Inherited Metabolic Disorders

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This booklet is a compilation of ***Clinical Practice Guidelines for Inherited Metabolic Disorders****. It is based on day to day experience of dealing with uncommon and relatively lessor known disorders of newborn and infants. A teamwork of Chemical Pathologists, Paediatricians and senior lab technologists have made it possible to diagnose these IMDs to a higher level than previously done. These Guidelines are by no means final words, but will require repeated revisions and modifications in the coming years.*

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Disclaimer: All efforts have been made to include most recent and reliable information in this booklet but knowledge and best practice in this field keeps on changing very rapidly. So it is the responsibility of the health practitioners to make decision regarding patient care based on their patient experience and any further update on the subject.

Authors of the booklet declare no conflict of interest of any sort or any nature.

Dedicated to the Great French Paediatrician

Jean-Marie Saudubray is Emeritus Professor of Pediatrics and Expert Metabolic Consultant in the Hopital La Pitié Salpétrière from the Université Pierre et Marie Curie in Paris.

From 1976 to 2007 he was head of the Pediatric service of Metabolism, Genetics and Neurology in the Dept. of Pediatrics at the Hopital Necker - Enfants Malades in Paris.

He not only provided excellent practice guidelines and clinical classification for these disorders but also wrote one of the most authentic books on the subject i.e. ***"Inborn Metabolic Diseases Diagnosis and Treatment",*** which is widely used as reference book.

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Foreword

It is our firm belief that nature does not make errors. “Inborn Errors of Metabolism” is not a true depiction of motive of nature to create individuals with genetic defects. Probably these disorders are there for us to appreciate the intricacies of metabolic networks operational in humans and other living things. So the term “Inborn Errors of Metabolism” is being replaced by ***“Inherited Metabolic Disorders”.*** This term has been adopted by many communities worldwide and aptly explains the etiology of the disorders. We have also adopted ***“Inherited Metabolic Disorders”*** abbreviated as IMDs. However, the term IEM will also remain in use and for the information of our students and young colleagues the two terms are synonyms.

Present book is a collection of PSCP Guidelines on IMDs. It contains the definition, types, clinical presentations and diagnostic approach. Then some individual disorders are discussed in some details with clinical scenarios.

In the present booklet we have adopted the clinical types and diagnostic criteria described by Prof Saudubray. However, keeping our peculiar circumstances in mind we have based our algorithms on basic tests and some advanced laboratory investigations available in tertiary care labs like AFIP Rawalpindi and Aga Khan University Karachi.
A very valid reservation may be raised here that why to talk of these rare disorders in a country where infections and communicable diseases are still rampant and children suffer a lot from diseases like infective diarroheas, pneumonias and meningitis. But we must not forget that due to high level of consanguinity in our community, we may be seeing only a tip of the iceberg in the form of some of these disorders seen in our clinical practice and a higher prevalence of IMDs are hidden than we anticipate. We can determine the epidemiology of these disorders only when we have newborn screening and diagnostic services available in at least some centers in the country. In the second stage we can start pre-natal diagnostic services and genetic counseling to avoid occurrence of these disorders in the family.

We hope the Practice Guidelines provided in this book will go long way in helping our General Physicians, Neonatologists, Paediatricians, and Chemical Pathologists in taking care of sick young children in whom no infective cause is found.

In addition to the Clinical Practice Guidelines, we have also provided some prototype cases of IMDs in the form of QADIS (Quick Assessment of Data Interpretation Skills). This portion is meant to be used as a tool of self-learning. Each patient record is followed by some space to write the answers. We have ensured that the correct diagnosis and other relevant answers are given on the next page. At the cost of some extra paper volume, this feature will make these Guidelines a 'workbook' for the students.

It will be unfair if we forget the efforts of our junior colleagues in compiling this book i.e. Dr Qurat Ul Ain Mustafa, Dr Afshan Awan, Dr Waqas Sheikh, all three are our FCPS Part II trainees.in Chemical Pathology. Well done doctors!!

We understand this is a very humble attempt and lack many aspects of the disorders as well as need a lot of corrections and modifications. *So we request all the readers to provide their valuable input to be included in the next editions*.

Aamir Ijaz
Muhammad Aamir
Ayesha Hafeez

Contents

Note: Beautiful title of this booklet has been designed by Lt Col Zujaja Hina Haroon, Consultant Chemical Pathologist, AFIP Rawalpindi.

Inherited Metabolic Disorders (IMDs): General Information

Overview:

- Metabolic disorders result from the absence or abnormality of an enzyme or its cofactor, leading to either accumulation or deficiency of a specific metabolite. Optimal outcome for children with inherited metabolic disorders (IMDs) depends upon early recognition of the signs and symptoms, prompt evaluation, and referral to a center familiar with the evaluation and management of these disorders. Delay in diagnosis may result in acute metabolic decompensation, progressive neurologic injury, or death.

- Individual IMD is not very common (1:5,000 to 1:10,000) .However, collectively as a group the incidence is around 1:800.

- Management of certain symptoms like hypoglycemia, hyperammonemia, and seizures must be initiated promptly before exact diagnosis to prevent long-term sequelae[1]

Initial Evaluation:

a. History*:*

(1) The history should focus on previous episodes of metabolic decompensation, identification of potential triggering events, and family history of metabolic disease or members with similar presentations.

(2) Antenatal /Birth history should be obtained in all cases and is especially significant for cases like non-ketotic hyperglycinemia, peroxisomal disorders, some lysosomal storage disorders, and disorders of cholesterol biosynthesis

(3) Recurrent vomiting and /or diarrhoea

(4) Intolerance to feeds

(5) Episodic abdominal pain

(6) Lethargy

(7) Failure to thrive/developmental delay

(8) Fits

(9) Recurrent hypoglycemia

(10) Family history should include history of consanguinity, history of similar complaints in siblings, early neonatal deaths etc[2].

(11) Age at presentation:

(a) Diseases like urea cycle disorders, non-ketotic hyperglycinemia, , and branched-chain organic acidemias often present during the first few hours of life

(b) During the first or second week, conditions like neonatal hemochromatosis, galactosemia, tyrosinemia and maple syrup urine disease are likely to manifest clinically.

(c) Conditions like alpha-1 antitrypsin deficiency, Niemann-Pick disease, and bile acid synthesis defects usually present after the third week

(12) Triggering events: In the evaluation of a child with suspected IMD it is important to ask about the following triggers:

- Are the symptoms aggravated by ingestion of certain kinds of meals e.g. carbohydrates ,protein rich meal, Complementary foods (eg, infant cereals, fruit juice, and pureed fruits, vegetables, or meats)

- Are the symptoms related to conditions like fever, infections?

- Is there any relation of aggravation of symptoms to any anesthesia, surgery or any specific type of medication?

b. Physical Examination:

(1) Examine general body habitus for any dysmorphism. Any coarse facial features,micro –or macrocephaly should alert the physician of any possible IMD.

(2) Hair and skin should be examined for any signs of alopecia, eczema, hypopigmentation, gingival hyperplasia, xanthomas, edema, hirsutism and/ or photosensitivity.

(3) Examine eyes for presence of any cataract, corneal opacities, Kayser-Fleischer ring or lens dislocation.

(4) Look for any evidence of hepatosplenomegaly

(5) A complete musculoskeletal and neurological examination should be undertaken to assess for any arthritis, dyatonia, myopathy, peripheral neuropathy hearing loss and parathesias.

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1. Saudubray JM, Desguerre I, Sedel F, Charpentier C A Clinical Approach to Inherited Metabolic Diseases. In Fernandes J, Saudubray JM, van den Berghe, Walter JH (Editors) Inborn Metabolic Diseases 4th Edition (2006). Springer Medizin Verlag. springer.com. PP 3-5

2. Inborn errors of metabolism: Identifying the specific disorder www.uptodate.com ©2016 UpToDate®

Laboratory Evaluation of IMDs:

A step-wise approach to evaluation, beginning with basic tests that are routinely available should be considered first, before obtaining specialized metabolic investigations. The confirmatory diagnosis of most IMDs requires specialized testing that may include detection of abnormal metabolites in the plasma, urine, and/or CSF; assay of enzyme activity in skin, red blood cells, white blood cells, skeletal muscle, or liver; and/or chromosome or DNA analysis.

1. Initial Lab Testing[1]:

Following battery of tests is suggested to be carried out initially in children suspected of having IMDs.

a. Blood Complete picture
b. Plasma glucose levels
c. Arterial blood gases
d. Plasma ammonia
e. Plasma lactate levels
f. Liver function tests
g. Electrolytes, urea and creatinine
h. Examination of the urine, including color, odor, dipstick, and presence of ketones/reducing substances

Sampling requirements and Clinical Significance of Initial Tests

a. Blood CP
    (1) Specimen requirement: 2 ml blood in K-EDTA container
    (2) Clinical significance: Hematologic manifestations of IMDs may involve any or all of the cell lines. The complete blood count also may provide a clue to sepsis, which may be the trigger for a metabolic crisis or

presenting manifestation of an IMD associated with increased risk of infection.

b. Plasma glucose levels

(1) Specimen requirement: 2 ml blood in Na-F container

(2) Clinical significance: Hypoglycemia typically occurs in fatty acid oxidation disorders (such as medium chain acyl-CoA dehydrogenase deficiency), glycogen storage diseases (GSD), gluconeogenic disorders, and hereditary fructose intolerance. It also may occur in amino acid disorders, organic acidemias, and mitochondrial disorders.

c. Arterial blood gases:

An arterial blood gas is used to detect acid-base disturbances. Metabolic acidosis with an increased anion gap is commonly associated with organic acidemias.

d. Plasma ammonia

Specimen requirement: 2 ml blood should be collected in lithium heparin tube, transported on ice and analyzed immediately.

Clinical significance: Early manifestations of hyperammonemia include anorexia, abdominal pain, headache, irritability, fatigue and later tachypnea, vomiting, lethargy, seizures, coma, and death. Significant elevations in ammonia (≥300 µmol/L) are most commonly associated with urea cycle disorders and certain organic acidemias. An elevated ammonia concentration (≥120 µmol/L in the newborn and ≥80 µmol/L in older infants and children) is neurotoxic and must be treated immediately. Additional tests that should be ordered if the plasma ammonia is elevated include quantitative plasma amino acid analysis, qualitative urine organic acid analysis, and liver function tests (if not obtained previously)

e. Plasma lactate levels

(1) Specimen requirement: 1 ml of blood to be collected in Na-F bottle transported on ice and analyzed immediately.

(2) Clinical significance: Lactic acidosis caused by abnormal oxidative metabolism is a frequent finding in mitochondrial disorders (e.g. disorders of oxidative phosphorylation), glycogen storage diseases, disorders of gluconeogenesis, and disorders of pyruvate metabolism. Elevated lactic acid also may be present in disorders of amino acid metabolism, organic acidemias, and fatty acid oxidation disorders.

f. Liver function tests: These should be performed as part of initial testing especially in cases having hyperammonemia to exclude liver disorder.

g. Electrolytes/urea/creatinine: The finding of hyponatremia and hyperkalemia may provide a clue to salt-wasting. Measurement of serum electrolytes may also be required to calculate the anion gap. A metabolic acidosis with an increased anion gap is commonly seen in organic acidemias..

h. Urine examination for ketones/reducing substances

(1) The presence of reducing substances in the urine is a clue to certain IMDs if the urine dipstick is negative for glucose. Children that have nonglucose reducing substances in the urine may have a carbohydrate intolerance disorder (e.g. galactosemia, hereditary fructose intolerance) or an amino acid disorder. However, the absence of reducing substances in the urine does not exclude these disorders. False-positive tests for urine reducing substances in children may occur in children who have taken penicillins, salicylates, ascorbic acid, or drugs excreted as glucuronides.

(2) The presence or absence of ketones in the urine is helpful in determining the etiology of hypoglycemia.

(3) The urine pH is helpful in determining the cause of metabolic acidosis, if metabolic acidosis is present. The appropriate physiologic response to metabolic acidosis is increased urinary acid excretion, with the urine pH usually falling below 5. A urine pH >5 is more suggestive of renal tubular acidosis than the disorders mentioned above.

2. Specialized Laboratory testing[2]:

These tests should only be performed as indicated by the clinical presentation and initial laboratory evaluation; the samples should be obtained at the time of acute presentation, if possible.

Sampling Requirements and Clinical Significance and

a. Plasma amino acids by HPLC:

(1) Sample requirement: 2-3 ml of blood in lithium heparin tube preferably transported on ice.

(2) Clinical Significance: Inherited defects of amino acid metabolism are clinically and biochemically heterogeneous with a variable and disease specific course. Characteristic amino acid profiles or the presence of low or normally undetectable amino acids may lead to or suggest a diagnosis. Some of the important amino acids and the disorders associated with excess/deficiencies in plasma are summarized in the Table 1.

b. Urine Amino acids analysis:

(1) Sample requirement: 10-20 ml of random urine in plain container without any preservative.

