DEPARTMENT OF MEDICAL GENETICS , J K LON HOSPITAL , SMS MEDICAL COLLEGE, JAIPUR

A TREATABLE METABOLIC DISORDER WITH LATE PRESENTATION

Presenter - Dr Anjali Sharma

Moderator - Dr Priyanshu Mathur

Experts - Dr Aradhana Dwivedi

Dr Gayatri Dhanger

Case history

- 10 year old
- Male child
- 2nd born of non-consanguineous marriage
- 17.8 kg weight on admission
- Hailing from, Shahpura, Jaipur
- Informant - father and reliability - good

Presenting illness

Complaint of

- Abdominal distension for 6 years
- Not gaining weight for two years
- Not gaining in height for two years
- Lower limb deformity for two years

History of presenting illness

- Patient was apparently normal six years back , then patient develop progressive abdominal distension, insidious in onset, gradually increasing in size , associated with the feeling of heaviness and early satiety. It was not associated with pain, vomiting or loss of appetite. it was also not associated with loose stool, greasy stool or constipation.

- Parents noticed of inadequate weight gain for the last two years. Parents also report loosening of clothes which previously fits perfectly . At age of four years patient weight was 15 kg but currently patient weights 17.8 kg.

- The parents reported that child has not been gaining height appropriately for past two years, child height was normal (98 cm) at age of four years, but linear growth has slowed compared to peers.

- The parents noticed inward angulation of both knees since the age of 8 years which has been gradually progressive. The deformity is bilateral and associated with difficulty in walking long distances, but not associated with pain, trauma or history suggestive of infection.

- No history of cough, breathlessness, oedema
- No history of recurrent cough , expectoration , hemoptysis or poor appetite
- No history of chronic diarrhoea or flatulence
- No history of polyuria , polydipsia or oliguria
- No history of skin or hair changes , night blindness, or bleeding gum
- No history of chronic steroid use or drug ingestion
- No history of blood transfusions

Past History

- Patient was admitted at 4 years of age due to complain of abdominal fullness for 2 days.

During hospitalization

GPE

PR - 90/min

BP - 100/70 mmhg

RR - 26/min

Temp - 98.6F

Anthropometry

Weight - 15 KG

(25th - 50th percentile)

Height - 98 cm

(10th - 25th percentile)

HC - 50 cm

MUAC- 14.5 cm

Abdominal examination

Abdomen was soft & distended.

Liver palpated at 4 cm under sub coastal margin , firm in consistency.

Spleen 3 cm under subcostal margin , firm in consistency.

Investigations

Hb	11.8gm/dl	**S Cholesterol**	152mg/dl
WBC	4400/Cum	**Triglycerides**	103mg/dl
PLT	**47K**	**S albumin**	4.2g/dl
PT/INR	**20/1.42**	**TTG- IgA**	<0.20AU/mL
SGOT	45IU/l	**APTT**	37.8
SGPT	27IU/l		

USG Abdomen

Suggestive of Chronic Liver Disease With Multiple Hepatic Nodules

Liver Biopsy

Single core of liver tissue, msg 1.2 cm.

Microscopic Description

Section examined show two cores of hepatic parenchyma with predominant mosaic pattern of hepatocytes, results from swollen hepatocytes compressing the sinusoids.

- The hepatocyte cell membranes are accentuated, and prominent glycogenated nuclei are seen.
- Evidence of compression of sinusoids by expanded hepatocytes noted.
- Portal inflammation is moderate. Mild portal fibrosis is seen on trichrome stain.

Diagnosis- Metabolic liver disease.

Histological features & Special stains suggest possibility of Glycogen Storage Disease.

- He was diagnosed as **CHRONIC LIVER DISEASE UNDER EVALUATION / ?STORAGE DISORDER / ?METABOLIC / ? OTHER CAUSE**

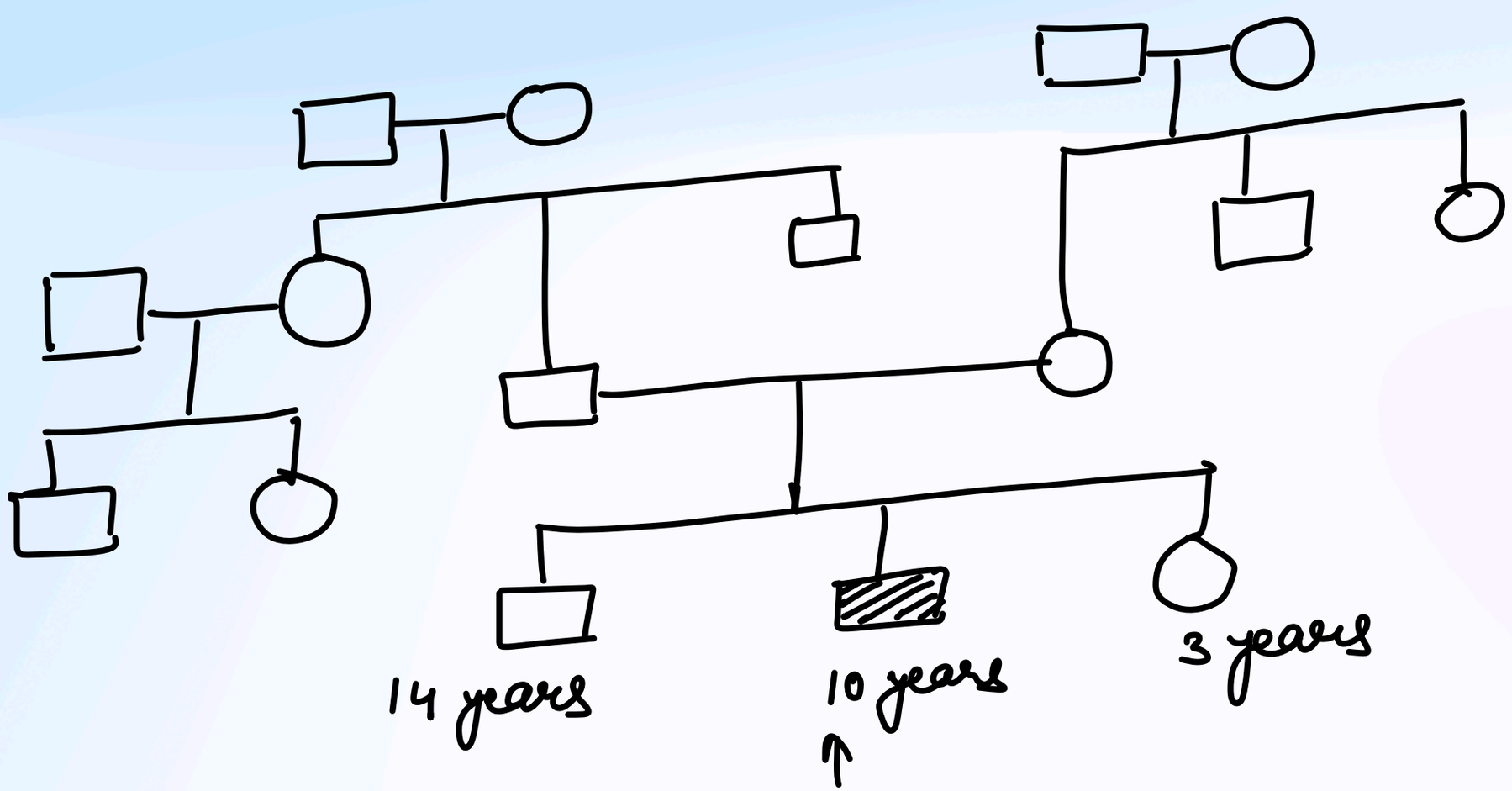
- Patient had multiple OPD visits for same complain but received symptomatic treatment.

