G9P8 ระหว่าง ANC มีปัญหา hypertension 140/90
Family history: ปฏิเสธโรคอื่น ๆ ในครอบครัว
Physical examination:
GA: A Thai female newborn infant, Marked jaundice with generalized edema
BT 36.7 oC, PR 160/min, BP 85/55, BW 3,480 g.
No Hepatomegaly, but splenomegaly with ascites
The picture as show below:

Basic investigations:
CBC : Hb 11.9 g/dl, WBC 10,450 cell/mm3, PMN 69% L 22% Baso 1% M 5% E 2% Atyp L 1%, Plt. 73,000 cell/mm3
UA: pH 6.5, Pro. +1, Glu. Negative, Bil. +3, WBC 3-5, RBC 0-1
BS: 85 mg/dl, BUN 9.8, Cr 0.28 mg/dl
Electrolytes: Na132 mmol/L, K 5.9 mmol/L, Cl 104 mmol/L, HCO3 19 mmol/L
BUN 15 mg/dl, Cr 0.3 mg/dl
LFT: TB 22.4 mg%, DB 15 mg%, AST 189 U/L, ALT 43 U/L, ALP 900 U/L, TP 2.7 g%, Alb 1.9 g%, GGT 15 (11-50) U/L. PTT >100 (control 27.1), PT 45.3 (11.9), INR 3.7

Plain abdomen:



The abdominal film shows - ascites

Ultrasound abdomen : The liver is relatively slightly small size. It shows coarse echogenicity without focal lesion. The spleen is enlarged 6.8 cm in size. No focal lesion. Moderate amount of ascites. Gall bladder, bile ducts, portal vein are normal.

Imp : Possible liver cirrhosis with portal hypertension.

Problem list:

Neonatal liver failure

Definitions:
A distinct clinical syndrome that is characterized by evidence of severe hepatic dysfunction in children who are < 30 days of age at the time of diagnosis.
Shneider BL. Curr Opin Pediatr 1996;8:495-501 .
Unlike its adult counterpart, encephalopathy is not necessarily a key feature of the syndrome.

Etiology of neonatal liver failure (33 cases)

	N (%)
Infection	6 (18)
HSV 1 and 2	5
HBV, HHV6, Enterovirus	0
Bacterial	1
Metabolic	5 (15)
Tyrosinemia 1	1
Urea cycle	1
Golactosemia	3
Neonatal hemochromatosis	16 (48)
Infiltrative storage HLH	4 (12)
Leukemia, tumors, Nieman-Pick C	0
Drug	1 (3)
Hypocortisolism	1 (3)

McClean P, Davidson SM. Semin Neonatol 2003;8:393-401.

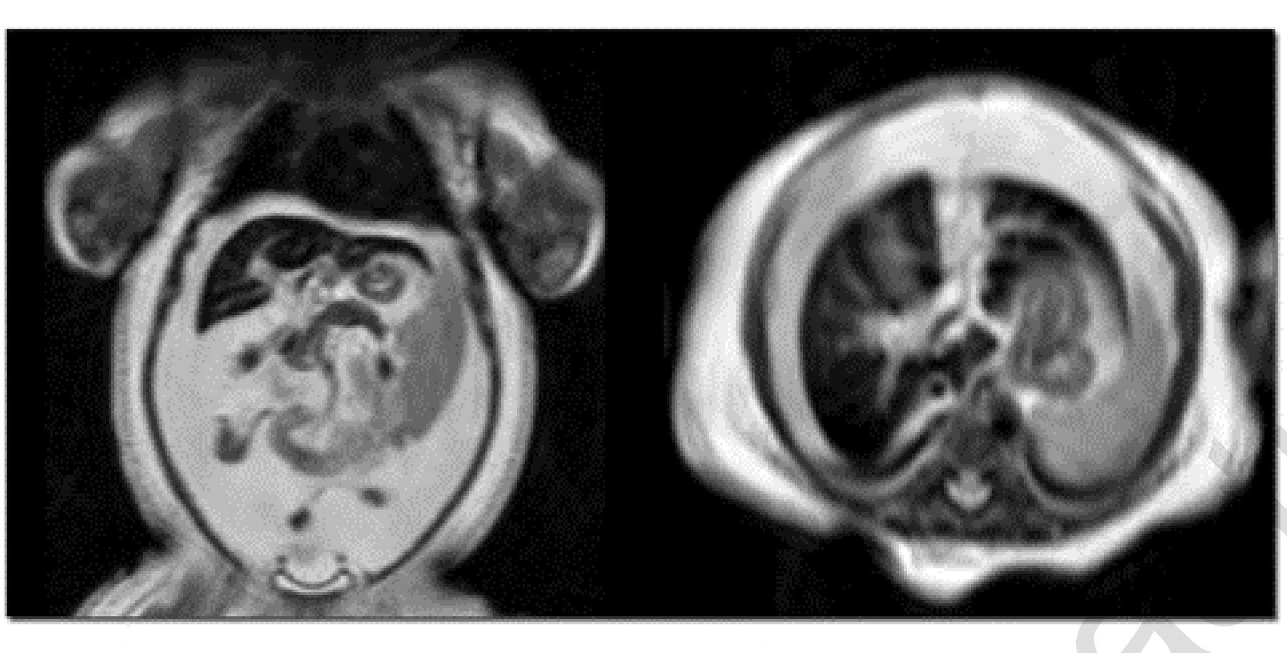
Further investigations :

