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Clinical report

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Twin-to-twin transfusion syndrome as a cause of neonatal acute liver failure

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Abstract

Background: Acute liver failure (ALF) is a rare condition during neonatal period.
Objective: To report a case of recipient twin with fulminant ALF secondary to hydrops fetalis caused by twin-to-twin transfusion syndrome (TTTS).
Method: The patient was admitted to the neonatal intensive care unit (NICU) for respiratory failure requiring mechanical ventilation and fulminant ALF with prolonged international normalized ratio (INR) and elevated liver enzymes with highest aspartate aminotransferase of 4,580 U/L.
Results: Laboratory investigation for secondary causes of liver failure was not revealing. Her liver enzymes and coagulation levels were dramatically normalized as the clinical symptoms of hypervolemia improved within 1 week.
Conclusion: TTTS can be a possible cause of neonatal ALF. Early detection with proper management of TTTS is important to avoid adverse outcomes. However, pathogenesis of hepatic dysfunction in TTTS is rarely described, and further studies are needed to help understanding the correlation between liver diseases and TTTS.

Keywords: acute/therapy; fetofetal transfusion; hydrops fetalis; liver failure; newborn

Twin-to-twin transfusion syndrome (TTTS) is one of the important complications in twin pregnancy, especially in monochorionic diamniotic (MCDA) twins. TTTS occurs in 10%–15% of twin pregnancy [1]. It is characterized by unbalanced placental blood flow between two fetuses within a shared placental circulation causing hypervolemia in recipient twin. This results in a release of atrial and brain natriuretic peptide (ANP and BNP) and fetal polyuria, eventually leading to polyhydramnios in the recipient's sac. Clinical presentation of TTTS can be varied from amniotic fluid (AF) discordance to demise of one or both twin. Other clinical manifestations of TTTS that have been described include hypertension, cardiac dysfunction, cerebral injury, and fetal hydrops in recipient twin. This article reports a case of newborn (twin B [recipient twin]) with TTTS resulting in hydrops fetalis (HF) and neonatal acute liver failure (NALF), a rare clinical manifestation of TTTS. She had markedly elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and ferritin level shorty after birth which improved within the first week of life. From our current knowledge, acute liver failure (ALF) in TTTS can be caused by hepatic infarction resulting from vascular sledging and peripheral ischemia due to the polycythemia–hyperviscosity syndrome and most of these injuries occur in recipient twins [2]. This article will discuss etiologies of NALF in this patient and the correlation between TTTS and NALF.

This study was approved by the Institutional Review Board of Faculty of Medicine Vajira Hospital, and was

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exempted from full board review (certificate of exemption no. 9/2018). The parents of the patient provided the written informed consent for publication of the case report.

Case report

Baby girl S (twin B) was born by emergent cesarean section due to twin pregnancy and HF of one twin at 36 4/7 weeks' gestation by ultrasound to a 36-year-old gravida VI para IV Thai women. The mother had only one antenatal care (ANC) visit at 32 weeks' gestation at Vajira Hospital, Bangkok, Thailand. A prenatal ultrasound was done and revealed HF of twin B with fetal ascites, increased skin thickness, cardiomegaly, and pleural effusion. Twin A had anhydramnios and twin B had polyhydramnios with single deepest pocket (SDP) of 10 cm. Prenatal screening revealed AB, Rh-positive maternal blood type, negative anti-HIV, negative hepatitis B surface antigen (HBsAg), and negative Venereal Disease Research Laboratory (VDRL) titer. Pregnancy was complicated by MCDA twin pregnancy, maternal amphetamine use, maternal anemia, and prenatal diagnosis of HF of twin B from ultrasound findings. The mother reported taking abortion pills and rice whisky earlier during first trimester. She also reported recent use of amphetamine 3 days prior to delivery. On a subsequent ANC visit, she was admitted to the hospital and later delivered the babies. She was given 2 g of ampicillin intravenously 30 min prior to delivery.

