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# Metabolic Disease: When Do We Suspect?

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Metabolic diseases affect around one in every 500 newborns. We need to rule out whenever signs or symptoms are unrelated or the patient show biochemical changes like persistent hypoglycemia or increase lactic acid or ammonia.

When do we really suspect of metabolic disease? In the neonatal period, birth asphyxia without an explanation, early seizures, hypotonia, microcephaly, dysmorphy, eye abnormalities (cataracts, cornea opacity, ophthalmoplegia and cherry red spots), cardiomyopathy are very important signs of metabolic diseases.

In older children, drowsiness, lethargy, vomiting and even coma are common clinical presentation in urea cycle defect. Regression of psychomotor skills appear in patients with storage and peroxisome disorders. Coarse face is a typical presentation of storage disorders and mostly these children are normal when they born and around 2-3 years of age, the face start to change and become coarse. Neurosensorial deafness is common in mitochondrial disease. Ataxia in preadolescent, after rule out intoxication, encephalitis and tumor, we need to consider metabolic disease. Early fractures in children is common in osteogenesis imperfect but if associated in the neonatal period with brittle hair and hypotonia, we need to exclude Menkes disorders. Icthiosis in the first months of life in boys is related with steroid sulphatase deficiency, particularly if you have family history. Angiokeratomas is linked to Fabry disease. Macroglossia associated with hypotonia and cardiomyopathy is frequent in Pompe disease. Hepatosplenomegaly is common in storage diseases. Splenomegaly with anemia is typical in Gaucher disease. If we found hepatomegaly alone, galactosemia, tyrosinemia type I, Wilson disease, a1-antitripsine deficiency, biliar acid transport and synthesis defect, peroxisome disorder and CDG are the main causes. Abnormal sexual differentiation appear in Smith-Lemli-Opitz syndrome. In this case, we can find 2-3 toes syndactyly and congenital microcephaly among others signs when the child born.

We can also diagnose metabolic diseases, using the Classification Table of inborn errors of metabolism in the neonatal period and early infancy (Table 1-4) or if the patient showed hypoglycemia, we can use the flow chart for the diagnosis (Table 5).

| Types | Clinical type | Most important Laboratory results | Most usual diagnosis |
|---|---|---|---|
| I | Neurological deterioration,<br>'intoxication' type<br>Abnormal movements Hypertonia | Acidosis 0<br>2,4-Dinitrophenylhydrazine (DNPH +++)<br>Acetest 0/± | ✓ MSUD<br>(specific odour) |
| II | Neurological deterioration,<br>'intoxication' type<br>Dehydration | Acidosis ++<br>Acetest ++ | ✓ Organic acidurias<br>(MMA, PA, IVA)<br>✓ Ketolysis defects |
| | Neurological deterioration,<br>'energy deficiency' type,<br>with liver or cardiac symptoms | Acidosis<br>++/±<br>Acetest 0 | ✓ Fatty acid oxidation and<br>(GAII, CPTII, CAT, VLCAD, MCAD,<br>✓ HMG-COA lyase) |

***Table 1:*** *Classification of inborn error of metabolism in neonatal and infancy.*

*MSUD: Maple Syrup Urine Disorder; MMA: Methylmalonic Aciduria; PA: Propionic Aciduria; IVA: Isovaleric Aciduria; GAII: Glutaric Aciduria II; CPTII: Carnitine Palmitoyltransferase II; CAT: Carnitine Transporter; VLCAD: Very Long –Chain Acyl-CoA Dehydrogenase; MCAD: Medium-Chain Acyl-CoA Dehydrogenase; HMG-COA lyase: 3-hydroxy-3-methylglutaril-(HMG-)CoA lyase*

| Types | Clinical type | Most important Laboratory results | Most usual diagnosis |
|---|---|---|---|
| III | Neurological deterioration, 'energy deficiency' type<br>Polypnoea<br>Hypotonia | Lactate<br>+++/+ | ✓ Congenital lactic acidosis (pyruvate carrier, PC, PDH, Krebs cycle enzymes, respiratory chain)<br>✓ MCD |
| IVa | Neurological deterioration, 'intoxication' type<br>(Moderate hepatocellular disturbances, Hypotonia, seizures, coma) | NH3 ↑ +/+++ | ✓ Urea cycle defects<br>✓ HHH syndrome |

***Table 2:*** *Classification of inborn error of metabolism in neonatal and infancy.*

*PC: Pyruvate Carboxylase; PDH: Pyruvate Dehydrogenase; MCD: Mitochondrial Disorder; HHH: hyperammonemia, hyperornithunemia, homocitrullinuria*

| Types | Clinical type | Most important Laboratory results | Most usual diagnosis |
|---|---|---|---|
| IVb | Neurological deterioration<br>(Seizures Myoclonic jerks Severe hypotonia) | No major metabolic disturbance | ✓ NKH, SO plus XO<br>✓ Neurotransmitter defects<br>✓ Peroxisomal defects<br>✓ Trifunctional enzyme<br>✓ Respiratory chain<br>✓ CDG<br>✓ Cholesterol biosynthesis |
| Va | Recurrent hypoglycemia with hepatomegaly | hypoglycemia | ✓ Glycogenosis type I (acetest -)<br>✓ Glycogenosis type III (acetest +)<br>✓ Fructose 1,6-biphosphatase<br>✓ Hyperinsulinism |