- At the age of 8 years patient visited orthopaedic OPD in view of limb deformity and suspected to have rickets. Patient was started on calcium and vitamin D supplements and treated for more than 1 year , without any significant improvement. No reports available.

Family History

- No history of similar illness in family members.
- No history of blood transfusion in family members.

Pedigree Chart



Dietary History

Recommended Average Requirement	Patient Daily Intake
Energy = 2220 Kcal Per Day	Energy = 1560 Kcal Per Day
Protein = 26.2 G per Day	Protein= 25 G per Day

Energy Deficit= 660 Kcal per Day

Protein Deficit = 1.2 G per Day

Developmental History

- Gross Motor - Runs , Jumps, Skips Well ,Good Balance and Coordination
- Fine Motor- Write Neatly With Good Hand Control ,Draws Detailed Figures ,Can Perform Complex Tasks Like Cutting and Crafting
- Language- Fluent, Grammatically Correct Speech , Age Appropriate Vocabulary, Understand Complex Commands ,Reads and Writes at Grade Level
- Cognitive Development- Understands Time, Money, Cause-Effect Relationship ,Good Attention Span and School Performance
- Social Development- Prefers Peer Group Activities, Cooperative , Understands Rules and Fairness
- Emotional Development- Express Feelings Appropriately, Show Empathy
- Activities of Daily Living- Independent in Dressing, Bathing ,Feeding and Toileting.

Birth History

- Mother is G3P3L3A0. Patient is second born full term through vagina delivery. Immediate cry at birth with birth weight 3.1 KG.
- There was no history of NICU Stay .
- Breastfeeding was initiated within two hours of life.

Immunisation History

- Immunisation completed as per national immunisation schedule.
- BCG scar mark is present.

Socio-economic history

According to New Kuppuswamy Scale 2025 -Lower Middle Class

1. Education - 6
2. Occupation - 5
3. Income - 3

Total Score = 14 (Lower Middle Class)

General Physical Examination

- Patient sitting comfortably on bed with poor built and undernourished.
- No Pallor , Icterus , Cyanosis , Clubbing , Lymphadenopathy or Oedema

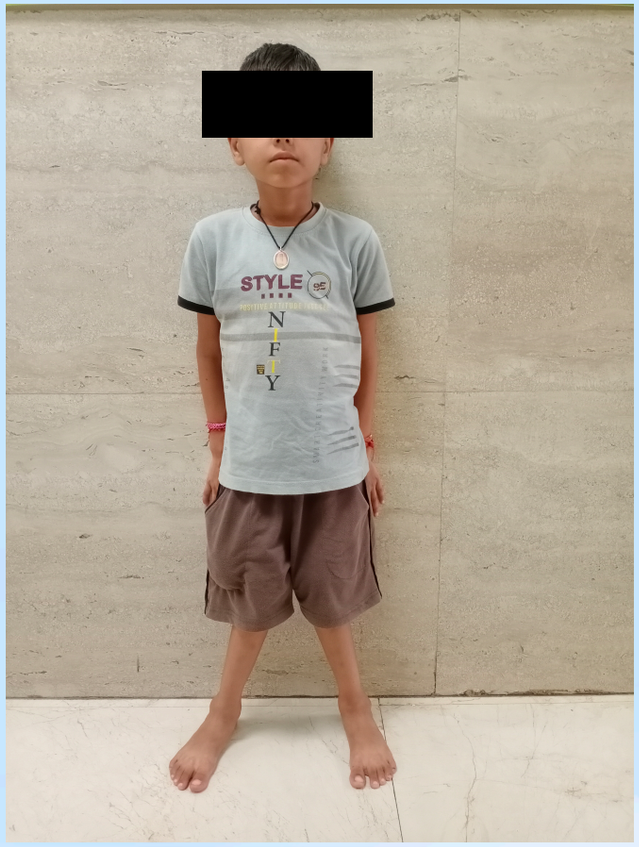
Vitals

- Pulse rate - 84 per minute palpated in right radial artery
- Respiratory rate- 22 per minute , Thoracic
- Blood pressure - 110/70 measured in right arm in sitting posture
- SPO2 - 99% on room air recorded in right index finger

Head To Toe Examination

Positive Findings

- Pectus Carinatum
- Widening of Bilateral Wrist and Bilateral Knee
- Genu Valgum
- Prominent Tibial Lower End



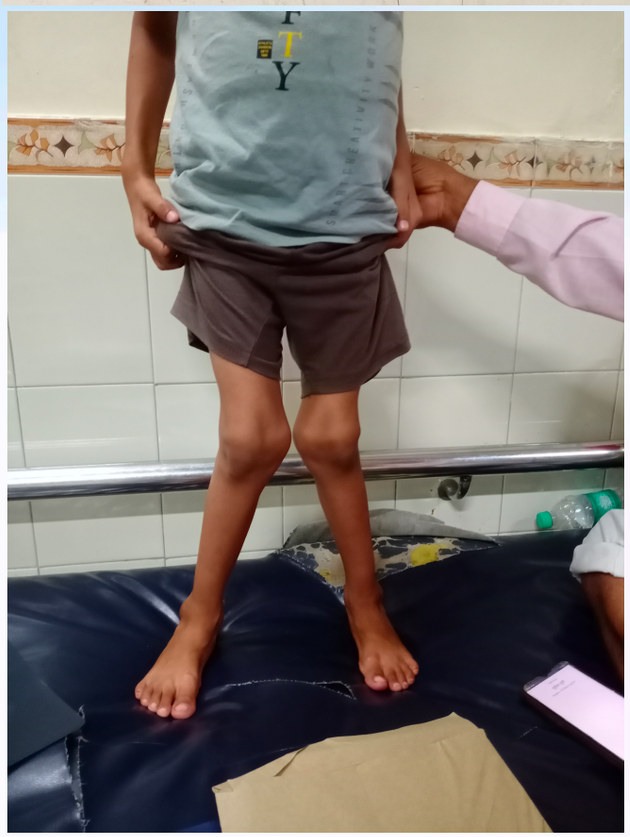


Image Showing Inward Angulation of the Bilateral Knees (Genu Valgum Deformity)

