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A Case of Early Neonatal Fulminant Liver Failure and Haemophagocytic Lymphohistiocytosis

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Abstract Both liver failure and haemophagocytic lymphohistiocytosis are rare conditions during the neonatal period. We report a case of fulminant neonatal liver failure that presented on the first day of life and was subsequently diagnosed to have haemophagocytic lymphohistiocytosis (HLH). Work up for secondary causes was not revealing and our patient might represent a case of familial HLH although the more definitive genetic testing was not performed. To our knowledge, this is the youngest reported case of HLH in this locality. HLH should be considered in cases of perinatal liver failure.

Key words Acute liver failure; Haemophagocytic lymphohistiocytosis; Neonates

Case Report

A full term baby girl born by normal vaginal delivery with birth weight 2.41 kg was admitted to our special baby care unit after birth because of low birth weight and moderately meconium stained liquor. The Apgar score was 9 at 1st minute and 10 at 5th minute of life. Antenatal history was unremarkable except her mother had a non specific skin rash at 13th and 26th week of gestation and had upper respiratory tract symptoms at 22nd week of gestation, all without fever. Her mother's antenatal screening for hepatitis B surface antigen, syphilis and human immunodeficiency virus antibodies were negative and her mother was rubella immuned. This was the first pregnancy of her mother. There was no parental consanguinity and the family history was unremarkable. On physical examination, her weight was at the 10th percentile, length and head circumference at the 3rd percentile. There was generalised papular rash over the body. She did not have any dysmorphic features. Cardiovascular examination revealed a pansystolic murmur of grade 3/6 over the left sternal border but normal apex and no abnormal precordial impulses. She was tachypnoeic without desaturation and had hepatosplenomegaly each 4.5 cm below costal margin.

Work up for sepsis and congenital infections was performed and she was put on intravenous penicillin and gentamycin. Initial blood test results showed thrombocytopenia with count 37 x 10^9/L, anaemia with haemoglobin (Hb) 11.3 g/dL but normal total white blood cell (wbc) count 15 x 10^9/L and differential counts. Liver function test (LFT) was deranged with aspartate transaminase(AST) 677 IU/L and alanine transaminase (ALT) 151 IU/L. Total bilirubin and conjugated bilirubin were raised (73 umol/L and 34 umol/L respectively at birth). The serum albumin was low 19 g/L. Clotting profile was mildly deranged with prothrombin time (PT) 19.3 seconds (normal 10-16 seconds), activated partial thromboplastin time (APTT) 39.8 seconds (normal 31-55 seconds) and an international normalised ratio (INR) 1.67. C-reactive protein (CRP) was elevated to 18.2 mg/L. There was hypoglycaemia with blood glucose 1.4 mmol/L before the start of intravenous fluid. Chest X-ray showed bilateral lung field hazziness. She was transferred to our neonatal intensive care unit for further management.

She developed fever since postnatal day 1 with temperature 38°C and also neutropenia since day 3 (Table 1) apart from the thrombocytopenia and anaemia. She had

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disseminated intravascular coagulopathy (DIC) with raised D-dimer (935 ng/ml Fibrinogen Equivalent Unit (FEU) on day 2, normal <500 ng/ml FEU) and decreased fibrinogen level (1.6 g/L on day 3, normal ranged from 2.3-3.9 g/L). Antimicrobials were changed to intravenous ampicillin and gentamycin since day 2. Ceftriaxone and acyclovir were added since day 4. Congenital infection screening was non revealing including for (i) bacteria, (ii) cytomegalovirus (CMV), (iii) herpes simplex virus (HSV), (iv) varicella zoster virus (VZV), (v) Epstein-Barr virus (EBV), (vi) parvovirus, (vii) rubella, (viii) toxoplasma, (ix) human immunodeficiency virus (HIV), (x) hepatitis A/B/C and (xi) syphilis (Table 2). Skeletal survey, ophthalmological assessment and bedside ultrasound brain were normal that showed no evidence for congenital infections. Echocardiography showed ventricular septal defect (VSD) 1.7 x 2.3 mm, patent ductus arteriosus (PDA) 1.4 mm and atrial septal defect/patent foramen ovale (ASD/PFO) 3.8 mm.