At birth, the infant was floppy with no respiratory effort. APGAR scores were 0, 5T, and 8T at 1, 5, and 10 min, respectively. Positive pressure ventilation was given due to bradycardia. At 3 min of life, she was intubated with improvement in her HR and respiration. She was subsequently transferred to the neonatal intensive care unit (NICU) at 10 min of life while on peak inspiratory pressure (PIP) of 25, positive end-expiratory pressure (PEEP) of 6 on a T-piece resuscitator with oxygen saturation of 95%. On arrival to NICU, she was put on mechanical ventilation.

At NICU, her physical exam was remarkable for a near-term infant with markedly distended abdomen, generalized edema, hepatomegaly, ascites, and without any dysmorphic features. Her birth weight was 2,350 g which was appropriate for gestational age and twin A's birth weight was 1,595 g which was small for gestational age, with 32% birth weight discordance. Her baseline blood pressure (BP) was elevated at 83/39 mmHg (95th percentile). Her body temperature (BT) was 36.8ºC and her heart rate (HR) was 136 beats/min. Initial chest X-ray showed normal pulmonary vasculature without any infiltration, normal cardiothoracic ratio, central displacement of bowel, and marked hepatomegaly. Bedside abdominal ultrasound revealed moderate ascites with hepatomegaly without any space occupying lesion. Spleen and visualized pancreas were unremarkable. An initial blood culture and complete blood cell (CBC) count with differential were obtained. The initial CBC count revealed a hematocrit (Hct) of 46.1%, hemoglobin (Hb) of 14.7 g/dL (twin A Hct 55%, Hb 18.2 g/dL), platelet count of 132,000 cell/mm^3, and a white blood cell count of 10,870 cells/μL. Due to prenatal diagnosis of HF and positive findings on physical exam, investigations were carried out to differentiate the causes of HF. Chromosomes sent on day of life 1 revealed normal 46XX. Brain ultrasound was unremarkable. Eye exam was normal. Ampicillin and gentamicin were initiated for suspected sepsis.

During her first 8 h of life, she had polyuria with urine output of 17.6 mL/kg/h and decreased to 15.5 mL/kg/h with in the next 8 h. She had multiple problems including hypoglycemia which needed multiple glucose injection with total peripheral nutrition, hypoalbuminemia for which she was given 20% albumin and metabolic acidosis. Due to the findings of hepatomegaly and HF, liver function tests were done and revealed markedly elevated liver enzymes with AST of 4,580 U/L and ALT of 792 U/L. Her coagulograms were also abnormal with elevated prothrombin time (PT) of 38.9 s and international normalized ratio (INR) of 3.5. The diagnosis of NALF was made. She was given fresh frozen plasma (FFP), cryoprecipitate, and vitamin K to correct her coagulopathy. There was no clinical bleeding and her liver enzymes improved over time as shown in **Table 1**.

Further evaluation to differentiate causes of NALF was done as shown in **Table 2**. On day of life 2, her systolic blood pressure (SBP) was 80–103 mmHg; her HR was 102–138 bpm; and her body weight (BW) was 2,033 g (decreased 13.5%). Her urine output decreased to 9.9 mL/kg/h. Metabolic acidosis and hypoglycemia resolved. On day of life 3, her SBP was 60–97 mmHg; HR was 134–154 bpm; her BW was 2,069 g; and her urine output was 6.1 mL/kg/h with net fluid input of 296.6 mL and net fluid output of 305 mL. Her respiration improved as ascites decreased. She was subsequently extubated and was able to maintain her respiration.

During the first 2 days of life, she demonstrated signs of hypervolemia including elevated BP, HR, and polyuria. After her diuresis, hypertension, respiration, and signs of edema improved. Within 1 week after birth, her AST decreased dramatically from 4,580 to 29 U/L and ALT decreased from 792 to 57 U/L. Her coagulopathy also gradually improved.