CMV Ig M - neg
Blood amonia - 174 (19-82) mg%
Protein electrophoresis (g%)
>> Alpha1 - 1.7 (2 - 6)
>>Alpha2 - 5.5 (6 - 13)
>> Beta 5.0 (8 - 15)
>> Gama 29.2 (10 - 20)
Urine succinylacetone - neg
Alpha-fetoprotein - 13,287 ng/ml

How likely is neonatal hemochromatosis (NH) the etiology in this neonate ?
Neonatal hemochromatosis (NH) :
Defined as a rare disorder that is characterized by neonatal liver failure with an in utero onset and is associated with hepatic and extrahepatic iron accumulation that spares the RE system.
Vohra P, et al. J Pediatr 2000;136:537-41

Diagnosis of NH
- Should be suspected in neonates who manifest liver disease antenatally or very shortly after birth.
- Hepatic and extrahepatic siderosis
>>>Tissue biopsy with iron staining (liver, oral mucosa)
>>>MRI (T2 - weighted) (If tissue biopsy is impossible)
- Hyperferritinemia, hypotransferrinemia, hypersaturation of transferrin

Evaluation of NH in this patients:
Ferritin 5,940 (7-140 ng/mL)
Transferrin 12 (23-43 mmol/L)
Serum iron 18 (9-27 mmol/L)
TIBC 18 (27-80.5 mmol/L)
% transferrin saturation (SI/TIBC) = 100% (< 80%)
Liver biopsy - not done due to severe coagulopathy
and a large amount of ascites



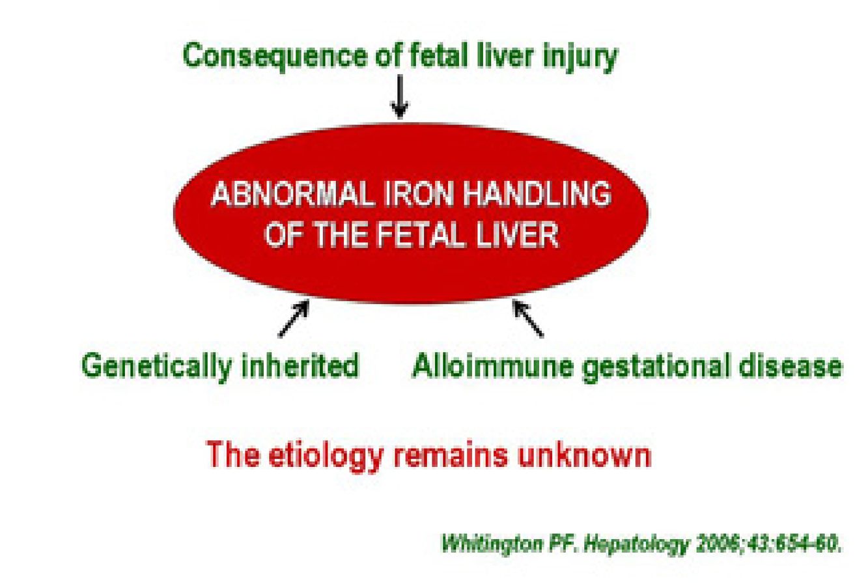
MRI (T2 Weighted): Small size liver with moderate splenomegaly. Markedly reduced signal intensity of hepatic parenchyma and pancreatic parenchyma on T2-Wi are evidence of parenchymal cell iron overload. The signal intensity of bone marrow and spleen are normal.

