Preceptorship Programme
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Case of acute liver failure in a 7 month child - A diagnostic dilemma.

7 month/male

Growing well

Exclusive breast feed

No H/O failure to thrive, vomiting, diarrhea, seizures, aversion to sweets, CAM intake

Term, Birth Weight 3 Kg, LSCS, No h/o NICU Stay

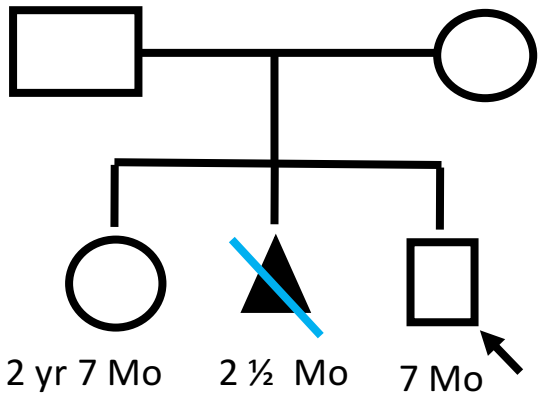
Fever (undocumented), Irritability, refusal to feed and lethargy x 12 days
Progressively increasing **jaundice** x 8 days

Birth | 3 months | 7 months | 8 months

Family History:

Non Consanguineous Marriage

H/o previous abortion +



Antenatal History:

Not significant

Natal & Post natal history:

Term, B.Wt 3 Kg, LSCS, No h/o NICU Stay

Received age appropriate vaccines

Development as per age

Examination

General examination

Weight: 6.5 kg (-1.89 Z)

Length: 70 cm (-0.18 Z score)

HC: 44 cm (- 0.49 Z score)

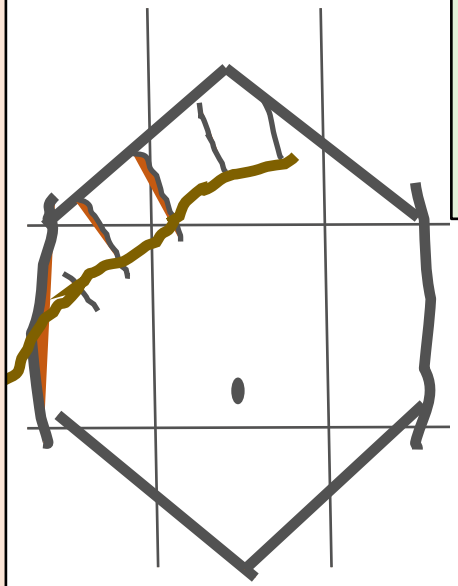
Pallor ++, Icterus ++

No cyanosis, clubbing, edema, lymphadenopathy

No CLD stigmata

No dysmorphic facies

Genitals normal



Per Abdomen: Liver 8 cm BRCM, firm, rounded margins, smooth surface, *span 12 cm* (> 97 % ile)

Spleen not palpable

No dilated abdominal veins

CNS Examination: Irritable, inconsolable cry, tone flaccid, pupil : NSNR – Hepatic encephalopathy stage : I / II

CVS Examination: S1, S2 Present, No murmur

Respiratory Examination: Bilateral air entry preset, clear

Summary

7 month old/ Male

Growing well

Rapidly progressive jaundice

Large, firm liver

Inconsolable cry, feed refusal, irritability with lethargy - Grade II Encephalopathy

Clinical Diagnosis

? Infantile liver failure

Jaundice with grade II encephalopathy

Etiologies of Acute Liver Failure in Neonates (King's College Hospital, London)

Neonates	N = 31
Neonatal hemochromatosis (NH)	15
Hemophagocytic lymphohistiocytosis (HLH)	4
Herpes simplex virus	5
Metabolic	4
Acetominorphen toxicity	1
Sepsis/ shock	1
Isolated cortiosol deficiency	1