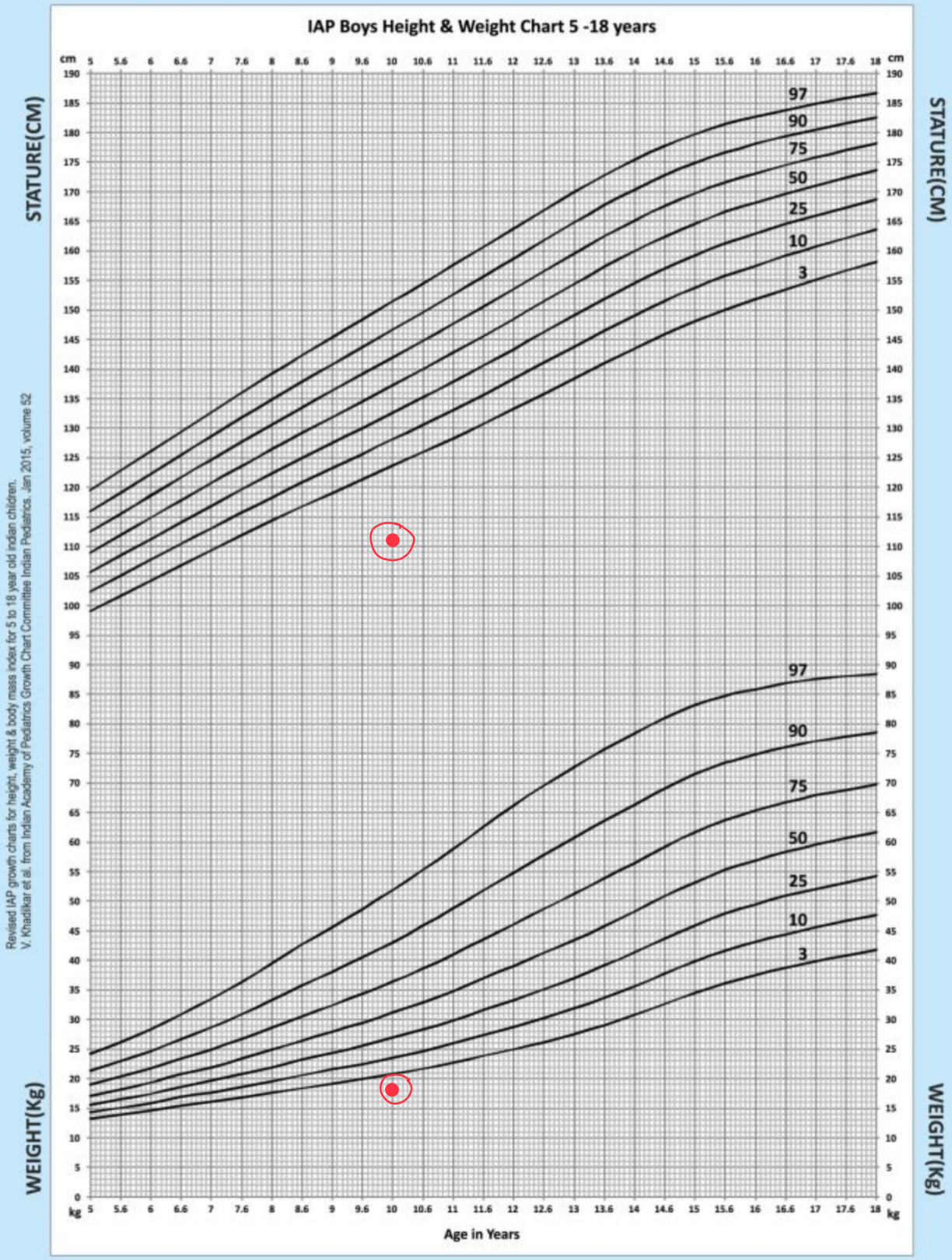
Anthropometry

- Head Circumference - 51 Cm
- Weight - 17.8 KG
- Weight for Age - <3rd Percentile (IAP Growth Charts)
- Height - 111 Cm , US - 59 Cm , LS - 52 Cm
- Height for Age - <3rd Percentile (IAP Growth Charts)
- US/LS Ratio - 1.13 (Disproportionate Short Stature)
- Arm Span = 110cm
- BMI - 14.47 Kg/M2 (10th -25th Percentile)

SMR (Tanner) Staging - SMR Stage 1

5 to 18 Years : IAP Boys Height and Weight Charts

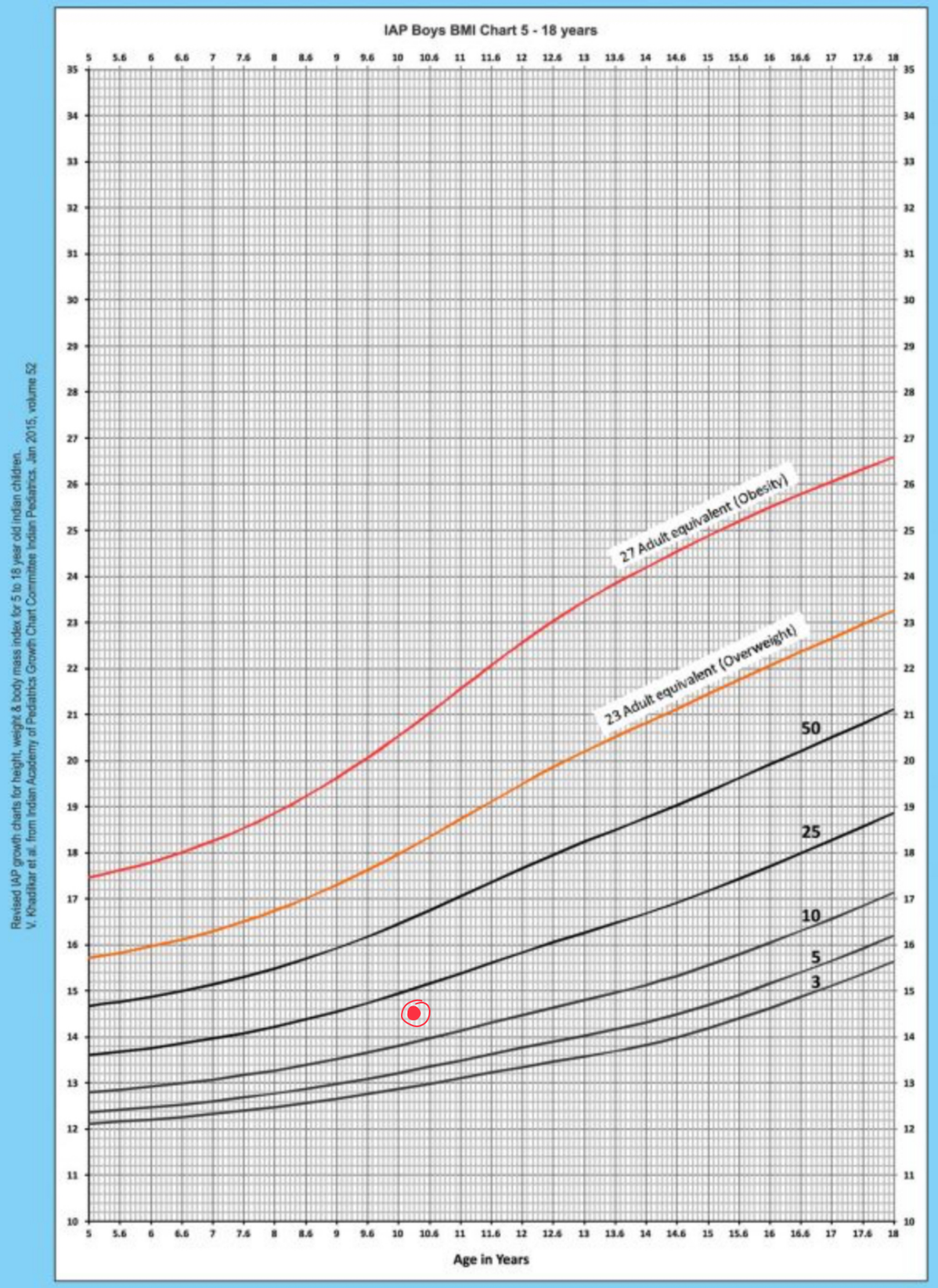
Father's Height_____, Mother's Height_____, Target Height_____



