RARE CAUSE OF CHOLESTATSIS IN AN INFANT

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BACKGROUND

- 3 ½ month old female infant, developmentally normal
- 4th born to 2nd degree consanguineous parentage
- H/o sibling death (first 2 male children, both expired at 3 months of age, etiology unclear)
- Born of NVD, birth weight was 2.64 kg, had no adverse perinatal events

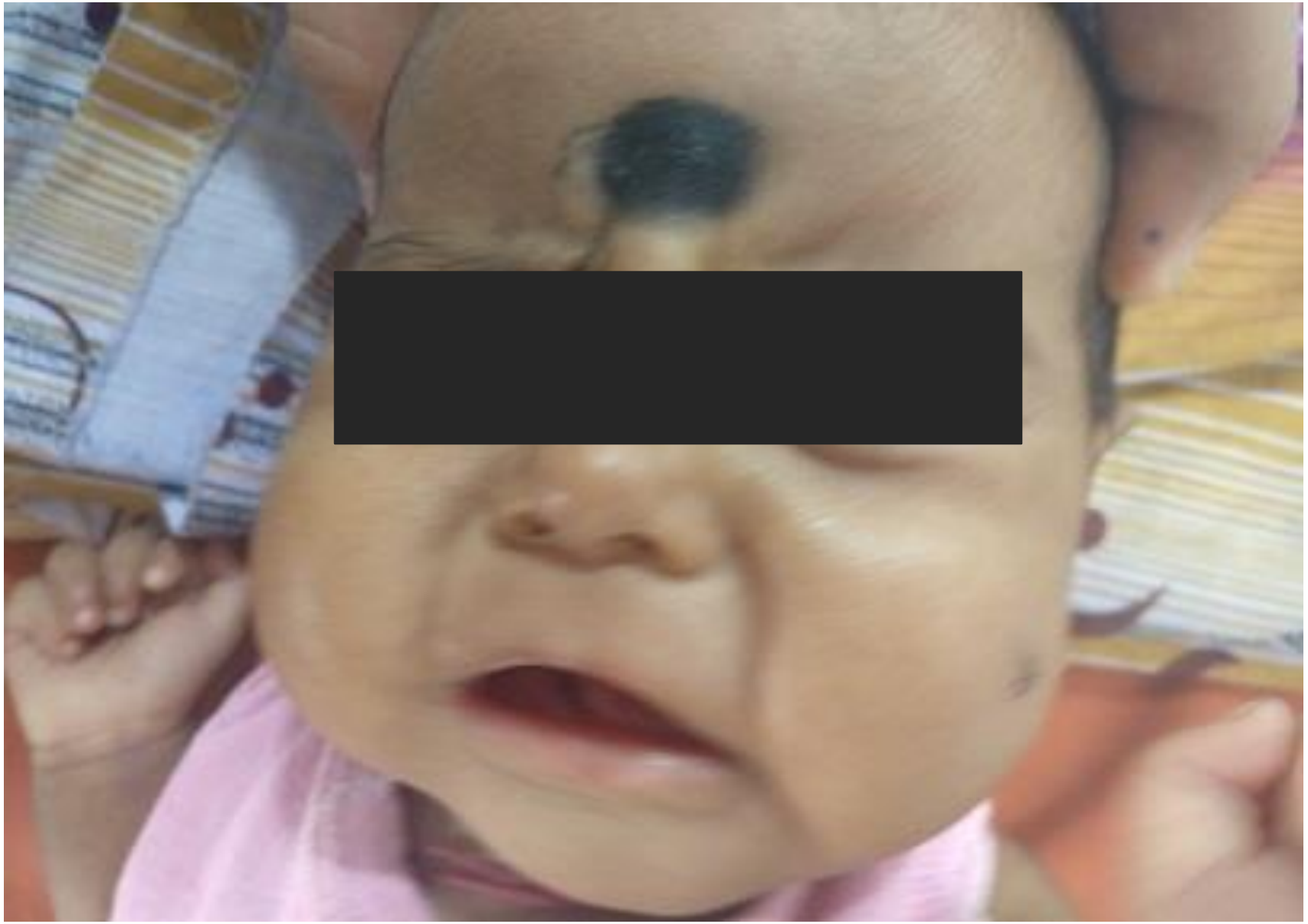
BACKGROUND

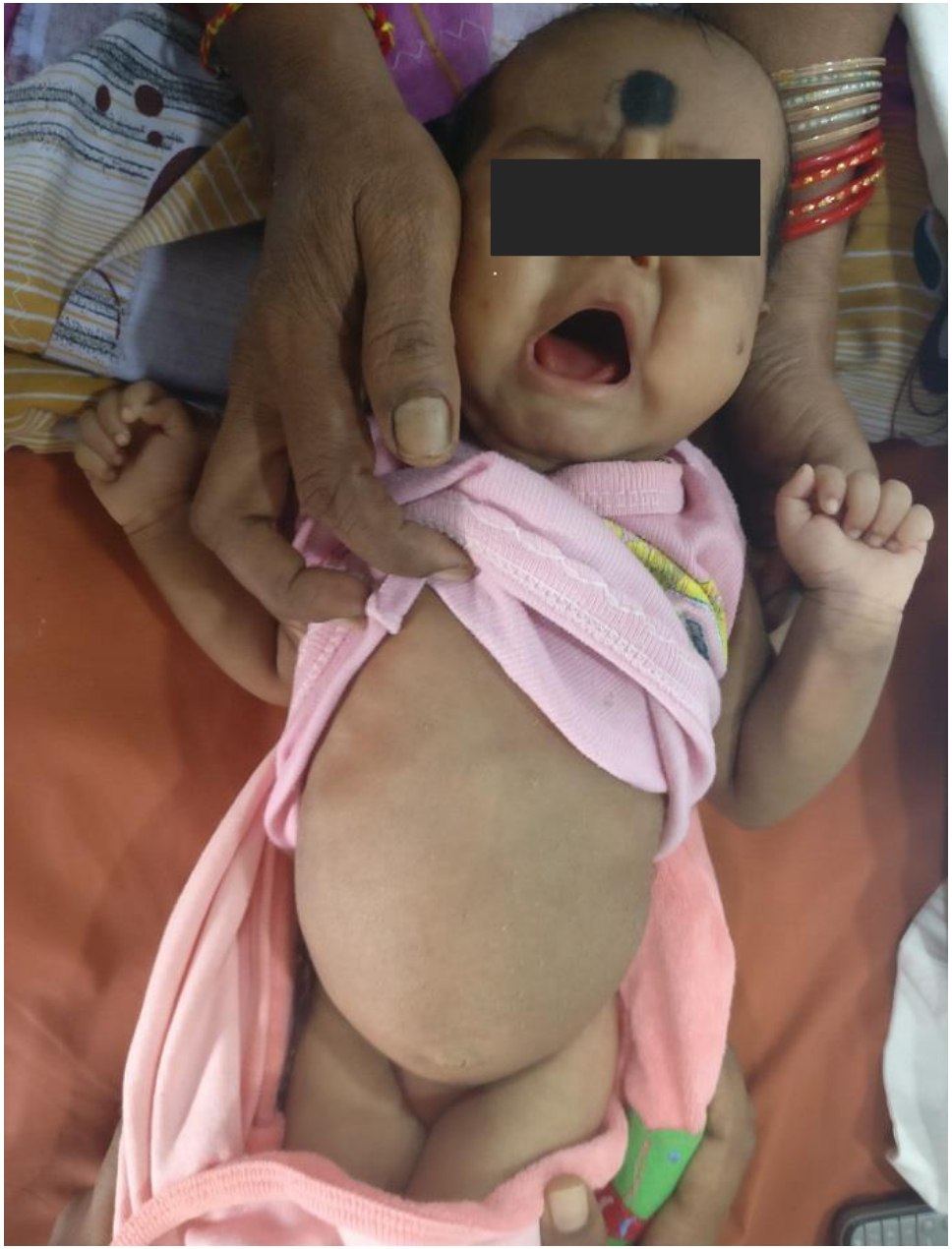
- 3 months of age → growth faltering → started on dexolac feeds

