Title: Fulminant liver failure in a neonate

Type of manuscript: Instructive Case

Authors: Naomi E Clarke MBBS BMedSci¹, Damien Gilby MBBS MRCPCH¹, Helen Savoia MBBS FRCPA², Mark R Oliver MBBS FRACP MD^{3,4,5}, Sheryle Rogerson MBBS MRCPCH FRACP¹

1. Department of Neonatology, Royal Women's Hospital, Flemington Road, Parkville, Victoria 3052
2. Department of Clinical Haematology, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052
3. Department of Gastroenterology, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052
4. Department of Paediatrics, University of Melbourne, Parkville, Victoria 3052
5. Murdoch Children's Research Institute, Parkville, Victoria 3052

Corresponding author:

Sheryle Rogerson
Department of Neonatology
Royal Women's Hospital
Flemington Road
Parkville VIC 3052
Australia
Email: Sheryle.Rogerson@thewomens.org.au
Tel: +61 3 8345 2673

Conflict of interest:

The authors have no conflicts of interest to declare.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/jpc.13090](https://doi.org/10.1111/jpc.13090)

Note: Naomi Clarke's present address is Research School of Population Health, Australian National University, Acton ACT 2601

Author Manuscript

Fulminant liver failure in a neonate

Case report

We describe the case of baby LJ, who was born to a 25-year-old primigravid woman at 27+6 weeks gestation. Severe intrauterine growth restriction ($< 3^{\text{rd}}$ centile) was noted at the 20 week morphology scan, associated with echogenic bowel and echogenic kidneys. Antenatal investigations including TORCH serology, karyotype and parental cystic fibrosis screening were normal, and microarray was normal other than showing evidence of a known high degree of parental consanguinity. Ongoing ultrasound surveillance demonstrated deterioration in umbilical artery Dopplers and minimal growth. Antenatal steroids were given at 27+4 weeks.

LJ was born via caesarean section at 27+6 weeks gestation. His birthweight was 591g ($< 3^{\text{rd}}$ centile), with Apgar scores of 2 and 7 (at 1 and 5 minutes, respectively). Early issues included respiratory distress syndrome requiring ventilation; hypoglycaemia; hypotension requiring inotropic support; tension pneumothorax and a patent ductus arteriosus. Routine cranial ultrasounds were normal. A two-week course of intravenous antibiotics was given from day 7 of life for presumed sepsis in the context of a significant clinical deterioration. No organism was grown on blood cultures. The patient stabilised by day 10 and was extubated on day 16.

LJ had a raised conjugated bilirubin (cBR) from day 1, with a total serum bilirubin (SBR) at 18hrs of 121 $\mu\text{mol/L}$, and cBR of 23 $\mu\text{mol/L}$. Phototherapy given in the first week of life lowered the SBR; however, cBR continued to rise and by day 18 cBR was 122 $\mu\text{mol/L}$. Liver enzymes were normal, abdominal examination was unremarkable, and liver ultrasound was normal other than a few tiny echogenic areas, with a normal gall bladder. Synthetic function was reduced with hypoalbuminaemia and coagulopathy (albumin 11g/L, INR 2.3, APTT 50 sec, fibrinogen 1.2g/L).

Over the next several weeks, there was progressive liver dysfunction, with unresponsive coagulopathy, hypoalbuminaemia, generalised oedema and renal impairment. Liver enzymes became mildly deranged (peak ALT 199IU/L, peak ALP 612IU/L, GGT normal) but subsequently normalised, and conjugated bilirubin decreased. Regular vitamin K and blood product support (including FFP, prothrombinex, cryoprecipitate and albumin) were given. On day 30, a significant clinical deterioration occurred secondary to *Klebsiella pneumoniae* sepsis, and the patient was re-intubated, recommenced on inotropes and commenced on broad-spectrum antibiotics. Synthetic liver function continued to worsen, with maximal INR of 9.7, APTT > 180 sec and fibrinogen $< 0.5\text{g/L}$.

LJ was extensively investigated for the cause of his liver failure – differentials and relevant investigations are summarised in table 1. Given the history of consanguinity, a metabolic aetiology was considered most likely; however, an extensive metabolic screen did not identify a cause. Based on clinical and biochemical findings, the most likely diagnosis was gestational alloimmune liver disease (GALD). The patient was too unwell to undergo definitive investigation with MRI or biopsy, so presumptive treatment with a double-volume exchange transfusion was planned on day 34 of life; however, due to difficult intravascular access only a single-volume exchange was given. Despite maximal intensive care, there was progressive multi-organ failure, and the infant passed away on day 40 of life.