(2) Clinical significance: The diagnostic utility of urinary amino acids is limited as compared to plasma analysis and should only be reserved for specific cases, as the testing is expensive and doesn't have an added advantage over plasma testing.

c. CSF amino acid analysis:

(1) Sample requirement: 1-2 ml of CSF sample collected in plain tube without any preservative and transported immediately to laboratory for analysis

(2) Clinical Significance: CSF amino acid analysis just like urinary analysis should be reserved for selected cases only. Quantitative CSF amino acid analysis whenever required should ideally be performed at the same time the sample is obtained for plasma amino acid analysis

in cases suspected of having Non ketotic hyperglycinemia. A CSF: plasma glycine ratio >0.08 is abnormal and consistent with nonketotic hyperglycinemia.

d. Urine organic acids[3]

(1) Sample requirement: 10-20 ml of random urine in plain container

(2) Clinical significance: Analysis of organic acids in urine is performed by gas chromatography/mass spectroscopy (GC/MS). A qualitative assay of these compounds is adequate because pathogenic organic acids (eg, methylmalonic or propionic acid) are not present in significant amounts in the urine of normal individuals. Clinically important organic acidemias include methylmalonic academia, propionic academia, isovaleric academia and glutaric acidemia type I.[1]

e. Acyl carnitine profile

(1) Sample requirements: Plasma or Dried Blood Spots (DBS)

(2) Clinical significance: Analysis of acylcarnitine conjugates is performed by LC/MS/MS and can be measured in a plasma sample or a filter-paper bloodspot. This test is used for the diagnosis of fatty acid oxidation disorders; it also may detect organic acidemias in which the acylcarnitine profile is abnormal (e.g. propionic acidemia, isovaleric acidemia)

f. Others

(1) Skin, skeletal muscle, or liver biopsy for enzyme assay

(2) Urinary glycosaminoglycans, oligosaccharides to evaluate the possibility of lysosomal storage disorders.

(3) Triglycerides and uric acid to detect elevations seen in some GSD

(4) Brain MRI to assess for leukodystrophy or basal ganglia changes found in lysosomal storage or mitochondrial disorders respectively

(5) Quantitative CSF lactate in individuals with disorders of mitochondrial energy metabolism who may have normal plasma lactate levels and therefore measuring lactate, either by direct analysis of the CSF or by measuring brain lactate by MR spectroscopy

(6) Serum very long-chain fatty acids to detect peroxisomal disorders

(7) Liver biopsy to evaluate the type and location of abnormal storage material with a frozen sample of unfixed liver saved for further diagnostic studies.

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2. Pasquali M, Longo N. Newborn Screening and Inborn Errors of Metabolism. In Burtis CA, Ashwood ER, Bruns DE [Ed} Teitz Textbook of Clinical Chemistry and Molecular Diagnostics 5th Ed. 2045-80.

3. Rinaldo P, Tortorelli S, Matern D .Recent developments and new applications of tandem mass spectrometry in newborn screening. Curr Opin Pediat 2004; 16:427-433

Biochemical Presentations and Diagnostic Approach

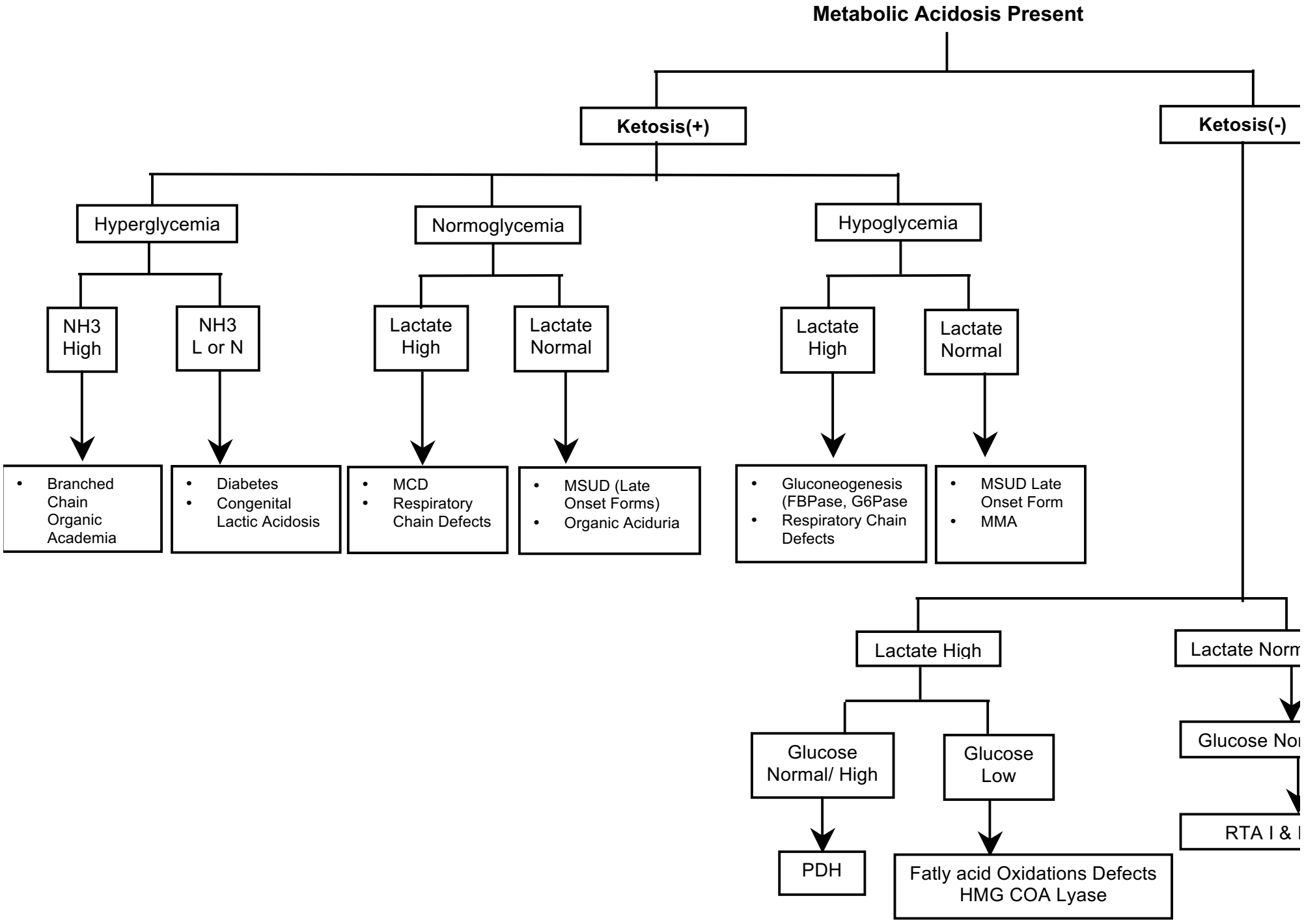
The description and algorithms in Guidelines/3/2016 are mainly adopted from Chapter 1 · A Clinical Approach to Inherited Metabolic Diseases in Saudubray JM, Desguerre I, Sedel F, Charpentier C A Clinical Approach to Inherited Metabolic Diseases. In Fernandes J, Saudubray JM, van den Berghe, Walter JH (Editors) Inborn Metabolic Diseases 4th Edition (2006). Springer Medizin Verlag. springer.com. PP 3-5

Metabolic Acidosis:

1. It should be noted whether metabolic acidosis is accompanied with ketosis or not.
2. In patients with metabolic acidosis without ketosis lactate levels should be seen. Metabolic acidosis with normal lactate and glucose levels is mostly seen in renal tubular acidosis. Patients with high lactate but normal glucose levels are suspected of having Pyrovate Dehydrogenase Complex Deficiency whereas those with low glucose levels may be suffering from fatty acid oxidation defects.
3. For patients with metabolic acidosis and ketosis, evaluate blood glucose lactate and ammonia levels:
    a. Hyperglycemia and hyperammonemia together is seen usually in branched chain organic aciduria.

    b. Hyperglycemia with normal or low ammonia levels is seen in diabetes/ketolytic defects.

    c. Metabolic acidosis with ketosis but normal lactate and glucose levels is seen in organic acidurias and late onset forms of MSUD. Metabolic acidosis associated with ketosis but hypoglycemia should be evaluated for lactate levels. A high lactate is seen in defects of gluconeogenesis and respiratory chain defects. Normal lactate levels will be seen in MSUD-late onset forms and methyl malonic aciduria.


Metabolic Acidosis Present
Ketosis(+)
Ketosis(-)
Hyperglycemia
Normoglycemia
Hypoglycemia
NH3 High
NH3 L or N
Lactate High
Lactate Normal
Lactate High
Lactate Normal
• Branched Chain Organic Academia
• Diabetes
• Congenital Lactic Acidosis
• MCD
• Respiratory Chain Defects
• MSUD (Late Onset Forms)
• Organic Aciduria
• Gluconeogenesis (FBPase, G6Pase
• Respiratory Chain Defects
• MSUD Late Onset Form
• MMA
Lactate High
Lactate Norm
Glucose Normal/ High
Glucose Low
Glucose No
RTA I &
PDH
Fatly acid Oxidations Defects
HMG COA Lyase

Hypoglycemia

1. Hypoglycemia typically occurs in fatty acid oxidation disorders (such as medium chain acyl-CoA dehydrogenase deficiency), glycogen storage diseases (GSD), gluconeogenic disorders, galactosemia, and hereditary fructose intolerance. It also may occur in amino acid disorders, organic acidemias, and mitochondrial disorders.
2. While considering the differential diagnosis in a patient with hypoglycemia associated findings like hepatomegaly, association with fasting, presence or absence of lactic acidosis and ketosis should be considered.
3. Hypoglycemia associated with IMDs usually presents with hepatomegaly.
    a. Galactosemia, tyrosinemia type I and hereditary fructose intolerance present with short fast hypoglycemia and permanent hepatomegaly. The later may also manifest as post prandial hypoglycemia and liver fibrosis.

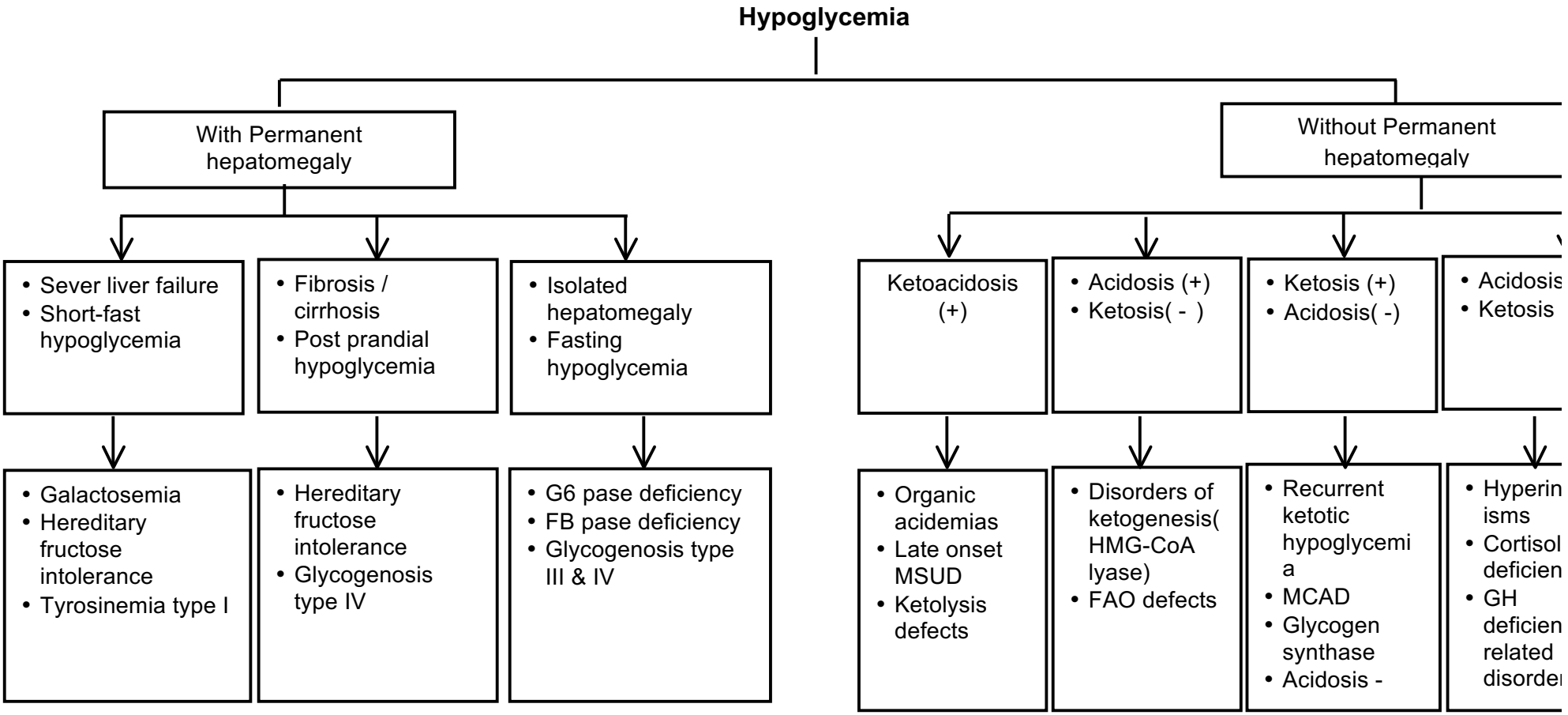
    b. Isolated hepatomegaly alongwith fasting hypoglycemia and ketosis is usually a feature of glycogenosis type III and VI.

    c. In patients which present with hypoglycemia but without permanent liver enlargement look for the presence or absence of ketosis and metabolic acidosis.
        (1) Patients with ketoacidosis will often show recurrent attacks of hyperlactemia as well. The differential diagnosis includes organic acidurias, late-onset MSUD and Ketolysis defects.

