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Inborn errors of metabolism: a clinical overview

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ABSTRACT

CONTEXT: Inborn errors of metabolism cause hereditary metabolic diseases (HMD) and classically they result from the lack of activity of one or more specific enzymes or defects in the transportation of proteins.

OBJECTIVES: A clinical review of inborn errors of metabolism (IEM) to give a practical approach to the physician with figures and tables to help in understanding the more common groups of these disorders.

DATA SOURCE: A systematic review of the clinical and biochemical basis of IEM in the literature, especially considering the last ten years and a classic textbook (Scriver CR et al, 1995).

SELECTION OF STUDIES: A selection of 108 references about IEM by experts in the subject was made. Clinical cases are presented with the peculiar symptoms of various diseases.

DATA SYNTHESIS: IEM are frequently misdiagnosed because the general practitioner, or pediatrician in the neonatal or intensive care units, does not think about this diagnosis until the more common cause have been ruled out. This review includes inheritance patterns and clinical and laboratory findings of the more common IEM diseases within a clinical classification that give a general idea about these disorders. A summary of treatment types for metabolic inherited diseases is given.

CONCLUSIONS: IEM are not rare diseases, unlike previous thinking about them, and IEM patients form part of the clientele in emergency rooms at general hospitals and in intensive care units. They are also to be found in neurological, pediatric, obstetrics, surgical and psychiatric clinics seeking diagnoses, prognoses and therapeutic or supportive treatment.

KEY WORDS: Inborn errors of metabolism. Metabolic inherited disease. Diagnosis.

INTRODUCTION

In 1904 the doctor Archibald E. Garrod described alkaptonuria, a disease he classified as a lifelong congenital chemical alteration. Later on, in 1909, he described other diseases: albinism, cystinuria, porphyria and pentosuria, which he named "Inborn Errors of Metabolism". Garrod's conclusions were completely correct in relation to the genetic basis of metabolic disorders and the gene-enzyme concept.¹

According to Scriver, in the foreword of "Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases",² the importance of Garrod's observation that inborn errors of metabolism (IEM) are manifestations of biochemical individuality was never recognized during his lifetime, nor has it been in our days, because many doctors still think of IEM as situations of extreme rarity that will never be seen in the typical medical practice. IEM produces manifestations in every organ, from the fetus to geriatric life and they are omnipresent in appearance, not respecting the doctor's qualifications as a generalist or specialist.

Inborn errors of metabolism cause hereditary metabolic diseases (HMD) and

classically they result from the lack of activity of one or more specific enzymes or defects in the transportation of proteins. The consequences can usually be the accumulation of substances present in small amounts, the deficiency of critical intermediary products, the deficiency of specific final products or furthermore the noxious excess of products of alternative metabolic pathways.³

The molecular basis of biochemical disorders in HMD are genetic mutations in enzymatic loci that affect activator proteins or co-factors for enzymes, protein transportation, carrier systems or recognition markers.^{3,4}

Incidence

More than three hundred human diseases are known today that are caused by inborn errors of metabolism and this number is constantly growing because of new identification techniques for the various biochemical phenotypes. However, the detection of HMD incidence has not been increasing in parallel, probably because its diagnosis is being underestimated. Faulty diagnosis of IEM is related to a series of factors: (1) they are individually considered rare and therefore many physicians do not consider IEM until most frequent conditions have been ruled out, (2) blood and urine samples for investigation of metabolic errors need to be collected at the right time in relation to the course of the disease, and (3) many metabolic diseases only produce intermittent abnormalities.^{3,5,6}

IEM are not rare diseases when we observe their cumulative incidence,⁷ which is about one in every 5000 live births. Nevertheless, the prevalence of each disease has many variables, especially relating to race. Examples of frequency for specific diseases include: 1 in 500 for familial hypercholesterolemia;⁸ 1 in 12,000 for phenylketonuria;^{4,9} 1 in 15,000 for organic acidurias;¹⁰ 1 in 60,000 for glycogen storage diseases;⁴ 1 in 45,000 for galactosemia;⁸ 1 in 100,000 to homocystinuria⁸ and 1 in 290,000 for maple syrup urine disease.¹¹

In Brazil the incidence of some specific

IEM disorders have been found to be: 1 in 11,818 to 1 in 15,000 for phenylketonuria;^{12,13} 1 in 43,000 for maple syrup urine disease;¹² and 1 in 125,000 for biotin deficiency.¹⁴

Inheritance Patterns

The majority of HMD are inherited autosomal recessive traits, i.e. they have a recurrence risk of 25% for each gestation of heterozygous parents. Some diseases are X-linked, that is, the mother is carrier of the mutation, with the risk of recurrence for each gestation in these cases being 50% for males and 50% for females to be carriers of the mutation who can pass it on to their children. There are in addition mitochondrial diseases, determined by mutations in mitochondrial DNA, in which the risk of recurrence is virtually 100% of the children of both sexes.³

CLINICAL CLASSIFICATION OF INBORN ERRORS OF METABOLISM

One of the most educational and clinical classifications of IEM is to be found in The Metabolic and Molecular Bases of Inherited Disease, 1995 edition,¹⁵ by Saudubray & Charpentier,⁵ which classifies IEM in accordance with the clinical phenotype and presents tables of signs and symptoms and flow charts that aid daily practice greatly. Table 1 shows a summary of the authors' classification.