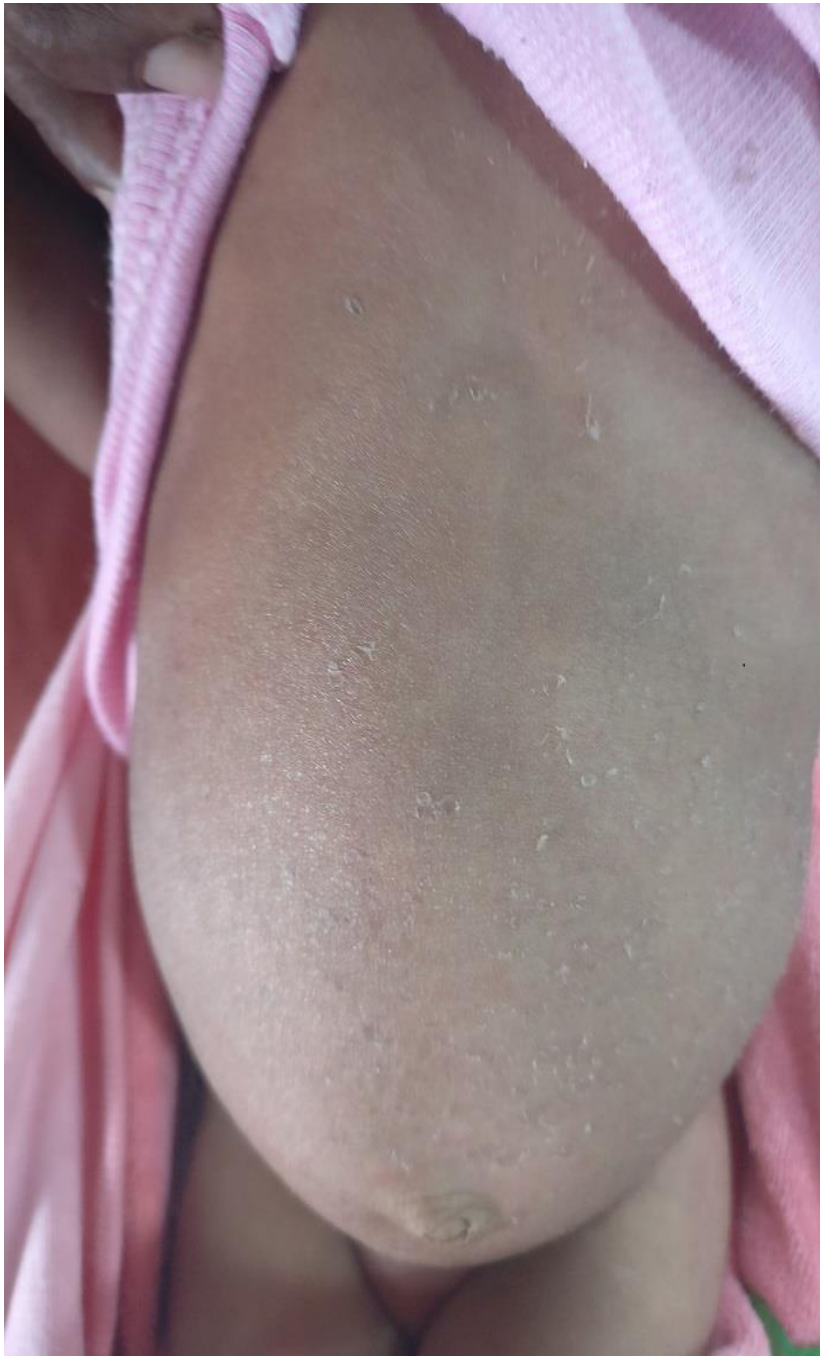
- Child was admitted outside and received albumin transfusion (edema, s. albumin = 2 g/dl) and PRBC transfusion (Hb = 5.2 gm/dl) and was referred to KKCTH for further management.