Discussion

In this case report, pregnancy is complicated by monochorionic diamniotic twins with AF and fetal weight discordance

Table 1. Laboratory results

	26/3	27/3	28/3	29/3	30/3	31/3	1/4	2/4	3/4	4/4	5/4	6/4	7/4	8/4	9/4
Hct (%)	46.1	36.7	50.4	42.2	35.4	40.5	39.3	32.9	40	41	34.6	32.4	31	36.2	34.3
Platelet (cell/mm^3)	132K	97K	105K	77K	69K	75K	81K	62K	45K	120K	85K	79K	88K	75K	82K
AST (U/L)	4,580	4,290	–	267	156	72	44	29	30	–	28	–	–	–	47
ALT (U/L)	792	650	–	193	166	111	86	57	51	–	24	–	–	–	18
ALP (U/L)	232	227	–	215	262	309	319	302	369	–	372	–	–	–	369
TP (g/dL)	5.8	6.3	–	10.20	5.7	6.1	6.3	7.6	7.2	–	7.7	–	–	–	7.4
Alb (g/dL)	2.6	3.1	–	2.6	2.7	2.8	2.9	4.3	2.9	–	3.2	–	–	–	3.2
Glb (g/dL)	3.2	3.2	–	3.2	3.0	3.3	3.4	3.3	4.3	–	4.5	–	–	–	4.2
TB (mg/dL)	2.19	4.46	–	5.8	12.72	12.38	10.22	7.6	6.68	–	8.43	–	–	–	13.57
DB (mg/dL)	0.30	0.37	–	1.60	3.08	5.06	4.68	4.3	4.3	–	5.64	–	–	–	9.09
IDB (mg/dL)	1.89	3.09	–	8.60	9.64	7.32	5.54	3.3	2.3	–	2.79	–	–	–	4.48
Fibrinogen	–	–	76.0	103.3	142.1	–	–	147.9	172.3	233.2	204	–	–	–	211
PT (s) (13.5–16.4)	38.9	45.3	39.1	27.6	25.0	–	23.0	17.2	18.5	18	16.4	15.7	15.7	15	15.6
PTT (s) (29.5–42.2)	42.8	43.9	56.6	54.6	53.7	–	51.0	36.5	44.1	47.3	46.1	45.2	51.3	43.7	44.6
INR (1.05–1.35)	3.50	4.11	3.52	2.44	2.20	–	2.02	1.49	1.6	1.56	1.41	1.35	1.35	1.29	1.34
LP-PRC	–	15 mL/kg · 1	–	–	–	–	–	10 mL/kg · 1	–	–	–	–	10 mL/kg · 1	–	–
LP-Plt	–	10 mL/kg · 1	–	10 mL/kg · 1	10 mL/kg · 1	10 mL/kg · 1	–	–	15 mL/kg · 1	–	–	–	–	–	–
Cryo	–	–	1 unit	1 unit	1 unit	–	–	1 unit	1 unit	–	–	–	–	–	–
FFP	–	10 mL/kg · 3	10 mL/kg · 3	10 mL/kg · 2	10 mL/kg · 2	10 mL/kg · 2	10 mL/kg · 2	10 mL/kg · 2	15 mL/kg · 1	15 mL/kg · 1	15 mL/kg · 1	–	10 mL/kg · 1	–	–

Hct, hematocrit; plt, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; TP, total protein; Alb, albumin; Glb, globulin; TB, total bilirubin; DB, direct bilirubin; IDB, indirect bilirubin; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; LP-PRC, leukocyte-poor packed red cell; LP-Plt, leukocyte-poor platelet concentration; Cryo, cryoprecipitate; FFP, fresh frozen plasma.

as well as with HF in larger twin. Since the patient met all criteria of TTTS, the diagnosis of TTTS (Quintero stage IV) was made as the cause of HF in this patient. Other investigations were done to exclude other causes of HF but were unrevealing. Twin anemia polycythemia sequence (TAPS) and selective intrauterine growth restriction (sIUGR) can cause difference in fetal sizes and may have some overlapping features of TTTS [3, 4]. TAPS can cause HF if fetus is severely anemic but our patient's hemoglobin was within normal limit at birth and there was no hemoglobin discordance between donor and recipient twin, so it is unlikely to be the cause of hydrops in this patient. sIUGR can have difference in AF volume but it is unlikely to cause fetal hydrops. The diagnosis criteria and staging of severity of TTTS are shown in **Table 3**.