Category 1

Diseases that only affect a functional or anatomical system or an organ, such as the endocrine system, immune system, coagulation factors or lipoproteins. The symptoms are uniform and the correct diagnosis is usually easy, because the basis of the biochemical defect incorporates the given consequence, for example, the tendency to bleed seen in cases of coagulation defects.

Category 2

Diseases in which the biochemical basis affects one metabolic pathway common to a great

number of cells or organs, such as in storage diseases due to lysosomal disorders, or is restricted to one organ with humoral and systemic consequences, such as hyperammonemia in defects of the urea cycle or hypoglycemia in hepatic glycogenesis.

Diseases in this category have great clinical diversity. The central nervous system (CNS) is frequently attacked and in the evolution of the disease many secondary abnormalities can appear, making the diagnosis more difficult. This category includes many errors in intermediary metabolism (carbohydrate defects; amino acid or organic acid metabolism with primary or secondary disturbances of vitamin or metal homeostasis; purine and peroxisome disorders), diseases of intracellular transport (endoplasmic reticulum and Golgi apparatus defects) and lysosomal disorders.

These diseases can be divided into three groups from a physiopathological perspective, greatly assisting in diagnostic reasoning.

Group I

Disturbances in the synthesis or catabolism of complex molecules. The symptoms are permanent, progressive, independent of incidental events and are not related to alimentary ingestion.

Lysosomal Disorders. Also called storage diseases. These lead to the progressive accumulation of undigested substrates, usually polymers, that cannot usually be hydrolyzed. The polymers accumulate in lysosomes, where they can be seen using optical or electron microscopy. The affected tissues are those in which the substance is usually catabolized in great quantities: circulating lymphocytes, fibroblasts, liver, spleen, conjunctiva, bone marrow and intestinal mucosa. The clinical manifestations in this group are generally hepatomegaly or hepatosplenomegaly; dysmorphic features (coarse facial features) that are present at birth (GM₁ gangliosidosis) or develop in the first years of life (mucopolysaccharidosis); ophthalmological, bone, joint and central nervous system (CNS) involvement.

Table 2⁴ lists lysosomal disorders.

Peroxisomal Biogenesis Disorders. Involving many anabolic functions. These include the biosynthesis of plasmalogen, which is a major myelin component, cholesterol and bile acids. Generalized peroxisomal β -oxidation deficiency results in a variety of disturbances that are still not well understood, partly because there is an overlap in function between the peroxisomes and other organelles such as the mitochondria and the endoplasmic reticulum. These multiple and complex biochemical abnormalities result in specific defects of neuronal migration with malformations and severe neurologic dysfunction, hypotonia, mental retardation and developmental regression. In contrast to lysosomal disorders, there is no intracellular accumulation of undigested polymers. A useful marker for their diagnosis is the accumulation of very long chain fatty acids in plasma, such as X-linked adrenoleukodystrophy ("Lorenzo's oil disease"). Table 2⁴ lists the diseases in this group.

Defects In Intracellular Transport. Involving defects in intracellular transport and protein processing. This group includes α_1 -antitrypsin deficiency and carbohydrate-deficient glycoprotein syndrome.

Group 2

Inborn errors of intermediary metabolism leading to acute and recurrent intoxication (metabolic acidosis, vomiting, lethargy, dehydration, thromboembolic complications) or

Table 1 - Clinical classification of inborn errors of metabolism⁵

Category 1	Involving a functional system
Category 2	Affecting metabolic pathways common to a great number of cells or organs
Group 1	Defects in the synthesis or catabolism of complex molecules
Group 2	Defects in the intermediary metabolism
Group 3	Deficiencies in energy production or utilization

chronic and progressive intoxication (developmental delay or ectopia lentis) from the accumulation of toxic compounds proximal to the metabolic block. In this group are the aminoacidopathies, organic acidurias, urea

cycle defects and sugar intolerance. The main characteristics of this group are the existence of periods free from symptoms and the relationship with alimentary ingestion. The clinical expression is late-starting, intermittent or related to the introduction of the noxious substratum. Table 3⁴ lists the diseases in this group.