PRESENTATION

- **Growth faltering**(2.64 kgs→3.1 kgs)
- **Cholestatsis** →High colored urine (staining diaper) and pale colored stools since 1 month of age
- **Pallor**
- **Edema**
- **Icthyosis**
- **Doll like facies (chubby cheeks)**
- **Hepatomegaly**







INVESTIGATIONS

Hb	**6.0**
TC	18900 (55/43/2)
Platelet	2.92 lakhs
PT/aPTT/INR	15/44/1.3
Total Bilirubin/Direct	**6.1/4.0**
OT/PT	132/39
Protein/albumin	**3.8/2.6**
GGT/SAP	77/153
RFT	Normal

USG abdomen- mild hepatomegaly, fatty changes + both kidneys towards lower limit , rest normal

ADDITIONAL FINDINGS

- Ophthalmology evaluation- **Corneal and Conjuctival Xerosis.** (treated with vitamin A)

- Thyoid Profile **- fT4- 1.37, TSH-19.52** (started on thyroid supplements)

- S. Ammonia-50, pyruvate-0.087, **Lactate-3.5**

DIFFERENTIAL DIAGNOSIS

- **CYSTIC FIBROSIS**

✓ FTT/neonatal cholestasis

✓ Fecal chymotrypsin (2 samples) – no activity

✓ CFTR gene panel (72 mutations) –negative

- **MITOCHONDRIAL HEPATOPATHY**

✓ Neonatal cholestasis/ lactate= 3.5

✓ No CNS /other system involvement

DIFFERENTIAL DIAGNOSIS

- **GLYCOGEN STORAGE DISORDERS**

✓ Hepatomegaly/ doll like facies

✓ No fasting hypoglycemia/lipid profile/uric acid –normal

- **FANCONI BICKEL SYNDROME**

✓ Hepatomegaly/doll like facies

✓ However no RTA/no renomegaly

So WHAT is the DIAGNOSIS ????

- History of consanguinity and sibling loss
- CHOLESTASIS with fat soluble vitamin deficiencies
- Failure to thrive
- Fatty liver
- Anemia
- Hypoproteinemia
- DOLL LIKE FACIES

CITRIN DEFICENCY

Neonatal Intrahepatic Cholestatsis a/w Citrin Deficiency (NICCD)

