Nutritional treatment

of inborn errors of metabolism

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Authors

MÓNICA RUIZ PONS

Unit of Pediatric Nutrition and Metabolism. Department of Pediatrics. Hospital Nuestra Señora de la Candelaria. Santa Cruz de Tenerife.

FÉLIX SÁNCHEZ-VALVERDE VISUS

Unit of Pediatric Gastroenterology and Nutrition. Department of Pediatrics. Hospital Virgen del Camino. Pamplona.

JAIME DALMAU SERRA

Unit of Pediatric Nutrition and Metabolopathies. Hospital Infantil de la Fe. Valencia.

Foreword

It is a great honor for me to write the prologue for the book entitled «*Nutritional Treatment of Inborn Errors of Metabolism*» by Drs. Mónica Ruiz Pons, Félix Sánchez-Valverde and Jaime Dalmau Serra.

The binomial relation between nutrition and metabolic diseases can be approached in a variety of manners: 1) Starting with nutrition and making changes to the primary food groups which are appropriate for each situation caused by metabolic disturbances; 2) Comparing the differences between normal children and those with inborn errors of metabolism and 3) Beginning with the main groups of metabolic diseases and their pathophysiology with the aim of determining the most adequate nutritional treatment. The last option, chosen by the authors of this text, is without question the most useful for general pediatricians. Indeed, there is no one better to undertake this task, given that these authors are experts in the two factors of this binomial equation. Their expertise in nutrition and broad experience in the treatment of metabolic diseases makes them especially suited to undertake this task.

After the introduction, the book begins with a chapter on general concepts that provides the reader with a better understanding of the problems of nutrition and more importantly, its inborn errors, which are subdivided according to the metabolic pathways of each of the three main nutrient classes (carbohydrates, fat and proteins/amino acids) or the specific cycle. Finally, the book provides an appendix with particularly useful tables.

Experts in metabolic diseases, as well as general pediatricians, will be pleased to have one more tool available for the treatment of this complex pathology. On behalf of all, I would like to express my profound gratitude to the authors.

Pablo Sanjurjo Crespo
Professor & Chair of Pediatrics

Summary

1 Introduction

One must always think about metabolism. When a child presents a clinical picture that doesn't appear to make sense, think about metabolism. This is an increasingly frequent reality in pediatric practice and this short textbook, aimed at pediatricians, attempts to analyze metabolism from the viewpoint of basic nutritional management of inborn errors of metabolism (IEM).

In recent years, the identification of IEM or congenital metabolic diseases has increased. Many diseases that could only be diagnosed according to syndromic characteristics or histopathology, can now be diagnosed biochemically. Indeed, not only enzymatic errors can be identified, but also the metabolic toxins produced or the lack of metabolites posterior to the enzymatic defect. In addition, given that many IEM are monogenic alterations, our ability to provide genetic diagnoses of many of these diseases is continuously improving.

Many IEM are related to the metabolism of the primary nutrients and their derived products. The human body is extremely sensitive to alterations in the availability of basic nutrients during the period of rapid growth during early childhood. Moreover, the undesirable results of metabolic alterations can often affect one or more vital organ (brain, liver, kidney, heart, etc). Thus, nutritional therapy is fundamental for the treatment of this type of disease, in order to ensure the adequate growth of the child while preventing the metabolic imbalances common to this disease.

In the treatment and diagnosis of all diseases there must be communication and coordination between various professionals, in this case, pediatricians. This joint professional care is of utmost importance in the treatment of IEM and requires continuous

communication. An initial or tentative diagnosis should be made at the primary level (Primary Care Clinic, Pediatric Emergency Room, Neonatology Department), followed by a long process of diagnosis, treatment and monitoring that will take place in the Department of Metabolism. This is where the nutritional and dietary monitoring of these patients is vital and should be managed by the hospital's Nutrition Department. Finally, it is fundamental that these patients and their condition be known at the primary health care level from which they were originally referred as these patients are prone to constant metabolic decompensations and require specific close monitoring by health care professionals.

This manual is centered on the most frequent and effective intervention and nutritional support techniques used for dealing with IEM. First, each disease will be introduced with its biochemical and clinical aspects, as well as comments on specific treatments employed in addition to nutritional therapy. For a more profound understanding of the IEM, the reader is referred to recent national and international literature where these diseases are dealt with in more detail. These references are provided at the end.

The objective of this manual is to increase the awareness of pediatricians about IEM, especially in terms of nutrition. Moreover, it is our intention to provide an introduction to metabolism which is as easy and clear as possible, something which has been lacking given the innate difficulties of this field. Evidently, the fundamental principal in the diagnosis of any disease is the awareness of its existence. This idea must extend to the awareness of the use of nutritional therapy in its treatment. The technological advances in the development of infant formulas in recent years has made it possible for nutritionists to have at their disposition an arsenal of specialized dietetic products making nutritional treatment possible.

We cannot finish without thanking SHS laboratories for their help in the creation of this manual and for their constant support in the nutritional management of patients, for whom this humble contribution is made.

2 General aspects

2.1. CONCEPT AND EPIDEMIOLOGY

Inborn errors of metabolism (IEM) are a group of diseases caused by a genetic mutation resulting in the production of an incorrect protein that alters the physiological functioning of the cell. Depending upon the altered function, this may result in the accumulation of a non-metabolized substrate, the production of substances through the metabolising of this substrate by alternative pathways, or phenotypes resulting from reduced or non-production of the final product. The pathophysiological effects of an accumulation of non-metabolized substrates depends on the amount of substance accumulated, as well as its level of toxicity. The employment of uncommon or alternative metabolic pathways may produce new substances that are potentially toxic, while the consequences of a deficiency in specific products depend on how essential this product is to the organism. The clinical manifestations of these altered proteins are broad and appear primarily during the early stages of life, although they may also become manifest during later periods.