As part of fetal hydrops work up, liver function tests and coagulograms were sent (Table 1). NALF was diagnosed in this patient based on pediatric diagnostic criteria of ALF [7]. NALF is a rare condition defined as loss of vital liver function in infants during the first month of life. Unlike ALF in older children, NALF is difficult and problematic to diagnose due to the lack of standard diagnostic criteria in neonates. We apply the diagnostic criteria of pediatrics ALF to NALF which include (a) coagulopathy (PT $\geq$ 20 s or INR $\geq$ 2.0) not corrected by vitamin K, (b) biochemical evidence of acute liver injury, and (c) no known evidence of chronic liver disease

[7, 8]. This patient had markedly elevated transaminases and coagulopathy since birth. The most common mechanism of ALF is acute hepatic necrosis which can be caused by infection, toxins, or other etiologies. Among many etiologies of ALF, the two most common causes of liver failure within the first week of life are neonatal hemochromatosis and viral infection [8, 9].

Neonatal hemochromatosis (NH) is a rare condition characterized by massive iron deposition in liver and extrahepatic tissues with sparing of the reticuloendothelial system. The etiology of NH is currently unknown but it is hypothesized to be an alloimmune process where maternal antibody directly attacks fetal liver antigen. This hypothesis is supported by the findings that exchange transfusion and high-dose intravenous immunoglobulin (IVIG) which remove antibodies from the fetal blood also improve the symptoms. NH presents with hypoglycemia, coagulopathy, elevated alanine aminotransferase, jaundice, high ferritin, and raised iron saturation levels [7]. Aminotransferase levels are nearly always below 100 IU/L and ferritin levels are almost always >800 ng/mL and <7,000 ng/mL. However, there is no single diagnostic biochemical test of NH [8]. Ferritin is an acute phase reactant and can be elevated in other etiologies of NALF. It can be confirmed only by the evidence of extrahepatic deposits sparing the reticuloendothelial system. In the study by Smith et al., a biopsy of salivary glands of the lips demonstrated hemosiderin accumulation within the epithelial cells of six of seven neonates with NH [10]. From the description of NH earlier, it is less likely that this patient has NH due to very high levels of aminotransferase and ferritin. Furthermore, the clinical symptoms of ALF in this patient improved without the treatment of IVIG and exchange transfusion.

Viral infection associated with NALF is commonly acquired at birth or right after birth so the neonates typically have no signs of intrauterine growth restriction. The most common organism is herpes simplex virus (HSV) which can cause both disseminated HSV or HSV isolated to the liver. Neonates usually present at 1 or 2 weeks of age with fever, lethargy, poor feeding, and abdominal distension. Other organisms that have been associated with NALF are human herpes virus 6 (HHV6) and cytomegalovirus (CMV) but with a less severity and better prognosis than that in HSV infection [8]. The diagnosis can be confirmed by polymerase chain reaction (PCR) of the blood, nasal swab, or feces. However, the treatment with high-dose parenteral acyclovir should be initiated while waiting for laboratory confirmation due to a high mortality rate. In this case, while waiting for PCR results and blood culture, the patient was treated with both antiviral and antibiotics drugs. Acyclovir was discontinued after the laboratory investigation of blood PCR for HSV become negative. Toxoplasmosis and Rubella titers as well as CMV PCR were also negative. Thus, the NALF caused by viral infection in this patient can be excluded.

Table 2. Causes of neonatal liver failure, assessment methods, and results

Cause	Assessment method	Result
Syphilis	Quantitative non-treponemal serological test	Negative
Toxoplasmosis	Serology (IgG and IgM)	IgG less than 1:16; IgM negative
Rubella	Serology (IgG and IgM)	Negative
Cytomegalovirus	Blood and urinary PCR	Negative
Herpes simplex virus	Blood PCR	Negative
Varicella virus	Blood PCR	Negative
Infection/sepsis	Blood culture	No growth
Hepatitis viruses A, B, and C	Serology (IgG and IgM)	Negative

PCR, polymerase chain reaction.

Table 3. Diagnostic criteria and severity staging (Quintero staging system) of TTTS [3, 5, 6]

Diagnostic criteria	Severity staging (Quintero staging system)
1. Presence of a monochorionic diamniotic pregnancy	a. DVP < 2 cm in donor sac; DVP > 8 cm in recipient sac b. The bladder is no longer visible in the donor twin
2. Polyhydramnios in the recipient with DVP of ≥8 cm and oligohydramnios in the donor with DVP < 2 cm	c. Critically abnormal Doppler in either twin: absent/reverse diastolic flow in the umbilical artery of the donor or recipient and/or absent/reverse flow in the ductus venosus or pulsatile flow in the umbilical vein of the recipient d. Hydrops in either fetus e. Demise of one or both twins

DVP, deep vertical pocket.