Over the next two week, she continued to deteriorate with a list of further investigations done yielding no definite cause for her fever, rash, hepatosplenomegaly, liver failure and pancytopenia. There was intermittent fever and rash, the pancytopenia showed worsening trend (Table 1). She became lethargic since day 4. She required continuous positive airway pressure (CPAP) support via nasal prung since day 7. Liver function continued to deteriorate with increasing hypoalbuminaemia (serum albumin 18 g/L on day 7), increasing hyperbilirubinaemia and increasing coagulopathy (Table 1), although the liver enzymes showed a decreasing trend (AST dropped to137 IU/L and ALT to 69 IU/L on day 9). The serum ammonia level remained normal that time. Further screening for infections including CSF for human herpes virus (HHV), stool and throat swab for enterovirus culture, blood smear for malaria, blood fungal culture, tracheal aspirate for acid fast bacilli (AFB) PCR, tracheal aspirate and CSF and blood for AFB smear and culture were all negative. Second serology titre for CMV, HSV, EBV and parvovirus did not suggest recent infections (Table 2). Skin biopsy performed on day 9 showed no inclusion body, no infiltration of acute or chronic

Table 1 Serial changes of blood cell counts, bilirubin, conjugated bilirubin, clotting profile (PT-prothrobin time, APTT- activated partial thromboplastin time, INR - international normalised ratio) and ammonia over time

Day	1	2	3	4-5	7-9	10-11	12-13	14-15	16-17	18-19	20-21	22-24	25-27
WBC (x 10^9/L)	15	6.7	3.6	3.7	4.5	–	2.8	1.9	–	1.1	0.7	1.1	0.2
Neutrophil (x 10^9/L)	4	2.4	1.4	1.6	2.1	–	1.1	0.0	–	0.1	0.1	0.1	0.0
Hb (g/dL)	11.3	10.3	–	9.7	6.7	6.3	–	6.8	–	–	4.1	6.9	7.4
Platelet (x 10^9/L)	27	31	–	38	40	24	26	7	11	–	9	12	13
Bilirubin (total) (umol/l)	72	–	190	295	374	416	529	–	592	–	520	363	428
Birubilin (conjugated) (umol/l)	34	–	102	183	229	261	304	–	308	–	284	–	–
PT(s)	19.3	–	–	21.4	24	–	47.2	–	36.8	–	25.7	91.4	23.4
APTT(s)	39.8	–	–	44.6	47.9	–	98.7	–	61.4	–	40.3	117.1	89.9
INR	1.67	–	–	1.8	2	–	3.87	–	3.06	–	2.15	7.34	1.96
Ammonia (umol/l)	–	46	–	–	69	48	–	–	75	–	97	224	164

Table 2 The list of work up (culture tests, serological tests, antigens detection) for congenital infections in patient and her mother

	Tests done on mother	**Tests done on patient**
CMV (cytomegalovirus)	- blood for IgM -ve, IgG +ve	- Urine CMV deaff x 2 times -ve - serum CMV IgM-ve - serum CMV PCR -ve - serum CMV 1st titre =40 on day 1, 2nd titre =20 on day 18 - CSF R/M, biochem normal; viral culture -ve
HSV (herpes simplex virus)		- CSF herpes PCR -ve - CSF HSV titre <4 - CSF viral culture -ve - serum HSV 1st titre = 20 on day1, 2nd titre = 10 day18
VZV (varizella zoster virus)		- CSF VZV titre <4 - CSF viral culture -ve
EBV (Epstein-Barr virus)	- serum monospot test x 2 times -ve	- serum EBV IgM -ve - polyvalent titre 1st and 2nd both=320 (day 1 and day 18) - CSF viral culture -ve
Parvovirus	- serum parvovirus IgM-ve, IgG +ve	- serum parvovirus IgM -ve , IgG +ve
Rubella	- antenatal serum rubella Ab +ve - postnatal serum rubella IgM -ve	- serum rubella IgM -ve
Toxoplasma	- serum toxoplasma tire <10	- serum toxoplasma titre <10 - serum IgM -ve
HIV (human immunodeficiency virus)	- antenatal serum HIV Ab -ve - repeat serum HIV Ab postnatal -ve	
Hepatitis B (HepB)	- antenatal serum HepBsAg -ve - repeat postnatal serum HepBsAg / Ab -ve	- serum HepBsAg / Ab -ve
Hepatitis C (HepC)		- serum HCV Ab -ve
Hepatitis A (HepA)	- serum HepA IgG +ve, IgM -ve	- serum HepA IgG +ve, IgM -ve
Syphilis	- antenatal VDRL -ve	- blood RPR -ve - CSF VDRL -ve
HHV 6 (human herpes virus type 6)		- CSF HHV6 -ve
Enterovirus		- stool and throat swab cultures -ve
Tuberculosis	- mantoux test -ve - CXR normal - sputum for AFB PCR -ve - sputum for AFB smear and culture x 3 times -ve	- CSF AFB smear x 2 -ve - blood ESR 10 - blood for TB culture -ve - tracheal aspirate for AFB PCR -ve - tracheal aspirate for AFB culture and smear x 3 times -ve
Bacterial	- maternal high vaginal swab -ve	- blood, CSF microscopies and cultures -ve (except one +ve blood culture likely represent contamination, please see text above)
Fungus		- blood fungal culture -ve
Malaria		- blood smear for malaria -ve

