An approach to :
Inborn Errors of Metabolism

Dr.Binod Kumar Singh

Professor of Pediatrics, Patna
Superintendent NMCH Patna-2020-2022
IAP State President, Bihar- 2019
IAP State Vice-President, Bihar- 2018
CIAP Executive board member-2015
NNF State president, Bihar- 2014
IAP State secretary,Bihar-2010-2011
NNF State secretary,Bihar-2008-2009
Fellow of Indian Academy of Pediatrics (FIAP)

Chief Consultant
Shiv Shishu Hospital
K-208, P.C Colony, Hanuman Nagar,
Patna - 800020
Web site : www.shivshishuhospital.org,Mob:-9431047667

What are IEMS?

- Disorders in which there is a block in normal metabolic pathway that is caused by genetic defect of a specific enzyme.
- Defect can be inherited or sporadic in nature.
- Deficiency of enzymes causes :

1. Decreased production / Absence of product
2. Excess of metabolites
3. Formation of abnormal mediators

When to suspect IEMS?

- Deterioration after a period of apparent normalcy
- Parental consanguinity
- Family history of neonatal deaths
- Rapidly progressive encephalopathy and seizures of unexplained cause
- Severe metabolic acidosis
- Persistent vomiting
- Peculiar odor(especially in urine)
- Acute fatty liver or HELLP during pregnancy

Clinical pointers towards specific IEM

Hepatomegaly	**Storage disorders , urea cycle defect**
Coarse facies	**Mucopolysaccharidosis** , GM1 gangliosides ,Pompe's disease
Cataract	Galactosemia(oil drop) , Wilson (sunflower)
Cherry red spot	Tay Sach's disease , Niemann pick dis , GM1 Gangliosidosis
Hypopigmentation	PKU , Albinism
Renomegaly	**Von Gierke disease** , Zellweger syndrome
Skin rash / eczema	Biotinase deficiency , Multiple carboxylase deficiency
Cardiomyopathy Retinitis pigmentosa	**Pompe's dis** , FAO defect , Mitochondrial ETC defect Mitochondrial disorder

Abnormal urine odors

Mousy odor	**Phenylketonuria**
Rancid	Tyrosinemia
Sweaty feet	Isovaleric acidemia
Cabbage like	Methionine defect
Tom cat urine	Multiple carboxylase deficiency
Sweet smell	Ketones
Maple syrup	MSUD

Patterns of presentation

- **Encephalopathy with or without metabolic acidosis**

predominant features of

- organic acidemias ,

-urea cycle defects , and

- congenital lactic acidosis .

Intractable seizures

-Pyridoxine dependency ,

- non ketotic hyperglycemia ,

-folinic acid responsive seizures

Patterns of presentation

- **Jaundice alone** – Gilbert syndrome , Criggler najjar syndrome
- **Hepatic failure** (jaundice , ascites , coagulopathy)- Galactosemia , Tyrosinemia , GSD – type 4
- **Neonatal cholestasis** – Alpha -1 antitrypsin def , Niemann pick disease.
- **Hypoglycemia** – Galactosemia , GSD , disorder of gluconeogenesis, FAO defects .

Screening for neonatal IEM(DBS method)