Adapted from Gratacós E, Ortiz JU, Martinez JM. A systematic approach to the differential diagnosis and management of the complications of monochorionic twin pregnancies. Fetal Diagn Ther. 2012; 32:145–55.

Other causes of NALF such as hemophagocytic lymphohistiocytosis (HLH) and toxins are less likely in this patient. HLH is caused by excessive immune activation (gene mutation of natural killer (NK) cells and T-cell functions). The diagnosis can be made by gene analysis or fulfilling the diagnostic criteria including fever, splenomegaly, cytopenias, hypertriglyceridemia/hypofibrinogenemia, hemophagocytosis in the bone marrow, abnormal NK cell functional assay, elevated soluble IL-2R alpha level, and elevated ferritin level (usually >20,000 ng/mL) [7, 11]. There was no fever and splenomegaly in this patient. Her triglyceride was 71 mg/dL and ferritin was 98,845 ng/mL. Her fibrinogen level was low at first but it spontaneously returned to normal level within 1 week. The diagnostic criteria that were not fulfilled together with the clinical improvement without chemotherapy made HLH less likely the cause of NALF in this patient.

Regarding toxins, in this patient there was a history of chronic maternal acetaminophen and amphetamine used. The metabolite of acetaminophen can cross placenta and produce hepatitis in the fetus. However, the dose of acetaminophen ingestion, which was 500 mg of acetaminophen a day in this pregnancy was not considered as an overdose. Furthermore, toxic exposures usually result from maternal intentional ingestion of paracetamol in 24 h prior to delivery with usually 10 times the therapeutic dose [12]. On the other hand, the amphetamine ingestion during pregnancy can affect the fetal development. Previous studies consistently showed the correlation between methamphetamine use and neonatal and childhood neurodevelopment abnormalities but not with liver injury [13, 14].

Inborn error of metabolism (IEM) does not affect the fetus but it is usually present in the postnatal period. Mitochondrial hepatopathy caused by mutation in gene required for cell respiration. The patient can present in the first week of life and the result of liver transplantation is extremely good if there is no major extrahepatic disease [9]. Galactosemia and tyrosinemia type 1 are important cause of severe liver function in the second and third weeks of life. The enzymology and DNA tests can be performed to make the diagnosis. IEM must be promptly investigated as specific treatment and dietary control can be lifesaving [15].

Since investigations of other possible causes of NALF were all negative and there was improvement of laboratory profiles without any specific treatment as clinical symptoms of hypervolemia resolved, we considered the cause of liver failure in this patient as multifactorial causes mainly hypervolemia from TTTS and ischemic process from perinatal depression. We concluded that hypervolemia causes decompensated heart failure which results in hepatomegaly and hepatic dysfunction known as cardiac hepatopathy [16, 17].

Since NALF is rare, there is no management guideline for this condition. Some recommendations are controversial such as indication for blood component transfusion. Based on our experience and literature review, we suggest algorithms for management of NALF (**Figure 1**).

Management

General management

A neonate with ALF should be transferred to a medical center that provides highly specialized tertiary level services, in intensive care unit for continuous monitoring, preferably with liver transplant facilities [17]. A central venous line should be placed in order to measure central venous pressure, to administer fluids, medications, and blood products, and to collect blood samples. It is recommended that patients should be carefully monitored for the following parameters: vital signs, urine output, continuous oxygen saturation, metabolic parameters (electrolyte, blood sugar, arterial blood gas), and neurological status (presence of encephalopathy). The frequency of these parameters assessment should be adjusted according to the status of the patient [18].

Medications that alter the level of consciousness should be avoided (unless the patients have to be mechanically ventilated) to prevent worsening of encephalopathy and to be able to assess the consciousness of the patient. If the sedation is necessary, 1–2 mg/kg of propofol can be given. Prophylactic proton pump inhibitors should be given in all cases of ALF to prevent gastrointestinal bleeding [18, 19].