inflammatory cells, no granuloma or vasculitis and was negative for special stains for parasite, virus and AFB. Ultrasonography (USG) of the abdomen on day 10 showed mild ascites, hepatosplenomegaly with multiple nonspecific right hepatic hypoechoic lesions, which could represent infective or regenerative foci. Therefore, intravenous metronidazole was added and a computerised tomography (CT) of the abdomen was arranged.

Work up for haematological conditions like haemophagocytic lymphohistiocytosis (HLH) and neonatal leukaemia was also done. Bone marrow aspirate on the posterior superior iliac crest on day 10 showed insufficient cells for diagnosis. Bone marrow aspirate was repeated on day 11 which revealed no evidence of malignancy or haemophagocytosis. Review of CSF showed no haemophagocytic cells also. Serum lactate dehydrogenate (LDH) was normal 662 IU/L. Serum fibrinogen was only slightly decreased 1.6 g/L and serum triglyceride was normal that time although serum ferritin was high (8927 ng/ml). No definite haematological diagnoses could be made.

Work up for inborn errors of metabolism which included urine for reducing sugars, nitrosonaphthanol test, succinylacetate and organic acid pattern was negative. Blood gas showed no metabolic acidosis. Blood amino-acid chromatography showed high cystathione which was a non specific change in liver failure. Blood lactate, carnitine, acylcarnitine, very long chain fatty acid, alphafetoprotein and α1 antitrypsin levels were all normal. Screening for autoimmune diseases was also negative included the patient's and maternal serum for anti-nuclear antibodies and anti-double strand DNA antibodies.

Patient was continued on supportive treatment for her pancytopenia and liver failure which included ursodeoxycholic acid, phenobarbitone, cholestyramine, vitamin K1 injection, intravenous ranitidine, intravenous N-acetylcysteine, empirical antibiotics and blood product transfusions. She continued to deteriorate further after the first two week of life. The patient became comatose with only little response to painful stimuli and developed generalised oedema and increasing ascites. There was increasing respiratory difficulty due to the grossly distended abdomen and she was intubated on day 14. Ventilation requirement was high. The pancytopenia became severe with neutrophil count dropped to 0 x 10^9/L, platelet dropped to less than 10 x 10^9/L and anaemia persisted (Table 1). Granulocyte colony stimulating factor (GCSF), intravenous immunoglobulin and intravenous methylprednisolone were given but there was no improvement. Intravenous amphotericin B was added since day 18 to cover for the severe neutropenia. Liver failure became more fulminant: the highest total serum bilirubin was 592 umol/L on day 17, the worst INR was 7.34 and serum ammonia started to rise since day 17. Lactulose, neomycin and sodium benzoate were added. CT abdomen was done on day 17 and it showed hepatosplenomegaly, gross ascites and mild hepatic steatosis suggested for metabolic or diffuse infiltrative processes. However, work up for inborn errors of metabolism or haematological diagnoses was so far negative. Liver biopsy was not performed due to the severe coagulopathy and patient's very unstable clinical condition. Local liver transplantation center was contacted but the case was considered unsuitable due to the small patient size and uncertainty of the underlying cause of acute liver failure. One of the blood cultures which was taken on day 18 from peripheral site yielded methicillin responsive coagulase negative staphylococcus but the blood culture taken from the arterial line simultaneously was negative. The positive blood culture might represent contamination only. Intravenous vancomycin was added. Further blood cultures were negative. Renal function started to deteriorate also with a highest serum urea of 17.3 mmol/L, creatinine 124 umol/L, estimated worst glomerular filtration rate (GFR) 14.5 ml/min/1.73 m^2 and oliguria since day 21. Nephrotoxic drugs were withheld (frusemide, spironolactone, vancomycin and amphotericin B) with the renal function and urine output improved afterwards.