These diseases are also known as hereditary diseases of metabolism or congenital errors of metabolism. The concept of «inborn errors of metabolism» was established at the beginning of the 20th century by Garrod, who described cystinuria, alcaptonuria, pentosuria and albinism[3]. Subsequently, our knowledge of this type of disease has increased progressively. Indeed, Garrod's first book identified four diseases, in 1983 Stanbury et al., described 200 and Scriver et al., in 1995, described 459 diseases. At present, there are more than 700 defined conditions[3-5]. This rapid advance in the number of identified IEMs is due to the possibility of genetic

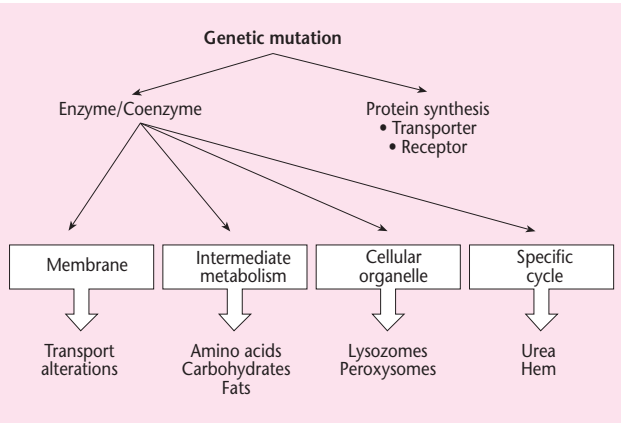

Figure 2.1. Etiological mechanism of the inborn errors of metabolism (Modified from Sanjurjo P et al.[2]).

diagnosis. While all human beings carry defective genes, this does not necessarily lead to the development of any symptom or disease as each individual has two copies of each gene, maternal and paternal, and one copy is generally intact. The majority of the IEM are monogenic, meaning only one gene is affected. Through the study of affected families, it is possible to detect the genetic mutation present in all members affected by an IEM and locate the altered gene. A single gene can be affected by a multitude of mutations and these tend to be linked to the type and intensity of the clinical manifestations of the IEM[6].

The genetic mutation underlying an IEM results in the production of an altered protein (enzyme or coenzyme), and therefore an alteration in its function. In summary, if physiology means the strict functional regulation of the cell and organism, a metabolic disease is «physiological chaos» (Fig. 2.1). On the other hand, recent advances in molecular biology have made the genetic diagnosis of many IEM possible, while these diagnoses were previously based solely on a clinical analysis and the accompanying

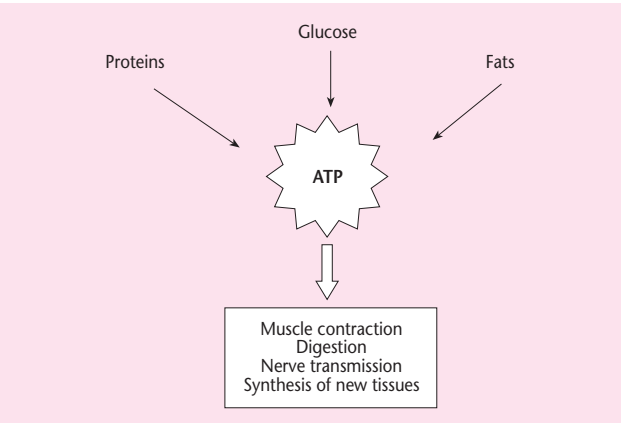

Figure 2.2. ATP is the direct energy source of all forms of biological work.

signs and symptoms. Although each individual IEM has a very low incidence rate, the combined incidence for this group of diseases is 1/500 live newborns. The prognosis of these diseases has clearly improved in recent years due to the possibility of early diagnosis and the availability of specific dietary products for each disease.

For all functions, the human organism must use the chemical energy stored in the glucose, fat and protein molecules found in food. The chemical chain reactions which occur on the cellular level when these primary nutrients are offered to the cell are called intermediate metabolism. Furthermore, during the paediatric period, part of this energy is anabolised for growth. Cells do not directly use glucose, fats and proteins, but instead their energy is derived from diverse metabolic intermediates, among which ATP (adenosine triphosphate) is the most important[5]. The potential energy accumulated and stored in this compound is later used for all forms of human energy expenditure including for example, muscle contraction, construction and repair of tissues, digestion, circulation, nerve transmission, glandular secretion, etc. (Fig. 2.2).

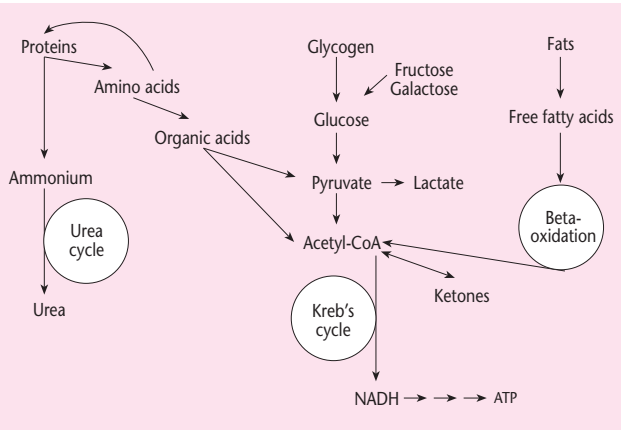

Figure 2.3. Overall view of the metabolic pathways and the incorporation of proteins, carbohydrates and fats into the Kreb's cycle.

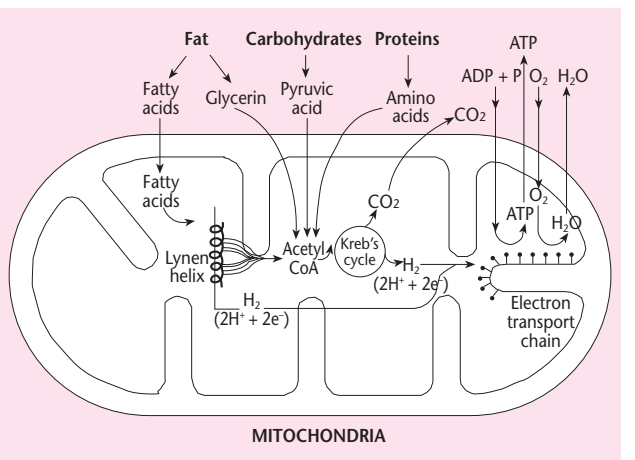

Figure 2.4. Overall view of the catabolism of carbohydrates, fats and proteins at the level of the mitochondria.

Figure 2.3 provides a general summary of the diverse metabolic pathways for proteins, carbohydrates and fats, and their incorporation

into the Kreb's cycle for the production of ATP. These intermediate metabolic reactions occur in the mitochondria (Fig. 2.4).

Until the development of a possible genetic therapy approach, dietary treatment remains the most important tool in the management of IEM[7-9]. As outlined above, in IEM there is an increase in the concentration of the non-metabolized substrate, a decrease in the formation of the final metabolite and/or the activation of alternative metabolic pathways that may result in toxic metabolites[5,9]. The treatment options for these diseases include:

1. Excess substrate or the production of toxic metabolites from this substrate requires the suppression or limitation of a nutrient, depending upon whether this is essential or not.
2. The decrease in the formation of a final metabolite may occasionally result in the need to administer this substance in sufficient quantities to maintain its physiological function.
3. When the alteration of an enzymatic reaction is due to a deficiency in a coenzyme, therapy includes the administration of this factor, if possible.