5 to 18 Years : IAP Boys Body Mass Index Charts

Name _____

DOB _____

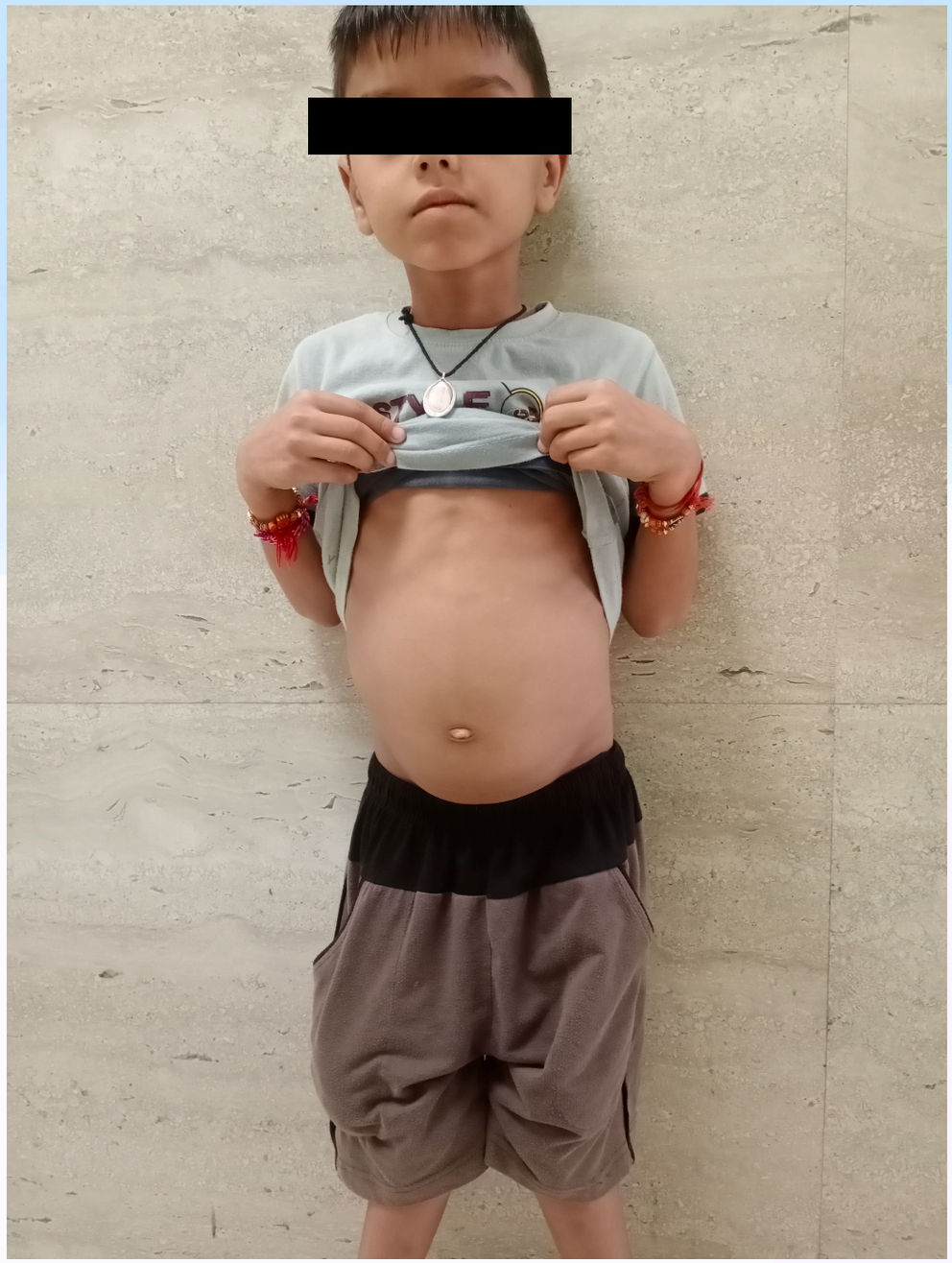


Revised IAP growth charts for height, weight & body mass index for 5 to 18 year old indian children.
V. Khadilkar et al. from Indian Academy of Pediatrics Growth Chart Committee Indian Pediatrics. Jan 2015, volume 52

Gastro-Intestinal System Examination

Inspection

- Abdomen is moderately distended.
- All quadrant moving equally with respiration.
- Umbilicus is everted and normal in shape.
- Skin over the abdomen is normal, no visible scar, sinus, pulsation, peristalsis or engorged veins.
- External genitalia appears normal. Bilateral testis present.



Palpation - Abdomen soft, no rigidity or gaurding

- Liver is palpable 4 cm under subcoastal margin , non-tender with firm consistency and margins are sharp.

- Spleen palpable 3 cm under left subcostal margin

Percussion - No shifting dullness

- Liver span is 14 cm

Auscultation - Bowel sounds normal

Provisional Diagnosis

10 year old male child with past history of chronic liver disease presented with abdominal distension, short stature, underweight, hepatosplenomegaly and clinical features of Rickets, most likely provisional diagnosis is metabolic liver disease.

Differential Diagnosis

1. Tyrosinemia type 1 (Chronic form)
2. Wilson Disease
3. Glycogen Storage Disease
4. Cystic Fibrosis
5. Alpha-1-Antitrypsin Deficiency
6. Lysosomal Storage Disorder

	Differentials	Favour	Against
1	**Tyrosinemia Type 1**	Chronic liver disease with Hepatosplenomegaly Failure to thrive Hypophosphatamic Rickets due to fanconi syndrome	Typically presents in infancy Usually more acute or severe early course
2	**Wilson Disease**	Chronic liver disease with Hepatosplenomegaly Growth failure , short stature Can cause renal tubular dysfunction-rickets	No h/o jaundice No h/o neuropsychiatric symptoms
3	**Glycogen Storage Disease**	Chronic liver disease with Hepatosplenomegaly Growth failure , short stature rickets due to metabolic acidosis / Vitamin D deficiency	Usually presents in infancy associated with hypoglycemia, doll-like face