Serum LDH subsequently rose to 2988 IU/ L on day 20, fibrinogen dropped to 0.8 g/L and triglyceride rose to 1.72 mmol/L, these supported the diagnosis of haemophagocytic lymphohistiocytosis (HLH). Peritoneal tapping to lessen the ascites was done on day 20 due to ventilation difficulty and the peritoneal fluid showed very occasional macrophages with intracytoplasmic nuclear structures suggestive of phagocytosed portion of a leukocyte (Figure 1). This provided further evidence for HLH although the number of phagocytic cells was too small for definitive diagnosis. Bone marrow examination was not repeated in view of the very unstable clinical condition. HLH was diagnosed based on the clinical criteria of fever, splenomegaly, cytopenias, hypofibrinogenaemia and hyperferritinaemia. After discussion with paediatric haematologist, chemotherapy with dexamethasone, etoposide and cyclosporin A was started on day 24.

However, there was uncontrolled haematemesis and pulmonary haemorrhage and the patient died on day 28. Parents refused paramortem and postmortem examinations.

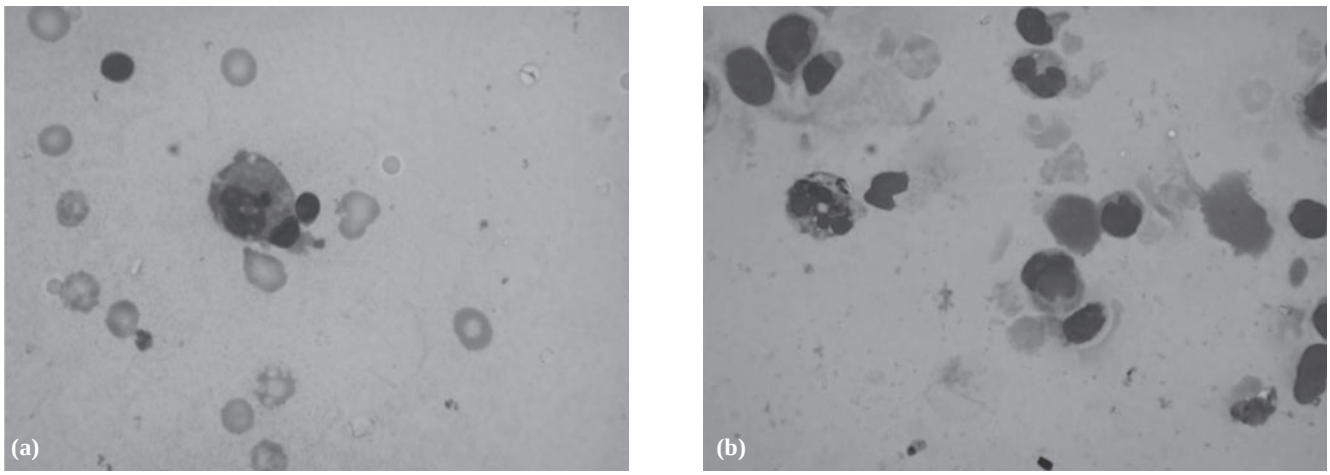

Figure 1 Peritoneal fluid on day 20: (a) a macrophage with intracytoplasmic nuclear fragments – suspicious of haemophagocytosis; (b) 2 cells with intracytoplasmic bodies – suspicious of haemophagocytosis

Discussion

Diagnosis

Acute liver failure (ALF) is traditionally defined as severe hepatic dysfunction and hepatic encephalopathy that developed within 8 weeks of onset of symptoms in a patient without a previous history of liver disease.[1] However, encephalopathy in children especially during infancy and neonatal period is difficult to diagnose and can happen late in the course of illness. The Pediatric Acute Liver Failure Study Group (PALFSG)[2] revised the diagnosis of ALF in paediatric patients, and in neonates it is defined as the presence of biochemical evidence of acute hepatic injury and an international normalised ratio (INR) >1.5 with encephalopathy or INR >2 without encephalopathy.[3]