Post-Mortem

Post-mortem examination of the liver showed extensive fibrosis, with proliferation of bile ductules and a positive Perls (iron) stain. Examination of the pancreas revealed extrahepatic siderosis with a positive Perls stain. These findings were highly suggestive of the diagnosis of GALD. Staining for C5b-9 complex in the liver was positive, confirming the presence of an alloimmune-mediated liver injury, and the diagnosis of GALD.

Discussion – gestational alloimmune liver disease

We report a case of severe and worsening neonatal liver failure, with a clinical and pathological (post-mortem) diagnosis of gestational alloimmune liver disease (GALD).

Gestational alloimmune liver disease – previously known as neonatal haemochromatosis – manifests as severe liver injury with accumulation of iron (siderosis) in hepatic and extrahepatic tissue. It is caused by sensitization of the mother to a fetal liver antigen, resulting in the development of specific anti-fetal liver IgG antibodies. These antibodies bind to the antigen in the fetal circulation and activate the terminal complement cascade, resulting in hepatocyte injury and death¹. The exact fetal antigen is unknown, but studies have shown involvement of complement in specific injury to fetal hepatocytes², and immunohistochemical staining for C5b-9 to nearly all hepatocytes is the defining feature of GALD¹.

GALD typically results in subacute fetal liver injury (as in the case we describe) and congenital cirrhosis, with siderosis a result of fetal liver dysfunction. In other cases it may produce hyper-acute severe liver injury leading to fetal demise, and autopsy findings in such cases reveal acute hepatocyte necrosis without fibrosis or siderosis³.

Affected neonates are generally growth-restricted and are often born prematurely due to medical intervention for growth restriction. The onset of disease is typically within hours or days, but can be up to weeks after birth, with marked coagulopathy, oedema, hypoalbuminaemia and oliguria⁴. Aminotransferase levels are generally relatively low for the degree of liver injury and synthetic dysfunction. Both conjugated and unconjugated bilirubin are typically raised. Ferritin is raised with hypersaturation of transferrin⁴. Diagnosis relies on the demonstration of extra-hepatic siderosis, which can be achieved through biopsy of oral salivary glands or T2-weighted MRI¹.

Treatment with intravenous immunoglobulin (IVIg) and exchange transfusion is the current standard of care for neonates with GALD. A case series of 16 affected infants, all of whom were treated with IVIg and 13 of whom also received double-volume exchange transfusion, showed survival of 12 infants without liver transplant. This survival rate of 75% was compared to 131 historical controls in the literature, who were treated with anti-oxidants, chelation and/or liver transplantation, and for whom the reported overall survival rate was 32%⁵. Coagulopathy can take 4-6 weeks to resolve following treatment.

Lethal recurrence rate in subsequent pregnancies is over 90% without treatment⁶. Maternal treatment with IVIg in weeks 14, 16 and weekly from week 18 of pregnancy shows good efficacy in reducing the recurrence of GALD, with a recent large case series of such pregnancies reporting survival of 138 out of 140 (99%) infants, and only five cases of liver disease⁴.

Discussion – neonatal liver disease

Acute liver failure is relatively uncommon in neonates, and should be considered in any case where there is sepsis (confirmed or presumed) and/or recurrent hypoglycaemia with abnormal liver function tests. If there is biochemical evidence of liver dysfunction and coagulation studies are abnormal, then liver failure should be suspected and vitamin K should be administered. If coagulation studies fail to normalise, this confirms liver failure and a referral should be made to a tertiary liver centre. Management which should be initiated in the referring centre includes changing to a lactose-free formula, fluid restriction to 2/3 maintenance (while maintaining blood glucose levels), and consideration of **empiric** antibiotics, including high-dose aciclovir until herpes simplex virus is excluded. Treatment with a proton pump inhibitor or H2 antagonist should also be considered.

Identifying the cause of neonatal liver disease will inform management, prognosis and risk of recurrence in subsequent pregnancies. Major causes of neonatal liver disease include GALD, infections (such as herpes simplex virus, enterovirus and cytomegalovirus), metabolic disorders (such as galactosaemia,

respiratory chain defects, tyrosinaemia and mitochondrial disorders), haemophagocytic lymphohistiocytosis, and ischaemic injury⁷. A prospective study of 148 infants with acute liver failure revealed significant differences in biochemical parameters (AST, ALT, conjugated bilirubin and INR) based on aetiology of acute liver failure. These patterns – summarised in Table 2 – may be used to guide further investigation and management⁸.