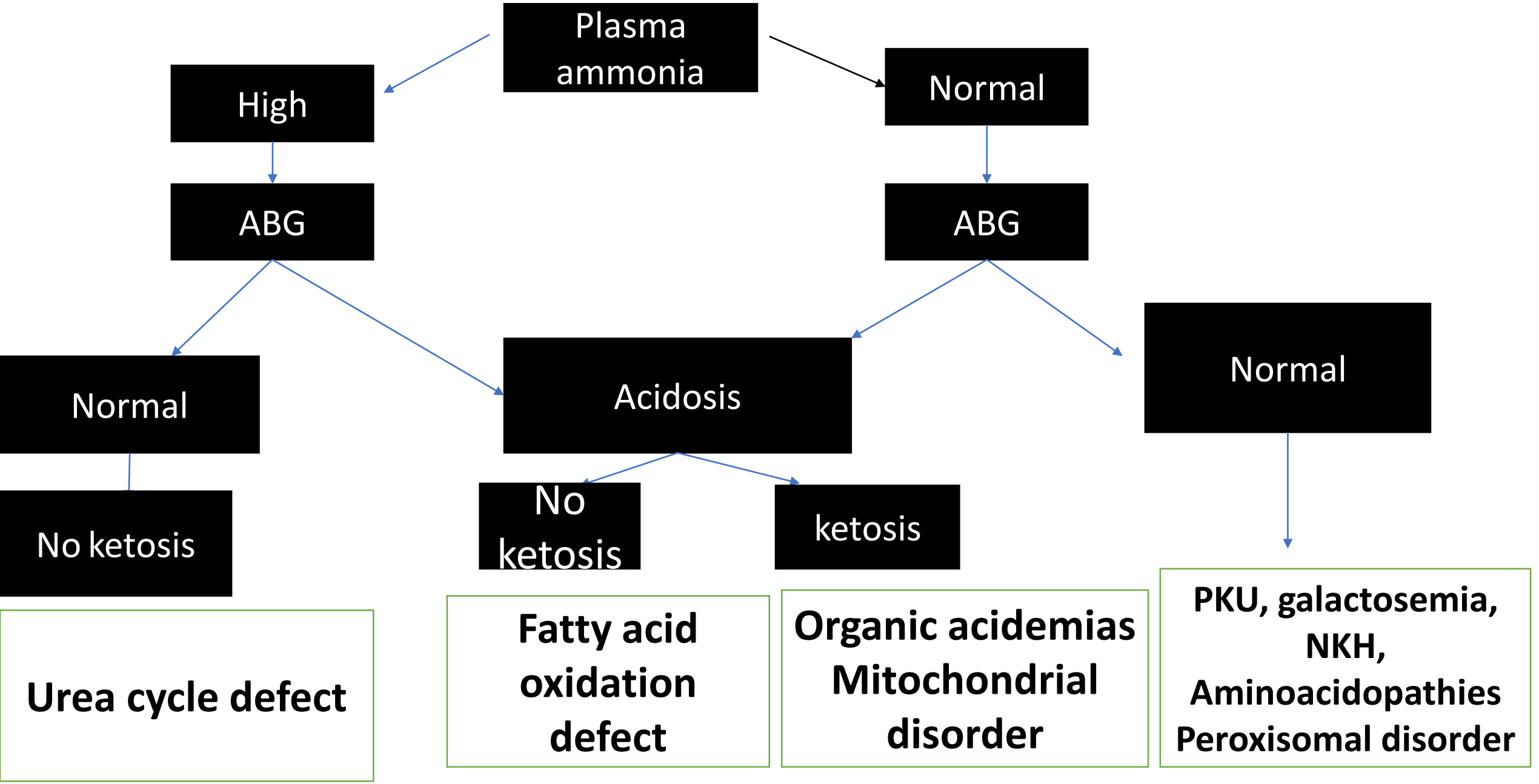
Dried blood spot is obtained by heel pad prick.

The dried blood spot is subjected to TMS.