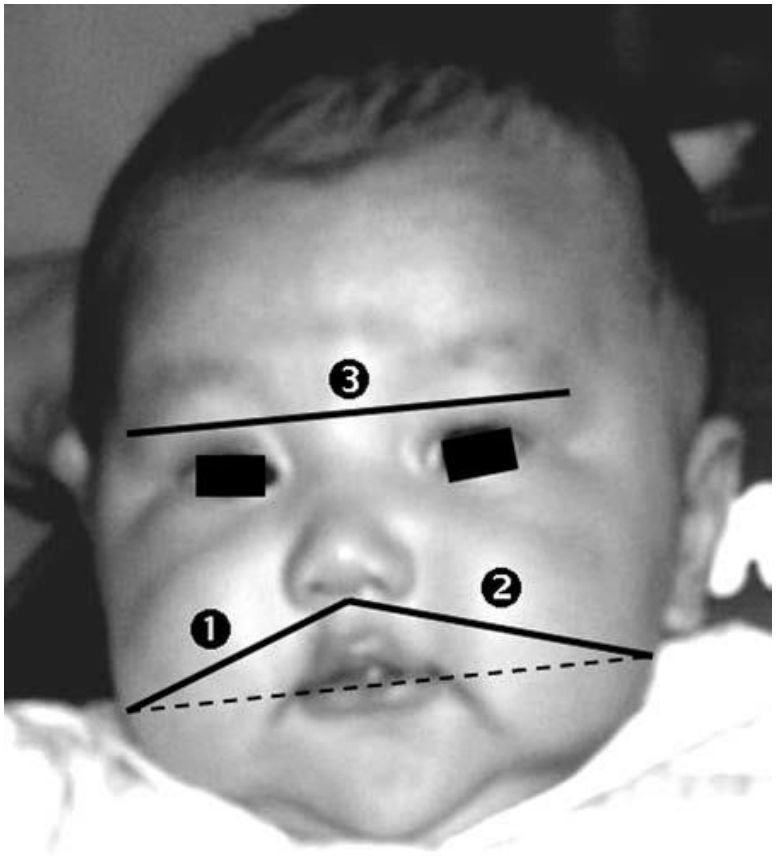
CHUBBY INDEX

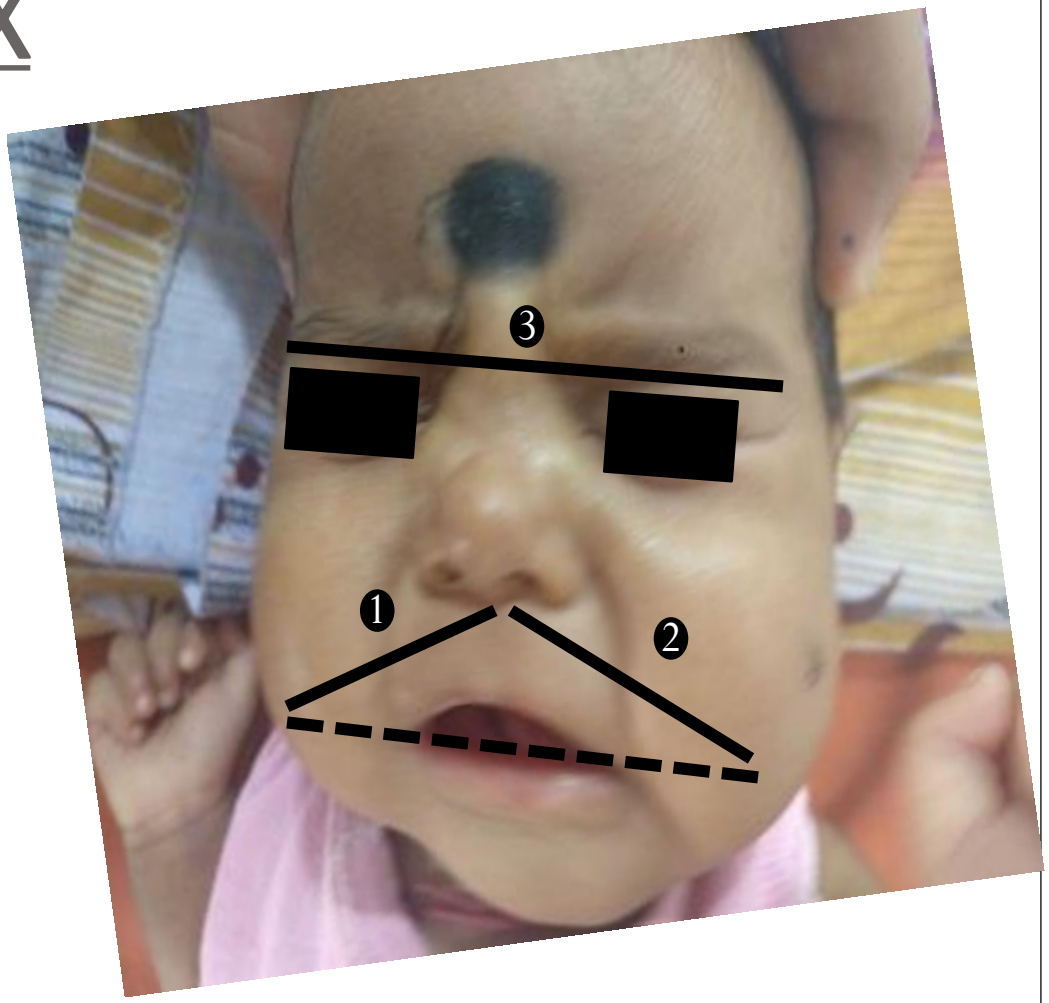
- Defined →the sum of the lengths of the bilateral cheeks (1+2) divided by the distance between the lateral ends of the eyebrows (3).

- At the age of 2 to 4 months, the **Chubby Index in the NICCD** group (**1.3310.071**,range 1.217–1.402) was significantly higher than that in the control group (1.0680.059, range 0.964–1.169) ($P<0.05$) *(Chen et al 2008)*

- Our patient →chubby index →1.3.

CHUBBY INDEX





Chen HW, Chen HL, NiYH, Lee NC, ChienYH, HwuWL, HuangYT, Chiu PC, Chang MH. Chubby face and the biochemical parameters for the early diagnosis of neonatal intrahepatic cholestasis caused by citrin deficiency. J Pediatr Gastroenterol Nutr 2008; 47: 187–92

Can LFTs predict ???