Clinical course:

Supportive care for liver failure
Antibiotic IV
Day-11th - Diagnosis of NH
>>Start Deferoxamine 30 mg/kg/day
>>N-acetylcysteine IV. 100 mg/kg/day
>>Vit E 25 IU/kg/day
Day 35th - Severe pulmonary hemorrhage and expired
Final diagnosis: Neonatal hemochromatosis

Neonatal Hemochromatosis (NH)

Etiopathogenesis of NH



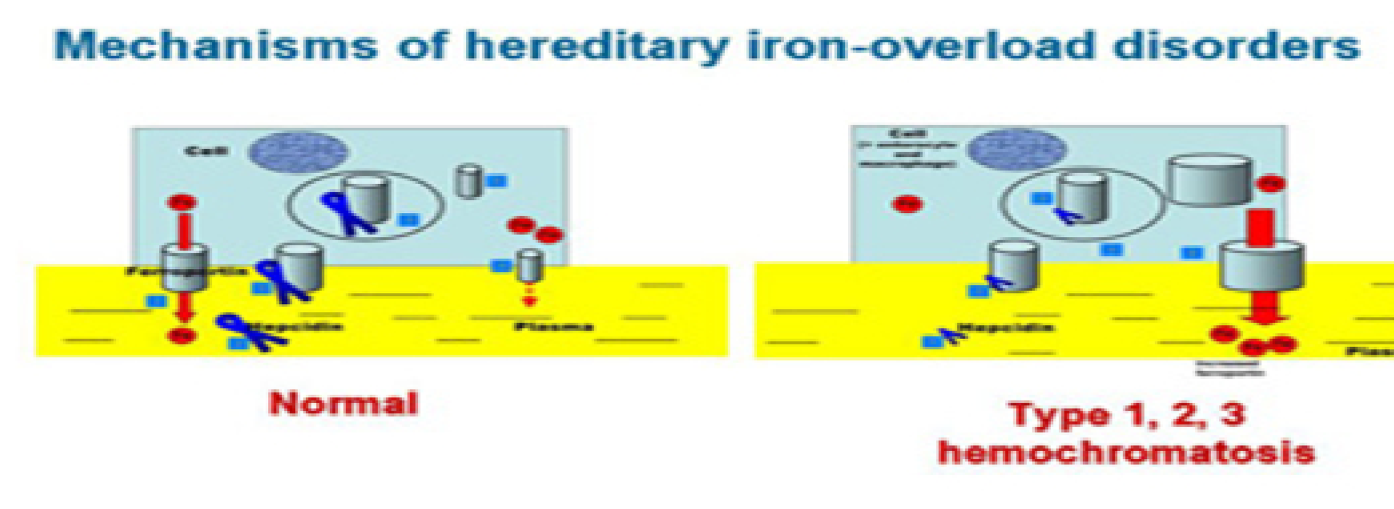
NH. vs. Hereditary hemochromatosis:
In terms of clinical feature, NH has iron accumulation in the liver and extrahepatic sites in a distribution similar to that seen in hereditary HFE-associated hemochromatosis. However, NH has no genetic relation with hereditary hemochromatosis.

Mutated genes in hereditary iron-overload disorders

Type	Gene	Protein	Inheritance	Age at onset (y)
1	HFE	HFE	AR	40-60
2A	HJV	Hemojuvelin	AR	15-25
2B	HAMP	Hepcidin	AR	15-25
3	TFR 2	TFR 2	AR	40-60
4	SLC 40A1	Ferroportin	AD	30-50

Andrews NC, et al. N Eng J Med 2005;353:189-98.