4	**Cystic Fibrosis**	Chronic liver disease with Hepatosplenomegaly Failure to thrive and underweight Rickets due to fat soluble vitamin deficiency	No history of recurrent respiratory infection No steatorrhea or pancreatic insufficiency symptoms
5	**Alpha-1-Antitrypsin Deficiency**	Chronic liver disease with Hepatosplenomegaly Growth failure	Rickets not typical Pulmonary symptoms (Emphysema) absent Usually presents early
6	**Lysosomal Storage Disorder**	Hepatosplenomegaly Growth failure Chronic course	No coarse facial features Rickets uncommon No neurological manifestation or bone pain features

Investigations

Hb	14.2 g/dl	**Na/ K/CL**	145/3.7/111 mmol/L
PLT	79k	**S creatinine**	0.27mg/dl
WBC	6.76 cells/uL	**S urea**	18.72 U/L
PT/INR	19/1.41	**S calcium**	8.93 mg/dl
LDH	531.44 IU/L	**S VIT D3**	19.7 ng/ml
GGT	30.58 IU/L	**S PTH**	40.9 pg/ml
S Alkaline	342.94IU/L	**S AFP**	41.4 ng/ml
S PHOSPHORUS	1.64 mg/dl	**S B HCG**	3.1mIU/ml
Direct bilirubin	0.20 mg/dl	**HBsAg**	Negative
Total bilirubin	0.63 mg/dl	**Anti HCV**	Negative
SGOT	32.78 IU/L	**Urinary calcium**	27.5 mg/dl
SGPT	22.79 IU/L	**Spot urine creatinine**	31.32 mg/dl
S total protein	6.5 g/dl	**Urine calcium creatinine ratio**	0.87 mg/g
S albumin	4.1g/dl	**HIV**	Non reactive