The aetiologies for NLF are different from those of ALF in older children in whom infectious or autoimmune hepatitis, drug overdose (e.g. paracetamol overdose) and metabolic disease (e.g. Wilson disease) are more common. Causes of neonatal ALF are listed in Table 3[4,5] and include inborn errors of metabolism, perinatal infections, hypoxic ischaemic insult, neonatal haemochromatosis, haematological conditions like congenital leukaemia or haemophagocytic lymphohistiocytosis and other miscellaneous causes. In PALFSG study[3] of 39 neonates (but age ranged 1-88 days with a median age of 33 days), up to 48.7% of the cases did not have a specific diagnosis, 23.1% was identified to have metabolic diseases (4 respiratory chain defects, 1 mitochondrial disorder, 1 galactosaemia, 1 Niemann Pick, 1 urea cycle defect and 1 tyrosinaemia), 10.2% was diagnosed to have neonatal haemochromatosis (NH), 7.7% had congenital infections (but all were herpes simplex infections) and 5.1% due to shock. In another series of 33 NLF patients by Aw et al[6] who documented patients <4 weeks only, 48% were due to NH, while 15% were accounted by congenital infections (again all were herpes simplex infections except one case of bacterial infection), another 15% by metabolic diseases (3 galactosaemia, 1 urea cycle defect and 1 tyrosinaemia type I) and 12% by HLH.

In our case, such an early presentation for liver failure on day 1 before the start of any feeding pointed to conditions like congenital infections, neonatal haemochromatosis, haemophagocytic syndrome, congenital leukaemia or hypoxic ischaemic insult. The birth history was unremarkable with good Apgar scores, so hypoxic ischaemic insult to the liver was unlikely. Inborn errors of metabolism generally do not present on day 1 of life and they did not present with fever and rash. The presentation before any feeding together with the negative urine reducing substances, normal ammonia level initially did not suggest diagnoses like galactosaemia, hereditary fructose intolerance or urea cycle defect. The negative urine nitrosonaphthanol test and succinylacetate for thrice also ruled out tyrosinaemia type 1. Mitochondrial diseases, fatty acid oxidation defects were unlikely with the normal serum lactate, carnitine, acylcarnitine pattern and urine organic acid pattern. Peroxisomal disorder was again unlikely with the normal blood very long chain fatty acid assay. Serum alpha-1-antitrypsin level was normal that ruled out alpha-

Table 3 Causes of acute liver failure in neonates[1,5]

Disease group	Disease entity
Inborn errors of metabolism	Hereditary tyrosinaemia type I
	Mitochondrial disease
	Galactosaemia
	Alpha-1-antitrypsin deficiency
	Urea cycle defect
	Fatty acid oxidation defect
	Peroxisomal disorder
	Inborn errors of bile salts synthesis
	Congenital disorder of glycosylation syndrome
	Hereditary fructose intolerance
Infection	Virus - hepatitis B, herpes simplex 1 and 2
	herpes zoster, CMV human herpes virus 6,
	adenovirus, enterovirus (echovirus, coxsackie virus), parvovirus etc.
	Bacterial (Listeria, tuberculosis etc.)
Haematological/infiltrative	Cogenital leukaemia
	Haemophagocytic lymphohistiocytosis
	Tumours
Others	Neonatal haemachromatosis
	Hypoxic/ischaemic
	Autoimmune hepatitis
	Hypocortisolism
	Vascular malformations
	Congenital heart disease
	Drugs, including maternal drug overdose