In general, diet will undergo: a) Quantitative modifications, which means that the proportion of the three main nutrient groups that make up the daily caloric intake will be altered, and/or b) Qualitative modifications, where specific nutrients that the subject cannot metabolize will be restricted, or c) Supplementing the diet with specific coenzymes (B vitamins, vitamin C, Coenzyme Q, etc.) or other beneficial substances even if their primary synthesis is not specifically affected, as increased quantities may be required due to their accelerated consumption. Additionally, for many of these diseases it is fundamental to quantify the intake of protein and/or amino acids.

2.2. CLASSIFICATION

IEM can be classified by taking into account diverse aspects, including the age of onset[10], the general clinical manifestations[5],

the most affected organic system, or using what are referred to as guiding symptoms[2,11]. These classifications use mainly clinical aspects in order to orient and facilitate the diagnosis of IEM. In our opinion, taking into consideration the difficulty in organizing 700 diseases in a manageable fashion, the simplest and most graphic classification of IEM is that which takes into account the main food group, enzymatic system or metabolic pathway affected. The classification presented in table 2.1, while not exhaustive, does represent the main diseases and groups of diseases included in IEM.

This type of classification helps one to understand the symptoms of the disease from a pathophysiological point of view and allows a global approach both in the clinic, as well as in nutritional treatment.

2.3. GENERAL PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS OF IEM

In general, the signs and symptoms of an IEM will provide a clinical picture that is intimately related to the pathophysiological mechanisms of the disease in question. Each clinical picture will depend upon the type of IEM and the organs affected. From a pathophysiological point of view, and depending upon the functions affected, the IEM can be classified, in a practical manner, into three main groups (Table 2.2)[11].

Group I: This group includes those diseases in which the synthesis or catabolism of complex molecules is altered. The symptoms are permanent, progressive and are not related to another disease process or food intake. These diseases have been classically defined as storage diseases. These diseases are malign and can affect all organs or functions of the body, although the most frequently affected are: the liver and spleen, producing progressive hepatosplenomegaly due to the accumulation of substances; the central nervous system, resulting in mental retardation, convulsions, etc.; muscle tissue, both skeletal and

TABLE 2.1. IEM Classification

Disease group	Specific diseases
IEM of carbohydrates	• Glucogenosis • Lactic acidemias • IEM of galactose • IEM of fructose
IEM of fats	• Disorders of beta-oxidation and carnitine system • Smith-Lemli-Opitz (SLO) syndrome
IEM of amino acids and proteins	• Hyperphenylalaninemia or phyenylketonuria • Tyrosinemia • Non-ketotic hyperglycinemia • Homocystinuria • Maple syrup urine disease • Methalonic and propionic acidemia • Type 1 glutaric aciduria • Isovaleric acidemia
IEM defects of specific cycles	• Diseases of the urea cycle • Purine metabolism disorders • Phorphyrias • Defects in cholesterol biosynthesis • Defects in bile acid biosynthesis • Mitochrondrial diseases or OXPHOS defects
IEM of complex molecules (lysosomal and peroxisomal diseases)	• Mucopolysaccharidosis • Oligosaccharadosis and mucolipidosis • Krabbe disease • Metachromatic leukodystrophy • Gaucher • Congenital defects of glycosylation
Transport defects	• Fanconi's syndrome • Protein intolerance with lysinuria • Cystic fibrosis of the pancreas • Congenital malabsorption of carbohydrates • Hemochromatosis
Other hereditary metabolic diseases	• Alpha-1-antitrypsin deficit • Hereditary diseases of neurotransmitters • Drepanocytosis • Imperfect osteogenesis

TABLE 2.2. Physiopathological Groups

	Mechanism	Clinical aspect	Specific analysis	Dietary treatment	Diseases
Group I	Alteration of complex molecule synthesis Deposit of complex cells	Permanent Progressive	No	No (Some peroxysomal diseases are treated with fatty Docosohexaenoic acid) SLO with cholesterol	Lysosomal Peroxisomal Transport diseases with intracellular processing
Group II	Acute and progressive intoxication	Neurological involvement Hepatic failure Growth failure Cardiomyopathy	Yes Acidosis Ketosis ↑ Ammonium Hypoglycemia	Yes	AMINO ACID DISEASES Phenylketonuria Maple syrup Homocystinuria Tyrosinemia ACIDURIAS Propionic Methyl-malonic UREA CYCLE INTOLERANCE TO SUGARS Galactosemia Fructosemia
Group III	Deficiency in energy production or usage	Hypotony Myopathy Failure to thrive Hepatic failure Infant sudden death syndrome	Yes Hypoglycemia Lactic acid Ammonium Hepatic profile disorder	Yes	Glucogenosis Defects in gluconeogenesis Congenital lactic acidemias Defects in beta-oxidation Diseases of the mitochondrial respiratory chain

cardiac, producing hypotonia and/or myocardiopathy and finally the kidney, associated with renal failure and tubulopathies. This group does not have an acute neonatal form, although on occasion the metabolic alterations at birth present stigma which is characteristic of the disease through polymalformation syndrome, as in the case of Smith-Lemli-Opitz syndrome. The majority of these conditions will not have dietary treatment, although it is being used in some cases. Peroxisome diseases (Zellweger syndrome, adrenoleucodystrophy) are currently being treated with

docosohexanoic acid (DHA)[12] while high doses of cholesterol is being used to treat Smith-Lemli-Opitz syndrome[13].

Group II: This group consists of entities that provoke acute and progressive intoxication. These conditions can be divided into three forms according to the age of debut and onset of the clinical symptoms: precocious or neonatal, intermediate or infantile, and finally a late onset form that can appear in late childhood or even during adulthood. In this group neurological affectation predominates, followed by liver and muscle complications. Both the severity of the clinical symptoms and the age of onset depend upon the underlying genetic mutation and the percentage of residual enzymatic activity.

Group III: This group includes IEM where the symptoms are largely due to a deficiency in energy production or use. The clinical manifestations are compatible with generalized organ failure, liver affectation, hypotonia, growth failure and myopathy. The clinical manifestations often begin with a series of symptoms which include vomiting, fever, prolonged fasting, reduced food-intake, etc, that require the patient to use alternative metabolic pathways that are not considered optimum. The child frequently presents various crises accompanied by these early symptoms.