        (2) No acidosis or ketosis will be seen in patients with hyperinsulinisms, cortisol deficiency and FAO defects. Unpredictable postprandial hypoglycemia or hypoglycaemia occurring after a very short fast (2–6h) is a feature in these disorders.

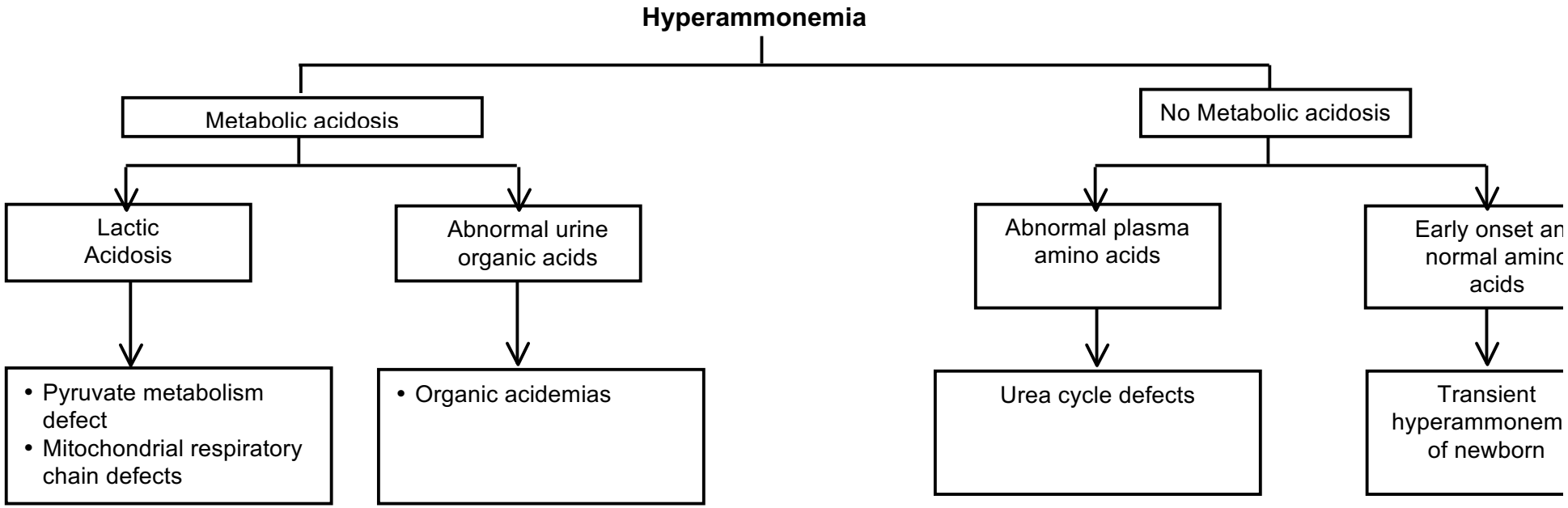
        (3) Severe hypoglycemia with metabolic acidosis and absence of ketosis, in the context of Reye syndrome, suggests HMG-CoA lyase deficiency, HMG-CoA synthase deficiency or fatty acid oxidation disorders.

(4) Fasting hypoglycemia with ketosis and in absence of metabolic acidosis suggests recurrent functional ketotic hypoglycemia. Also all types of adrenal insufficiencies and MCAD deficiency can on occasions present in this manner.


Hypoglycemia
With Permanent hepatomegaly
Without Permanent hepatomegaly
• Sever liver failure
• Short-fast hypoglycemia
• Fibrosis / cirrhosis
• Post prandial hypoglycemia
• Isolated hepatomegaly
• Fasting hypoglycemia
Ketoacidosis (+)
• Acidosis (+)
• Ketosis(-)
• Ketosis (+)
• Acidosis(-)
• Acidosis
• Ketosis
• Galactosemia
• Hereditary fructose intolerance
• Tyrosinemia type I
• Hereditary fructose intolerance
• Glycogenosis type IV
• G6 pase deficiency
• FB pase deficiency
• Glycogenosis type III & IV
• Organic acidemias
• Late onset MSUD
• Ketolysis defects
• Disorders of ketogenesis(HMG-CoA lyase)
• FAO defects
• Recurrent ketotic hypoglycemia
• MCAD
• Glycogen synthase
• Acidosis -
• Hyperin isms
• Cortisol deficien
• GH deficien related disorde

Hyperammonemia

1. A plasma ammonia level should be obtained for any child with unexplained vomiting, lethargy, or other evidence of an encephalopathy.
2. Hyperammonemia is a characteristic finding in urea cycle defects, organic acidemias, fatty acid oxidation defects, and liver dysfunction
3. In patients with raised ammonia levels, look for the presence or absence of metabolic acidosis
4. Those with metabolic acidosis and raised lactate levels may be suspected of having pyruvate metabolism defects or mitochondrial respiratory chain Defects, while those with abnormal urinary organic acid levels may be having organic acidemias.
5. In children with hyperammonemia and absence of metabolic acidosis, urea cycle disorders may be suspected, especially if the plasma amino acid profile is also indicative. Transient Hyperammonemia of Newborn is suspected especially if the amino acid profile does not suggest any IMD.


Hyperammonemia
Metabolic acidosis
No Metabolic acidosis
Lactic Acidosis
Abnormal urine organic acids
Abnormal plasma amino acids
Early onset an normal amino acids
• Pyruvate metabolism defect
• Mitochondrial respiratory chain defects
• Organic acidemias
Urea cycle defects
Transient hyperammonem of newborn

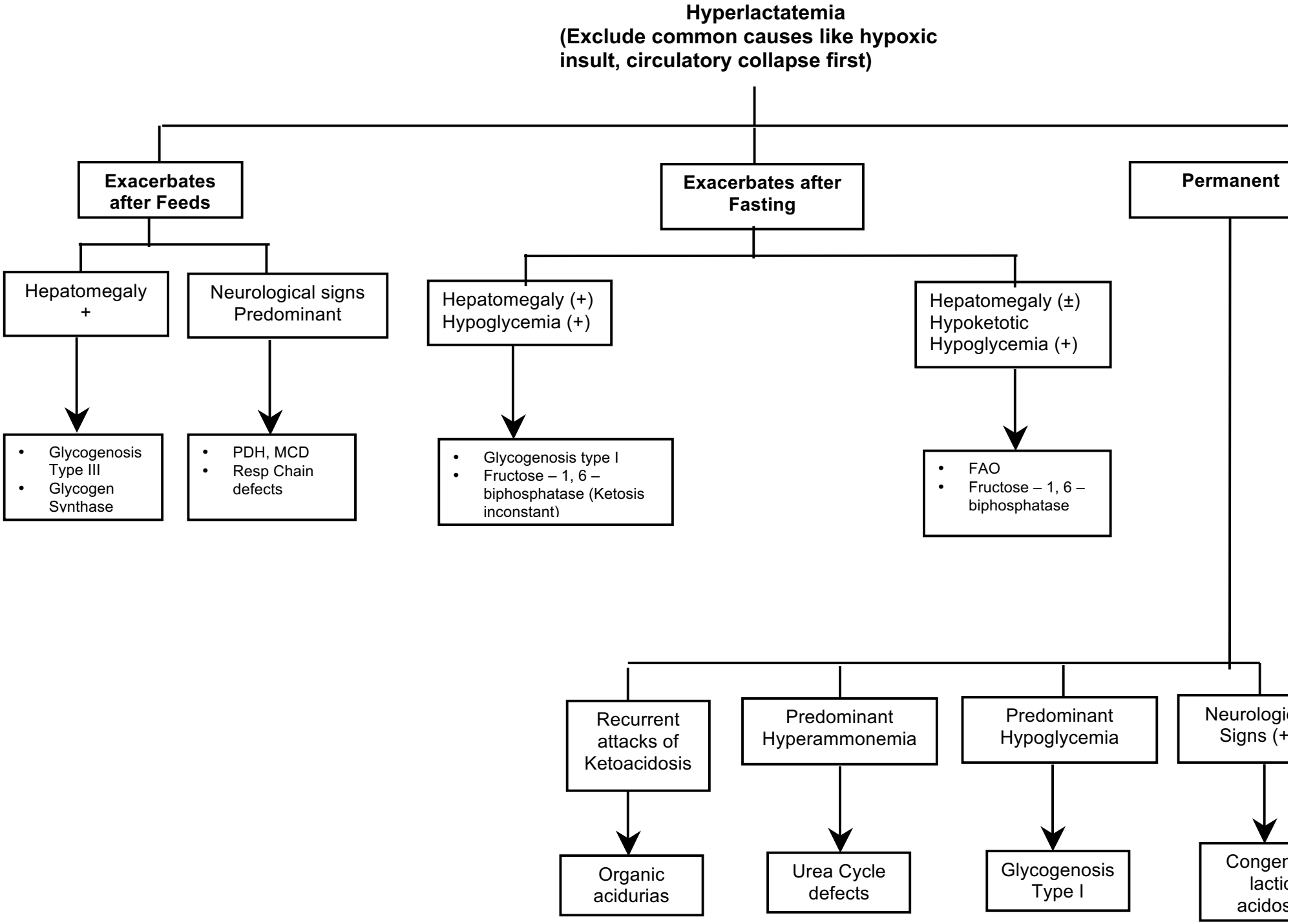
Hyperlactatemia

1. Conditions like circulatory collapse, hypoxic insult, diarrhea, persistent infections, hyperventilation, and others involving failure of cellular respiration must be excluded in a child before an IMD of lactate-pyruvate oxidation is sought as blood lactate levels are often raised in such conditions.
2. Lactic acidosis caused by abnormal oxidative metabolism is a frequent finding in mitochondrial disorders (eg, disorders of oxidative phosphorylation), glycogen storage diseases, disorders of gluconeogenesis, and disorders of pyruvate metabolism
3. Look for the presence or absence of ketosis and whether the hyperlactatemia is permanent or exacerbates only after fasting/feeding.
    a. If the hyperlactatemia exacerbates only after feeding and hepatomegaly is the prominent sign, Glycogenosis type III or Glycogen synthase deficiency is suspected.

    b. Post feed hyperlactatemia associated with neurological signs is suggestive of either pyruvate dehydrogenase or multiple carboxylase deficiency.

    c. Hyperlactatemia only after fasting(or exacerbated with fasting) is suggestive of glycogenosis type I, fructose 16 biphosphatase deficiency or fatty acid oxidation defects.