- NICCD was related to
- ✓ **AST/ALT ratio >2**
- ✓ **D-BIL/T-BIL ratio < 0.67.** (*Chen et al 2008*)

- In our patient
- ✓ AST/ALT ratio→132/39 →**3.4**
- ✓ D-BIL/T-BiL ratio →4.0/6.1→**0.65**

- In NICCD → **serum bile acids >200** (*Kobayashi et al. 2006*), which was similar to the finding in our patient.

FISCHERS RATIO

- Fischer ratio → (branched-chain amino acids [BCAAs] Val+Leu+Ile / aromatic amino acids [AAAs] Tyr+Phe) → decreased from ~3.4 to **~2 in citrin deficiency**.

(Saheki T, Song YZ. Citrin Deficiency. 2005 Sep 16. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.)

- In our patient the Fischers ratio was **1.63.**

- **The above test is usually positive in the asymptomatic phase of the disease.**

CITRIN DEFICENCY

CITRIN DEFICIENCY

- Autosomal recessive

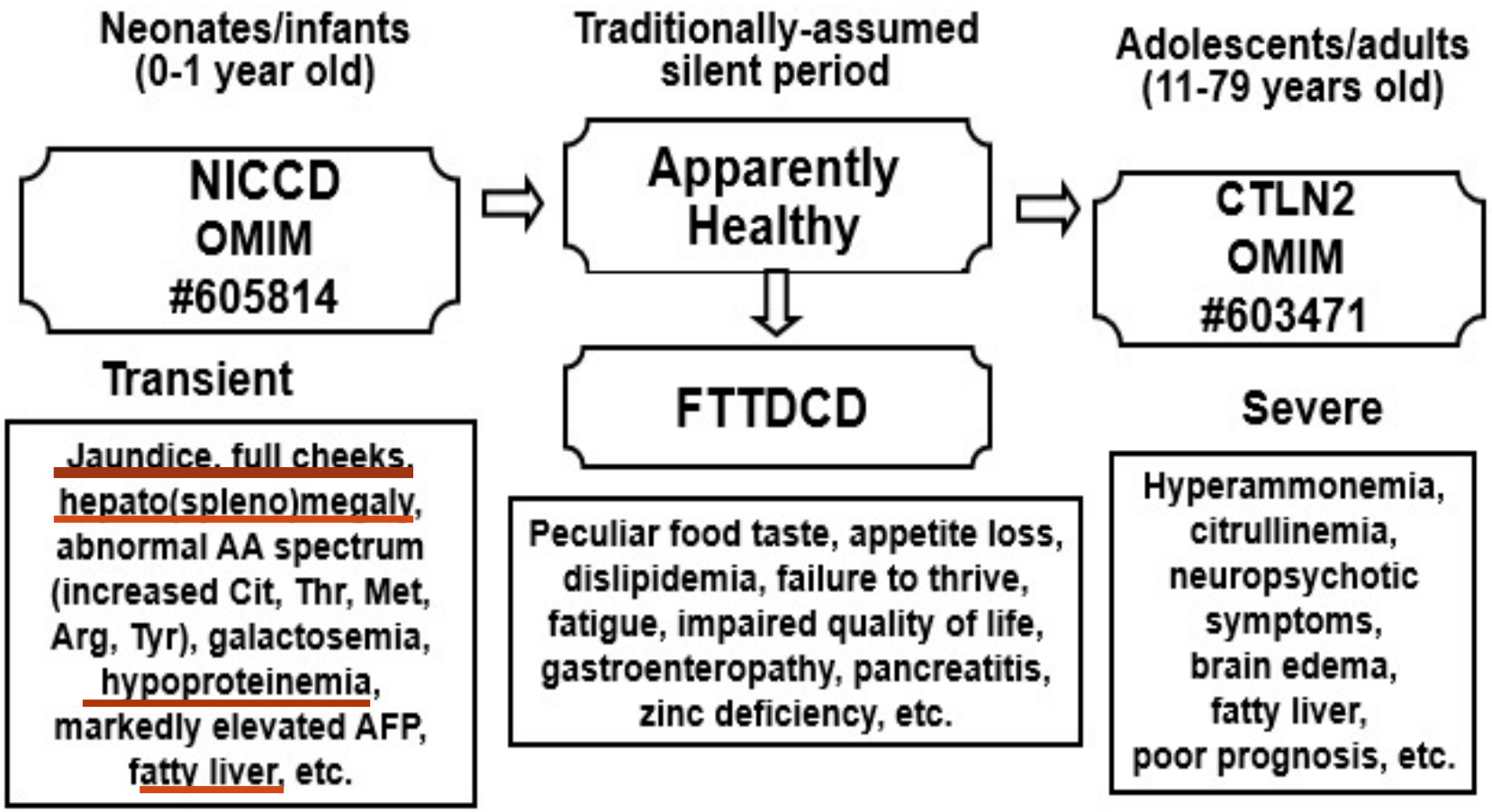
- Disease of **EAST ANCIENT ANCESTRY (**carrier rates in Japan, China, Taiwan and Korea are 1:65, 1:65, 1:48 and 1:112) → Disease of **PAN ETHNIC ORIGIN** (Israel, Pakistan, the United States, the United Kingdom and the Czech Republic)