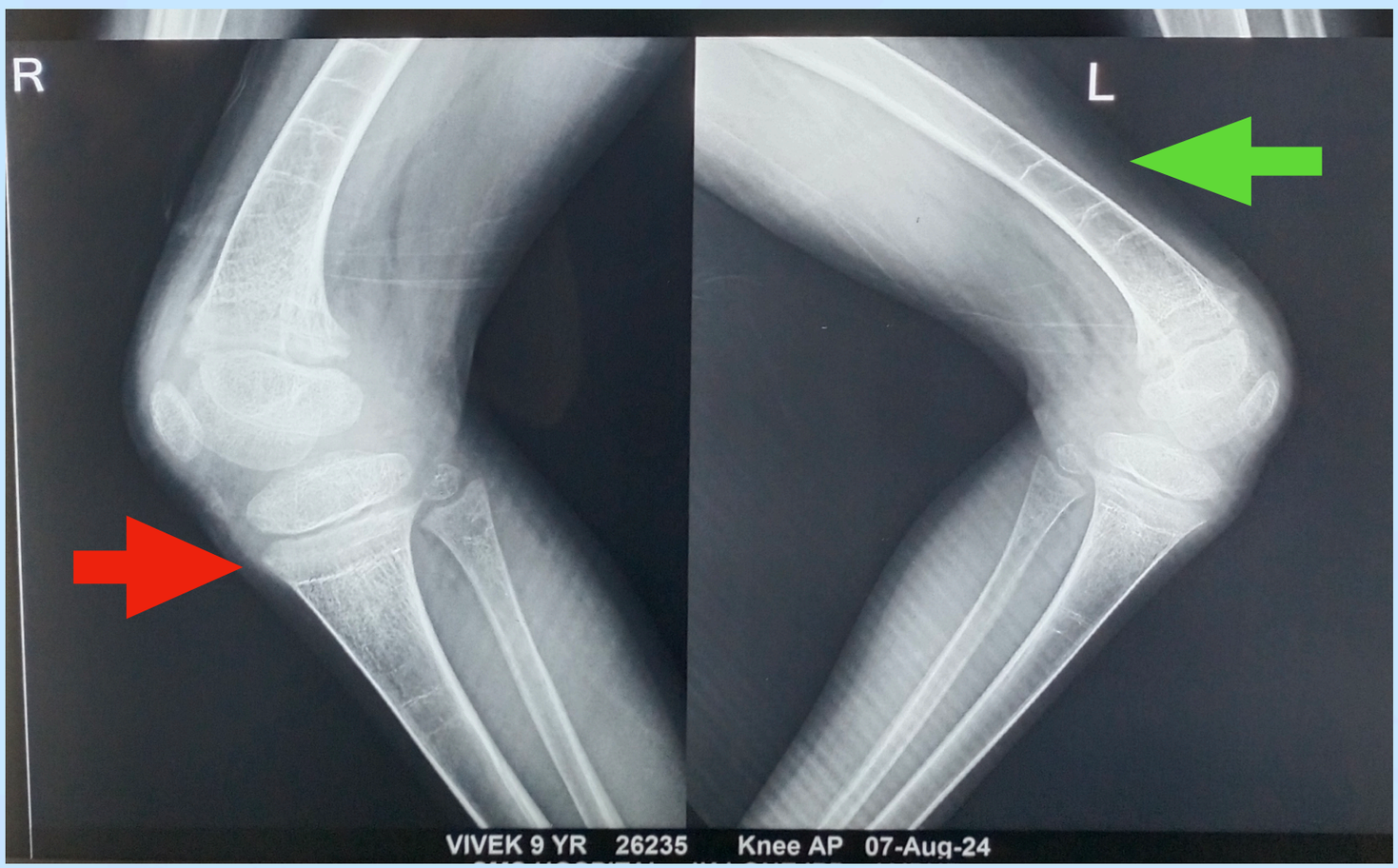
USG Abdomen

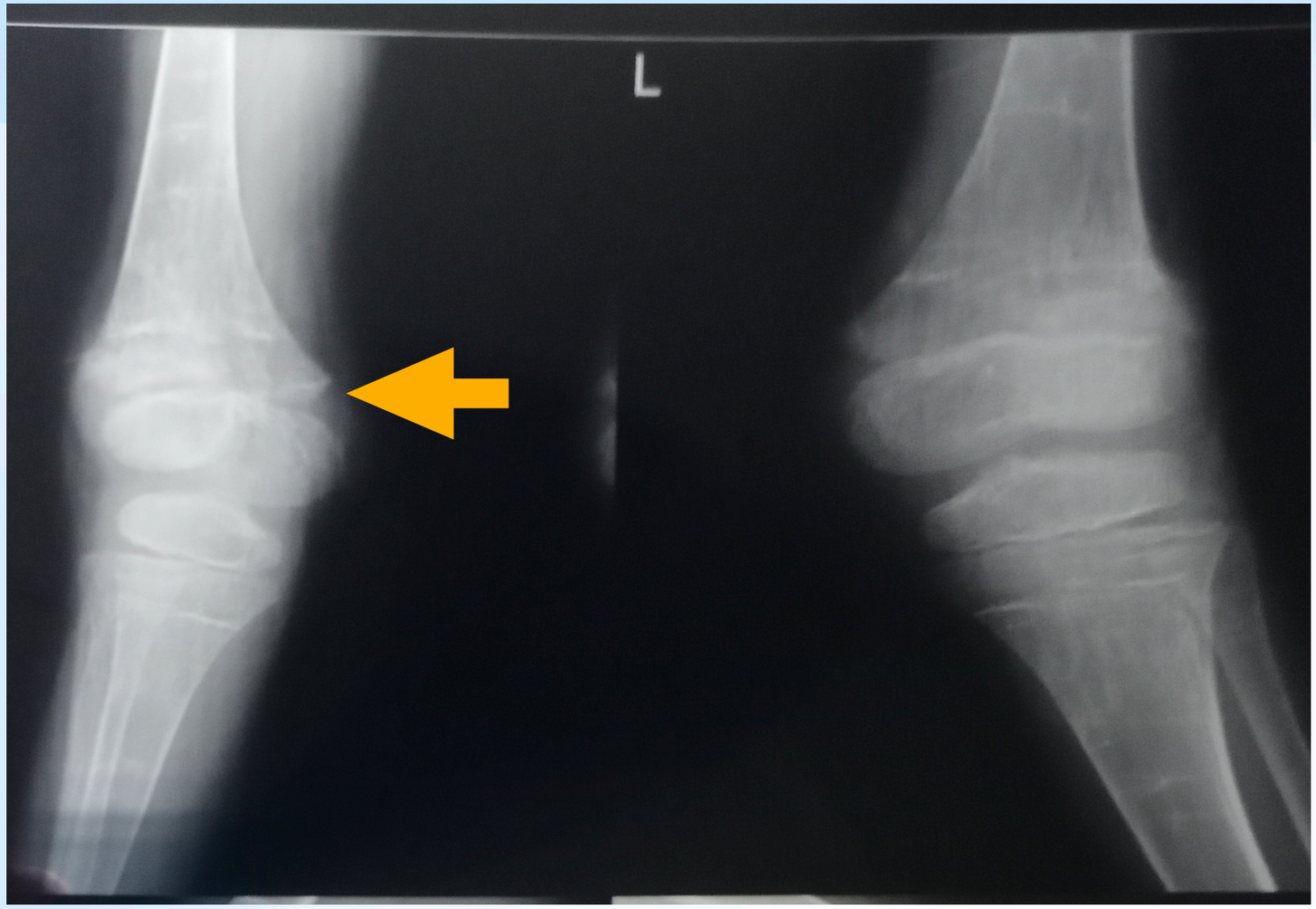
- Liver Is Enlarged (Size 14cm) , Coarse Echotexture , Focal Nodular Lesion in Right Lobe 30x30 mm, No Vascularity, Pinpoint Calcification

- Bilateral Bright Kidneys

- Spleen Enlarged (Size 11.4 Cm)

Impression - Chronic Liver Disease With Hepatosplenomegaly





X-ray Knee

- Widened growth plates (physes) at the proximal tibia and distal femur
- Metaphyseal cupping, fraying, and splaying,
- Poorly defined metaphyseal margins
- Mild bowing deformity of the long bones around the knee region
- Bone density appears reduced compared to normal

CEMRI TRIPLE PHASE ABDOMEN

Altered signal intensity lesion measuring approx. 29 x 30 mm is noted in the peripheral location of right lobe of liver and just abutting adjacent kidney and diffusion restriction and containing peripheral capsule and central scar which is showing linear enhancement in arterial phase however significant enhancement is noted in the delayed venous phase could be hemangioma - ? nature. advise: CECT triple phase will be more informative.

CECT SCAN WHOLE ABDOMEN (TRIPLE PHASE)

Ill defined soft tissue density lesion with early arterial phase enhancement is noted in subcapsular location of right lobe of liver, measuring approx. 31 x 27 x 39 mm surrounded by perifocal edema and persist upto delayed venous phase with centripetal contrast filling - possibility includes: - hepatoblastoma /atypical hemangioma.

TMS-GCMS

Urine Succinylacetone levels - Increased (122mmol/mol creatinine)

Whole Exome Sequencing

Gene[#] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[$]
***FAH* (+)** (ENST00000561421.6)	Exon 2	c.192G>T **(p.Gln64His)**	Likely compound Heterozygous	Tyrosinemia, type I (OMIM#276700)	Autosomal recessive	Pathogenic **(PS3,PS4)**
	Exon 2	c.101T>G **(p.Val34Gly)**				Uncertain Significance **(PM2,PP3)**

Whole Exome Sequencing Shows Mutation in FAH(+) on Exon 2 Pathogenic Variant c.192G>T Confirmed Tyrosinemia Type 1 .