Table 2 - Clinical classification of inborn errors of metabolism^{5*} - Group 1

Lysosomal disorders

Mucopolysaccharidosis (mps)	I-H - Hurler I-HS - Hurler - Scheie I-S - Scheie II - Hunter III - Sanfilippo IV - Morquio VI - Maroteaux - Lamy VII - Sly
Sphingolipidoses	GM ₁ Gangliosidosis Tay - Sachs Sandhoff Fabry disease Shindler disease
Lactosylceramidosis	Gaucher disease Farber disease Niemann-pick disease Krabbe disease Metachromatic leukodystrophy Multiple sulfatase deficiency

Mucopolysaccharidoses

Glycoproteinoses	Fucosidosis Mannosidosis Sialidosis Aspartylglucosaminuria
Disturbances of membrane transport	Sialic acid storage disease Salla disease Cystinosis
Others	Carnavan disease Pompe disease Acid lipase deficiency
Peroxisomal biogenesis disorders	Zellweger syndrome Adrenoleukodystrophy Refsum disease Hyperoxaluria, type I

*Modified

Group 3

Energy deficiency diseases. The symptoms are at least partially caused by deficiency in energy production or utilization resulting from

Table 3 - Clinical classification of inborn errors of metabolism^{5*} - Group 2

Disorders of amino acids	Cystinuria Phenylketonuria Tyrosinemia Homocystinuria Non-ketonic hyperglycinemia Maple syrup urine disease
Organic acidurias	Isovaleric acidemia 3-methylcrotonyl-CoA carboxylase deficiency 3-methylglutaconic acidemia 3-hydroxy-3-methylglutaric acidemia Propionic acidemia Methylmalonic acidemia Multiple carboxylase deficiency Glutaric acidemia, type I
Urea cycle defects	Carbamoyl phosphate synthetase deficiency Ornithine transcarbamylase deficiency Citrullinemia Arginosuccinic aciduria Argininemia Lysinuric protein intolerance
Sugar intolerances	Classical galactosemia Galactokinase deficiency Epimerase deficiency Hereditary fructose intolerance Hereditary fructose-1,6- biphosphatase deficiency

*Modified

defects in intermediary metabolism in the liver, myocardium, muscles or brain. This group includes glycogenosis, glyconeogenesis defects, congenital lactic acidemias, fatty acid oxidation defects and mitochondrial diseases. The diseases of this group present overlapping clinical manifestations that may result in the accumulation of toxic components or deficiency in energy production.

The common symptoms include hypoglycemia, hyperlacticemia, severe generalized hypotonia, myopathy, cardiomyopathy, growth retardation, cardiac failure, circulatory collapse and sudden infant death syndrome. Congenital malformations indicating abnormal processes in fetal energy pathways are also in this group, as observed in pyruvate dehydrogenase complex deficiency. Table 4⁴ lists the diseases in this group.

CLINICAL MANIFESTATIONS

Neonatal Period And Childhood

The clinical findings for patients with HMD

presenting life-threatening acute metabolic crises are nonspecific and include poor feeding, vomiting, dehydration, lethargy, hypotonia and seizures. This picture is similar to that of septicemia, which may also be present, since IEM predisposes to infectious conditions. When a child with undiagnosed HMD dies, this fact is attributed in general only to the sepsis, resulting in an error of diagnosis. The autopsy findings in such cases are frequently nonspecific, not allowing for the diagnosis of a HMD.^{5,6}

There are some symptoms that are unusual in HMD, like the case of inspiratory stridor in an 11-month-old boy¹⁶ that became progressively worse over a period of 4 weeks, needing assisted ventilation. Ethylmalonic-adipic aciduria was diagnosed, a mild variant of multiple acyl-CoA dehydrogenation. The child greatly improved with riboflavin supplementation. The authors suggest research into organic aciduria in the presence of unexplained laryngeal stridor.¹⁶ There is furthermore a description of transitory visual symptoms in a

Table 4 - Clinical classification of inborn errors of metabolism^{5*} - Group 3

Fatty acid oxidation defects	Medium chain acyl-CoA dehydrogenase deficiency
	Long chain acyl-CoA dehydrogenase deficiency
	Short chain acyl-CoA dehydrogenase deficiency
	Long chain 3-OH-acyl-CoA dehydrogenase deficiency
	Multiple acyl-CoA dehydrogenase deficiency (glutaric acidemia, type II)
	Carnitine plasma transport defect
	Carnitine palmitoyl transferase deficiencies
Mitochondrial disorders	Pyruvate dehydrogenase complex deficiency
	Oxidative-phosphorylation (respiratory chain) defects (MERRF) (MELAS)
	Pyruvate carboxylase
	Phosphoenolpyruvate carboxykinase deficiency
Glycogen storage disorders	HEPATIC FORMS Type 0; I; III; IV; VIII; IX; X
	MUSCLE FORMS Type V; VII