Liver Transplantation, Vol 14, No 10, Suppl 2 (October), **2008**: pp S80-S84

Characterization and Outcomes of Young Infants with ALF, (USA/UK/CANADA)

J Pediatr **2011**;159:813-8)

Diagnosis	Number (n = 148) (%)
Metabolic diseases	28 (18.9)
Galactosemia	12 (8.1)
Respiratory chain defect	5 (3.4)
Tyrosinemia	3 (2.0)
Neiman Pick type C	3 (2.0)
Mitochondrial disorder	3 (2.0)
Urea cycle defect	1 (0.7)
NH	20 (13.5)
Viral Infection	24 (16.2)
Other etiologies	19 (12.8)
HLH	4 (2.7)
Acetaminophen	2 (1.4)
Indeterminate	56 (37.8)

India

Neonates	Alam et al. 2014	N = 30 (%)
Metabolic Liver Disease		10 (33%)
Galactosemia		4 (13.3%)
tyrosinemia		1 (3.3%)
HFI		2 (6.6%)
Urea Cycle Defect		2 (6.6%)
Glycogenetic defect		1 (3.3%)
HLH		5 (16.6%)
Virus		5 (16.6%)
Hepatitis A		3 (10%)
EBV		1 (3.3%)
Varicella Zoster		1 (3.3%)
DILI		3 (10%)
Others		4 (13.3%)
AIH		2 (6.6%)
Neonatal hemochromatosis		1 (3.3%)
Budd Chiari syndrome		1 (3.3%)
Indeterminate		3 (10%)

Clinical Diagnosis

- **? Infantile liver failure**
- Jaundice with grade II encephalopathy

Metabolic Liver Disease
- Tyrosinemia
- Mitochondriopathy
- FAOD
- ~~Galactosemia~~
- ~~HFI~~

~~**Neonatal Hemochromatosis**~~
~~**HSV hepatitis**~~

~~**Hemophagocytic Lymphohistiocytosis**~~

~~**Sepsis**~~

Initial workup

Parameter	Value	Ref. Range	UNIT
Hb	9.5	11-14	g/dL
TLC	8.99	5-15	10^3/uL
PLATELETS	178	200-450	10^3/uL
INR	**5.3**	0.87 – 1.03	
T.BIL / D.BIL	**19.6 / 13.2**	0.2-1.2 / 0-0.05	Mg/dL
ALBUMIN	2.4	0-0.05	Mg/dL
AST/ALT	**1457 / 986**	5-34 / 0-55	IU/L
ALP	191	<500	IU/L
GGT	199	12-64	IU/L
BUN	9.31	5.1-16.8	Mg/dL
Creatinine	0.45	0.7-1.25	Mg/dL

Further Workup

Metababolic workup	Result	Ref. Range
AFP	**11244 IU/ML**	0-74 IU/ML
Urine Succinyl acetone	< 0.13	0-20 u mol/L
CPK	48	30-200 IU/L
Lactate	**160.1 Mg/dL**	4.5-20 Mg/dL
pH	**7.2**	
TMS	Negative	
Ammonia	42	18-72 Umol/L
Urine for reducing substance	Negative	
FBS (6 hours)	**45 (Low)**	> 60 Mg/dl
S. Ferritin	1664	21-274 ng/ml
Fibrinogen	0.53	2-4 g/L
Total cholesterol	<170	<170 mg/dl
Triglyceride	<150	<150 mg/dl

Radiological Workup

USG:

Liver: Enlarged (10.3 cm), ***Altered echotexture with Grade I fatty liver***

Portal vein 4 mm

Spleen non palpable

Mild ascites

Causes of MLD Presenting as ALF

Disease	Points in favor	Points against
Mitocondriopathy	High lactate, Fatty Liver	No multi system involvement
FAOD	High lactate fatty liver	No history of ALF during previous episodes of fever
Tyrosinemia	ALF	Urine for succinyl acetone Negative