1-antitrypsin deficiency. The work up for congenital infections was negative although congenital infections could not be totally ruled out based on the fact that serology results might be affected if there was abnormal immune response like in HLH and PCR tests which were more sensitive were only done for serum CMV and CSF HSV in our case. Neonatal haemochromatosis (NH) and haemophagocytic lymphohistiocytosis (HLH) were two highly probable diagnoses with the high serum ferritin level and severe liver failure soon after birth. However, NH usually presents as acute decompensated end stage liver disease with small liver and often normal serum transaminases; whereas in our case, there was marked hepatomegaly and increase in serum transaminases. The features of fever, cytopenias and hypertriglyceridaemia in our case are not features of NH. The serum transferrin saturation in our case was 91%, outside the range of 95-100% which is more specific for NH.[7] A lip or salivary gland biopsy for any extrahepatic iron deposits sparing the reticuloendothelial system was not done on our patient due to unstable clinical condition. For the diagnosis of HLH, although we failed to demonstrate haemophagocytosis in bone marrow, it is known that haemophagocytosis can be absent at presentation in two-thirds of patients finally diagnosed to have HLH and serial bone marrow examinations may be needed.[8] Again, due to the unstable clinical condition, further bone marrow examinations were not feasible in our patient. Liver biopsy was not done due to the severe coagulopathy. The clinical features of fever, splenomegaly, pancytopenia, hypofibrinogenaemia and high serum ferritin already fulfilled the clinical criteria for diagnosis of HLH according to the diagnostic guidelines of the Haemophagocytic Lymphohistiocytosis Study Group treatment protocol 2004 (Table 4).[9] Together with the subsequent demonstration of haemophagocytosis in peritoneal fluid, the diagnosis of HLH was made.

Table 4 Diagnostic guidelines for HLH (HLH-2004)[9]

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled.

1. A molecular diagnosis consistent with HLH.
2. Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below):
   A) Initial diagnostic criteria
      - Fever
      - Splenomegaly
      - Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):
        haemoglobin <90 g/L, platelets <100 x 10^9/L, neutrophils <1.0 x 10^9/L (in infants <4 weeks: haemoglobin <100 g/L)
      - Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥3.0 mmol/L, fibrinogen ≤1.5 g/L)
      - Haemophagocytosis in bone marrow or spleen or lymph nodes
        No evidence of malignancy
   B) New diagnostic criteria
      - Low or absent NK-cell activity (according to local laboratory reference)
      - Ferritin ≥500 microgram/L
      - Soluble CD25 (i.e. soluble IL-2 receptor) ≥2400 U/ml

HLH can be primary (genetic) which is further classified into a group of autosomal recessive familial HLH (FHLH) and a group of inherited immunodeficiencies with strong predilection for HLH including Chediak-Higashi syndrome 1 (CHS-1), Griscelli syndrome 2 (GS-2) and X-linked proliferative syndrome (XLP).[10] It can also be acquired secondary to infections (the most frequent being EBV, CMV or other herpes viruses, Leishmania and parvovirus 19), malignant or autoimmune diseases.[11] Acquired HLH can occur in all age groups but usually at a later age than FHLH.[11] The onset of illness is usually below 1year old for FHLH (70-80% of cases) with a median age of 2.9 months and diagnoses at a median age of 4.9 months.[12] Specifically, about 10% present in the neonatal period and a few may already present at birth.[10,13] Therefore, in our case of neonatal onset HLH, primary HLH should be likely. CHS-1, GS-2 is characterised with albinism which was not present in our case. Our case was a female patient that XLP was also unlikely. FHLH was strongly suspected. FHLH has an estimated incidence of 1 in 50,000-300,000 live births.[12] There are several known genetic mutations identified associated with FHLH. The first to be described is the perforin gene mutations in 1999[14] which account for 13-50% of FHLH (FHLH-2) patients depending on the ethnic origin. Perforin is responsible for the induction of apoptosis by introducing cytolytic effector molecules into the target cells.[10] The second identified responsible gene comes to UNC13D gene. It is described in 17-30% of FHLH patients (FHLH-3)[15] and UNC13D mutations lead to impairment of vesicle priming and granule exocytosis. Recently, another involved gene, syntaxin 11, was reported but syntaxin 11 mutations have only been found in inbred kindreds from Turkish patients which account for 19% of FHLH (FHLH-4) in them.[16] The syntaxin 11 encoded protein is involved in intracellular trafficking but its exact role to clinical HLH remains unknown. However, these genetic tests are not available in Hong Kong and our patient could not be confirmed with the diagnosis of FHLH. It is also important to note that most FHLH is often triggered by infections, especially the herpes type viruses such as EBV and VZV. As mentioned above, congenital infections were not totally ruled out in our case and so our case might represent a FHLH with/without triggering by infections although acquired HLH secondary to infections could still be a possibility. There is few data specifically about neonatal HLH with most being case reports. Imashuku et al 2005[17] described a series of 96 HLH patients <1 year of age. In that series, 11 HLH had disease onset before 1month old, 2 of them was due to FHLH, 3 was secondary to HSV infections, 4 was secondary to enterovirus infection and the remaining 2 with unknown causes. Case reports of neonatal HLH associated with CMV and EBV infections have also been reported.[18,19]