*modified

Table 5 - Clues suggesting an inborn error of metabolism^{3,6}

Positive family history	Metabolic acidosis
Consanguinity	Neutropenia and/or thrombocytopenia
Loss of developmental milestones	Hepato and/or splenomegaly
Siblings with unexplained infant/neonatal death	Unusual odor (urine or sweat)

patient with X-linked adrenoleukodystrophy as an initial manifestation of the disorder.¹⁷

Among the clinical findings of HMD there are descriptions of dysmorphic features present at birth,¹⁸ generally when fetal energy is affected,^{2,5} or developed during the first years of life as in lysosomal diseases.¹⁹

Clinical experience of HMD has shown that when we have difficult or peculiar cases that cannot be explained by known disease physiopathologies, we should think of IEM as an etiology, because there is probably a very large variety of symptoms beyond those that have been described. When we talk about the clinical picture of HMD, it is always in a general way, because within one disorder there is individual variation in symptoms and severity. Table 5^{3,6} lists clues suggesting an IEM and Table 6 lists frequent signs and symptoms in neonates and infants.^{6, 18, 20}

Clinical Manifestation - Adult Life

The clinical manifestations of IEM are not limited to childhood and adolescence: they can also appear in adult life.²¹ Patients detected via neonatal screening tests, who receive early treatment, progress to adult life with a series of complications and incidental symptoms as a consequence of base diseases such as phenylketonuria,^{21,23} or may present a greater longevity as in cystic fibrosis,²⁴ but whatever the case, they will need to seek

general medical care.

Pregnant mothers with phenylketonuria face problems in that they need rigorous diet control so as not to affect the fetus.²⁴⁻³⁰ There are also women who have hyperphenylalaninemia without phenylketonuria and do not need to diet because the phenylalanine levels do not harm them. However, these levels are sufficiently elevated during pregnancy to provoke microcephaly or mental retardation in the fetus, and so these women also are going to need diet control.^{31,32}

Therapeutic progress in glycogen storage disease, especially after uncooked cornstarch therapy,³⁴ has decreased the need for hepatic transplantation and consequently the numbers of individuals that survive until adult life have been increasing.^{35,36}

In addition to cases of individuals detected in the neonatal or childhood periods such that they can reach adult life, as described above, there is HMD that is only diagnosed in adult life. This may occur because of one of the following reasons:

1. Mild clinical manifestations in childhood and adolescence. Examples: propionic acidemia in a boy that had vomiting in childhood for 2-3 days, improved with fasting at home without medical attendance and in adult life presented chorea and progressive dementia;³⁷ patients with hereditary fructose intolerance who developed an aversion to

Table 6 - Clinical manifestations of hereditary metabolic diseases in neonates and infants^{6,18,20}

Failure to thrive	Vomiting and/or diarrhea
Lethargy or coma	Hypo or hypertonicity
Seizures	Hepatomegaly and/or hepatopathy
Respiratory distress and/or apnea	Jaundice
Grotesque facial features	Unusual odor (urine, sweat)
Dysmorphic features	Abnormal hair
Macroglossia	Abnormal eye findings*
Growth failure	Myopathy
Frequent infections	Development delay
Symptom-free interval	Recurrent disturbances

*Cataract, retinopathy and others

sweet food, then spending the whole life without symptoms until fructose-containing solutions were used during a surgery, when the patient had a severe metabolic crisis;³⁸⁻⁴³ hyperammonemia episodes, even fatal, especially in women receiving protein overload or under stress, as in childbirth, because they are carriers of the ornithine transcarbamylase (OTC) mutation, a urea cycle defect of X-linked inheritance;⁴⁴⁻⁴⁷ hyperammonemia coma in two young siblings with lysinuric protein intolerance, both having been underweight with intermittent gastrointestinal symptoms.⁴⁸

2. Diseases with clinical manifestation at the onset of adulthood. Examples: alkaptonuria involving large joints and spine in the third or fourth decades of life;⁴⁰⁻⁵¹ hypoglycemia crisis in a young adult with glutaric aciduria type II;⁵² glycogen storage disease type I,

normally detected in childhood, can be seen in an adult with symptoms of hypoglycemia⁵³⁻⁵⁴ or cardiomyopathy in glycogen storage disease type II;⁵⁵ McArdle's disease or glycogen storage disease type V

Table 7 - Clinical manifestations of hereditary metabolic diseases in adult life⁵

Progressive paraparesis	Muscular weakness
Hemiparesis	Ophthalmoplegia
Dystonia	Visual deficit #
Epileptic crisis	Behavioral disturbances *
Non myoclonic epilepsy	Hepatomegaly and/or hepatopathy
Chorea	Splenomegaly
Ataxia	Hypoglycemia

optical atrophy; cherry red spot; corneal opacities; * dementia; depression; aggressiveness; psychosis; personality and character changes