Clinical Diagnosis

- **? Infantile liver failure**
- Jaundice with grade II encephalopathy

Metabolic Liver Disease

~~Tyrosinemia~~

Mitochondriopathy

FAOD

~~Galactosemia~~

~~HFI~~

~~Neonatal Hemochromatosis~~

~~HSV hepatitis~~

~~Hemophagocytic Lymphohistiocytosis~~

~~Sepsis~~

Final Diagnosis

Infantile Liver Failure (INR 5.6) with HE I/II

Etiology - Likely **MITOCHONDRIOPATHY / FAOD**

Meeting KCH for liver transplant – **4 / 5**

Management

Parents counselled for Liver Transplant

Meanwhile, Rapid Exome sequensing sent for mitochondriopathy

Supportive measures started including NAC

No further deterioration in HE

Follow Up

	DOA 1	DOA 12	Unit
Hemoglobin	9.5	9.0	g/dL
TLC	8.9	16.1	10^3/uL
Platelets	178	45	10^3/uL
INR	**5.35**	3.22	
T.Bil / D. Bil	**19.63 / 13.28**	**33.91 / 24.19**	Mg/dL
AST / ALT	1457 / 986	277 / 165	IU/L
ALP	191	162	IU/L
Albumin	2.44	3.45	Mg/dL
Lactate	**160.1**	80	Mg/dL
Ammonia	42	39	Umol/L

Supportive management - UDCA / IV Antibiotics / NAC/ Lactulose

Whole Rapid Exome Sequencing

Gene	Variant	Location	Zygosity	Disease	Inheritance	Classification
TRMU	c.1019-2A>G	Intron 9	Heterozygous	Transient infantile liver failure	Autosomal recessive	**Likely Pathogenic**
TRMU	c.835G>A	Exon 8	Heterozygous	Transient infantile liver failure	Autosomal recessive	**Pathogenic**

TRMU gene mutation causes ***transient liver failure without recurrence***

Parents were offered option of conservative treatment ***without liver transplant***

Following which child improved

Clinical features of the liver failure patients caused by TRMU pathogenic variants

Clinical features	N = 24 (%)
Hyperlactatemia	24 (100%)
Hepatomegaly	17 (70.8%)
Splenomegaly	3 (12.5%)
Elevated Alpha Fetoprotein	20 (83.3%)
Jaundice	18 (75%)
Coagulopathy	18 (75%)
Hypoglycemia	11 (45.8%)
Poor feeding	17 (70.8%)
Cholestasis	5 (20.8%)
Spontaneously recovery	17 (70.8%)
Died	7 (29.1%)

Elevated lactate was the most prominent symptom.

Qin Z, Yang Q, Yi S, Huang L, Shen Y, Luo J. Whole-exome sequencing identified novel compound heterozygous variants in a Chinese neonate with liver failure and review of literature. Mol Genet Genomic Med . 2020;8:e1515. https://doi.org/10.1002/mgg3.1515

Hospital stay

	DOA 1	DOA 12	DOA 56	Follow up	Ref Range	Unit
Hemoglobin	9.5	9.0	9.2	12.8	11-14	g/dL
TLC	8.9	16.1	17.8	6.5	5-15	10^3/uL
Platelets	178	45	25.0	304	200-450	10^3/uL
INR	**5.35**	3.22	2.56	**1.09**	0.87 – 1.03	
T.Bil / D. Bil	**19.63 /13.28**	**33.91/24.19**	12.9/8.4	**0.37/0.16**	0.2-1.2	Mg/dL
AST/ALT	1457/986	277/165	73/71	80/50	5-34/0-55	IU/L
ALP	191	162	395	263	<500	IU/L
Albumin	2.44	3.45	2.86	4.28	0-0.05	Mg/dL
Lactate	**160.1**			**37**	4.5-20	Mg/dL
Ammonia	42	39	56	59		

NAC

Supportive management

Clinical Question

1. In all indeterminate ALF in infancy should exome sequencing be sent?