From a dietary point of view, the diseases in Groups II and III are susceptible to dietary and nutritional intervention, as discussed below.

2.4. SYSTEMATIC DIAGNOSIS OF IEM

IEM are under-diagnosed and it is important that the pediatrician initially suspects the possibility of one of these conditions in order to start the diagnostic process[14]. Indeed, the clinician must consider the possibility a child may have a metabolic disease in order to send the patient to a specialist for the pertinent studies to be performed. When an IEM is suspected, there are a series of basic analyses, shown in table 2.3, that help

TABLE 2.3. Initial biochemical protocol

Urine	Smell
	Color
	Ketone bodies (Combur test)
	pH (Combur test)
	Reducing substances (Clinitest)
	Ketoacids (DNPH)
	Sulfites (Sulfitest Merck)
	Brandt Reaction
Blood	Complete blood test
	Electrolytes, anion GAP
	Blood gases
	Glucose, calcium
	Uric acid
	Hepatic tests (transaminases, alkaline phosphatases, bilirubin, albumin)
	Coagulation tests
	Ammonium
	Lactic acid, pyruvic acid
	3-hydroxybutyrate, acetoacetate

to orient the initial diagnosis towards the most probable generic type of IEM.

Given the non-specific nature of IEM symptoms, many are common to other illnesses, if the symptoms persist a basal biochemical study can be performed at any hospital. This should also be done during the neonatal period if symptoms are present. This study should consist in an analysis of pH levels, blood gasses, glycemia, ammonia, lactic acid and ketone bodies. The combination of symptoms and the most highly altered analytical results will orient suspicions towards IEM. For example, the presence of metabolic coma, hyperammonemia and normal blood glucose levels suggests an alteration in the urea cycle. When the patient presents with multisystemic affectation with hypotonia, metabolic acidosis, no acetonemia, elevated lactic acid and very low glycemia an alteration in the β-oxidation of fatty acids should be suspected. There are distinct algorhythms that can aid in the diagnosis of IEM,

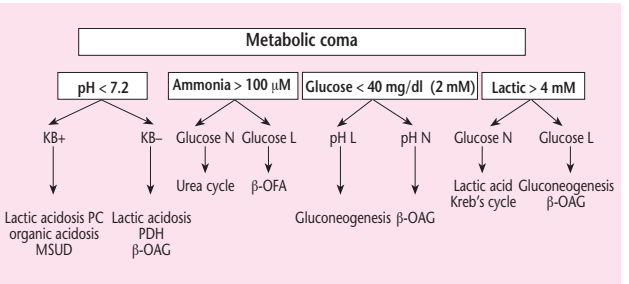

Figure 2.5. Differential diagnosis of metabolic comas. H: high; L: low; N: normal; KB: ketone bodies; PC: pyruvate carboxylase; PDH: pyruvate deshydrogenase; β-OFAG: alteration in β-oxidation of fatty acids; MSUD: maple syrup urine disease.

one of which is presented in Figure 2.5. However, one must keep in mind that algorhythms have their limitations, and should therefore be used with caution. In any case, they can help to confirm the initial suspicion of an IEM, and the patient can then be sent to a reference center for further study and treatment.

Subsequently, specific studies should be ordered to provide a more exact diagnosis among the various IEM (Table 2.4).

If the patient's condition is serious, samples of biological liquids should be collected and stored at -20 °C. These samples should be collected by an expert in biochemistry. The complete study should include:

a. Blood: Hematogram, electrolytes, anion Gap, pH and gases, coagulation factors, transaminases, ammonium, lactic and pyruvic acids, as well as β-hydrooxibutiric and ketonic acids as indications of the oxidation-reduction status of the cytoplasm and mitochondria, respectively. Following the results of these analyses, studies should be continued on the reserved blood sample and include: amino acids (AA), carnitine, acylcarnitines, succinylacetone (suspicion of tyrosinemia), organic acids (suspicion of acidemias), free fatty acids (suspicion of alterations in the β-oxidation of fatty acids), etc.

TABLE 2.4. Specific biochemical diagnosis

Urine	Amino acids Carnitine, acylcarnitines Orotic acid (suspicion of urea cycle disorder) Mono-disaccharides (suspicion of galactosemia or hereditary intolerance to fructose) Oligosaccharides (suspicion glucogenosis/lysosomal disease) Organic acids Succinylactone (suspicion of type I tyrosinemia)
Plasma	Amino acids Total and free carnitine, acylcarnitines Disialotransferrin (suspicion of carbohydrate deficient glycoprotein syndrome) Organic acids
CSF	Amino acids Lactic, plyruvic (L/P)
Others	Overload tests Stress tests Fasting test Skin biopsy (fibroblasts) Muscle, liver biopsy

b. Urine: General characteristics (smell, color), ketone bodies, pH levels, reducing substances (clinitest), ketoacids, Brand test for sulfurated AA, electrolytes. Subsequent studies can be performed of orotic acid (suspicion of disruption of the urea cycle), organic acids (suspicion of acidemias/organic acidemias), oligosaccharides (suspicion of lysosomal diseases), etc.
c. Cerebral spinal fluid. AA, ammonium, lactic and pyruvic acids.
d. Depending upon the initial symptoms and the urgency of the case, an ECG, cardiac ultrasound, EEG, magnetic resonance or tomography, etc. should be ordered.

It is very important to have a urine sample stored at -20 °C, plasma in a heparinized tube and stored at -20 °C, blood spotted on filter paper and, if possible, 10-15 ml of whole blood for molecular studies, 1 ml of cerebral spinal fluid and the possibility of a skin biopsy for fibroblast cultures. These analyses will allow

the diagnosis of each specific IEM, which cannot be performed initially when the most important issue is the treatment of the patient.

Currently, tandem mass spectrometry can provide an analysis of acylcarnitines and amino acids in plasma, in dried blood samples, in a few hours, allowing a rapid diagnosis of defects in the oxidation of fatty acids, alterations in amino acid and organic acid metabolism and some errors of the urea cycle. The last two groups of diseases can also be recognized by their typical amino acid profile in plasma. An analysis of organic acids in urine can identify abnormal metabolites that indicate organic acidopathies and defects in beta oxidation. Free fatty acids and ketone bodies (acetoacetate, 3-hydroxybutirate) are especially important if one does not have the acylcarnitine profile by tandem mass spectrophotometry available. To avoid delays, these studies should be ordered in parallel and the results should be available in 24 hours. Depending on the clinical symptoms and the basic test results, other studies to detect insulinemia, homocysteine, etc., should be performed.