Table 8 - Urine tests to inborn errors of metabolism⁸⁶⁻⁸⁹

Benedict	Galactosemia, fructose intolerances, alkaptonuria, Lowe syndrome. Positive also for: diabetes mellitus, renal glycosuria, Fanconi syndrome, lactase deficiency, pentosuria, vitamin C excessive ingestion, sulfonamides, tetracycline, chloramphenicol and p-amino salicylic acid
Ferric chloride	Phenylketonuria, tyrosinemia, histidinemia, maple syrup urine disease, hyperglycinemia, alkaptonuria. Positive also for: pleochromocytoma, carcinomatosis, hepatic cirrhosis, transitory tyrosinemia, conjugated hyperbilirubinuria, L-dopa metabolites, pyruvic acidosis, salicylates, acetoacetic acid, phenothiazines, methionine malabsorption, melanoma, lactic acidosis and isoniazide excretion
Dinitrophenylhydrazine	Phenylketonuria, maple syrup urine disease, histidinemia, methionine malabsorption, hyperglycinemia, glycogen storage diseases I, III, V and VI, lactic acidosis and pyruvic acidosis
Nitrosophthalol	Hereditary tyrosinemia, transitory tyrosinemia, liver disease, fructosemia and galactosemia
p-nitroaniline	Methylmalonic aciduria
Ctma bromide	Mucopolysaccharidoses. Positive also for: Marfan syndrome, arthritis rheumatoid, cretinism and carcinomatosis
Cyanide-nitroprusside	Homocystinuria, cystinuria
Nitroprusside silver*	Homocystinuria, cystinuria
Toluidine blue spot test*	Mucopolysaccharidoses. Positive also for: Marfan syndrome, rheumatoid arthritis, cretinism and carcinomatosis.
Erlich*	Porphyria
Paper chromatography	Disorders of amino acids

*These are not part of the minimum screening, but they should be done for confirmation as complementary tests, or in specific cases such as porphyria.

characterized by exercise intolerance and myoglobinuria, usually appearing from the third decade of life;⁵⁶⁻⁶² adult-onset Tay-Sachs disease or gangliosidosis GM₂ with several variants with neuropsychiatric manifestations;⁶⁴⁻⁶⁷ X-linked adrenoleukodystrophy in the adult-onset form of adrenomyeloneuropathy with progressive paraparesis;⁶⁸⁻⁷¹ Wilson's disease or hepatolenticular degeneration can occur in an adult with chronic hepatic cirrhosis progressing to hepatic failure, renal dysfunction, hemolytic anemia and neurologic symptoms such as dysarthria and deterioration of voluntary coordination movements;⁷²⁻⁷⁴ adult-onset Nieman-Pick disease with progressive dementia, dysarthria, ataxia and seizures starting from the second or third decades;⁷⁵⁻⁷⁶ mitochondrial diseases can be adult-onset with myopathy, encephalopathy, lactic acidosis and stroke-like episodes;^{77,78} subacute necrotizing encephalomyelopathy, Leigh's syndrome, in the juvenile form with chronic sensory motor neuropathy,⁷⁹ ataxia, deafness and retinitis pigmentosa;⁸⁰ cholesterol ester storage disease variant diagnosed in two unrelated women, 43 and 56 years with chronic liver disease;⁸⁰ the adult forms of metachromatic leukodystrophy with progressive mental deterioration as the first

symptom;⁸¹ hemochromatosis, usually diagnosed in the fourth decade with cirrhosis, arthritis, liver disease and diabetes;^{82,83} amyloidosis with progressive dementia and leukoencephalopathy;⁸⁴ a new familial leukodystrophy with dementia and abnormal glycolipid storage⁸⁵ among other diseases. Table 7 lists the more common signs and symptoms of adult-onset IEM.⁵

DIAGNOSIS

The exact diagnosis of an HMD often depends on specialized enzyme assays and/or identification of molecular defect. These methods are not very widely available, especially in our country. Such tests are however only suitable when there is a strong and more specific suspicion of IEM diagnosis.^{3,20}

In fact, what is more important than the exact tests for the HMD diagnosis is the clinical judgement capable of leading towards a probably safe diagnosis via identifying the group that the disease belongs to. A lot of information can be gained from the history, physical examination, and more commonly available laboratory tests, allowing the treatment to be started as soon as possible, when such therapeutic treatment exists.³

The initial laboratory evaluation suggested in the HMD literature varies in relation to the