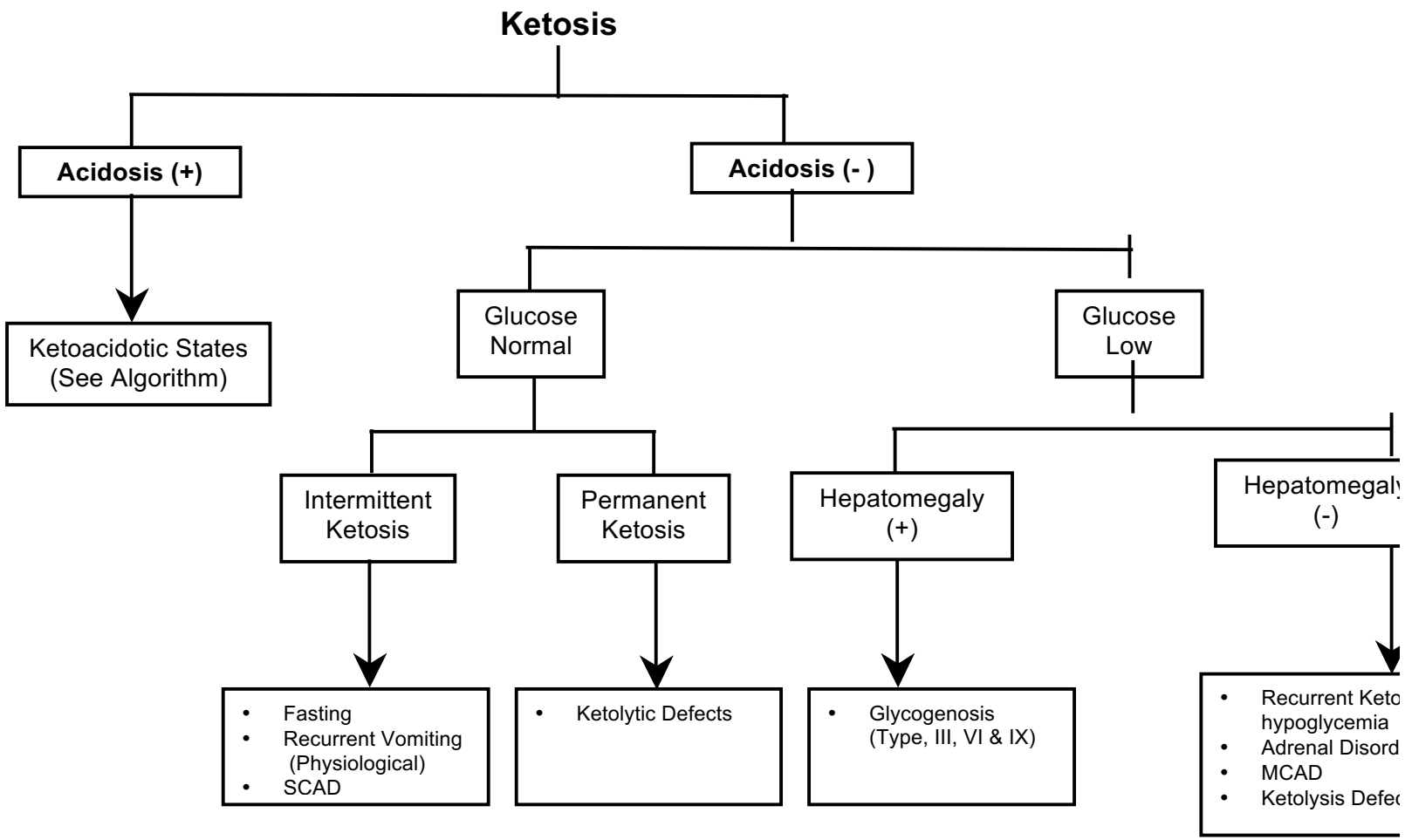
    d. Permanent hyperlactatemia in the setting of recurrent attacks of ketoacidosis is due to organic acidurias, that with predominant hyperammonemia is mostly due to urea cycle defects, predominant hypoglycemia is seen with glycogenosis type I, fructose 16 biphosphatase deficiency. Presence of neurological signs alongwith hyperlactatemia (usually >10mM) is suggestive of congenital lactic academia.


Hyperlactatemia
(Exclude common causes like hypoxic insult, circulatory collapse first)
Exacerbates after Feeds
Exacerbates after Fasting
Permanent
Hepatomegaly +
Neurological signs Predominant
Hepatomegaly (+) Hypoglycemia (+)
Hepatomegaly (±) Hypoketotic Hypoglycemia (+)
• Glycogenosis Type III
• Glycogen Synthase
• PDH, MCD
• Resp Chain defects
• Glycogenosis type I
• Fructose – 1, 6 – biphosphatase (Ketosis inconstant)
• FAO
• Fructose – 1, 6 – biphosphatase
Recurrent attacks of Ketoacidosis
Predominant Hyperammonemia
Predominant Hypoglycemia
Neurologi Signs (+
Organic acidurias
Urea Cycle defects
Glycogenosis Type I
Conger lactic acidos

Ketosis

a. Please note whether ketosis is accompanied by metabolic acidosis or not.
b. If the ketosis is not associated with metabolic acidosis, look for presence or absence of hypoglycemia and/or hepatomegaly.
c. Ketosis without acidosis or hypoglycemia, is likely to be a normal physiological reflection of the nutritional state (fasting, catabolism, vomiting, medium-chain triglyceride enriched or other ketogenic diets).
d. Ketosis without acidosis but presenting with hypoglycemia and with predominant hepatomegaly is usually a feature of glycogensosis type I, III and IX.
e. Ketosis without acidosis but presenting with hypoglycemia without hepatomegaly is usually seen with recurrent ketotic hypoglycemia,adrenal disorders, MCAD and ketolysis defects.

Fere


Ketosis
Acidosis (+)
Acidosis (-)
Ketoacidotic States
(See Algorithm)
Glucose
Normal
Glucose
Low
Intermittent
Ketosis
Permanent
Ketosis
Hepatomegaly
(+)
Hepatomegaly
(-)
• Fasting
• Recurrent Vomiting
(Physiological)
• SCAD
• Ketolytic Defects
• Glycogenosis
(Type, III, VI & IX)
• Recurrent Keto
hypoglycemia
• Adrenal Disord
• MCAD
• Ketolysis Defec

Clinical Types of IMDs[1]

Group 1: Disorders that give rise to intoxication:

This group includes IMDs that lead to acute or progressive intoxication from accumulation of toxic compounds proximal to the metabolic block. This group includes

Aminoacidopathies e.g. phenylketoneuria (PKU), Maple Syrup Urine Disease (MSUD) and tyrosinaemia,

Organic acidaemias e.g. methylmalonicacidaemias, propionic acidaemias and isovalericacidaemia,

Sugar intolerance e.g. galactosaemia.

Urea cycle disorders

Group 2: Disorders involving defects in energy metabolism

Signs and symptoms in these disorders are caused partly by a deficiency in energy production or utilization in the liver, myocardium, skeletal muscle, or brain. Disorders in this category also may have signs or symptoms related to accumulation of toxic compounds.This category includes following disorders:

Hypoglycemic Disorders

Glycogenolysis defects

Gluconeogenesis defects

Hyperinsulinism

Fatty Acid Oxidation Defects

Congenital Lactic Acidemias

Pyruvate carboxylase deficiency

Krebs citric cycle defects

Mitochondrial respiratory chain defects

Group3: Disorders Involving Complex Molecules

This group includes diseases that involve defects in the synthesis or the catabolism of complex molecules.These include:

1. Lysosomal Disorders:
    - Mucopolysaccharidoses
    - Sphingolipidoses
    - Glycoproteinoses
    - Disorders of lysosomal enzyme transport
2. Peroxisomal Disorders
3. ? Golgi apparatus Disorders
4. Inborn Errors of Cholesterol Synthesis

References

1. Saudubray JM, Desguerre I, Sedel F, Charpentier C A Clinical Approach to Inherited Metabolic Diseases. In Fernandes J, Saudubray JM, van den Berghe, Walter JH (Editors) Inborn Metabolic Diseases 4th Edition (2006). Springer Medizin Verlag. springer.com. PP 3-5

QADIS

(Quick Assessment of Data Interpretation Skills)

Cases of IMDs

Patient No 1

A 20 days newborn presented with lethargy, poor feeding and seizures few hours after his birth. Child was brought to pediatrician who advised different lab tests. His laboratory investigations revealed:

- Fasting plasma Glucose: 2.2 mmol/L
- Plasma Lactate: 1.5 mmol/L (< 2.0)
- Serum ALT: 65 U/L
- Fasting Insulin: >36 pmol/L (< 20)
- C peptide: > 0.6 ng/ml (< 0.3)
- Urine for glucose: Negative
- Urine for ketone bodies Negative

a. What is most likely diagnosis?
b. Name one biochemical test which may be helpful in the diagnosis

Write your answers here

Answers

Patient No 1

a. Persistent Hyperinsulinaemic Hypoglycaemia of Infants
b. Inappropriate glycemic response to glucagon at the time of hypoglycemia.

Explanation[1]

Persistent Hyperinsulinaemic Hypoglycaemia of Infants (PHHI)

a. Most common cause of persistent hypoglycaemia of the neonates
b. It's a genetic dysregulation of insulin secretion with sporadic or familial presentation
c. Biochemical Features:
   (1) Blood Glucose < 2.2 mmol/L in response to short fasting
   (2) Inappropriately high or normal insulin in the face of hypoglycaemia
   (3) Low FFA and ketone in spite of hypoglycaemia
   (4) Inappropriate glycaemic response to glucagon i.e. increase of glucose by 1.7mmol/L indicates retention of hepatic glycogen and hyperinsulinaemia

References

1. Pathogenesis, clinical features, and diagnosis of Persistent Hyperinsulinaemic Hypoglycemia of infancy. www.uptodate.com ©2015

Patient No 2

An infant presents with progressive neurological impairment with mental retardation (IQ not improving with age). He also has mousy odour, skin pigmentation and abnormal physical growth. His biochemical findings are:

- Acidosis: Negative
- Ketones : +
- Ammonia (NH3): Normal
- Lactate: Normal
- Glucose: Normal
- Calcium: Normal

Plasma Amino Acid Analysis by HPLC *: Phenylalanine Markedly Raised*

a. What is the most probable diagnosis?
b. Name ONE biochemical test which can be used for screening and diagnosis of this disease

Write your answers here

Answers

Patient No 2

a. Phenylketonuria
b. Serum Phenylalanine Level

Explanation[1]

Phenylketonuria

a. PKU is an important part of Newborn Screening part in many countries
b. PKU (MIM#261600) is a disorder with accumulation of amino acid phenylalanine.
c. It results from a deficiency of phenylalanine hydroxylase (PAH)
d. If untreated is characterized by intellectual disability (mental retardation).
e. Tyrosine concentration is normal or low normal.

(For more details, please see Page No 54)

References

1. Overview of phenylketonuria. WWW.UpToDate.com 2015

Patient No 3

A 9 hours of age newborn is reported to have poor feeding and hypothermia.

- Plasma glucose: 1.4 mmol/L

His plasma glucose came within reference range (for the age) at 3rd day and the baby was discharged fit.

a. What is the most probable diagnosis?
b. Write THREE likely causes of this condition.

Write your answers here

Answers

Patient No 3

a. Transient Hypoglycaemia of Newborn
b. Causes[1]:
    (1) Prematurity, intrauterine growth retardation
    (2) Asphyxia, hypothermia
    (3) Sepsis
    (4) Infant of diabetic mother
    (5) Erythroblastosis fetalis

References

1. Update on Investigating hypoglycemia in childhood. Ann Clin Biochem 2011: 1–12. DOI: 10.1258/acb.2011.011012

Patient No 4

An infant has been brought to a Pediatrician with history of poor feeding, lethargy and rapid breathing. There is also history of poor muscle tone, seizures abnormal eye movements and poor visual tracking. He has severe neurological deterioration and brain malformations has been demonstrated on neuroimaging. His biochemical findings are:

- Acidosis: +++
- Ketones : +
- NH_3: +
- Lactate: +++
- CSF Lactate: ++++
- Glucose: Normal
- Calcium: Normal
- Gutherie`s Test Negative

a. What is the most probable diagnosis?
b. What special precautions in diet should be taken while managing this case?

Write your answers here

Answers

Patient No 4

a. Pyruvate Dehydrogenase Complex Deficiency (Congenital Lactic Acidosis also taken as correct answer)
b. Ketogenic diets, with high fat and low carbohydrate

Explanation[1]

Congenital Lactic Acidosis

a. Congenital Lactic Acidosis is the broad category of IMDs
b. Inherited mitochondrial diseases are the commonest causes of congenital lactic acidosis i.e. ***Pyruvate Dehydrogenase Complex Deficiency*** and ***Pyruvate Carboxylase Deficiency***
c. Other Causes:
    (1) Biotin deficiency
    (2) Glycogen storage disease
    (3) Sepsis etc.

Point For Further Discussion

How to differentiate between ***Pyruvate Dehydrogenase Complex Deficienc***y and ***Pyruvate Carboxylase Deficiency*** based simple biochemical tests like lactate and pyruvate.

Answer: By Carrying out Pyruvate: Lactate Ratio

(Please see Page No 81 for further details)

References

1. NORD. http://rarediseases.org/rare-diseases/congenital-lactic-acidosis/

Patient No 5

A 3 days old newborn presented with refusal to feed, hypotonia, failure to thrive and seizures. His laboratory investigations revealed:

- pH: 7.32 (7.35 - 7.45)
- PCO_2: 33 mmHg (35 – 45)
- HCO_3 : 18.2 mmol/L (20 – 28)
- Plasma glucose (R) 2.2 mmol/L (>2.0)
- Serum potassium : 4.2 mmol/L (3.6–5.2)
- Serum Sodium: 139 mmol/L (132-145)
- Urine Ketones: Negative
- Plasma Aminoacids (By HPLC): Glycine 938 µmol/L (<330)
- CSF Aminoacids (By HPLC): Glycine 813 µmol/L (<7.5)

a. What is the most probable diagnosis?
b. Name ONE important differential diagnosis.