Finally, specific biochemical studies can be performed to detect the enzymatic alterations and by using molecular biology techniques genetic studies can be performed to detect genetic mutations that will conclude the identification of the hereditary metabolic disease affecting the patient[15].

The definitive diagnosis of an IEM is complex and time consuming task, in this situation, the physician and dietician must evaluate the patient's condition and establish a series of dietary rules to prevent, as far as possible, the harmful effects of a lack of some nutrient or the toxicity of some anomalous metabolic product, while at the same time supplying sufficient energy to prevent situations that could cause a metabolic crisis and to ensure the adequate growth of the child.

When IEM is the suspected cause of death, it is crucial that adequate samples for post mortem analysis are obtained including urine, plasma and blood samples on paper, for the tests indicated

above, cerebrospinal fluid for neurometabolic studies, whole blood collected in EDTA for DNA analysis, fibroblasts for enzymatic studies and tissue biopsies (muscle, liver, kidney).

2.5. GENERAL EMERGENCY TREATMENT

The reality in this situation is generally to be confronted with a child in critical condition suffering from a suspected metabolic illness but without an exact diagnosis until test results are received. In the case of suspected IEM, treatment should be started immediately, and in the majority of cases, before the definitive diagnosis is known. For this reason it is necessary that the initial treatment, at least to a certain degree, is non-specific. The medication and dosages considered essential for acute emergency treatment, and which should be available in the Intensive Card Unit, Emergency Room and Neonatology Unit are indicated in tables 2.5 and 2.6. The general protocol to be employed in these cases is s the following[16-18]:

1º Elevate glucose levels

An infusion of glucose and electrolytes can be started before any laboratory results are received, but one must ensure that samples for metabolic studies have been collected beforehand as pathological metabolic parameters may be normalized rapidly with treatment (e.g., hypoglucemia). The intake of any potentially toxic compound (e.g., proteins, fats, galactose, fructose) should be suspended. Initial treatment should start with intravenous glucose at a concentration of 10% and a rate of 150 ml/kg/day, which represents an energy administration of 60 kcal/kg/day. Overhydration does not usually pose a problem as the majority of metabolic crises are accompanied by some degree of dehydration.

This treatment is generally sufficient under conditions of reduced fasting tolerance; the pathophysiological mechanisms generally subside with administration of glucose at a rhythm similar

TABLE 2.5. Alternative treatment pathways in hyperammonemia

Drug	Initial infusion (90 min)	Maintenance Infusion (24 h)	Commercial name
	Administer them with 10% glucose (20 ml/kg) They are administered in addition to the drepanocytosis daily liquid and calorie requirements		
L-Arginine	1-2 mmol/kg (3-6 mmol/kg in AS,AL)[a] 100-150 mg/kg/día (CPS; OTC) to 700 mg/kg/día (AS,Al)	1-2 mmol/kg (3-6 mmol/kg in AS,AL)[a]	SHS (orally) Arginine hydrochlorate (i.v. ampoules, Pharma International)
Sodium benzoate	250-500 mg/kg	250 mg/kg	NA[b]
Sodium phenylacetate	250 mg/kg	250 mg/kg	NA[b]
Sodium Phenylbutyrate	600-700 mg/kg/day orally		Ammonaps (Orphan Europe)

[a]AS, arginosuccinate synthetase deficiency (citrulinemia); AL, arginocucchinate lyase deficiency. [b]NA, not available in Spain.

to normal hepatic production (7-8 mg/kg/min in newborns). In contrast, it is generally not sufficient in cases with endogenous intoxication, which demand higher energy intake to cause anabolism and frequently require specific detoxification measures.

This treatment is potentially dangerous in cases with altered energy metabolism (specifically in pyruvate dehydrogenase complex deficiency) where the elevated administration of glucose can worsen lactate acidosis. However, given that this disease is very rare and has a very poor prognosis, starting with the administration of high glucose is justified, as long as the balance of acid-base and lactate levels is regularly monitored.

2º Adapt the treatment to the results of the basic laboratory results

If the laboratory results and clinical findings indicate a condition that provokes endogenous intoxication, the treatment should

TABLA 2.6. Additional drugs used in metabolic emergencies (alphabetically)

Drug	Disease	Doses (in 3 doses except when specified to the contrary)	Commercial Name
Betaine	Homocysteine metabolism disorders	250-mg/kg/day orally	Cystadane (Orphan Europe)
Biotine	Holocarboxylase synthetase deficiency, multiple of carboxylase Biotinidase deficiency Hyperlactacidemia	10-20 mg/day orally	Medebiotin
L-Carnitine	Organic acidurias Carnitine transport defects MCAD deficiency Mitochondrial diseases	50-200 mg/kg/day i.v./orally	Carnicor (syrup, i.v. ampoule, drinkable vials) Secabiol (syrup)
Diazoxide	Hyperinsulinism	15 mg/day orally	Proglicen, 25 & 100 mg tablets
Folic acid	Homocysteine metabolism disorders	15 mg/kg/day orally/i.v.	
Folinic acid	Seizures responding to folinic acid	3-5 mg/kg/day i.v.	Folidan, Lederfolin
Glucagon	Hyperinsulinism	Bolus: 30-100 μg/kg (max.1 mg) after 5-10 μg/kg/h i.v.	
Hydroxycobalamin	Methylmalonic aciduria Cobalamine metabolism disorders Transcobalamine II deficiency Homocysteine metabolism disorders	1-2 mg/day i.m./i.v.	Megamibedoce (i.m. ampoule)
Insulin	All diseases with endogenous intoxication	Begin 0.05-0.1 U/kg/h	
NTBC	Type I tyrosinemia	1 mg/kg/day orally	Orphan Europe
Pyridoxin	Seizures responding to pyridoxine Homocysteine metabolism disorders	50 mg/day i.v. 100-500 mg/day i.v./orally	Benadon Roche
Ribofavin	Type I and II glutaric aciduria	150 mg/day/i.v/v.o	Magistral formula (orally)
Thiamine	Hyperlactacidemia Hyperlactacidemia, maple syrup	150 mg/day i.v/v.o.	Benerva Roche
N-Carbamylglutamate	Hyperammonemias	Initial bolus 200 mg/kg After 100 mg/kg/day	Carbaglu (Orphan)

Modified by Prietsch V, Lindner M. Zschocke J., Nyhan WL, Hoffmann G.F. Emergency management of inherited metabolic diseases. J Inher Metabol Dis 2002; 25: 531-46.

be intensified even without a definite diagnosis. Anabolism must be induced and measures taken to start detoxification.