Table 9 - Urinary odor in metabolic inherited disease^{18,86}

Disorder	Odor	Compound
Classical phenylketonuria	Musty, mousy	Phenylacetate
Hereditary tyrosinemia	Musty, cabbage-like	2-hydroxybutyric acid
	Rancid butter	2-oxo-4-methylbutyric acid
Maple syrup urine disease	Burnt sugar or	2-oxo-3-methylvaleric acid
	Maple syrup	2-oxoisocaproic acid
	Maggi curry	2-oxoisovaleric acid
Isovaleric Acidemia	Sweaty feet or	Isovaleric acid
3-Hydroxy-3-methylglutaric aciduria; multiple acyl-CoA dehydrogenation defects	Cheese	
3-Methylcrotonyl CoA carboxylase deficiency; multiple carboxylase deficiency	Cat urine	3-hydroxyisovaleric acid
Methylmalonic acidemia	Acid smell	Methylmalonic acid
Cystinuria	Sulfurous	Hydrogen sulfide

number and type of tests and it is generally accomplished in a progressive way, according to the results that are to be obtained, as indicated below.^{4-7,18,20,86} The investigation of an IEM could begin with simple urine and blood tests (Table 8),⁸⁸⁻⁸⁹ because a negative urine analysis does not rule out the HMD hypothesis and the two screenings are complementary in beginning the diagnostic reasoning.

Urine tests for IEM are not done very much in major diagnosis centers, although they are still of great importance for small laboratories and in countries where higher technical sophistication is not available. Some tests are not specific, but a positive test can direct the investigator towards one or more specific tests.⁸⁶

Looking at and smelling urine samples should be routine practice for good metabolism laboratories and Table 9 lists some peculiar urine odors.^{18,86} Urine chromatography for

aminoacids⁹⁰ or sugars form part of the initial urinary tests.

The investigation of organic acids in urine chromatography, mass spectrometry⁹¹ and plasma amino acid analysis⁹² are requested in accordance with clinical and laboratory indications.²⁰ All the urinary and plasma analyses for IEM are influenced by the use of medication such as acetaminophen, ampicillin/amoxicillin, carbamazepine and the patient's state of health.^{86,91,92}

The blood tests^{4-7,10,18,86} include complete blood count, blood gases, blood electrolytes (Na, K, Cl, P, Ca), lactate, glucose, ammonia, liver function testing, cholesterol, triglycerides, pyruvate, urea, creatinine and uric acid. The lactate/pyruvate ratio (normal < 25) is useful in lactic acidosis, organic acidurias, urea cycle defects and fatty acid oxidation defects. The Anion Gap is fundamental $[Na + K] - [HCO_3 +$

Table 10 - Clinical findings in hereditary metabolic diseases⁴

Clinical Manifestations and Laboratory Findings	Group of disorders								
	A	B	C	D	E	F	G	H	I
Episodic nature	++	++	++	++	+	+	-	-	-
Poor feeding	++	+	++	+	+	+	+	-	-
Abnormal odor	+	+	-	+	-	-	-	-	-
Lethargy, coma	+	+	+	+	+	+	-	-	-
Seizures	+	+	+	-	+	+	+	-	+
Developmental regression	-	+	+	-	+	-	+	++	+
Hepatomegaly	+	+	+	+	+	+	+	+	+
Hepatosplenomegaly	-	-	-	-	-	-	-	+	+
Splenomegaly	-	-	-	-	-	-	-	-	+
Hypotonia	+	+	+	+	+	+	+	-	+
Cardiomyopathy	-	+	-	+	+	+	-	+	-
Grotesque facial features	-	-	-	-	-	-	-	++	-
Hypoglycemia	+	+	-	+	+	+	-	-	-
Metabolic acidosis	+	++	-	+	+	+	-	-	-
Hyperammonemia	+	+	++	+	-	-	-	-	-
Ketosis	+	+	+	-	-	+	-	-	-
Hypoketosis	-	-	-	+	-	-	-	-	-

Abbreviations: A = amino acidopathies; B = Organic acidopathies; C = Urea cycle defects; D = Fatty acid oxidation defects E = Mitochondrial disorders; F = Carbohydrate disorders; G = Peroxisomal disorders; H = Mucopolysaccharidoses; I = Sphingolipidoses ; ++ = usually present; + = may be present - = usually not present

Cl⁻]: values of 12 ± 4 are considered normal, and a value above 16 is suggestive of organic aciduria.⁹³

Magnetic resonance imaging of the CNS is generally superior to computed tomography in HMD, allowing evaluation of the demyelination that is frequent in these diseases. Electroencephalography, electroretinography, electromyography, cerebrospinal fluid analysis and evoked potential are indicated in specific cases.^{27,28}

The study of cells and tissues obtained via biopsy has been particularly useful in the characterization of many IEM: in the storage diseases, establishing the nature of the accumulated material; in diseases producing alterations in the organelles such as mitochondria or peroxisomes, performing morphologic studies; and in diseases with tissue markers suggestive of metabolic diseases. The chronic hepatic diseases common to a series of IEM are an example of the last group.⁹⁴

Table 9 lists a summary of clinical manifestations and laboratory findings of some groups more commonly found among hereditary metabolic diseases, which may be helpful in directing the diagnosis.⁴

TREATMENT

The treatment of HMD depends on the IEM, the clinical manifestation and the metabolites accumulated that were responsible for the patient's decompensation. The combined diagnostic and resuscitative measures do not preclude a search for other etiologies. Complete evaluation for sepsis is needed in neonates because several HMD predispose towards sepsis.