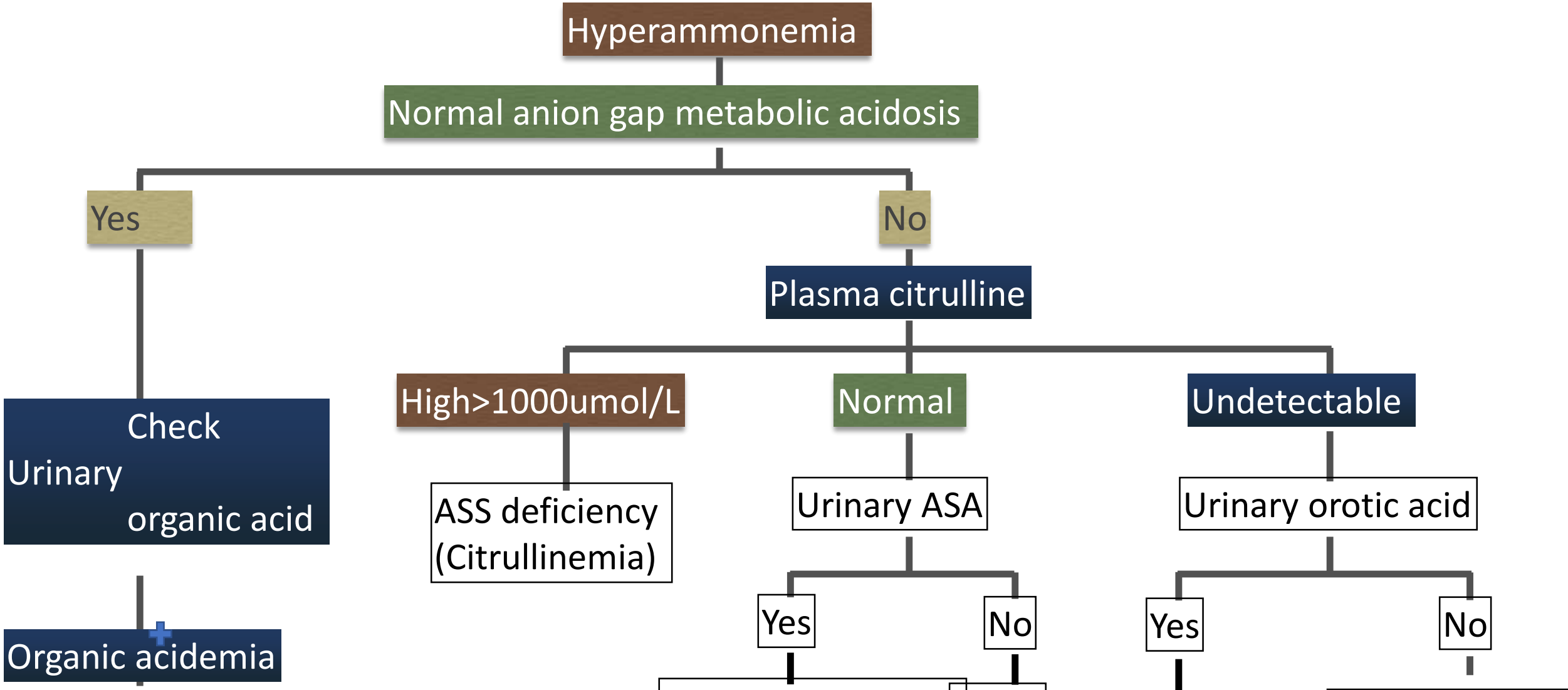
First line investigation important for developing approach