Write your answers here

Answers

Patient No 5

a. Non-ketotic Hyperglycinameia
b. Organic Acidaemias

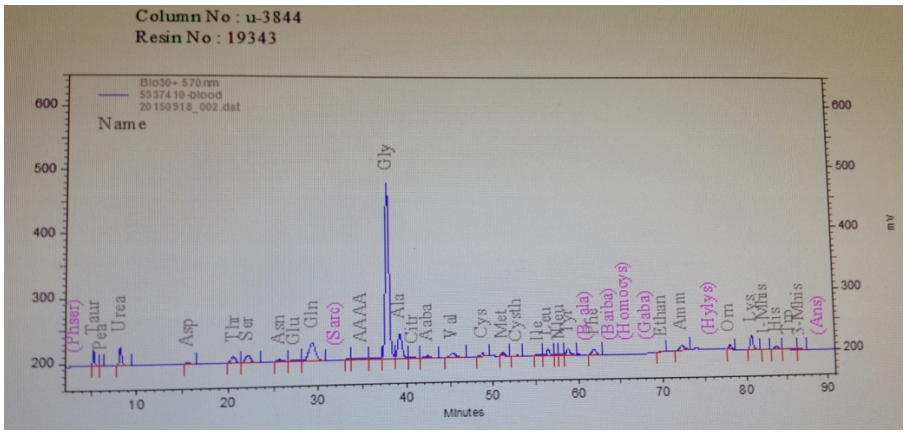
Explanation[1]

Non-ketotic Hyperglycinameia

a. First remember it is not 'Hyperglycaemia'!
b. It is due to defective metabolism of amino acid Glycine which accumulates in toxic concentrations
c. High CSF and serum glycine is the hallmark of the disorders

At AFIP Rwp this was the first case diagnosed on newly installed HPLC (biochrome) system for Amino Acid analysis

"Glycine Peak" on HPLC



(Please see Page No 66 for further details)

References

1. Non-Ketotic Hyperglycinaemia: NORD. www. National Organization for Rare Diseases.com

Patient No 6

A 3 days old baby girl presented with lethargy, anorexia, hypoventilation, hypothermia and seizures. and coma. Her biochemical investigations revealed

- pH: 7.48 (7.35 - 7.45)
- PCO_2: 44 mmHg (35 – 45)
- HCO_3 : 32 mmol/L (20 – 28)
- Plasma glucose (R) 5.9 mmol/L (5.6-6.9)
- Serum potassium : 4.4 mmol/L (3.6–5.2)
- Plasma Ammonia: 874 mmol/L (<35)
- Plasma Amino Acid Analysis reveals:
    - Citrulin: Decreased
    - Ornithine: Decreased
    - Glutamine Increased

a. What is most probable group of Metabolic Disorders present in this baby?
b. Name a urine test which can be helpful in finding the exact biochemical defect.

Write your answers here

Answers

Patient No 6

a. Urea Cycle Defect
b. Urine Orotic Acid

Explanation[1]

Urea Cycle Defects

a. Disease usually present during first a few days of life
b. Usual symptoms include somnolence, inability to maintain normal body temperature, and poor feeding, followed by vomiting, lethargy, and coma.
c. Very high Plasma Ammonia (>100 mmol/L) is an important finding
d. Absence of Metabolic Acidosis distinguishes it from other inherited metabolic disorders. Metabolic Alkalosis (not in all cases) may be present.
e. Amino acid pattern in plasma helps in diagnosis of various enzyme deficiencies. Following is an example
f. Decreased Citrulin, Decreased ornithine and increased Glutamine may be due to deficiency of either carbamyl phosphate synthetase (CPS) or ormithine transcarbamylase (OTC).
g. Urine Oratic acid level can differentiate the two conditions (Please see the PDF document *"Diagnostic algorithm for initial evaluation of hyperammonemia"*

References

2. Evaluation of female infertility. WWW.UpToDate.com 2015

(Please see Page No 70 for further details)

Patient No 7

An infant has been brought in a Paediatric Clinic with history of attacks of hypoglycemic featured by lethargy, nausea, and vomiting which rapidly progresses to coma within 1–2 h. Seizures also occur. His biochemical findings during the attacks are usually like following:

- Hypoglycaemia precipitated by fasting
- Acidosis: +
- Ketone bodies: Inappropriately Low
- Lactate: +
- Fasting Insulin: Normal
- Postprandial total acylcarnitine levels: <25-50% of normal

What is the most probable diagnosis?

Write your answers here

Answers

Patient No 7

Fatty acid oxidation disorder

Explanation[1]

Fatty acid oxidation (FAO) disorders usually present in early infancy as acute life-threatening episodes of hypoketotic, hypoglycemic coma induced by fasting or febrile illness. These include carnitine deficiency, fatty acid transportation defects, and defects of beta-oxidation enzymes.

Classification:

1. Carnitine cycle defects
2. ß-Oxidation Defects
    - Very-long-chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency
    - Medium-chain Acyl-CoA Dehydrogenase (MCAD) Deficiency
    - Short-chain Acyl-CoA Dehydrogenase (SCAD) Deficiency.
3. Electron Transfer Defects
4. Ketogenesis defects

References

1. Wanders RJA, Vreken P, den Boer ME et al (1999) Disorders of mito- chondrial fatty acyl-CoA -oxidation. J Inherit Metab Dis 22:442- 487

(Please see Page No 79 for further details)

Patient No 8

An 8 months old baby is admitted in a hospital as he is failing to thrive.

Urine Amino Acids By HPLC Analysis shows:

Urine Homocystine/Creat ratio: 9 µmol/mmol (0 - 5)

Urine Organic Acids By GC/MS shows:

Urine Ketones: Negative by Multistix

Urine *MMA/Creatinine ratio: 1413 µmol/mmol (0 - 30)

Urine Methylcitrate/Creat ratio: 50 µmol/mmol (0 - 25)

Urine Creatinine : 1.3 mmol/L

*MMA: Methyl Malonic Acid

What is the most probable diagnosis?

Write your answers here

Answers

Patient No 8

Organic Aciduria (Methyl Malonic Aciduria)

Explanation[1]:

a. Organic acidemias, also known as organic acidurias, are a group of disorders characterized by increased excretion of organic acids in urine. They result primarily from deficiencies of specific enzymes in the breakdown pathways of amino acids. Enzyme deficiencies in beta oxidation of fatty acids or carbohydrate metabolism cause elevated levels of non-amino organic acids.

b. Types
   (1) Branched-chain organic acidemias
   (2) Multiple carboxylase deficiency
   (3) Glutaric acidemia (or aciduria) type 1 (GA1) ●
   (4) Abnormal organic acid levels in Fatty acid oxidation defects

c. Methylmalonic academia (MMA) is a type of organic acidaemia characterized by impaired metabolism of methylmalonic acid that is generated during the metabolism of certain amino acids (isoleucine, methionine, threonine, or valine) and odd-chain fatty acid

   Lab Investigations: includes measurement of pH, carbon dioxide tension, bicarbonate, ammonia, lactate, pyruvate, glucose, electrolytes, creatinine, urea, and ketones. Infants typically have severe metabolic acidosis with an increased anion gap, ketosis, and hyperammonemia. Other common findings include hypoglycemia and electrolyte and other abnormalities associated with volume depletion

   Finding of Specific organic acid in the urine: is pathognomic of the disorder e.g. Methyl Malonic Acid in MMA.

References

1. Organic acidemias: www.UpToDate.com 2015

(Please see Page No 72 for further details)

Patient No 9

A 14 month child has repeated upper airway obstruction and frequent ear, nose and throat infections. She has short stature, hepatosplenomegaly, increasing facial dysmorphism, cardiac disease, progressive learning difficulties and corneal clouding. Her biochemical findings are :

- Urine heparan sulfate : Increased
- Urine keratan sulphate: Increased

What is the most probable diagnosis?

Write your answers here

Answers

Patient No 9

Mucopolysaccharidoses

Explanation[1]

The mucopolysaccharidoses (MPS) are lysosomal storage disorders caused by the deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs), previously known as mucopolysaccharides. Fragments of partially degraded GAGs accumulate in the lysosomes, resulting in cellular dysfunction and clinical abnormalities.

Types:

a. Soft tissue storage and skeletal disease with or without brain disease (MPS I, II, VII)
b. Soft tissue and skeletal disease (MPS VI)
c. ●Primarily skeletal disorders (MPS IVA, IVB)
d. ●Primarily central nervous system disorders (MPS III A-D)

Lab Diagnosis:

a. Measurement of urinary glycosaminoglycan (GAG) concentration
b. Fractionation of GAG by electrophoresis or chromatography,
c. Analysis of oligosaccharides for the identification of types of MPS,
d. Definitive diagnosis requires assay of enzyme activity, usually in peripheral blood leukocytes.
e. Azurophilic cytoplasmic inclusions (Alder-Reilly granules) have been described in some patients and are another potential clue to the diagnosis.

References

1. Mucopolysaccharidoses: Clinical features and diagnosis www.UpToDate.com 2015

(Please see Page No 83 for further details)

Patient No 10

A 10 months child presents with protruded abdomen, truncal obesity, short stature, hepatomegaly, and growth delay. His biochemical findings are :

- Attack of hypoglycaemia on brief fast
- Ketones : +
- NH3: Normal
- Lactate: +++
- Triglycerides: Increased
- Insulin: Normal

What is the most probable diagnosis?

Write your answers here

Answers

Patient No 10

Glycogen Storage Disease (GSD) Type I

Explanation[1]:

Glucose-6-phosphatase deficiency (G6PD, MIM #232200), also known as von Gierke disease, is a glycogen storage disease (GSD). It was the first GSD to have the responsible enzyme defect identified, and therefore is designated GSD I

Biochemical Features of GSD

a. Plasma Glucose levels: Hypoglycemia is the hallmark finding in patients with GSD I. Affected individuals have poor fasting tolerance, especially infants and young children, and may develop hypoglycemia
b. Plasma Lactate: A marked increase in blood lactate concentration is also found in GSD1
c. Hyperuricemia — Many patients have hyperuricemia, which is secondary to decreased renal clearance and increased production via degradation of adenine nucleotides. Gout rarely develops before puberty.

   Hyperlipidemia — There can be marked hyperlipidemia, especially hypertriglyceridemia, occurs and can lead to xanthoma formation and pancreatitis.
d. Molecular Analysis: DNA testing for common mutations may be carries out for all suspected cases for confirmation.
e. Enzyme Assays: The enzymatic diagnosis is based on the demonstration of specific enzyme deficiency in liver, muscle, fibroblasts, or leukocytes.

References

1. Glucose-6-phosphatase deficiency (glycogen storage disease I, von Gierke disease) www.UpToDate.com 2015

(Please see Page No 76 for further details)

Examples of IMDs

PSCP Guidelines 5/2016

Phenylketonuria

Phenylketonuria(PKU), first described by Følling in 1934 as "*Imbecillitas Phenylpyruvicais* is a rare inherited disorder that causes amino acid, phenylalanine (PHE) to build up in body due to deficiency of phenylalanine hydroxalase enzyme, which is essential for phenylalanine breakdown[1].

Clinical features:

a. Delayed mental and social skills
b. behavioural problems which include hyperactivity, purposeless movements,
c. stereotypy, aggressiveness, anxiety and social withdrawal
d. Seizures and tremors
e. Skin rashes (eczema)
f. Head size much smaller than normal (microcephaly)
g. Poor bone strength
h. Musty odour in child's breath, urine or skin.
i. Delayed development

Most severe form of the disease is called classic PKU. Children with less severe forms of PKU, in which some of the enzyme function is retained, there is not a risk of significant brain damage.

Causes:

Genetic mutation in the PAH gene located on the long arm of chromosome

12 that causes build up of phenylalanine in body. It is inherited in autosomal recessive pattern.

Classification:

The disorder is usually classified according to the concentration of PHE in blood when patients are on a normal protein containing diet or after a standardized protein challenge[i]:

a. Classical PKU (PHE >1200 µmol/l; less than 1% residual PAH activity),
b. Hyperphenylalaninaemia or mild PKU (PHE >600 µmol/l and <1200 µmol/l; 1–5% residual PAH activity),
c. Non-PKU-HPA or mild hyperphenylalaninaemia (PHE ≤ 600 µmol/l; >5% residual PAH activity)[2].

Diagnosis :

a. Blood PHE levels:

Blood PHE is normal at birth in infants with PKU but rises rapidly within the first days of life. Diagnosis is based upon the finding of an elevated plams concentration of phenylalanine. There is variation between different countries and centres in the age at which screening is undertaken (day 1 to day 10), in the methodology used (Guthrie microbiological inhibition test, enzymatic techniques, HPLC, or tandem mass spectro metry).

b. PHE/tyrosine ratio:

The level of blood PHE that is taken as a positive result requiring further investigation (120 to 240 µmol/l) but with some laboratories are also using a PHE/tyrosine ratio >3 to be diagnostic. The advantage of HPLC is that additional amino acids including tyrosine can be measured simultaneously. A high concentration of PHE together with low to low-normal tyrosine concentration may assist in making the diagnosis of PKU[3].

c. Molecular Analysis:

Molecular analysis can be used to demonstrate mutations at the PAH locus in peripheral blood leukocytes or for carrier detection or prenatal diagnosis in families in whom the mutation is known.