The basic principles for emergency treatment management in patients who may have an IEM can be summarized as follows:^{3,7,20}

1. Take appropriate diagnostic action: have urine and blood samples collected to investigate the IEM, as described above.
2. Treat acute metabolic decompensation such as dehydration, metabolic acidosis,

- hypoglycemia and, electrolyte disturbances.
3. Provide adequate calories and fluid to prevent catabolism.
 4. Remove toxic metabolites such as ammonia, propionic and methylmalonic acid, performing peritoneal or blood dialysis. Blood exchange transfusion has been performed in some centers where dialysis could not be instituted. Increasing the excretion of toxic metabolites can be achieved by using alternative pathways, such as sodium benzoate, phenylacetate, and phenylbutyrate to improve the excretion of waste nitrogen in hyperammonemia. Carnitine and glycine are useful for eliminating organic acids. These can be administered via nasogastric tube if necessary.
 5. Discontinue all protein and carbohydrate (fructose or galactose) intake for about 24 hours, maintaining glucose and intravenous lipid.
 6. Supplement with indicated co-factors to increase the residual enzyme activity when possible, such as thiamin, riboflavin, biotin, pyridoxine, cobalamin, and carnitine in accordance with the disorder.

Once the acute crisis has been controlled, attention must be turned to chronic management, limiting the intake of the offending substance, if possible, via manipulation of the diet. In accordance with the diagnosis, formulas free of certain amino acids, or restricting total protein intake and specific carbohydrates could be used.

Bone marrow transplantation has been accomplished in some cases of mucopolysaccharidosis, such as MPS I-H (Hurler), mild variant MPS II (Hunter) and MPS V (Maroteux-Lamy). Early transplantation leads to intelligence level stabilization and disappearance of the organomegaly, coarse facial features and the chronic profuse watery rhinitis that is high in glycosaminoglycans and could produce sleep apnea. It also prevents heart manifestations. The orthopedic problems are not prevented by the

transplantation, but the progression in skeletal involvement is slower. The transplant of bony medulla is still indicated in metachromatic leukodystrophy, adrenoleukodystrophy and globoid cell leukodystrophy before the start of clinical manifestations.⁹⁷⁻¹⁰⁰

Enzyme replacement therapy in Gaucher disease type I has resulted in gradual normalization of blood counts, decrease in the size of liver and spleen, and decrease in skeletal symptoms. The results are better if the therapy is early.¹⁰¹⁻¹⁰³

Enzyme replacement and gene therapy represent the great hope in treatment for other storage diseases, and are still at the experimental stage, but it is hoped that they may be used in the future.^{104,105}

Supportive treatment is very important in reducing the morbidity of IEM and in giving better quality of life even with the disorders that do not have specific treatment. In these cases, orientation for supportive treatment is indicated relating to general medicine, nutrition (to provide appropriate caloric intake), gastroenterology and speech therapy (for evaluation of deglutitive pharyngo-esophageal function and dysphagia), psychology (for the family and patients) and physiotherapy.¹⁵

IEM are hereditary in nature, and so the family should have formal genetic counseling, including prognosis for the patient, risk of recurrence, possibility of prenatal diagnosis, and screening of other family members, especially for carriers of X-linked mutations.^{3,7}

BIOCHEMICAL BASIS FOR HEREDITARY METABOLIC DISEASES - MINI REVIEW

The understanding of IEM is quite difficult, especially while we still cannot fully visualize the metabolism of the human organism as a whole and the connections that exist among the various metabolic reactions, which are crucial in the maintenance of the basic functions of our body.

Metabolism is basically energy production and consumption, obeying certain priorities.

Energy is needed primarily for the basal rate of metabolism, which is the energy spent by an individual at rest and in an absorptive state for the normal corporal functions such as breathing, blood flow and maintenance of muscle integrity. The thermal response to alimentary ingestion may represent 5 to 10% of the total energy expenditure for the body. Finally, physical activity provides largest variation in energy expenditure, with a highly active individual's energy expenditure being up to 100% greater than the basal rate of metabolism.⁹⁶

The largest deposits of energy in the organism are glycogen and the triglycerides and there are two priorities during fasting: (1) the maintenance of plasma glucose levels for cerebral metabolism and other tissues that request glucose and (2) the need to mobilize fatty acids from lipid storage and ketone bodies from the liver so as to liberate energy for all other tissues. In the absence of food, plasma glucose, amino acid and triglyceride levels drop, causing a decline in insulin secretion and an increase in glucagon liberation. The low insulin/glucagon ratio and the low availability of circulating substrates create a catabolic state during the period of nutrient deprivation, characterized by triglyceride, glycogen and protein degradation.⁹⁶