Neonatal acute liver failure has a 70% mortality rate without liver transplantation⁷. In a large, multi-centre study of infants and children with acute liver failure, 41% of infants with acute liver failure were listed for transplant. Overall graft survival in those who received a transplant was 76% and patient survival was 87.8% at 12 months post-transplant⁸.

As our case illustrates, the cause of neonatal liver disease can be difficult to identify, and intensive supportive care is required. Gestational alloimmune liver disease is an important differential and treatment with IVIg and/or exchange transfusion should be considered if the diagnosis is likely on clinical grounds.

Learning points

- Coagulation tests should be performed in all infants with biochemical evidence of liver dysfunction (excluding those situations in which a clear cause is apparent, such as raised alkaline phosphatase [ALP] associated with altered bone growth of prematurity, and elevated unconjugated bilirubin in neonatal jaundice)
- Failure to normalise coagulation after administration of vitamin K indicates liver disease and warrants immediate referral to a tertiary liver centre
- Causes of neonatal liver failure include gestational alloimmune liver disease (GALD), viral infections, metabolic disorders, haemophagocytic lymphohistiocytosis, and ischaemic injury
- Medical management of GALD includes intravenous immunoglobulin and exchange transfusion which can lead to favourable outcomes
- Mothers of infants with GALD should be referred for specialist management with IVIg in subsequent pregnancies

Multiple-choice questions

1. If there is biochemical evidence of liver dysfunction in a neonate, which of the following investigation results confirms neonatal liver failure?

- A) Prolonged PT/INR which normalises after vitamin K administration
- B) Prolonged PT/INR which does not normalise after vitamin K administration
- C) Low serum albumin
- D) Hypoechoic areas on liver ultrasound
- E) None of the above can confirm liver failure

Answer: B. Prolonged PT/INR which does not normalise after vitamin K administration confirms liver failure. Prolonged PT/INR that normalises after vitamin K administration is suggestive of vitamin K deficiency. Low serum albumin can be due to liver failure but also numerous other causes. Hypoechoic areas on liver ultrasound are a non-specific finding which do not indicate liver failure.

2. If acute liver failure in a neonate is confirmed, what management should be instigated?

- A) Fluid restriction to 2/3 maintenance
- B) Intravenous acyclovir
- C) Changing to a lactose-free formula
- D) Referral to a tertiary paediatric liver centre
- E) All of the above

Answer: E. All neonates with liver failure should be managed with acyclovir and lactose-free formula until the diagnoses of herpes simplex virus and galactosaemia (respectively) have been excluded. Fluids should be restricted and referral to a tertiary liver centre made for further management.

3. Which of the following statements regarding gestational alloimmune liver disease is correct?

- A) Risk of recurrence in subsequent pregnancies to the same mother is 25% due to autosomal recessive inheritance
- B) Onset is typically weeks to months after birth
- C) Medical treatment of affected infants includes immunoglobulin and exchange transfusion
- D) Conjugated bilirubin is typically normal
- E) All of the above

Answer: C. Intravenous immunoglobulin and exchange transfusion can result in survival of infants without need for liver transplantation, although it can take 4-6 weeks for coagulation to normalise following this treatment. There is a lethal recurrence rate of 90% in subsequent pregnancies due to maternal allo-antibodies, but maternal treatment with IVIg can dramatically reduce this risk. Onset is typically within hours to days of birth, and conjugated bilirubin is typically raised.

References

1. Whittington PF. Gestational alloimmune liver disease and neonatal hemochromatosis. *Semin. Liver Dis.* 2012; 32: 325-32.
2. Pan X, Kelly S, Melin-Aldana H, Malladi P, Whittington PF. Novel mechanism of fetal hepatocyte injury in congenital alloimmune hepatitis involves the terminal complement cascade. *Hepatology* 2010; 51: 2061–8.
3. Whittington PF, Pan X, Kelly S, Melin-Aldana H, Malladi P. Gestational alloimmune liver disease in cases of fetal death. *J. Pediatr.* 2011; 159: 612–16.
4. Feldman AG, Whittington PF. Neonatal hemochromatosis. *J. Clin. Exp. Hepatol.* 2013; 3: 313–20.
5. Rand EB, Karpen SJ, Kelly S, et al. Treatment of neonatal hemochromatosis with exchange transfusion and intravenous immunoglobulin. *J. Pediatr.* 2009; 155: 566–71.
6. Whittington PF, Kelly S. Outcome of pregnancies at risk for neonatal hemochromatosis is improved by treatment with high-dose intravenous immunoglobulin. *Pediatrics* 2008; 121: e1615–21.
7. Dhawan A, Mieli-Vergani G. Acute liver failure in neonates. *Early Hum. Dev.* 2005; 81: 1005–10.
8. Sundaram SS, Alonso EM, Narkewicz MR et al. Characterization and outcomes of young infants with acute liver failure. *J. Pediatr.* 2011; 159: 813–18.