Mechanisms of hereditary iron-overload disorders



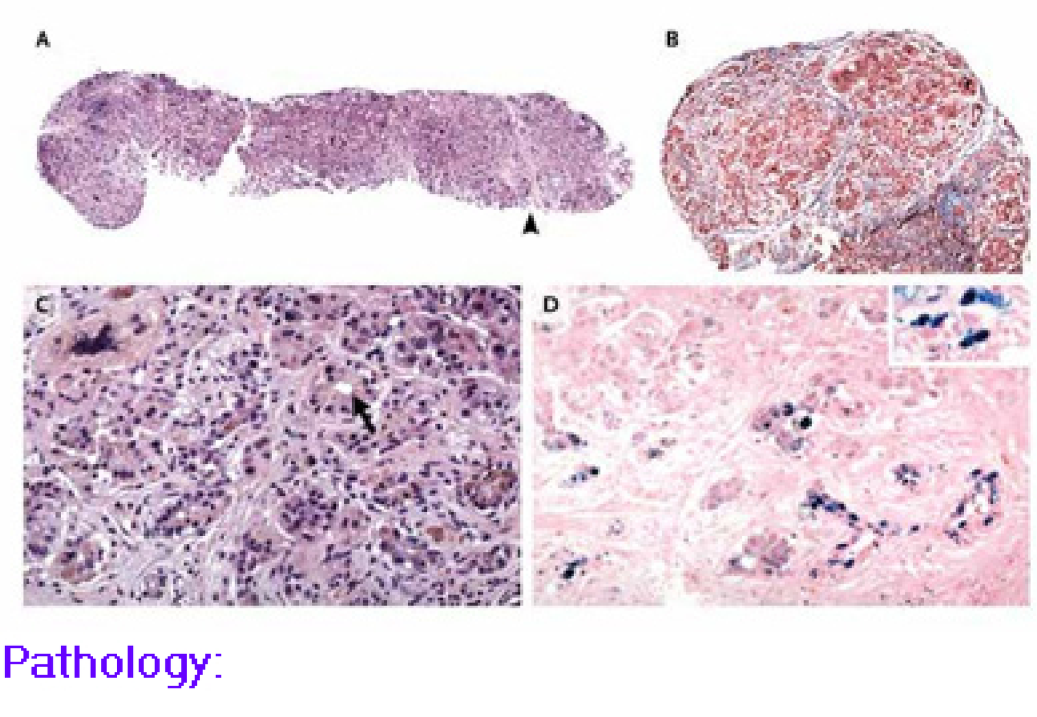
Brissot P, et al. Blood Reviews 2008;22:195-210.

>>NH is the most frequently cause of liver failure in neonates.

>>NH phenotype has been found in associated with Tyrosinemia, trichohepato-enteric syndrome, GARCILE syndrome, parvovirus B 19 infection, Congenital rubella, renal-hepatic-pancreatic cystic dysplasia of Ivemark

>>No precise cause can be identified in the vast majority of cases.

Clinical features of NH
>Severe fetal liver injury, presenting with late second and third trimester fetal loss, IUGR, Premature birth
>Acute liver failure develops at early onset within hours of birth or rarely takes a subacute course and manifests days to weeks after birth.
>Hypoglycemia, marked coagulopathy,
>Hypoalbuminemia, ascites, jaundice
>Frequently misdiagnosed as having severe sepsis
>Serum aminotransferases are disproportionately low for the degree of hepatic injury.
>Very high AFP
>There is a high recurrent rate (80%) within families.



Pathology:

oHepatic siderosis and cirrhosis is universally described.
oBridging and pericellular fibrosis with focally nodular pattern.
oPseudoglandular formation
oMultinucleated giant cell transformation
oSiderosis may affect any of extrahepatic organs including exocrine pancrease, myocardium, thyroid, oral mucous and salivary gland.

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Treatment:

oSupportive care of liver failure
oMedical treatment with a cocktail of antioxidants and iron chelator
—>Acetylcysteine, Vit E, Selenium, PGE1
—>Desferrioxamine
oLiver transplantation

Outcomes of treatment

	Rodrigues, et al. (Liver transpl 2005) N = 19	Grabhorn, et al. (Pediatrics 2006) N = 16
Antioxidants/chelation [N;(%)]	10	10
Survive	1 (10)	4 (40)
Dead/LT	9 (90)	6 (60)
Supportive care only [N;(%)]	9	6
Survive	1 (11)	1 (16.6)
Dead/LT	8 (89)	5 (83.4)
Total LT [N;(%)]	10	8
Survive	5 (50)	6 (75)
Overall death [N;(%)]	12 (63)	5 (31.3)