The use of energy by our organism and the metabolism during fasting mentioned above refer to healthy adults. In children in a growth phase and/or during an infection, there is a significant increase in the basal rate of metabolism. When there is an IEM in a child with an infection, we may imagine the profound metabolic alterations that occur and understand the gravity of metabolic decompensation, with its high mortality and great difficulty in treatment.¹⁰⁸

All metabolic events are driven by enzymes that are catalytic proteins and their main function is to increase the speed of reactions, without being altered during that process. The enzymes possess a highly specific active site that links to one or some specific substrates and catalyzes only one type of

chemical reaction. Some enzymes associate with a co-factor (metallic ions or coenzyme) needed for the enzyme activity.^{96,107}

Most IEM are a consequence of enzyme deficiencies. In glycogen storage disease Type I, for example, there is an inability to liberate glucose from the liver, neither as a product of glycogenolysis nor gluconeogenesis. Thus, accentuated hypoglycemia occurs. During fasting, the humoral response to hypoglycemia provokes phosphorylase activation and hepatic glycogenolysis. As there is no glucose liberation, glycolysis continues with production of great amounts of pyruvate and consequently lactate. The elevation of glycerol, acetyl-coenzyme A and nicotinamide adenine dinucleotide (NADH) levels generated by the increased flow in the glycolytic pathway contribute to the increase in triglyceride and cholesterol synthesis. The glucagon stimulus mobilizes outlying reserves of fat, elevating the circulating levels of free fatty acid. Therefore, innumerable metabolic alterations occur as a consequence of enzyme deficiency and obviously in the case of a child in a growth phase and with a larger number of viral or bacterial infections,¹⁰⁹ the control of these disturbances is worse.

CONCLUSION

IEM are frequently underestimated by the doctor in neonatal and intensive care units of national health clinics or in private clinics. The increase in the rate of identification of these disorders is directly related to clinical judgement and the habit of thinking of those diseases not as rarities but as possibilities, in the light of cases that cannot be explained by more familiar physiopathologies. From this step forward, advances in knowledge and biochemical techniques will really be able to increase the rate of diagnosis.

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Acknowledgements - To staff of the multidisciplinary outpatient clinic for research into hereditary metabolic diseases and to the IEM laboratory of the Center for Genetic Medicine of UNIFESP for their collaboration.

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Sources of funding: FAPESP for supporting the IEM investigation, grant no. 97/10838-7

Conflict of interest: Not declared

Last received: 5 January 1999

Accepted: 21 September 1999

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RESUMO

CONTEXTO: Os erros inatos do metabolismo (EIM) causam as doenças metabólicas hereditárias (DMH) e classicamente resultam da falta de atividade de uma ou mais enzimas específicas ou defeitos no transporte de proteínas. **OBJETIVOS:** Revisão clínica sobre Erros Inatos do Metabolismo (EIM) voltada para o médico na sua prática diária, com tabelas e figuras que sumariam as diversas doenças que fazem parte deste assunto. Uma pequena revisão das bases bioquímicas suficiente para compreensão da fisiopatologia dos EIM. **FONTES DOS DADOS:** Pesquisa bibliográfica utilizando livros de textos sobre os EIM e suas bases bioquímicas (Scriver, CR et al, 1995), revisão da literatura que abrangeu os artigos clássicos e aqueles publicados nos últimos dez anos, fornecendo assim referências atualizadas sobre as diversas doenças metabólicas hereditárias (DMH). **SELEÇÃO DOS ESTUDOS:** Foi realizada seleção de textos de autores consagrados pelo conhecimento e experiência na área dos EIM e descrição de casos clínicos com suas manifestações clínicas mais peculiares e marcantes. **SÍNTESE DOS DADOS:** Os EIM são doenças subdiagnosticadas pela falta de hábito do médico geral, neonatologista e intensivista em pensar nesta hipótese. Na revisão são descritos os mecanismos de herança, as principais características clínicas e os achados laboratoriais dos EIM, dentro de uma classificação que fornece uma visão geral sobre o assunto. São abordadas sumariamente as formas de tratamento existentes para os diversos grupos de EIM. **CONCLUSÕES:** Os EIM não são doenças raras como se pensava no passado e pacientes portadores de DMH fazem parte do atendimento geral nos pronto-atendimentos, nas clínicas cirúrgicas, obstétricas, pediátricas, neurológicas e psiquiátricas, aguardando diagnóstico, prognóstico e tratamento terapêutico e/ou de suporte.

PALAVRAS-CHAVE: Erros inatos do metabolismo. Doença metabólica hereditária. Diagnóstico.