***Table 3:*** *Classification of inborn error of metabolism in neonatal and infancy*

*NKH: Non-Ketotic Hyperglycinia; XO: Xantine Oxidase; CDG: Congenital Disorders Glycosylation*

| Types | Clinical type | Most important Laboratory results | Most usual diagnosis |
|---|---|---|---|
| Vb | Hepatomegaly<br>Jaundice<br>Liver failure<br>Hepatocellular necrosis | NH3 N or ↑<br>Lactate +/++<br>Glucose N or ↓ ++ | ✓ Galactosaemia Tyrosinaemia type I OXPHOS defects<br>✓ Mitochondrial DNA depletion |
| Vc | Hepatomegaly<br>Cholestatic jaundice<br>± failure to thrive<br>± chronic diarrhoea<br>± osteoporosis<br>± rickets | No major<br>metabolic<br>disturbance | ✓ Alpha-1-antitrypsin,<br>✓ Inborn errors of bile acid metabolism<br>✓ Peroxisomal defects<br>✓ CDG I and II<br>✓ Niemann-Pick type C<br>✓ LCHAD<br>✓ Mevalonic aciduria<br>✓ Cholesterol metabolism<br>✓ Cerebrotendinous xanthomatosis<br>✓ Citrin deficiency |
| V d | Hepatosplenomegaly<br>'Storage' signs (coarse facies, ascites, hydrops fetalis, macroglossia, bone changes, cherry red spot, vacuolated lymphocytes)<br>**± failure to thrive**<br>**± chronic** diarrhoea<br>**±** haemolytic anaemia | Hepatic signs<br>±/++ | ✓ Erythropoietic porphyria<br>✓ GM1 gangliosidosis<br>✓ Sialidosis type II<br>✓ I Cell disease<br>✓ Niemann-Pick type A/C<br>✓ MPS VII<br>✓ Galactosialidosis<br>✓ Glycosylated transferrin<br>✓ Mevalonic aciduria |

***Table 4:*** *Classification of inborn error of metabolism in neonatal and infancy.*

*CDG: Congenital Disorders Glycosylation; LCHAD: Long-Chain Hydroxyl Acyl-CoA Dehydrogenase; MPS VII: Mucopolysaccharidoses VII*

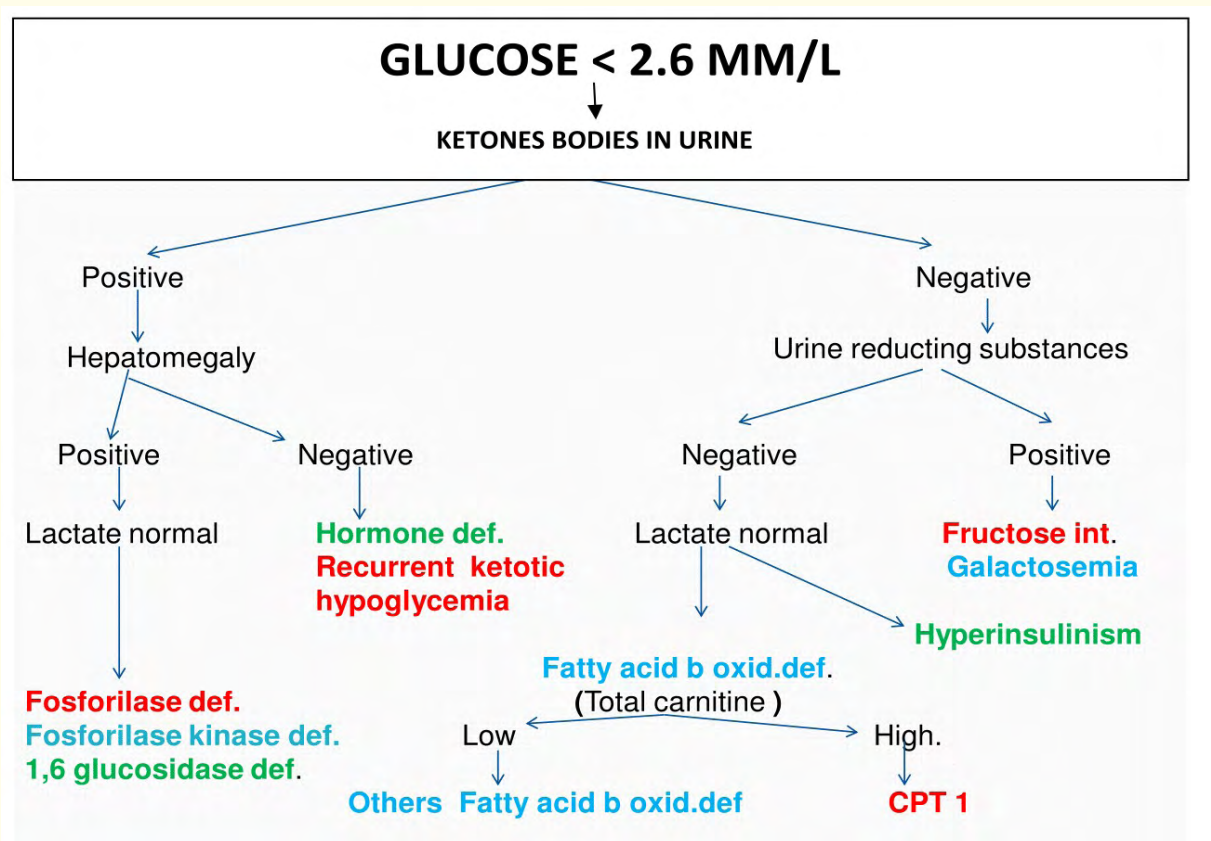


***Table 5:*** *Flow chart of hypoglycemia.*

*CPT 1: Carnitine Palmitoyltransferase 1*

Why we need to find a diagnosis? We can treat the child as soon as possible and offer the couple prenatal diagnosis and genetic counseling for the future pregnancy.

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