Management

The managements of NLF and HLH are both challenging and require early diagnosis and treatment. Treatment of HLH should be partly guided by the severity of the

condition and the underlying etiologies although HLH can be rapidly fatal but some may present with less severe signs and symptoms which may also be transient. The immediate treatment aim is to suppress the hyperinflammation which could be life threatening. The potential triggering factors, such as infections and malignancies should be treated. HLH -94 treatment protocol includes initial 8 week treatment of dexamethasone and etoposide and in patients with FHLH or incomplete responses or relapses, it will be followed by maintenance with cyclosporin A and alternating pulses of etoposide and dexamethasone until stem cell transplantation (SCT).[20] In the current HLH-04 protocol study,[9] cyclosporin A was introduced at the beginning of therapy rather than at week 8 of treatment based on the observation that many patients experienced relapses when dexamethasone was tapered after 2 weeks. For presumed secondary or less severe HLH, corticosteroid and high dose immunoglobulins have been used but etoposide should be added without delay once the disease show significant progression. For those with refractory or progressive diseases despite above treatments, alternative therapies including antithymocyte globulin, TNF-α inhibitors, anti-CD25 (aclizumab), anti-CD52 (alemtuzumab), fludarabine and treatment protocols for lymphomas have been reported but there is a lack of concrete evidence about the effectiveness of these treatment.[11]

In our patient, chemotherapy for HLH was started on day 24 once with the diagnosis of HLH made based on clinical criteria and after discussion with local haematological centers but the patient succumbed due to severe upper gastrointestinal and pulmonary haemorrhage 4 days afterwards. HLH was not diagnosed earlier in our case as the initial presentation fulfilled only 4 out of the 8 diagnostic criteria while the bone marrow result was normal, although it could be argued that treatment of HLH could be initiated earlier once there was a strong clinical suspicion without waiting for diagnostic studies results as HLH can be rapidly fatal.[21]

For the management of NLF, it often involves multisystem dysfunction, which was well illustrated in our case. Many of the interventions are extrapolated from experience in older children without good randomised studies in neonates. General principles involve i) early recognition of the condition; ii) provision of general supportive measures including quiet environment, avoidance of hypoglycaemia, judicious fluid therapy and feeding regimen, adequate caloric diet and use of N-acetylcysteine;[1] iii) identification and treatment of complications including hepatic encephalopathy, infection, clinical bleeding, hepatorenal syndrome and ascites; iv) treatment of the underlying causes if identified; v) and finally timely referral for assessment for liver transplantation which is feasible in newborn babies due to advances in surgical techniques although liver transplantation is not indicated in certain conditions like multiorgan failure, uncontrolled sepsis, haemophagocytic lymphohistiocytosis, malignancies and generalised mitochondrial diseases. New treatment strategies like extracorporeal liver support system and hepatocyte transplantation may act as transient supports and buy time for regeneration of the native liver or for liver transplantation, but their role in neonates remains to be determined.

Prognosis

NLF carries poor prognosis with a mortality rate of 70% without liver transplantation[4] which improves to 54-60% with liver transplantation.[3,5] From the HLH-94 protocol study, HLH had a survival rate of 55%, but 20-25% of the patients died during the period waiting for SCT. FHLH was invariably fatal, with a median survival of <2 months after diagnosis if left untreated. There was no familial case survived without SCT but with SCT, survival was 51% for verified familial cases.[20] There is no data on the mortality or survival rate specifically to neonatal HLH with only case reports about individual cases of survival or mortality which was largely guided by the disease severity. In the Imashuku et al series mentioned above,[17] it was only specifically mentioned for neonatal HLH that all the 3 cases associated with HSV infection died.

In conclusion, we reported a rare case of neonatal HLH with fulminant liver failure. To our knowledge, this is the youngest case of HLH reported in this locality that presented since birth. Both neonatal HLH and liver failure are rare and challenging to manage with different underlying etiologies. Early recognition of the conditions, prompt initiation of treatment and identification of concomitant treatable conditions are keys to success.

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