Table 1. Differential diagnoses, investigations performed and results

Differential diagnosis	Investigations	Result
Viral infections		
Enterovirus	Enterovirus PCR (serum)	Negative
Adenovirus	Adenovirus PCR (serum)	Negative
Human herpes virus 6 (HHV6)	HHV6 PCR (serum)	Negative
Herpes simplex virus (HSV)	HSV PCR (serum)	Negative
Hepatitis B	Hepatitis B Sag	Negative
Hepatitis C	Hepatitis C antibodies	Negative
Cytomegalovirus (CMV)	CMV PCR (urine)	Negative
Epstein-Barr virus (EBV)	EBV antibodies	IgG positive, IgM negative
Metabolic disorders		
Galactosaemia	Hexose-1-phosphate uridyl transferase activity	Normal†
Tyrosinaemia	Serum tyrosine	156.5 µmol/L (high; ref range 32-124)
	Urine succinyl acetone	0.03 µmol/mmol of creatinine (normal; ref range <0.14)
Others (urea cycle defect, respiratory chain defect)	Serum ammonia	52 µmol/L (slightly high; ref range <50)
	Serum lactate	1.1 mmol/L (normal; ref range 1.0-1.8)
	Urine amino acids	Normal amino acid profile for neonate
	Urine organic acid screen	Homovanillic (HVA) + 4-hydroxyphenyl lactic ++ Vanil lactic + Consistent with abnormal liver function
	Urine total glycosaminoglycans	32.9mg/mmol of creatinine (normal; ref range <73.1)
	Urine bile acid screen	Increase in bile acids typical of cholestasis; no diagnostic pattern
	Plasma amino acids	Raised methionine (87 µmol/L, RR 6-36) – consistent with liver dystrophy
Other		
Gestational alloimmune liver disease‡	Serum transferrin	0.3 g/L (low; ref range 2.1-4.3)
	Serum ferritin	4797 pmol/L (no ref range)
	Iron-binding capacity	8.3 µmol/L (low; ref range 44-80)
	% Saturation	125% (high; ref range 20-55)
	Serum alpha-fetoprotein	74500 µg/L (normal; ref range 50-100000)
Haemophagocytic lymphohistiocytosis	Serum triglycerides	0.6mmol/L (low; ref range 0.9-2.0)
	NK cell function (CD107a expression)	Normal
	Perforin expression	Normal
	Plasma soluble CD25	3644 pg/L (normal; ref range 239-7887)
	Lymphocyte subsets	Consistent with B-lymphopenia§

X-linked lymphoproliferative syndromes	SAP and XIAP expression on CD8+ T cells	Normal
Alpha-1-anti-trypsin deficiency	Alpha-1-anti-trypsin level	1.27g/L (normal; ref range 0.9-2.4)

† Difficult to interpret given multiple blood transfusions

‡ Iron studies were performed on day 18 of life

§ Likely prematurity-related

Author Manuscript

Table 2.

Patterns of biochemical parameters according to aetiology of acute liver failure⁸

Aetiology	Pattern of biochemical parameters
Gestational alloimmune liver disease	Severe coagulopathy Relatively normal transaminases
Viral-induced liver failure	Extremely high transaminases Severe cholestasis Severe coagulopathy
Metabolic-induced liver failure	Moderately elevated transaminases Moderate cholestasis Moderate coagulopathy

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Clarke, NE;Gilby, D;Savoia, H;Oliver, MR;Rogerson, S

Title:

Fulminant liver failure in a neonate

Date:

2016-03-01

Citation:

Clarke, N. E., Gilby, D., Savoia, H., Oliver, M. R. & Rogerson, S. (2016). Fulminant liver failure in a neonate. JOURNAL OF PAEDIATRICS AND CHILD HEALTH, 52 (3), pp.338-341. <https://doi.org/10.1111/jpc.13090>.

Persistent Link:

<http://hdl.handle.net/11343/291012>