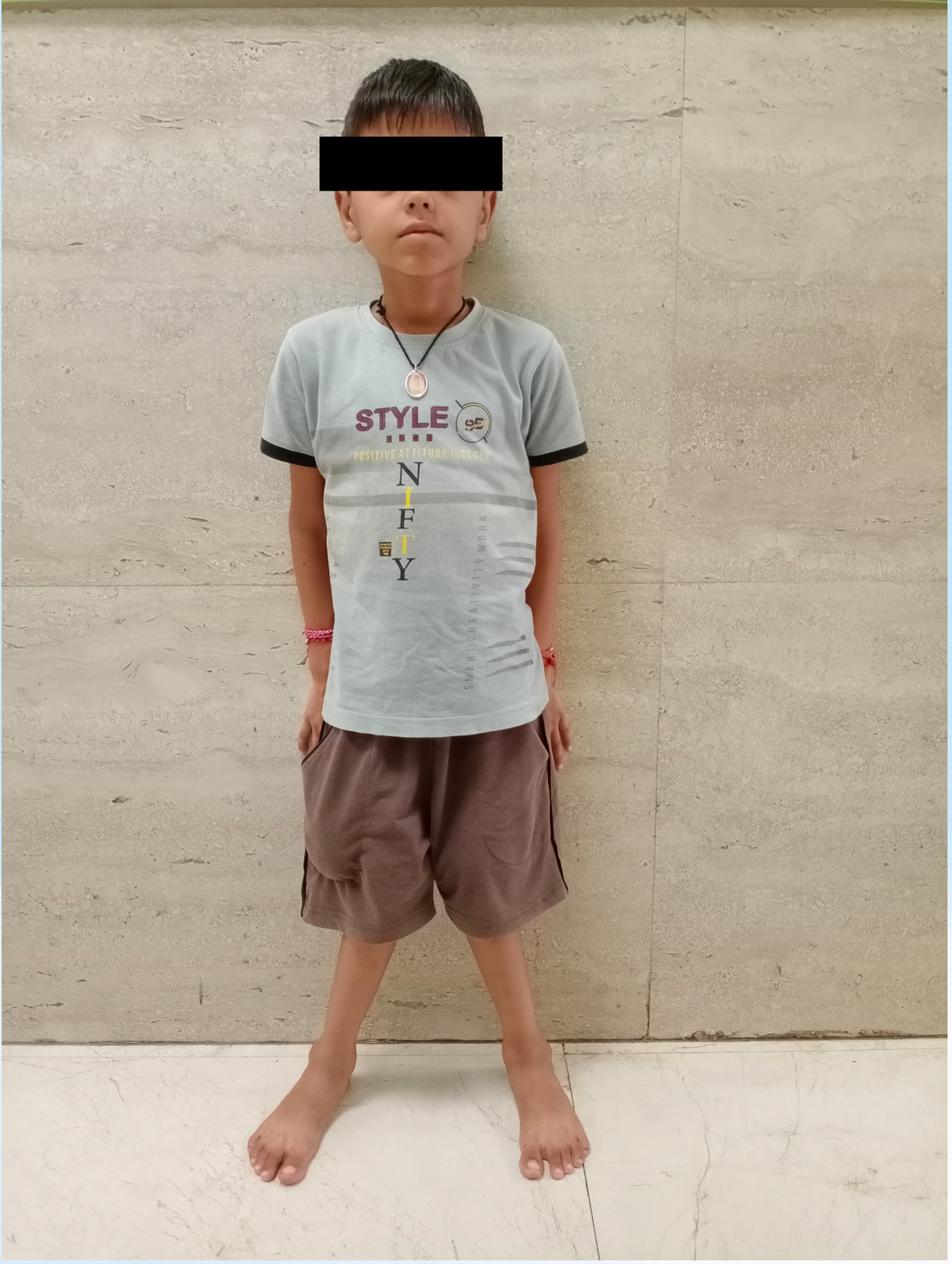
Final Diagnosis

10 year old male child with Chronic liver disease presented with Hepatosplenomegaly, Short stature, Underweight, and Hypophosphatemic Rickets due to Compound Heterozygous Mutation in FAH gene .

Final diagnosis is TYROSINEMIA TYPE 1

Management

- Patient Was Started on Tab NITISINONE 10 Mg BD
- High-Protein Restricted Diet
- Strict Low-Tyrosine & Low-Phenylalanine Diet Advised , Special Amino-Acid Formula (Tyrosine-Free, Phenylalanine-Restricted)
- Cap Calcitriol 0.25mcg EOD
- Phosphate Supplements



Date- Aug/2024
Height - 111cm
Wt- 17.5 kg

Date-Dec/2025
Height - 118 cm
Wt - 22 kg

DISCUSSION

Tyrosinemia Is an Inborn Error of Tyrosine Metabolism.

- Types
  - Tyrosinemia Type I
  - Tyrosinemia Type II
  - Tyrosinemia Type III

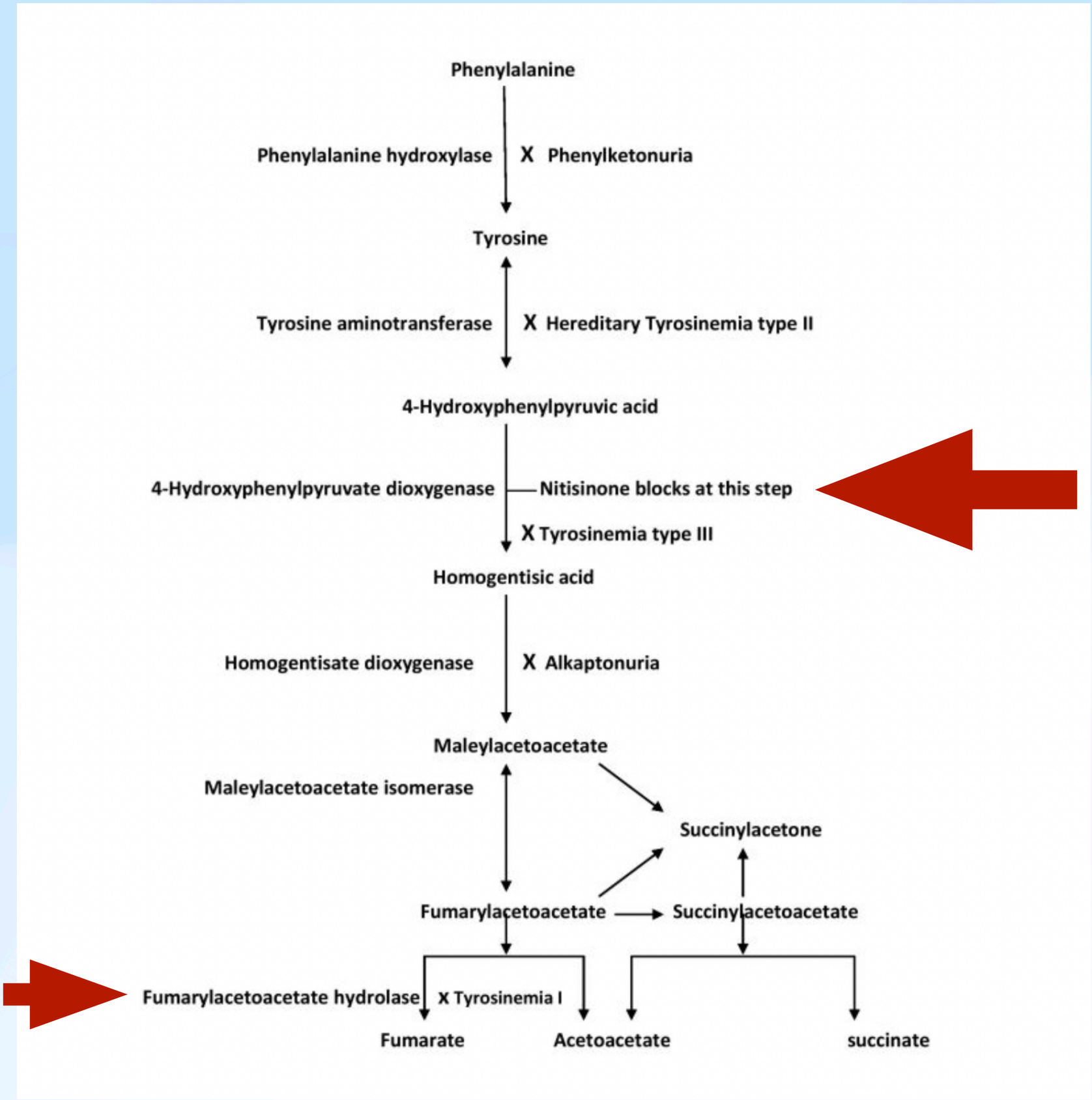
Tyrosinemia Type I

- Most severe form
- Usually begins in the first few months of life
- Clinical features - Failure to thrive , jaundice, a cabbage-like odour and an increased tendency to bleed .
- Liver and kidney failure
- Softening and weakening of the bones (rickets)
- Risk of liver cancer (hepatocellular carcinoma).

Acute form (0-6 month)	Sub-acute form (6-12 month)	Chronic form (>1 year)
-Manifestations of severe liver failure (mostly the younger age between 0-2 months) -Hypoglycemia, jaundice, bleeding diathesis, hepatomegaly progress to ascites -High susceptible to infections with rapid deterioration. -Mild proximal tubular disorder	-Less severe than in acute form -The main features are Coagulopathy ,Tubular dysfunction and hypophosphatemic rickets -Hepatosplenomegaly -Cabbage-like odour -Intercurrent infection precipitate hepatic crisis.	-Mainly with liver and/or renal disease. -Hepatomegaly secondary to cirrhosis -Tubulopathy with Fanconi syndrome leading to rickets and renal failure -Infrequent cardiomyopathy and neurological problems such as porphyria-like episodes

Tyrosinemia Type II	Tyrosinemia Type III
• Begins in early childhood • Affects the eyes, skin, and mental development. • Eye pain and redness, excessive tearing, photophobia, and palmoplantar hyperkeratosis. • About half of individuals have some degree of intellectual disability.	• Rarest • The Characteristic Features Include Intellectual Disabilities, Seizures, and Periodic Loss of Balance and Coordination (Intermittent Ataxia).