- CBC (neutropenia & thrombocytopenia seen in Propionic & Methylmalonic acidemia)
- blood glucose, ABG with lactate levels & Anion gap
- Serum electrolytes
- Plasma ammonia
- Serum uric acid
- Liver function test
- Urine ketones
- Urine reducing substances

Approach to IEM on the basis of ammonia level

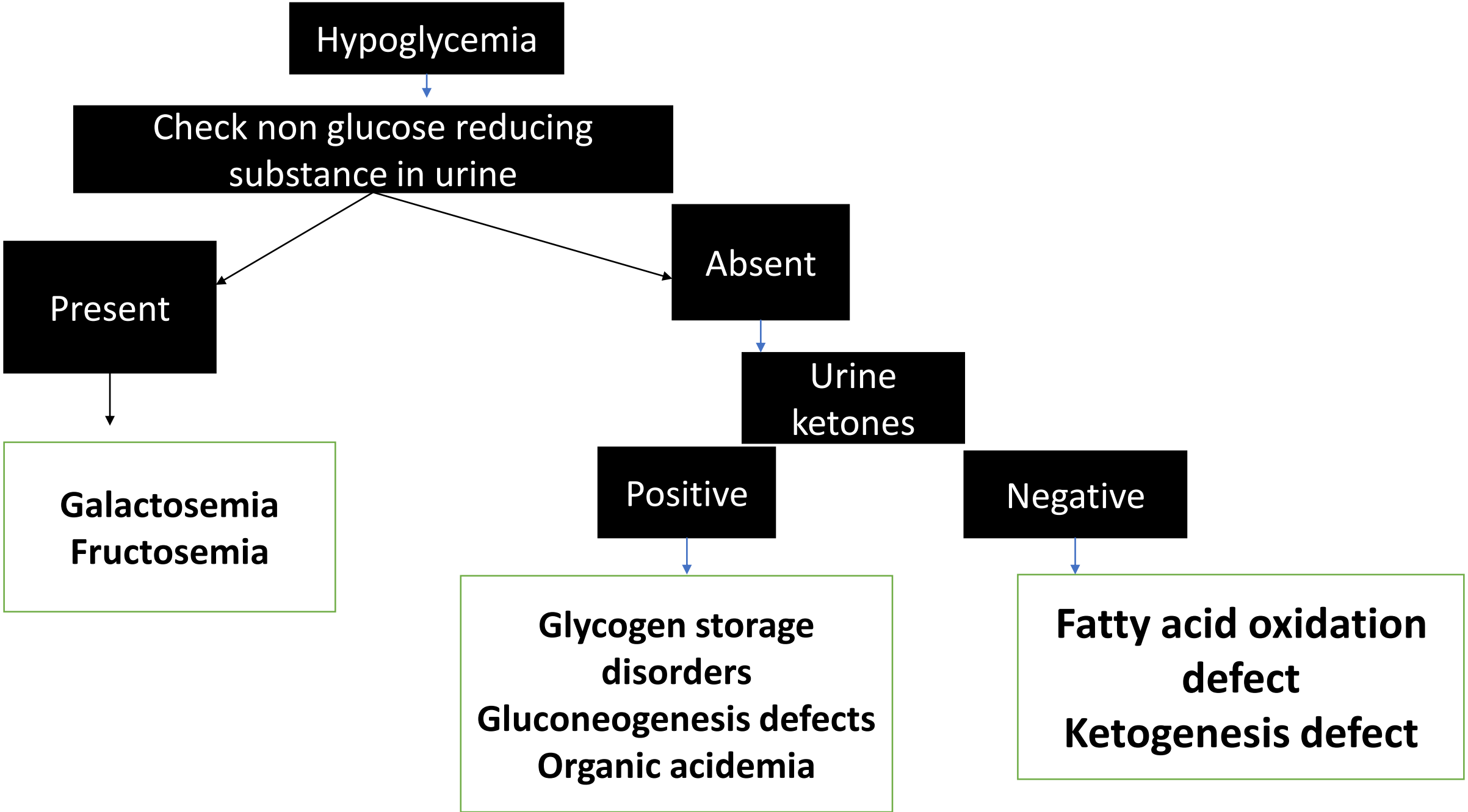


➢ Approach to symptomatic Hyperammonemia :



ASS – ARGINOSUCCINATE SYNTHASE
ASL – ARGINOSUCCINATE LYASE
CPS – CARBAMOYL PHOSSPHATE SYNTHATASE

Approach on the basis of hypoglycemia (recurrent / refractory)



❖ Differential diagnosis of metabolic disorders :

Diagnosis	Acidosis	Ketosis	Plasma Lactate	Plasma Ammonia	Plasma Glucose
Aminoacidopathies	+/-	+	N	N	N
Organic Acidemia	+++	+++	Inc.	Inc.	Dec.
Mitochondrial disorders	+	+/-	+++	N	N
Urea cycle disorders	N	N	N	+++	N
Fatty acid oxidation defect	+/-	N	+/-	-	Dec.

Second line investigation(ancillary and confirmatory test)

1.Urine gas chromatography mass spectrometry(urine GCMS) – Organic acidemias.

2.Plasma tandem mass spectrometry(plasma TMS)- for diagnosis of urea cycle defect ,FAD defects , Organic acidemias , Amino – acidopathies.

3.High performance liquid chromatography (HPLC) : for quantitative analysis of amino acids in blood or urine ; required for diagnosis of organic acidemia and Aminoacidopathies.

4. Lactate/pyruvate ratio - in case of elevated lactate.

5. Urinary orotic acid - in case of hyperammonemia for classification of urea cycle defect.

6. Enzyme assay: required for definitive diagnosis but not available for most IEM

Biotinidase assay - suspected biotinidase deficiency (intractable seizures, seborrheic rash , alopecia)

GALT (G-1-P uridyltransferase) assay - suspected Glactosemia (hypoglycemia, cataract, reducing sugar in urine)

7.Neuroimaging : MRI may provide helpful pointers

Zellweger syndrome : diffuse cortical migration and sulcation abnormalities.

Menke's disease/pyruvate de carboxylase deficiency - agenesis of corpus callosum.

MSUD - brain stem and cerebellar lesion.

8. Magnetic resonance spectroscopy : lactate peak in mitochondrial disorders and leucine peak in MSUD.
9. EEG : can be suggestive of IEM : E.g. comb like rhythm in MSUD

10. Plasma very long chain fatty acid (VLCFA) : elevated in peroxisomal disorders.
11. Mutation analysis
12. CSF amino acid analysis
    CSF glycine level increased in NKH
    serine level increased in disorder of serine biosynthesis

Biochemical Autopsy :

Done in **severely ill or dying child** with suspected but undiagnosed IEM.

SPECIMEN :

- Clinical photograph and infantogram
- Blood : 5ml in heparin, separated and stored -70C ; 5-10 ml EDTA blood (CBC),refrigerated and not frozen ; few blood spots on filter paper (acyl carnitine analysis).
- Urine : 5-10 ml frozen in plain sterile tubes.