Treatment:

The principle of treatment in PAH deficiency is to reduce the blood PHE concentration sufficiently to prevent the neuropathological effects. Dietary restriction of phenylalanine is the mainstay of therapy in PKU and Use of medical foods including phenylalanine-free protein substitutes)that supply approximately 75 percent of protein requirements (except phenylalanine) is recommended. Continuation of dietary restriction throughout life appears to be necessary for optimal outcome, as demonstrated by Koch et al [ii] in a long-term follow-up study of newborns with PKU who participated in a trial of dietary management[3].

Out come and prognosis:

Blood concentrations of phenylalanine should be monitored frequently, especially during infancy. The outcome for PKU is dependent upon a number of factors like blood PHE levels at presentation, age at start of treatment, and duration of periods of blood PHE deficiency. Longitudinal studies of development have shown that start of dietary treatment within the first 3 weeks of life with average blood PHE levels ≤400 µmol/l in infancy and early childhood result in near normal intellectual development[4].

References

1. Folling I. The discovery of phenylketonuria. Acta Paediatr1994 Suppl 407:4-10
2. Scriver CR, Kaufman S (2001) Hyperphenylalaninemia: phenylalanine hydroxylase deficiency. In: Scriver CR, Beaudet AL, Sly WS,Valle D (eds) The metabolic and molecular bases of inherited disease. McGraw-Hill, New York, pp 1667-1724.
3. MacDonald A. Diet and compliance in phenylketonuria. Eur J Pediatr 2000; 159 Suppl 2:S136.
4. Koch R, Burton B, Hoganson G, et al. Phenylketonuria in adulthood: a collaborative study. J Inherit Metab Dis 2002; 25:333.

PSCP Guidelines 6/2016

Maple Syrup Urine Disease

Maple syrup urine disease (MSUD, MIM #248600) also known as branched-chain ketoaciduria, is a disorder affecting the aliphatic or branched-chain amino acids. It is caused by a deficiency of branched-chain alpha-ketoacid dehydrogenase complex (BCKDC), the second enzyme of the metabolic pathway of the three branched-chain amino acids, leucine, isoleucine, and valine. It is characterized by psychomotor retardation, feeding problems, and a maple syrup odor of the urine.
[1].

Classification:

There are three main clinical presentations:

1. A severe neonatal-onset form with metabolic distress
2. An acute, intermittent, late-onset form
3. A chronic, progressive form presenting as hypotonia, failure to thrive, and developmental delay.

Clinical Features:

Newborns with classical MSUD typically develop ketonuria within 48 hours of birth and present with irritability, poor feeding, vomiting, lethargy, and dystonia. Patients with intermittent MSUD present during episodes of catabolic stress, including intercurrent illnesses (eg,otitis media). During these episodes, ataxia, lethargy, seizures, and coma may ensue. Children with chronic progressive forms may either present with anorexia vomiting and failure to thrive(gastrointestinal presentation) or with severe hypotonia and muscular weakness(Chronic Neurological Presentation)[1].

Diagnosis:

1. Plasma amino acid analysis:

Measurement of plasma amino acid concentrations by HPLC in affected patients shows elevated levels of branched-chain amino acids (leucine, isoleucine, and valine).Performing HPLC analysis is of significance in these cases as alloisoleucine, a metabolite of leucine, can also be detected simultaneously in affected individuals and this alongwith 2-oxo-3-methylvaleric acid is diagnostic for MSUD. However, alloisoleucine may not appear until six days of age, even when leucine levels are elevated[2]

2. Urinary organic acids:

   IVA, PA and MMA are diagnosed by their specific urinary organic acid profiles using GC-MS. Urine organic acid measurement will detect elevated levels of branched-chain ketoacids, lactate, and pyruvate.

3. Measurement of enzyme activity:

   BCKD enzyme activity can be measured in lymphocytes or cultured fibroblasts. However, this test is not necessary for diagnosis. Prenatal diagnosis can be performed by measuring enzyme activity in cultured amniocytes or choriovillus cells.

4. Molecular Analysis

   Mutation analysis should be performed in all patients with MSUD, especially when prenatal diagnosis is anticipated for future pregnancies[3ß].

Treatment :

For acute phase management in the newborn, episodes of metabolic decompensation must be treated aggressively. Plasma and tissue concentrations of leucine should be lowered rapidly by inhibition of protein catabolism and enhancement of protein synthesis. The mainstay in the treatment of MSUD is dietary restriction of branched-chain amino acids and the main goal is to achieve normal plasma concentrations of branched-chain amino acids and reduce the accumulation of toxic metabolites. Dietary restriction is maintained throughout life[2].

Outcome and prognosis:

The best outcomes occur in patients who begin therapy before they become symptomatic or are treated rapidly after symptoms develop.. Hoffmann B et al. in 2006 in one retrospective review of patients with classic MSUD, reported that median plasma leucine concentrations during the first six years of life were indirectly correlated with IQ at six years of age.

References

1. Overview of maple syrup urine disease. www.UpToDate.com @UptoDate2016
2. Morton DH, Strauss KA, Robinson DL, et al. Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics 2002;109:999.
3. Hoffmann B, Helbling C, Schadewdaldt P,Wendel U. Impact of longitudinal plasma leucine levels on the intellectual outcome in patients with classic MSUD.Pediatr Res 2006;59:17.

PSCP Guidelines 7/2016

Tyrosinaemia

Tyrosine an aromatic amino acid derives from two sources, diet and hydroxylation of phenylalanine and is important in the synthesis of thyroid hormones, catecholamines, and melanin. Impaired catabolism of tyrosine is a feature of several acquired and genetic disorders that may result in elevated plasma tyrosine concentrations[1].

Classification:

1. Hereditary Tyrosinemia
    a) Tyrosinaemia type I (Hepatorenal Tyrosinaemia)
    b) Tyrosinaemia type II (Oculocutaneous Tyrosinaemia/Richner-Hanhart syndrome)
    c) Tyrosinaemia type III
2. Acquired Tyrosinemia
    a) Transient tyrosinemia of the newborn
    b) Hepatocellular dysfunction

Tyrosinemia Type I:

Also known as hepatorenal tyrosinemia, it is characterized by severe progressive liver disease and renal tubular dysfunction. Most patients present in early infancy with failure to thrive and hepatomegaly. Renal tubular dysfunctionwhen present is manifest as the Fanconi syndrome with renal tubular acidosis, aminoaciduria, and hypophosphatemia (due to phosphate wasting).[iii]

Tyrosinemia Type II:

It is also known as oculocutaneous tyrosinemia or Richner-Hanhart syndrome, is characterized by early development of eye and skin abnormalities.

Tyrosenemia Type III:

A rare autosomal recessive disorder type III tyrosinemia is caused by deficiency of 4-hydroxyphenylpyruvate dioxygenase . Most affected patients have neurologic dysfunction, including ataxia, seizures, and mild psychomotor retardation, but no other systemic involvement .

Diagnosis:

a. Plasma amino acids

   The plasma tyrosine concentration in Type II tyrosinemia is typically >1000 µmol/L whereas the levels in Type III are also raised but typically remain below 500 µmol/L.

b. Liver function tests:

   In symptomatic patients of type I tyrosinemia, liver function tests are usually deranged in particular, liver synthetic function is severely affected – coagulopathy and/or hypoalbuminemia are often present even if other tests of liver function are normal.

a. Urine organic acids

   The most important diagnostic test for Type I tyrosinemia is the measurement of urine organic acids. The presence of succinylacetone in urine is pathognomonic for the disorder.

b. Enzyme assays:

   The diagnosis of type I tyrosinemia is confirmed by measurement of FAH enzyme activity in cultured skin fibroblasts. The diagnosis for type II tyrosinemia can be confirmed by enzyme assay on liver biopsy or by mutation analysis.

c. Molecular analysis:

The diagnosis of Type II is confirmed by detection of mutations in the TAT gene in cultured skin fibroblasts or blood. The diagnosis of Type III is confirmed by detection of mutations in the HPD gene in cultured skin fibroblasts or blood.

Newborn Screening:

Screening using tyrosine levels alone is not recommended due to high rate of both false positives and false negatives. Tandem mass spectrometry can reliably detect diagnostic quantities of succinylacetone.[iv] Molecular screening is possible in populations in which one or few mutations account for the majority of cases[2].

Treatment[3]:

Initially Dietary treatment with foods having low or absent phenylalanine, tyrosine, and methionine and restriction of natural protein was used but recently its use is recommended in conjunction with Nitisinone (formerly known as NTBC)therapy to prevent the complications related to hypertyrosinaemia. Nitisinone inhibits 4-OH phenylpyruvate dioxygenase (HPD), an early step in the tyrosine degradation pathway. The aim of management of tyrosinemia type II is to keep plasma tyrosine levels below 500 µmol/L and consists of a diet low in tyrosine and phenylalanine. Early dietary intervention may prevent cognitive impairment[v] and resolution of the skin and eye lesions. Likewise diet low in tyrosine and phenylalanine is recommended for type III tyrosinemia, but whether this diet can prevent or reverse the neurologic symptoms is uncertain.

Transient tyrosinemia of the newborn:

It is the most common acquired cause of increased plasma tyrosine levels and is due to immaturity of hepatic pyruvate dehydrogenase and occurs in about occurs in approximately 10 % of preterm infants and some term infants. In the past, affected patients could develop lethargy, poor feeding, metabolic acidosis, and prolonged jaundice. Symptoms responded rapidly to ascorbic acid, a cofactor of HPD, and decreased protein intake. Hypertyrosinaemia usually resolves spontaneously by 4–6 weeks.

Hepatocellular dysfunction:

Elevated plasma tyrosine level may be seen in hepatocellular dysfunction of any etiology but the tyrosine levels usually are <500 µmol/L and patients usually do not manifest symptoms of hypertyrosinemia. However, the association can cause diagnostic

confusion in a child who presents with unexplained liver disease in whom elevated plasma tyrosine could reflect Type I tyrosinemia[4].

References

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2. Sander J, Janzen N, Peter M, et al. Newborn screening for hepatorenal tyrosinemia: Tandem mass spectrometric quantification of succinylacetone. Clin Chem 2006;52:482.
3. Al-Essa MA, Rashed MS, Ozand PT. Tyrosinaemia type II: an easily diagnosed metabolic disorder with a rewarding therapeutic response. East Mediterr Health J 1999;5;1204.
4. Mohan N, McKiernan P, Preece MA et al .Indications and outcome of liver transplantation in tyrosinaemia type 1. Eur J Pediatr.1999;158[Suppl 2]:49-54.

PSCP Guidelines/8/2016

Alkaptonuria

Alkaptonuria is an autosomal recessive disorder resulting from deficient activity of homogentisic acid dioxygenase ,an enzyme in tyrosine degradation. The gene encoding HGD has been mapped to chromosome 3q21-q23 and over 40 mutations have been identified. [vi]There is accumulation of homogentisate and its oxidised derivative benzoquinone acetic acid, the putative toxic metabolite and immediate precursor to the dark pigment, which gets deposited in various tissues[1].

Clinical Features:

Some cases of alkaptonuria are diagnosed in infancy due to darkening of urine when exposed to air. However, clinical symptoms first appear in adulthood. During the third decade, deposits of the brownish or bluish pigment become apparent, typically first in the ear cartilage and sclerae. Additional pigment is deposited in the large joints and the spine, especially the lumbosacral region. The most prominent symptoms relate to joint and connective tissue involvement; significant cardiac disease and urolithiasis may be detected in the later years.[vii]

Diagnosis:

1. Urine Examination

   The urine of the patients with this disorder appears normal when fresh, but turns dark brown or black if left standing or after alkalinization. The dark color is caused by oxidation of homogentisic acid, and alkaptonuria has also been called black urine disease. Cloth diapers that are washed in alkaline solutions will have dark brown staining.
2. Homogentisic acid measurement in urine

   Organic acid screening by GC-MS can specifically identify and quantify homogentisic acid. Homogentisate may also be quantified by HPLC and by specific enzymatic methods .

Treatment:

Dietary restriction of tyrosine and phenylalanine usually reduces the excretion of HGA. No effective therapy is available for AKU. The arthropathy mostly is not reversible, although diet may prevent further progression. Ascorbic acid is sometimes given, and it acts by inhibiting the enzyme those catalyses the oxidation of HGA to the polymer with affinity for collagen but its efficacy has not been demonstrated for ochronosis [48]. Clinical trial assessing the efficacy of Nitisinone in blocking the the accumulation of HGA have been carried out[viii] showing that that urinary HGA levels were eliminated with low doses of nitisinone with subjective improvement in symptoms like joint pains[2].