Hepatic encephalopathy

It is important to recognize encephalopathy earlier and give appropriate treatment to the patient with hepatic encephalopathy to avoid complications associated with cerebral edema and intracranial hypertension. We recommend keeping patient in quiet environment with minimal stimulation. Induction of hypernatremia with hypertonic saline (HTS) (3%–30%) to keep serum sodium at 145–150 mmol/L has been shown to reduce brain edema. Mannitol is not recommended in NALF because of the lack of data to support its use. Moreover, it is not used in patient with hypotension, renal failure, or a serum osmolarity >320 mOsm/L. At present, there is no sufficient data to support the use of therapeutic hypothermia,

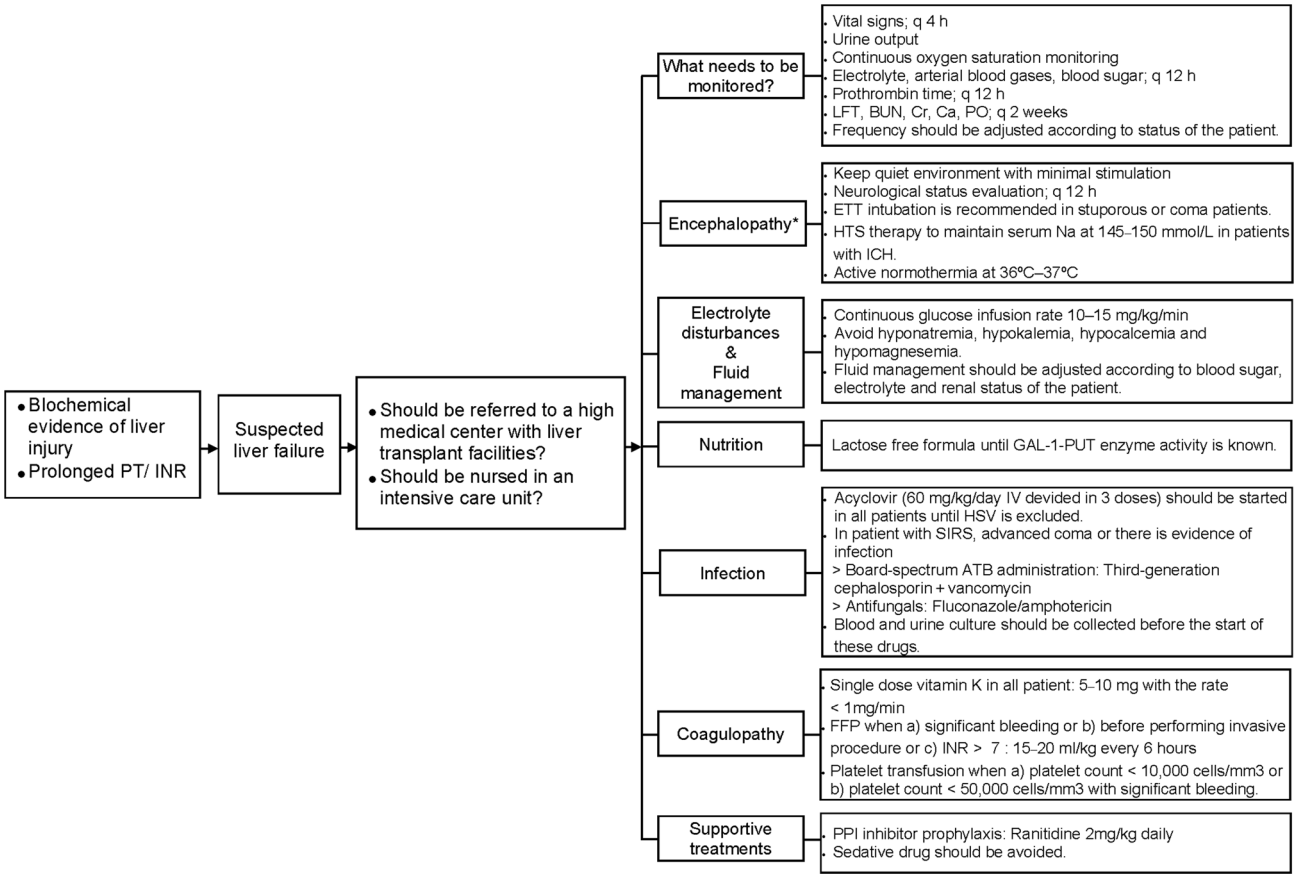

Figure 1. General management of NALF [15, 16, 18]. *Hypertonic saline (3%–30%) is preferred over mannitol in management of ICH. There is no enough evidence to support the use of mannitol and therapeutic hypothermia in NALF.
PT, prothrombin time; INR, international normalized ratio; q, every; h, hours; LFT, liver function test; BUN, blood urea nitrogen; Cr, serum creatinine; Ca, calcium; PO, phosphate; ETT, endotracheal tube; HTS, hypertonic saline; Na, sodium; ICH, intracranial hypertension; GAL-1-PUT, Galactose 1-phosphate uridyl transferase; IV, intravenously; HSV, Herpes simplex virus; SIRS, systemic inflammatory response syndrome; ATB, antibiotics; FFP, fresh frozen plasma; PPI, proton pump inhibitor

hyperventilation, and prophylactic anti-seizure drug in the management of NALF [20].

Coagulopathy

Platelet dysfunction, vitamin K deficiency, and hypofibrogenemia are commonly found in patients with ALF. Prothrombin time (INR) should be tested 12 hourly as it is an indicator of severity of liver damage and dictates physician when to list for transplantation. Thus, coagulopathy should not be routinely corrected as it will obscure the trend of INR unless the patient is already listed for transplantation, before performing invasive procedure or in severe coagulopathy with INR >7. Single dose of vitamin K (5–10 mg, infusion with the rate no more than 1 mg/min) is recommended in all patients with ALF. Fresh frozen plasma (FFP) can be given 15–20 mL/kg every 6 h or as a continuous infusion at 3–5 mL/kg/h. Patients with significant hypofibrinogenemia (<100 mg/dL) may benefit from cryoprecipitate. Platelet transfusion is recommended when platelet count is <10,000 mm^3 or <50,000 mm^3 with significant bleeding [18].

Infection