- In India only 2 cases of NICCD have been published so far.

CITRIN DEFICIENCY

- Newborns or infants - neonatal intrahepatic cholestasis caused by citrin deficiency **(NICCD)**
- Older children - failure to thrive and dyslipidemia caused by citrin deficiency **(FTTDCD)**
- Adults - as recurrent hyperammonemia with neuropsychiatric symptoms in citrullinemia type II **(CTLN2).**

Presentations of Citrin Deficiency



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LAB PARAMETERS IN NICCD

Assayed Item (NICCD)	Median (25%-75% range) (mg/dL)	Control Range (mg/dL)
TB	4.9 (2.8-8.0)	0.2-1.0
DB	2.5 (1.5-3.7)	0-0.4
TB/DB ratio	**0.55 (0.41-0.66)**	—
TBA	**239 (172-293)**	5-25
AFP	**91,900 (33,200-174,700)**	260-6,400 [1, 2] 2-55 [2, 3]

Kobayashi et al (2006)

In our patient TB/DB ratio was less and serum bile acids was >200 , however AFP =1837.

LAB PARAMETERS IN NICCD

Phenotype (Age)	Blood or Plasma Concentration of Ammonia (µmol/L)	Plasma or Serum Concentration of:		**Plasma or Serum Threonine-to-Serine Ratio**
		Citrulline (µmol/L)	**Arginine** (µmol/L)	
Control	18-47 [3]	17-43 [3]	54-130 [3]	1.10
NICCD (0-6 mos)	60	**300**	**205**	**2.29**
FTTDCD (>1-11 yrs)	Normal or slightly elevated	Normal or slightly elevated	Usually normal	Unknown
CTLN2 (11-79 yrs)	152	418	198	2.32