References

1. Phornphutkul C., Introne WJ, Perry MB et al . Natural history of alkaptonuria. N Engl J Med.2002; 347:2111-2121.
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PSCP Guidelines/9/2016

Non-ketotic Hyperglycinemia

Glycine-cleavage system (GCS) is an important pathway for catabolism of glycine , an essential amino acid. GCS degrades glycine into NH3 and CO2 and, thereby, also converts tetrahydrofolate into 5,10-methylene tetrahydrofolate. Nonketotic hyperglycinemia (NKH) or glycine encephalopathy is an autosomal recessive disorder due to mutations in the GCS and characterized by the accumulation of large amounts of the amino acid glycine in blood, urine and, particularly, the CSF and has a rapidly progressive course in the neonatal period or early infancy. The metabolic block occurs in the conversion of glycine into smaller molecules[1].

Classification/Grouping:

- Neonatal form
- Infantile form
- A mild-episodic form
- Late-onset form.

Clinical Features:

- Symptoms include muscular hypotonia, seizures, apneic attacks, lethargy and coma. Most patients die within a few weeks, whereas survivors show severe psychomotor retardation.
- Most of the cases with neonatal form appear normal at birth but develop a progressive encephalopathy within a few hours. It is characterised by lethargy, axial and limb hypotonia, and a depressed Moro response.
- Children with late onset NKH develop nonspecific neurological symptoms to varying degrees[2].

Diagnosis:

a. Plasma & CSF Amino acids by HPLC:

Detectin of raised levels of glycine in plasma and in CSF are key to the diagnosis of NKH. The diagnosis is based on finding of either an increased absolute value of glycine in CSF or an increased CSF to plasma glycine ratio (Ref:<0.02). In classical neonatal NKH this ratio is very high (>0.08), whereas it is only slightly elevated (0.04–0.10) or even normal in late onset,milder or atypical cases .

b. Enzyme assays:

Measurement of GCS activity in liver biopsy is confirmatory. However it is not commonly used as clinical presentation followed by plasma amino acid analysis is usually sufficient for diagnosis.

Treatment:

No effective treatment is available for NKH. Various treatment options including therapy with sodium benzoate and Pantothenic acid administration has been proposed but are usually ineffective. Research on enzyme replacement therapy is ongoing.

Prenatal Diagnosis:

Genetic counseling is recommended for families of children with non-ketotic Hyperglycinemia.Measuring GCS activity on crude chorionic villi tissue has been a attempted. Mutation analysis can be done on DNA extracted from foetal cells obtained by either amniocentesis (14–16 weeks)or chorionic villus sampling (10–12 weeks).

References

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2. Non-Ketotic Hyperglycinaemia: NORD. www. National Organization for Rare Diseases.com

PSCP Guidelines/10/2016

Cystinosis

Cystinosis can present as Type II RTA and Fanconi Syndrome. It is an inherited (autosomal recessive) lysosomal storage disorder caused by defective transport of the amino acid cystine out of lysosomes. The stored cystine is poorly soluble and crystallizes within the lysosomes of many cell types, leading to widespread tissue and organ damage[1].

Three types of cystinosis have been described based on the age at diagnosis and magnitude of cellular cystine deposition i.e. infantile onset adolescent onset, and adult onset

Infantile onset: Patients with the infantile nephropathic form of cystinosis (the most common and the most severe) develop symptoms early in life and, if left untreated, develop end-stage kidney failure by late childhood[2]

Signs and symptoms of nephropathic infantile cystinosis include the following:

a. Multiorgan involvement: May be mild to severe
b. Polyuria, polydipsia, dehydration, vomiting, metabolic acidosis
c. Hypophosphatemic rickets
d. Constipation
e. Failure to thrive, poor/loss of appetite
f. Craves salty and hot and spicy foods; prefers specific food textures
g. May have recurrent bouts of fever and manifestations of heat intolerance
h. Left untreated, renal failure develops by age 7-10 years

Laboratory tests

The following laboratory studies may be used to assess patients suspected of having cystinosis[3]:

a. Serum electrolyte levels: To detect Type II RTA i.e. acidosis (hyperchloremic, normal anion gap) and hypokalemia and hyponatremia, hypophosphatemia, and low bicarbonate concentration Blood gases: To detect metabolic acidosis and the degree of respiratory compensation

b. Urine testing: Findings include low osmolality, glycosuria, and tubular proteinuria (including generalized amino aciduria)

c. Urine electrolyte levels: To detect the loss of bicarbonate and phosphaturia

d. Cystine levels in polymorphonuclear leukocytes or cultured fibroblasts (for fetuses: chorionic villi or cultured amniotic fluid cells): Confirms diagnosis of cystinosis

Reference:

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PSCP Guidelines/11/2016

Urea cycle Disorders

The urea cycle is the main pathway that converts nitrogen to urea for excretion from the body. Deficiency of an enzyme in the urea cycle causes a urea cycle disorder[1] (UCD). All these defects are characterized by hyperammonaemia and disordered amino acid metabolism. Six inherited disorders of the urea cycle are well described. These are the deficiencies of carbamoylphosphate synthetase (CPS), ornithine transcarbamoylase(OTC), argininosuccinate synthetase, argininosuccinate lyase, arginase, and N-acetylglutamate synthetase (NAGS).

Clinical Features:

a. The early symptoms are often non-specific and initially, therefore, the diagnosis is easily overlooked. The new born usually appears well for the first 24 to 48 hours after birth and becomes symptomatic after feeding has started because human milk or infant formula provides a protein load. Common early symptoms are poor feeding, vomiting, lethargy and/or irritability and tachypnoea.
b. During infancy Irritability and behavioural problems may be present alongwith failure to thrive and poor development.
c. Patients who have partial enzyme deficiencies may have atypical presentations after the newborn period[1].

Diagnosis:

a. Plasma Ammonia: The most important diagnostic test in urea cycle disorders is measurement of the plasma ammonia concentration. If the plasma ammonia concentration is greater than 100 to 150 µmol/L, further testing is performed to establish a diagnosis. Mild elevations below this threshold should be interpreted in the context of the clinical course and followed to ensure resolution.
b. Arterial Blood gases: Absence of metabolic acidosis is suggestive of UCD.
c. Plasma Amino acids: In all urea-cycle disorders, there is accumulation of glutamine and alanine and, in citrullinaemia, argininosuccinic aciduria and

arginase deficiency, the changes in the amino acids are usually diagnostic. Orotic aciduria with raised plasma glutamine and alanine concentrations suggests OTC deficiency. Argininosuccinic acid is absent in the argininosuccinate synthetase deficiency and elevated in rgininosuccinate lyase enzyme deficiency whereas citrulline concenteration is raised in both.

d. Urine Orotic Acid: Urine orotic acid measurement may differentiate OTC and CPS deficiencies if citrulline is increased. . Orotic acid can be increased to more than 1000 µmol/mol creatinine (Ref:1-11 µmol/mol creatinine) in the former and is low in the latter.
e. Enzyme assays: Enzyme assays may be carried out in Liver biopsy for CPSI, OTC, and NAGS deficiencies, in Fibroblasts from skin biopsy for ASS and ASL deficiencies.
f. Molecular analysis:DNA testing for OTC deficiency should be considered in patients with a suspected UCD, especially if the plasma amino acid pattern is not diagnostic, and more than 150 mutations, most of which are single-base substitutions, have been reported . Detection of a pathogenic mutation in an asymptomatic patient may preclude the need for a liver biopsy to confirm the diagnosis.

Newborn screening:

Testing for UCDs and other IMDs by tandem mass spectrometry is now included in most newborn screening programs.

Treatment:

The aim of treatment is to correct the biochemical disorder and to ensure that all the nutritional needs are met. The major strategies used are to reduce protein intake, to utilize alternative pathways of nitrogen excretion and to replace nutrients that are deficient.

References

1. Leonard JV, Morris AA. Urea cycle disorders. Semin Neonatol 2002;

PSCP Guidelines/12/2016

Organic Acidemias

Organic acidemias, characterized by increased excretion of organic acids in urine, result primarily from deficiencies of specific enzymes in the breakdown pathways of amino acids or from enzyme deficiencies in beta oxidation of fatty acids or carbohydrate metabolism. Organic acids also are found in the urine of some patients with mitochondrial disease[1]

Clinical Features:

They can present clinically as a severe neonatal onset form of metabolic distress, an acute, and intermittent, late-onset form, or a chronic progressive form presenting as hypotonia, failure to thrive, and developmental delay.

Isovaleric Aciduria, Propionic Aciduria, Methylmalonic Aciduria are the three clinically important organic academia/aciduria. Dehydration is a frequent finding in these children and moderate hepatomegaly may be observed.

Diagnosis:

1. Arterial blood gases:
   The arterial blood gases show metabolic acidosis (pH <7.30) with increased anion gap and ketonuria. However, ketoacidosis can be moderate and is often responsive to symptomatic therapy.
2. Anion gap:
   Anion gap is increased owing to the presence of organic acids.
3. Plasma Ammonia:
   Hyperammonemia is a constant finding. When the ammonia level is very high (>500 µmol/l), it can induce respiratory alkalosis and lead to the erroneous diagnosis of a urea-cycle disorder.
4. Urinary organic acids:

The organic acidurias are characterized by their specific urinary organic acid profiles using GC-MS or abnormal acylcarnitines on tandem MS e.g. In Propionic Acidemia there is increased concentrations of free propionic acid in blood and urine, multiple organic acid byproducts(propionylcarnitine,3-hydroxypropionate, and methylcitrate) appear in urine.

Newborn Screening: Newborn screening for this group of organic acidurias can be performed by tandem MS [ix]An increased leucine/ isoleucine peak in blood spots taken at 24 or 36 h of age requires immediate notification to the peadiatrician.

Treatment: Acute phase management consists of treatment of the metabolic decompensation, followed by continuing care after recovery . It includes intravenous hydration and correction of metabolic acidosis, hyperammonemia, hypoglycemia, and electrolyte abnormalities. Other associated illnesses, such as infections, also are treated.

a. The aim of dietary treatment in isovaleric aciduria is to reduce the isovaleric acid burden to a minimum and to keep the urine free of metabolites. Similarly, the goal of treatment of methylmalonic and propionic acidema is to reduce the production of methylmalonic or propionic acid by means of natural protein restriction, carnitine supplementation (100 gm/kg/day) and reduction of intestinal production of propionate by metronidazole. In all cases the diet should be supplemented with an amino acid mixture that excludes the offending amino acids.
b. Plasma carnitine levels are usually low in patients with organic acidemia . L-carnitine is given to enhance the formation and excretion of acylcarnitine conjugates thought to be toxic to the brain, liver, and kidneys.

Reference:

1. Organic acidemias: www.UpToDate.com 2015

PSCP Guidelines/13/2016

Galactosaemia

Galactosemia can result from deficiencies of three different enzymes, Galactose-1-phosphate uridyl transferase (GALT), Galactokinase or Uridine diphosphate galactose 4-epimerase. The most important is classic galactosemia due to GALT deficiency.

Clinical Features:

Infants with galactosemia have normal weight at birth but signs and symptoms appear at initiation of breast milk or cows' milk-based formula feedings and they fail to regain birth weight. Symptoms appear in the second half of the first week and include refusal to feed, vomiting, jaundice, lethargy, diarrhea and hepatomegaly. Symptoms are milder and the course is less precipitous when milk is temporarily withdrawn and replaced by intravenous nutrition.

Diagnosis:

1. Urine reducing substances detection:
   If a symptomatic infant tests positive for reducing substances in urine, it may raise the clinical suspicion enough to trigger further evaluation and empiric treatment. A repeat of the test should be negative on switching the baby to soya milk. Due to lack of newborn screening programmes, this test has great utility in our set up, though it has got low specificity and sensitivity. .
2. RBC GALT activity
   The gold standard for diagnosis is the demonstration of nearly complete absence of GALT activity in RBCs [x] . Quantitative assay of RBC GALT activity is necessary to confirm the diagnosis.

Newborn Screening:

In many countries, newborns with galactosemia are discovered through mass screening for blood galactose, the transferase enzyme or both; this screening is performed using dried blood spots usually collected between the second and seventh days.

Treatment:

The main goal of long-term treatment of classic galactosemia is to minimize dietary galactose. This must be started immediately after the disorder is suspected clinically or following a positive newborn screening results even before the results of diagnostic tests are available. Once solid foods are introduced, ingredients containing lactose and galactose should be minimized .When a lactose-free diet is instituted early enough, symptoms disappear promptly, jaundice resolves within days, cataracts may clear, liver and kidney functions return to normal and liver cirrhosis may be prevented.

References

1. Galactosemia: Clinical features and diagnosis www.UpToDate.com 2016.

PSCP Guidelines/14/2016

Glycogen Storage Diseases

The glycogen storage diseases (GSDs) and related disorders are caused by defects of glycogen degradation, glycolysis and, paradoxically, glycogen synthesis. They are all called glycogenoses, although not all affect glycogen breakdown.