Empirical antibiotics administration is recommended when the likelihood of sepsis is high or when there is evidence of infection. It is also recommended in patients listed for liver transplantation since uncontrolled infection is a relative contraindication for liver transplantation [21]. Broad-spectrum antibiotics with third-generation cephalosporin, vancomycin, acyclovir, and fluconazole are recommended wherever indicated.

Electrolyte disturbances and fluid management

Hyponatremia, hypokalemia, hypocalcemia, hypophosphatemia, and hypomagnesemia often occur in patients with ALF. Hypoglycemia is also common due to failure of hepatic gluconeogenesis and secondary bacterial infection. Fluid management should be tailored according to blood sugar, electrolyte, and renal status of the patient [20, 22].

Liver transplantation

It is more difficult to make a decision for liver transplantation in neonates because they will need a lifetime immunosuppression. Furthermore, the outcome of ALF after liver transplantation is fairly poor compared with those with chronic end-stage liver disease [19]. There are no definitive criteria for listing infants and children for liver transplantation. However, liver transplantation should be considered if INR >4 or factor V concentration <25% [18]. Contraindications for liver transplantation are uncontrolled systemic infection or sepsis, multiple organs failure which will not improve with liver transplantation, unresectable extrahepatic malignancy, mitochondrial diseases, and irreversible neurological impairment [19-22].

Conclusion

We reported a recipient twin baby girl who had a fulminant liver failure associated with HF caused by TTTS. Her hepatic dysfunction was correlated with the improvement of her volume status. NALF is rare and challenging to manage with different etiologies. To our knowledge, this is the first case of TTTS complicated with NALF. The pathogenesis of hepatic dysfunction in twin-to-twin transfusion is rarely described. This article reiterates the need for more research to help understanding the correlation between liver diseases and TTTS.

Author contributions. All the authors contributed substantially to the conception and design of this study, acquired the data, and interpreted them. CP and DL drafted the manuscript. VP critically revised it. All the authors approved the final version submitted for publication and they take responsibility for statements made in the published article.

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Conflict of interest statement. The authors have completed and submitted the International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. None of the authors disclose any conflict of interest.

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