- Cerebrospinal fluid : 3-5 ml in 1-2 aliquots frozen and stored at -70C

- Skin biopsy : ~3mm diameter of skin (including dermis) from flexor aspect of the forearm or anterior thigh. Stored at 37C or refrigerated in culture medium or saline with glucose.

- Liver, Muscle, Kidney, Heart biopsy : At least 2 tissue biopsies of about 1mm3 , one immediately frozen in liquid nitrogen and other in glutaraldehyde.

Principles of Management :

Specific treatment is directed towards reversing the basic pathophysiological process causing the disease.

It includes :-Reduction of substrate accumulation for a deficient enzyme

- Reduce accumulated toxic metabolites
- Replace deficit enzyme
- Residual enzyme activity enhancement

Management of hyperammonemia :

1.Stop oral feed and provide adequate calories by i.v glucose and lipids. Maintain GIR 8-10 mg/kg/min. Start i.v lipid 0.5 g/kg/day(upto 3g/kg/day). After stabilization add protein 0.25g/kg upto 1.5g/kg/day.

2.**Hemodialysis** is initiated if plasma ammonia 500 - 600ug/dL for rapid removal.

3.Alternative pathways for **nitrogen excretion-**:

Sodium benzoate (IV or oral)- loading dose 250 mg/kg then 250-400 mg/kg/day in 4 divided doses.

Sodium phenyl butyrate -loading dose 250 mg/kg followed by 250-500 mg/kg/day.

L-arginine (oral or IV)- 300 mg/kg/day

Acute management of newborn with suspected organic acidemia :

1) The patient is kept NPO and IV glucose is provided.

2) Supportive care: hydration, treatment of sepsis, seizures, ventilation.

3) Carnitine: 100 mg/kg/day IV or oral.

4) Treat acidosis: Sodium bicarbonate 0.35-0.5mEq/kg/hr (max 1-2mEq/kg/hr)
5) Start Biotin 10 mg/day orally.

6) Start Vitamin B12- 1-2 mg/day I/M (useful in B12 responsive forms of methylmalonic acidemias)

7) Start Thiamine 300 mg/day (useful in thiamine-responsive variants of MSUD

Management of congenital lactic acidosis :

1) Supportive care: hydration, treatment of sepsis, seizures, ventilation. Avoid sodium valproate.

2) Treat acidosis: sodium bicarbonate 0.35-0.5mEq/kg/hr (max 1-2mEq/kg/hr)

3) Thiamine: up to 300 mg/day in 4 divided doses.

4) Riboflavin: 100 mg/day in 4 divided doses.
5) Add co-enzyme Q: 5-15 mg/kg/day
6) L-carnitine: 50-100 mg/kg orally.
7) Biotin 10 mg/day. (Biotin responsive Multiple carboxylase deficiency may present with unexplained lactic acidosis)

Treatment of newborn with refractory seizures with no obvious etiology (suspected metabolic etiology) :

1) In persistent SZ inspite of 2 or 3 AED in adequate doses, consider trial of pyridoxine 100 mg IV. If IV prep not available, oral pyridoxine can be given (15 mg/kg/day).

2) If SZ persist despite pyridoxine, give trial of biotin 10 mg/day and folinic acid 5mg twice daily (folinic acid responsive seizures). Trial of pyridoxal phosphate 10 mg/kg/dose X 2 doses is also recommended.

3) Rule out glucose transporter defect: measure CSF and blood glucose. In glucose transporter defect, CSF glucose level is equal to or less than 1/3rd of the blood glucose level. This disorder responds to the ketogenic diet.

Prevention :

Genetic counselling and prenatal diagnosis:

- Most of the IEM are single gene defects,
- inherited in an autosomal recessive manner, with a 25% recurrence risk.
- prenatal diagnosis can be offered
- samples required are chorionic villus tissue or amniotic fluid.

Modalities available are:

- **Substrate or metabolite detection**: useful in phenylketonuria, peroxisomal defects.
- **Enzyme assay**: useful in lysosomal storage disorders like Niemann-Pick disease, Gaucher disease.
- **DNA based (molecular) diagnosis**: Detection of mutation in proband/ carrier parents is a prerequisite.

Message

IEM is not a rare disease.

High index of suspicion is a key factor for the diagnosis of IEM.

Routine screening of all NB for at least 6 Common IEMS should be done.

- **TFT**
- **Galactosemia**
- **CAH**
- **PKU**
- **Biotinase deficiency**
- **G6PD deficiency**


THANK YOU
We're on Track For a Cure