Anabolism is an important objective during the entire course of treatment. This is primarily achieved by the administration of glucose, which is going to require a central pathway and possibly insulin. Fats should not be administered until defects in the oxidation of fatty acids have been ruled out.

Detoxification is more important in hyperammoniemia as its duration and severity is directly related to neurological damage. L-arginine becomes an essential amino acid in all cases of urea cycle defects (except for arginase deficiency). It is administered with sodium benzoate and/or sodium phenylacetate as alternative pathways for nitrogen excretion as they conjugate with glycine and glutamine, respectively. Sodium phenylbuterate is administered enterally as a source of phenylacetate. There is some debate as to whether sodium benzoate or phenylbuterate/sodium phenylacetate should be used for ammonium detoxification once the diagnosis as there is a theoretical risk of additional depletion of intramitochodrial CoA in organic acidopathies. However, this treatment is employed in many metabolic centers with no apparent adverse effects.

When ammonium levels exceed 400 μmol/l, or if they do not diminish adequately with conservative treatment, external detoxification may be necessary. This is especially necessary in the case of multiorgan failure, given that alternative treatments require intact liver and renal functions for the formation and secretion of conjugates. The choice of method will depend on the availability and experience of the medical team.

The correction of metabolic acidosis with sodium bicarbonate should be performed with caution in cases of hyperammoniemia due to the risk of ammonium disassociation and its toxicity. Carnitine is administered to compensate for the secondary carnitine deficiency caused by the urinary excretion of organic acids bound to carnitine. If a defect is suspected in the oxidation of long chain

organic acids, many centers do not perform bolus administration of carnitine due to the rapid accumulation of toxic long chain acylcarnitines and the risk of fatal cardiac arrhythmias.

Treatment monitoring

Due to the administration of high concentrations of glucose, glucose and lactate levels and acid-base equilibrium should be monitored closely (every 1-2 hours). Serum sodium levels should remain well above 135 mmol/l to avoid complications such as cerebral edema. Potassium levels may drop after the administration of benzoate or phenylbuterate/pheynlacetate, and should be maintained above 3.5 mmol/l. Ammonium levels should be reduced below 200 µmol/l in 12-24 hours.

Support treatment

Ventilation or circulatory support may be necessary, as well as anti-convulsion treatment. Antibiotic treatment is recommended in all patients as sepsis is an important component in the differential diagnosis and may be present, causing even greater catabolism.

3rd Treatment based on the results of specific metabolic tests

Once the disease has been identified, specific treatment should be started. These treatments, however, share some fundamental aspects which are described below:

Energy

In cases where anabolism is required (Group II), glucose and insulin administration should be continued. Once a defect in the oxidation of fatty acids has been ruled out, fats should be administered (2-3 g/kg/day) to augment caloric intake in diseases of protein catabolism (diseases of the urea cycle and alterations of organic acid and amino acid metabolism). Intermediate chain triglycerides may be beneficial as an alternative energy source in cases with defects of long chain fatty acid oxidation, especially for

the heart. However, there is no unanimous agreement on the indications and long-term application of this treatment (as it does not include essential fatty acids, a deficit of these may occur, they are ketogenic, etc). Little is known concerning the absolute energy requirements during metabolic decompensation. Theoretically, the minimum daily energy requirements according to age should be provided. Increases in the expenditure of basal energy of 30 to 40% have been reported during metabolic decompensation; however, when the patient is stabilized this expenditure is reduced up to 80%, such that, in addition to low expenditure due to greatly reduced physical activity, anabolism can be achieved with low energy administration. However, in situations of multiorgan failure and metabolic acidosis, anabolism may be very difficult to achieve due to reduced glucose tolerance and systemic insulin resistance. Human growth hormone has been beneficial in inducing anabolism in a variety of organic acid disorders and could be useful, at a dose of 0.05 mg/kg/day, in treatment of acute metabolic decompensation, although more studies are necessary.

In cases of high energy intake, fluid intake must be carefully balanced. During the first few days, the patient's weight can serve as a monitor of fluid intake, and later to determine if anabolism has been achieved. Continuous enteral feeding through a nasogastric tube should be started as soon as possible, beginning slowly and increasing progressively. If continuous vomiting occurs, treat with ondansetron (Zofran®) at 0.15 mg/kg during 15 min i.v., up to 3 times a day or granisetron (Kytril®) at 40 µg/kg every 24 hours.

In the case of reduced tolerance to fasting (Group III), the administration of glucose at a rate similar to that normally produced by the liver (7-8 mg/kg/min in newborns) is sufficient.

For energy metabolism disorders, the deterioration of lactic acidosis may on occasion require the administration of glucose be limited to 3-5 mg/kg/min while the early addition of fats to the treatment (2-4 g/kg/day) may be beneficial.

Protein restriction in protein catabolism disorders

Proteins must be added to the diet in order to allow anabolism to occur. For infants in coma due to hyperammoniemia, maple syrup disease or organic acid metabolism disorders, the intake of natural proteins or of specific amino acids should be suspended, with a period of 24-36 hours generally considered to be optimum. Under these circumstances, the daily monitoring of plasma amino acid concentrations is indispensable as protein malnutrition can prolong the state of catabolism. Natural proteins are administered in the form of maternal milk or infant formulas. In disorders of the urea cycle, a mixture of synthetic essential amino acids, starting with a protein equivalence of 0.5-0.8 g/kg/day, helps to reduce the nitrogen load. The prime objective is to achieve an intake of the daily protein requirement while testing individual protein tolerance. It must be kept in mind that the initial requirements may exceed the daily dietary recommendations due to rapid protein synthesis and growth recuperation. Low levels of essential amino acids indicate that a higher level of protein intake is required.

For the treatment of acute crises in maple syrup disease, a mixture free of branched amino acids is necessary. Their use in the synthesis of systemic proteins reduces plasma levels of leucine, isolucine and valine. In other disorders of organic acid metabolism, toxic metabolites are not recycled during protein synthesis. For this reason, a mixture free of amino acid precursors will not be beneficial for the metabolic crisis and may even worsen the hyperammoniemia due to excess nitrogen. For this reason, this treatment should only be started once catabolism has been reversed. Some amino acids should be administered separately as they limit protein synthesis, such as valine and isoleucine in maple syrup disease.