Tyrosine Metabolism Pathway



- The diagnosis of tyrosinemia can be established by determination of succinylacetone in urine or serum and by assay of FAH activity in lymphocytes and fibroblasts .
- Confirmation - Molecular Testing

Management

Medication and Procedures	Diet	Treatment for acute liver failure
1. Nitisinone (NTBC) is administered orally. The standard dose is 1 mg/kg/day, but in acute liver failure, the dose is increased to 2 mg/kg/day.	A special milk formula (tyrosine and phenylalanine free) e.g., Tyros 1®, Tyrex-1®, or Anamix TYR.	supportive measures including clotting factors, albumin, electrolyte correction, plasma, correction of acid base status and hyperammonia , treatment of infection, Vitamin K, respiratory support and appropriate fluid management.
2. Treatment of hypophosphatemic rickets with phosphate orally and Vitamin D.	Food pattern: Protein-restricted diet (a low tyrosine and phenylalanine diet) maintain plasma tyrosine level below 500 umol/l and phenylalanine level in the normal range (30-80 umol/ l)	
3. Supplement vitamins and micronutrients.		
4. Carnitine deficiency with L-Carnitine		
5. Liver transplantation		

NITISINONE

Pharmacodynamics

- **Mechanism of Action:** Nitisinone is a potent, competitive, and reversible inhibitor of the enzyme **4-hydroxyphenylpyruvate dioxygenase (4-HPPD)**.
- **Effect in HT-1:** By blocking 4-HPPD, it prevents the formation of toxic metabolites like maleylacetoacetate and fumarylacetoacetate, which otherwise lead to severe liver and kidney damage.
- **Effect in AKU:** It stops the conversion of 4-hydroxyphenylpyruvate into homogentisic acid (HGA), thereby reducing the systemic accumulation of HGA that causes joint and heart valve damage.

Pharmacokinetics

- **Absorption:** Rapidly absorbed after oral administration; peak plasma concentrations (Cmax) are reached in approximately **3.5 hours** for capsules and **15 minutes** for oral suspension.
- **Distribution:** Highly protein-bound (>95%) with an apparent volume of distribution of approximately 8.2 L in healthy adults.
- **Metabolism:** Primarily stable in the liver, with minor metabolism possibly mediated by the **CYP3A4** enzyme.
- **Elimination:** It has a long terminal half-life of approximately **52–59 hours**. Renal elimination is a minor route, with only about 3% excreted unchanged in urine.

Cost in India (2026)

The cost of nitisinone treatment in India has seen a significant reduction with the introduction of domestically manufactured versions.

- **Domestic Brands:** Annual treatment with local brands, such as Lasinone and Brunity, is approximately ₹2.5 lakh per year for 10 kg children.

- **Imported Brands:** The cost for imported brands like Orfadin was previously considerably higher, reaching up to ₹2.2 crore per year.

Availability

- **Local Supply:** Generic versions, including Lasinone from Laurus Labs and Brunity from Brawn Rare Disease, are accessible through specialized pharmaceutical distributors.
- **Importation:** International brands like Orfadin can still be obtained through Personal Use Import Permits, which require a doctor's prescription. Facilitators such as the Indian Pharma Network can assist with this process.
- **Government Support:** Patients may also be able to access nitisinone through Rare Disease Centers of Excellence (CoE) or specific government programs that support treatment for certain rare diseases, including HT-1.

Side effect of Nitisinone

Comman	Uncomman	Rare
Thrombocytopenia Leucopenia Granulocytopenia Conjunctivitis Photophobia Corneal opacity Keratitis Eye pain	Blepharitis Pruritus Exfoliative dermatitis Erythematous rash Leucocytosis	Bloated abdomen Dark urine Abdominal pain Feeling of tiredness or weakness Headache Light-colored stools Loss of appetite Weight loss Vomiting Jaundice

Special Milk Formulas

Nutritional Information (per 100g powder)

Nutrients	Amount
Calories	500kcal
Protein equivalent	16.7 g*

Nutritional Information (per 100g powder)

Nutrients	Amount
Calories	480kcal
Protein equivalent	15g

Tyrosine rich food

Animal-Based Sources

- **Meats & Poultry:** Chicken, turkey, beef, pork, lamb.
- **Fish:** Salmon, cod, tuna, and other types.
- **Dairy:** Cheese (especially aged), milk, yogurt.
- **Eggs:** A great source of tyrosine and other nutrients.

Plant-Based Sources

- **Soy Products:** Soybeans, tofu, soy milk.
- **Nuts & Seeds:** Sesame seeds, pumpkin seeds, almonds, peanuts.
- **Legumes:** Beans, lentils.
- **Whole Grains:** Quinoa, oats, wild rice.
- **Fruits & Vegetables:** Avocados, bananas, spinach, broccoli.

Low tyrosine food

- **Fruits:** Apples, pears, cherries, apricots, peaches, berries (avoid overripe/dried).
- **Vegetables:** Most fresh vegetables (spinach, carrots, potatoes, broccoli, squash).
- **Grains:** Most cereals, pasta, white rice, bread (avoid sourdough).

- **Indication of liver transplant**

  Severe liver failure at presentation and failure to respond to nitisinone therapy

  Have documented evidence of the malignant changes in hepatic tissue

- Transplant recipient require long term immunosuppression . Mortality in liver transplant recipient is 10%
- Transplant recipient also benefit from low dose nitisinone therapy to prevent continued renal and glomerular dysfunction resulting from succinylacetone generated in renal tissue

Monitoring

Every 3–6 months

- Liver function tests
- Serum tyrosine & phenylalanine
- Succinylacetone
- Renal function, electrolytes
- Alkaline phosphatase, phosphate

Every 6 months

- Alpha-fetoprotein (AFP)
- Abdominal ultrasound

Annually

- MRI liver (if AFP elevated or Ultrsound suspicious)
- Developmental assessment

Take Home Message

- Think metabolic in chronic liver disease with rickets: Hepatosplenomegaly, growth failure, and hypophosphatemic rickets in a child should raise suspicion of Tyrosinemia Type 1, **even beyond infancy.**
- Early treatment is life-saving: Prompt initiation of nitisinone (NTBC) with a tyrosine- and phenylalanine-restricted diet can **halt** disease progression and **reverse** renal tubular dysfunction and rickets.
- High risk of hepatocellular carcinoma: Lifelong surveillance for liver malignancy (AFP and imaging) is essential, **even on treatment.**
- Liver transplantation is curative for the metabolic defect and is indicated in treatment failure, advanced cirrhosis, or HCC.
- Family screening and genetic counseling are crucial due to autosomal recessive inheritance.

Thank you