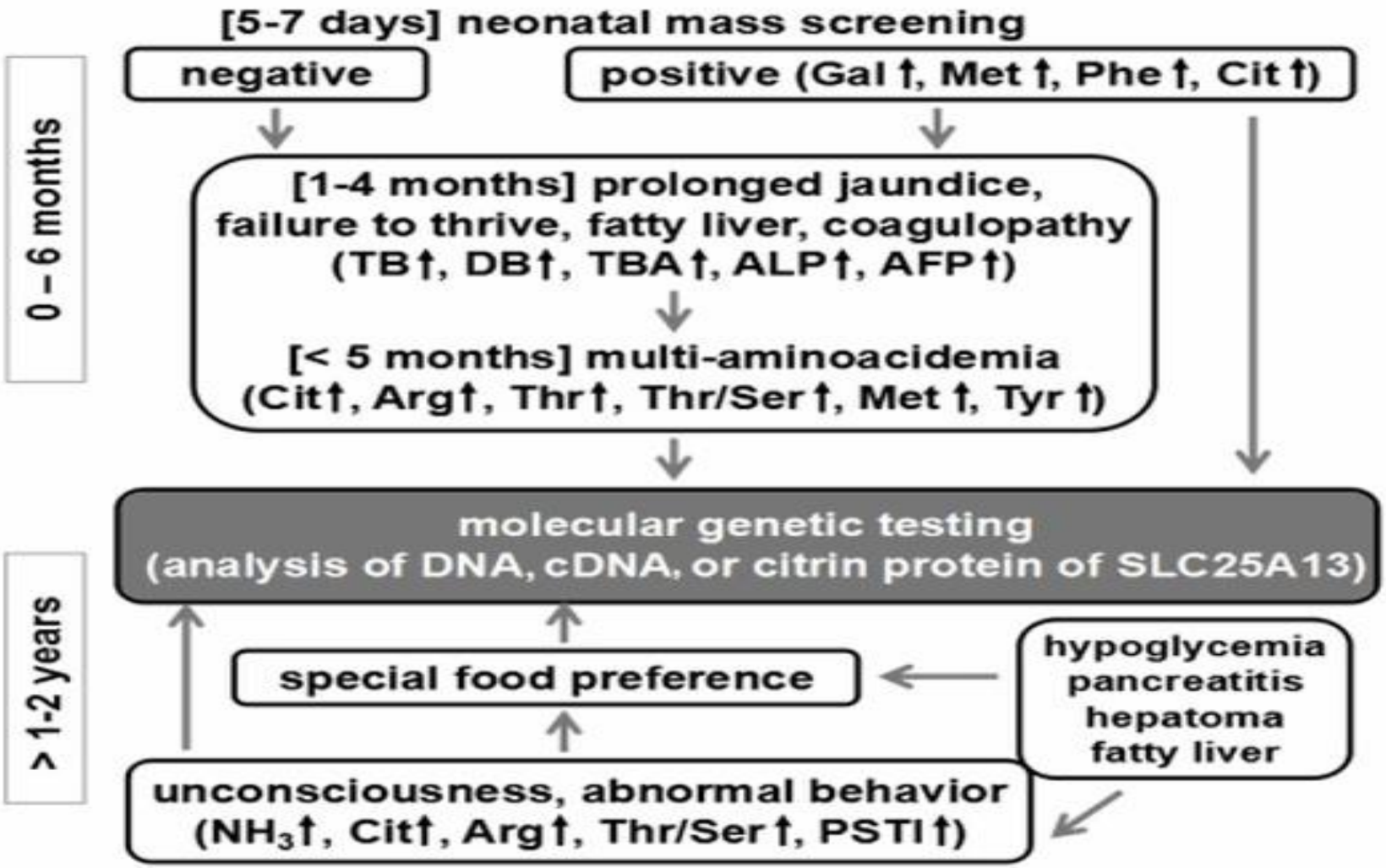
Kobayashi et al (2006)

In our patient aminoacidogram and threonine- serine ratio was normal

CONFIRMED DIAGNOSIS

- Gene analysis involving identification of biallelic pathogenic variants in **SLC25A13** .

HOW TO DIAGNOSE ???



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PITFALLS IN DIAGNOSIS

- Natural history of disease is unclear.

- Misdiagnosed as **Galactosemia and Tyrosinemia**.

- **Plasma amino acids** show
  - ✓ inconsistent and varied elevation.
  - ✓ The newborn screening is ineffective.
  - ✓ **Normal during asymptomatic phase** (as in our case)

- **Gene test not widely available in India.**

MANAGEMENT

- **NICCD**

✓ Fat soluble vitamins

✓ Lactose-free and MCT-enriched therapeutic formulas

✓ Usually self limiting

- **FTTDCD**

✓ Dietary preferences

✓ Sodium pyruvate

- **CTLN2**

✓ Arginine supplementation

✓ Sodium pyruvate

✓ Liver transplantation

TAKE HOME MESSAGE

- **Cholestasis with chubby cheeks with unexplained hypoproteinemia** – consider **Citrin deficiency**

- Plasma aminoacidogram may be normal during asymptomatic phase, however Fischers ratio will be <2.

- **Transient condition**, managed by dietary intervention (**avoid lactose and provide high protein**)


ngiyabonga
рахмат
danke
謝謝
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teşekkür ederim
Баярлалаа
mersi
kia ora
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tapadh leat
спасибо
faafetai lava
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nanni
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