Detoxification/administration of vasoactive drugs

For disorders of endogenous intoxication, detoxification measures should be maintained. In diseases of the urea cycle, treatment with

L-arginine, sodium benzoate and phenylacetate/sodium phenylbutirate should be continued. During the neonatal period, levels of plasma sodium benzoate should be monitored, especially in infants with ictericia, although this analysis is not available in the majority of centers. The risk of sodium benzoate and phenylacetate/phenylbutirate toxicity is low when administering the doses shown in table 2.5, but higher doses may be necessary if there are no positive results. In addition to ammonia, plasma amino acid levels should be monitored during detoxification; the goal here is to achieve a glutamine concentration below 800-1,000 µmol/l. Arginine levels should remain above 80 µmol/l. In cases of arginine succinic liaise deficiency, high doses of L-arginine (6 mmol/kg/day) may be sufficient for detoxification. Citrate may be added to compensate for its loss secondary to the formation of intermediate compounds of the Krebs cycle, although there has been debate regarding this treatment. High doses of L-arginine may also be required in situations of citrulinemia. For ornitincarbamyltransferase and carbamylphosphate synthetase deficiencies oral citruline treatment may be beneficial instead of L-arginine. In N-acetylglutamate synthetase deficiency, the treatment of choice is N-acetylglutamate. In organic acid metabolism disorders, treatment with carnitine is maintained at 100-300 mg/kg/day. This re-establishes free CoA levels in the mitochondria and promotes the excretion of short chain acylcarnitines. Serum levels of free carnitine should be in the upper limits of normal levels. Sodium bicarbonate may be necessary if metabolic acidosis exists, but should be administered with caution in cases of hyperammoniemia. In the case of severe hyperammoniemia (which mcommonly appears in cases of propionic acidemia) arginine may be given to stimulate the urea cycle through activation of N-acetylglutamate synthetase. However, depending upon ammonium levels, the administration of benzoate and sodium phenylbuterate/phenylacetate may also be necessary. In patients with metylmalonic or propionic acidemia, treatment with N-carbamylglutamate may be effective in reducing ammonium levels.

In some acidopathies treatment with the cofactor should be attempted. For example, in all cases of methylmalonic acidemia, hydroxycobalamine should be used. Biontine is the treatment of choice for deficiencies of holocarboxylase synthetase and biotinidase, while Riboflavin should be used in glutaric acidemias types I and II. Any severe metabolic decompensation with severe lactic acidosis accompanied by insufficient food intake, should be treated with thiamine. In methylmalonic acidemia, forcing diuresis and alkalinizing the urine with sodium bicarbonate helps to eliminate the methylmalonic acid. In propionic and methylmalonic academia, metronizadol suppresses the intestinal bacterial production of propionate. For cases of isovaleric acidemia and methylcrotonyl-CoA carboxylase deficiency, glycine in combination with carnitine can be used to promote the excretion of glycine conjugates. This is very useful in the long-term treatment of these conditions. In emergency situations, carnitine alone is used as it is essential to compensate the secondary carnitine deficiency.

In maple syrup urine disease extra-corporal detoxification may be necessary if leucine levels exceed 1,500 µmol/l (20 mg/d) and clinical neurological signs exist. As in hyperammoniemia, continuous venovenosa or arteriovenosa hemodialysis, hemofiltration and hemodiafiltration have shown to be effective. The response to thiamine must always be monitored. For tyrosinemia type I, NTBC (2-[2 nitro-4 trifluoro-methylbenzoyl]-. 1,3, - cyclohexanedione) is the treatment of choice to prevent the production of toxic metabolites.

Conditions which are accompanied by hyperhomocystinemia, such as homocystinuria and diseases affecting the transfer of methyl groups (including methylentertrahydrofolate reductase deficiency), may require treatment with hydroxycobalamine, folic acid, pyridoxine, betaine or methionine, depending on the underlying enzymatic defect.

For disorders in the oxidation of long-chain fatty acids, care must be taken in the administration of carnitine as there is a risk

of the formation of toxic acylcarnitines, although severe secondary deficiency of carnitine must be carefully treated with oral carnitine. For other diseases of fatty acid oxidation, including defects in the carnitine transporter and MCAD deficiency, early treatment with carnitine can be beneficial to compensate for the primary or secondary deficiency and promote the excretion of acylcarnitine esters.

The initial treatment of hyperinsulinism may require, in addition to high concentrations of glucose, the administration of glucagons and/or diazoxides.

In congenital lactic acidemias, there are few strategies that have proven to be effective. Treatment with thiamine (cofactor of the pyruvate 3-dehydrogenase complex), riboflavin (cofactor of the I complex) and biotin (cofactor of pyruvate carboxylase) should be tried. Secondary carnitine deficiency is treated with L-carnitine, the metabolic acidosis with sodium bicarbonate and, if sodium levels exceed 160 mmol/l, with trometabol.

In cases of epileptic encephalopathy, pyridoxine and folic acid should be tried. If metabolism dysfunctions are suspected, some medications should be restricted for acute emergencies where no other effective treatment is available as they may inhibit the mitochondrial function. This includes sodium valproate, chloral hydrate, chloramphenicol, tetracyclines and salicylates.

Precaution before discharging the patient from the hospital

The child's parents should know the causes and signs of early metabolic disequilibria, and should be shown how and when to administer emergency treatment at home. Every patient should receive a written emergency treatment protocol, describing the individual steps that should be followed at home and in the health center or emergency room where it is unlikely that a specialist in metabolic diseases will be on duty. The child's pediatrician should also be made aware of this written protocol. Gastrostomy or nasogastric feeding tubes allows enteral alimentation rich in calories, as well as

TABLA 2.7. Nutritional follow-up of IEM

Clinical	• Weight, Height, cephalic perimeter, subcutaneous folds • Specific clinical aspects • Psychomotor development
Biochemical	• Specific metabolites of IEM (aa, organic acids, etc.) • Blood, hepatic, renal functions • Carnitine • Specific biochemical analysis (succinylacetone, etc.)
Nutrition and dietary	• Nutritional intake • Elaboration of individual diets • Plasma AA (in protein restricted diets) • Essential fatty acids (in fat restricted diets) • Hemoglobin, Hematocrit and ferritin • Oligoelements (zinc and selenium) • Liposoluble vitamins

pharmacological treatment in the case of a refusal to eat. The introduction of a portable catheter system may be very useful and allows for an immediate central pathway for emergency treatment.