Classification:

1. GSDs affecting liver
    - GSD Type Ia(Glucose-6-phosphatase)
    - GSD Type Ib (Glucose-6-phosphate translocase)
    - GSD Type III(Debranching enzyme and subtypes)
    - GSD Type IV(Branching enzyme)
    - GSD Type VI(Liver phosphorylase)
2. GSDs affecting muscle
    - GSD Type V(Myophosphorylase)
    - GSD Type VII(Phosphofructokinase)
    - GSD Type X(Phosphoglycerate mutase)
    - GSD TypeXI(Lactate dehydrogenase)
3. Generalized GSDs
    - GSD II(Lysosomal α-glucosidase)
    - GSD IIb(Lysosomal-associated membrane protein 2)

Clinical Features:

a. Glyycogen is most abundant in liver and skeletal muscle, which are most affected by disorders of glycogen metabolism. The main role of glycogen in the liver is to store glucose for release to tissues that are unable to synthesize significant amounts during fasting.
b. Children with GSDs usually present with fasting hypoglycemia and ketosis, with or without hepatomegaly, and symptoms usually improve with eating or

glucose administration . These children may have poor weight gain, but are usually developmentally normal.

c. The major manifestations of disorders of glycogen metabolism affecting muscle are muscle pain, cramps, exercise intolerance and easy fatigability, progressive weakness, and myoglobinuria.

Diagnosis:

1. Plasma Lactate:

   A marked decrease in blood lactate concentration from an elevated level at zero time indicates a gluconeogenesis disorder, including GSD I, whereas an increase in blood lactate concentration suggests one of the other hepatic GSDs.

2. Plasma Glucose levels:

   Fasting hypoglycemia which appears in infancy or early childhood may be the first symptom in some of the GSDs like Glycogen Storage Disease Type 0.

3. Molecular Analysis:

   DNA testing for common mutations may be carries out for all suspected cases for confirmation. For example, for GSD II, alpha-1,4-glucosidase gene sequencing is necessary for diagnosis.[xi]

4. Enzyme Assays:

   The enzymatic diagnosis is based on the demonstration of specific enzyme deficiency in liver, muscle, fibroblasts, or leukocytes.

5. Supportive tests:

   a. Lipid profile:

      Though not required for diagnosis yet it should be carried out in patients suspected of certain subtypes like GSD type I(hyperlipidemia is a common feature) as the biomedical target in management is serum triglyceride concentration <6.0 mmol/L.

   b. Liver transaminases:

      Liver transaminases are elevated in hepatic forms of GSD Type IV and prothrombin and thromboplastin generation times are derranged.

   c. Muscle enzymes:

Serum creatine kinase is elevated in GSD Type II

Treatment:

a. The goal of treatment varies with the type of disorder, but usually it focuses on maintenance of physiologic glucose levels. Other biochemical parameters, such as lactic acidemia and hypertriglyceridemia, improve in parallel with improved glucose control.
b. For patients with GSD I carbohydrates such as lactose, galactose, fructose, and sucrose, should be minimized in the diet since they also depend upon glucose 6-phosphatase activity for metabolism. In GAD III ,restriction in fructose and galactose is unnecessary and dietary protein intake can be increased since no renal dysfunction exists.

References

1. Glucose-6-phosphatase deficiency (glycogen storage disease I, von Gierke disease) www.UpToDate.com 2015

Fatty Acid Oxidation defects:

Fatty acid oxidation (FAO) disorders usually present in early infancy as acute life-threatening episodes of hypoketotic, hypoglycemic coma induced by fasting or febrile illness. These include carnitine deficiency, fatty acid transportation defects, and defects of beta-oxidation enzymes.

Classification:

5. Carnitine cycle defects
    - Carnitine Transporter Defect
    - Carnitine Palmitoyltransferase-1 (CPT-1) Deficiency
    - Carnitine/Acylcarnitine Translocase (TRANS) Deficiency.
    - Carnitine Palmitoyltransferase-2 (CPT-2) Deficiency
6. ß-Oxidation Defects
    - Very-long-chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency
    - Medium-chain Acyl-CoA Dehydrogenase (MCAD) Deficiency
    - Short-chain Acyl-CoA Dehydrogenase (SCAD) Deficiency.
7. Electron Transfer Defects
    - ETF/ETF-DH Deficiencies
8. Ketogenesis defects
    - 3-hydroxy-3-methylglutaryl-CoA synthase
    - 3-hydroxy-3-methylglutaryl-CoA lyase

Clinical Presentation:

Clinical presentation of most of the FAO defects is similar. The affected children present with signs mainly of hepatic, cardiac, and skeletal muscle involvement. Cardiac failure is seen as the major presenting manifestation only in Carnitine Transporter Defects. During the first years of life, extended fasting stress may provoke an attack of hypoketotic, hypoglycemic coma.

Diagnosis:

a. Plasma glucose levels:

   Hypoglycemia is precipitated by fasting in FAO defects.

b. Plasma/Urine acylcarnitine profile:

   The assay of the plasma or urine acylcarnitine profile by tandem mass spectrometry is available. In all of the other defects, except HMG-CoA synthase deficiency, total carnitine levels are reduced to 25-50% of normal (secondary carnitine deficiency)

c. Enzyme assays:

   Enzyme assays in cultured skin fibroblasts or cultured lymphoblasts are used to measure the in vitro activities of specific steps in the fatty acid oxidation pathway.

Treatment:

a. Since most of these disorders usually present as episodes of hypoketotic, hypoglycemic coma induced by fasting or febrile illness, the mainstay of therapy is to prevent recurrent attacks by adjusting the diet to minimize fasting stress. Hepatic presentation of fatty acid oxidation disorders are most life-threatening aspect of these diseases so mostly treatment focuses on managing these.

b. In acutely ill patients, treatment with intravenous glucose should be given immediately in order to provide to provide sufficient glucose to
   stimulate insulin secretion to levels that will not only suppress fatty acid oxidation in liver and muscle, but also block adipose tissue lipolysis.

c. For long term dietary therapy, it is essential to prevent any period of fasting which would be sufficient to require the use of fatty acids as a fuel.

d. In FAO carnitine therapy might help to remove metabolites whereas it improves cardiac and skeletal muscle function to nearly normal within a few months in thoe with carnitine transporter defect.

References

1. Wanders RJA, Vreken P, den Boer ME et al (1999) Disorders of mito- chondrial fatty acyl-CoA -oxidation. J Inherit Metab Dis 22:442- 487

PSCP Guidelines/16/2016

Pyruvate Dehydrogenase Complex Deficiency

Pyruvate dehydrogenase complex (PDC) deficiency is a genetic mitochondrial disorder commonly associated with lactic acidosis, progressive neurological and neuromuscular degeneration and, usually, death during childhood. There has been no recent comprehensive analysis of the natural history and clinical course of this disease. Together with pyruvate carboxylase deficiency it is an important cause of congenital lactic acidosis .

Pathogenesis:

PDC deficiency specifically interferes with production of energy from carbohydrate oxidation as it impairs the mitochondrial oxidation of pyruvate and promotes conversion of pyruvate to lactate rather than its utilization in acetyl-CoA, the gateway for complete oxidation of carbohydrate via the TCA cycle. Overall the conversion of glucose to lactate yields less ATP that would be derived from complete oxidation of glucose via the TCA cycle and the respiratory chain.

Clinical Features: Patients present with delayed development and hypotonia, seizures and ataxia. Neuroradiological abnormalities such as corpus callosum agenesis and dilated ventricles or in boys basal gangliaand midbrain abnormalities are often found.

Diagnosis:

1. Plasma Lactate: Hyperlactatemia is a frequent finding early in the disease process. It ranges from severe lacticacidosis acid appearing shortly after birth to

a mildly elevated level which usually follows a meal high in carbohydrates. In some cases elevation of blood lactate levels is seen only during the acute episodes. Plasma Lactate to pyruvate ratio

2. Plasma lactate to pyruvate ratio: A blood lactate: pyruvate ratio is usually normal or low(≤20), in contrast to pyruvate carboxylase deficiency where a high lactate/pyruvate ratio is seen. Usefulness of the L:P ratio for differentiating non-PDH and PDH-D increases at higher lactate concentrations.
3. Plasma amino acid analysis:

   Amino acid levels vary with the general metabolic state of the patient; a catabolic state, in which gluconeogenesis is activated and proteins are degraded, elevates many amino acids, leading to a nonspecific amino acid profile.
4. Enzyme assay in fibroblasts:

   PDHC assays can be performed is cultured skin fibroblasts. PDHC can also be assayed in fresh lymphocytes, but low normal values might make the diagnosis difficult.

Treatment: Treatment is usually ineffective for most forms of pyruvate dehydrogenase complex deficiency; resolution of the lactic acidosis may occur, but cessation of the underlying progressive neurological damage is rare. A diet low in carbohydrates and high in fat (Ketogenic diets) have been used to control lactic acidosis with minimal success. Cofactor supplementation with thiamine, carnitine, and lipoic acid is the standard of care.

References

1. NORD. http://rarediseases.org/rare-diseases/congenital-lactic-acidosis/

Mucopolysaccharidoses

The mucopolysaccharidoses (MPS) are chronic, progressive multisystem disorders. They are a type of lysosomal storage disorders caused by the deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs).[xii] Fragments of partially degraded GAGs accumulate in the lysosomes, resulting in cellular dysfunction and clinical abnormalities.

Classification:

MPS grouped into four broad categories according to their dominant clinical features:

- Soft tissue storage and skeletal disease with or without brain disease (MPS I, II, VII)
- Soft tissue and skeletal disease (MPS VI)
- Primarily skeletal disorders (MPS IVA, IVB)
- Primarily central nervous system disorders (MPS III A-D)

Clinical features:

Clinical presentation is variable and is according to the group the MPS belongs to. Affected infants are usually normal at birth and the disease is only diagnosed as the phenotype evolves with time. Facial dysmorphism is seen with MPS IH (Hurler),MPS II (Hunter), MPS VI ((Maroteaux-Lamy).Patients with MPS III present with learning difficulties, behavioral disturbance and dementia and those with MPS IV have a severe bone dysplasia.

Diagnosis:

1. Urinary Glycosaminoglycan concentration
   In a child with coarse facial features, hepatosplenomegaly, and bone disease, with or without central nervous system (CNS) abnormalities,raised urinary

GAG(heparin sulphate/keratan sulphate) may suggest the diagnosis of MPS. Both a quantitative test of total GAG and a fractionation method, such as electrophoresis or chromatography, should be performed.

2. Analysis of oligosaccharides:
   Analysis of oligosaccharides can identify the types of MPS, oligosaccharidoses, and other storage disorders.
3. Enzyme assays:
   Definitive diagnosis requires assay of enzyme activity, usually in peripheral blood leukocytes,although fibroblasts or other cell types can be tested.
4. Others:
   - An ophthalmologic examination should be performed to assess corneal clouding and glaucoma.
   - Radiographic studies of the neck in flexion and extension should be obtained to assess cervical instabilityAlso look for vertebral slippage and kyphoscoliosis.

Treatment:

These disorders are usually not amenable to treatment and Palliative care remains an important aspect of management. Multidisciplinary management is essential and patients are best managed in specialist centres with access to a comprehensive range of clinical and supporting services.

References

1. Mucopolysaccharidoses: Clinical features and diagnosis www.UpToDate.com 2015

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Pakistan Society of Chemical Pathologists (PSCP)

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PSCP is a registered professional organization established to promote knowledge and best practices in the field of Clinical Chemistry (Chemical Pathology) in Pakistan. It is a PMDC accredited society for CME. Established in 2003, it has now nearly 200 members from all over the Pakistan. It holds annual ***scientific conferences*** and ***CME courses*** on the topics related to the fields of Chemical Pathology and Endocrinology. Two ***Distance Learning Programmes (DLPs)*** have been successfully conducted by PSCP in 2013 and 2014 and ***Structured Assessment of Skills (SAS)*** was conducted in 2015 to impart knowledge and skills in the field of Chemical Pathology.

PSCP is also a forum of scientific publications. ***"The Spectrum"*** is its newsletter published regularly since 2012 and up to now four editions have been published.

PSCP Clinical Practice Guidelines on Endocrinology were published in 2015 on the occasion of 6th Annual Course. This year two scientific publications are being issued. **'QADIS Book'** is a compilation of 120 patient records. Each record comprises clinical information and biochemical data, followed by correct diagnosis and a brief description of the condition.

These Clinical Practice Guidelines on Paediatric Inherited Metabolic Disorders have been written keeping our peculiar conditions in mind and more emphasis is given on the the use of clinical features as well as those routine laboratory facilities which are easily available in our hospitals. The sophisticated techniques like HPLC, GC/MS/MS and LC/MS/MS have also been mentioned as these are now available in our tertiary care centres. This is by no mean a textbook on IMD but just a short handbook for quick reference in clinical practice.