2.6. NUTRITIONAL MONITORING FOR IEM

The IEM are one of the most interesting challenges for Departments of Pediatric Nutrition and Metabolism. For these diseases, a correct diet may prevent all symptoms, and on many occasions is the only treatment that improves the definitive prognosis. For this reason, the development of special diets for each IEM requires a constant nutritional monitoring of every patient to ensure adequate nutrition and development. We must keep in mind that the treatment of many IEMs includes a low-protein diet, and that the main objective is to provide the patient with the maximum intake of protein possible to ensure proper growth without triggering the metabolic alteration.

As these patients are on special diets, frequent and regular monitoring is essential (Table 2.7):

- Clinical.
- Biochemical.
- Dietary.

Clinical controls

Periodic monitoring of the child's anthropometric parameters, including weight, height, head circumference, brachial perimeter and subcutaneous skin-folds (subscapular and triceps), should be performed in the clinic. In addition, the appearance of symptoms related to the IEM should be evaluated. These symptoms may be neurological (mental retardation, convulsions, loss of or lack of acquisition of psychomotor skills, etc.), digestive or related to the liver (appetite, vomiting, choluria, acholia, ictericia), cardiological, renal, or may affect the skin, nails and hair. The examination of the patient should also be oriented towards detection of the principal symptoms and complications that can arise in IEM.

Analytical controls. Biochemistry

The periodic evaluation of diverse biochemical parameters must also be performed. In all IEM, it is necessary to perform a basic hematogram, coagulation tests, general biochemistry, and hepatic and renal function profiles. Periodic monitoring of amino acids, carnitine and organic acids in blood and urine are the basis of the evaluation and monitoring of many amino acid disorders. Additionally, an analysis of the levels of diverse metabolic toxins that produce the symptoms of IEM should be performed regularly, since the purpose of dietary treatment is precisely to regulate these substances. For tyrosinemia for example, succynilacetone levels must be monitored, while for organic acidemias levels of propionate, methylmalonate, etc., should be controlled. On the other hand, the periodic monitoring of protein compartmentalization by determining the levels of proteins with a short half-life, such as prealbumin or retinal binding protein, should be performed in diets that include protein restrictions. Moreover, these restrictive diets

require periodic monitoring of vitamin levels and a variety of related micro-nutrients such as iron, zinc, selenium and vitamin B_{12}. In diets where fat intake is restricted and when there is liver affectation with or without cholestasis, the levels of lipid-soluble vitamins must also be determined.

Diet

Patients with an IEM must follow their specific diet religiously, since this diet constitutes the principal and sometimes the only treatment. In order to follow these diets, diverse specialized food preparations and specific units of each food group are currently available. These are listed in appendix 1 along with commercially available products. The diet must be tailored to each patient, taking into account the basic needs of the child and the characteristics and nutritional restrictions specific to the IEM in question. In addition, the likes and dislikes of the child should be taken into consideration. Thus, when a diet is designed, it should be based on the general considerations of each IEM and then adjusted to the characteristics of each child. In the dietary treatment of IEM, two important parameters demonstrating the effects of the diet should be monitored, the physical development of the child and the biochemical analyses specific to the IEM in question.

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3 Inborn errors of carbohydrate metabolism

3.1. GLYCOGENOSIS

Glucose is the only monosaccaride that can be used in human cellular metabolism to obtain ATP. Thus, all tissues of the body can use glucose to produce energy through glycolysis and the Kreb's cycle. It is very unusual that glucose be a source of carbohydrates in a normal diet. In general, carbohydrates are ingested in the form of fructose, galactose, lactose, sacarose, and starches, which are incorporated through the glycolytic pathway of the liver to be metabolized. A genetic defect in one of these conversion processes can lead to the accumulation of intermediate substances which are toxic to the organism. Additionally, the inability to convert other carbohydrate sources into glucose results in the loss of a possible energy source for the organism, which can be very serious if it is the endogenous carbohydrate (glycogen) that cannot be metabolized to glucose[1].

The majority of the body's glycogen stores are found in muscle tissue and the liver. In muscle, as in other tissues, glycogen is used as local cellular glycolytic fuel, while the glucose produced through glycogenolysis in the liver is secreted into the extracellular fluid to help maintain circulating glucose levels, especially during early fasting, and for use by other tissues.

Figure 3.1. provides a metabolic flowchart which shows the principal alterations present in glycogenosis.

Alterations in glycogenolysis which are susceptible to dietary treatment comprise a group of diseases characterized by an increase in intracellular glycogen, mainly in hepatocytes and muscle fibers. This is a result of an enzymatic deficiency at some point along the glycogenolytic or glycolytic pathway which impedes glycogen

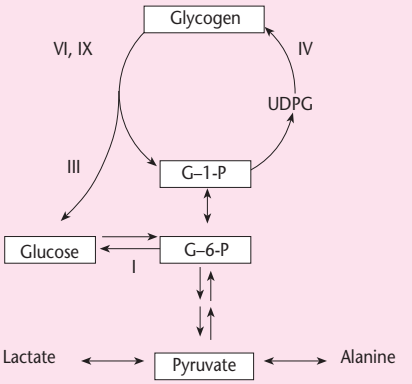

Figure 3.1. Types of glycogensis with abbreviated glycogenolytic, glycolitic and glyconeogenic pathways: I = glucose-6-phosphatase deficiencies; III = debranching enzyme deficiency; IV = branching enzyme deficiency; VI = liver phosphorylase complex deficiency; IX = phosphorylase b-kinase deficiency; G-6-P: glucose-6-phosphate; G-1-P: glucose-1-phosphate.

TABLE 3.1. IEM of carbohydrates. Glycogenosis

Glycogenosis[2] **(Different enzymatic deficits)**	
Pathophysiological group	• Type III
Incidence (cases/NB)	• 1/25,000
Debut Age	• Infant • Early childhood
Clinical aspects	• Hypoglycemia • Hepatomegaly • Prominent abdomen • Short height • Doll face • Muscle disorder (hypotony) • Cardiac, renal disease
Treatment	• Avoid hypoglycemia • Biotin • Liver transplant
Prognosis and complications	• Hepatic tumors • Osteoporosis • Renal failure

TABLE 3.2. Dietetic treatment objectives of type I glycogenosis. Biochemical parameters

	Parameter	Value
Blood	Preprandial glycemia	≥3.9 mm/l (70 mg/dl)
	Lactate	2-5 mm/l (18-45 mg/dl)
	Uric acid	< 0.4 mmol/l (7 mg/dl)
	Triglycerides	< 6 mmol/l (< 545 mg/dl)
	Base excess in venous blood or	> - 5 mmol/l
	bicarbonate in venous blood	> 20 mmol/l
Urine	Lactate (12 hour urine)	0.2-0.6 mm/l
	Lactate/creatinine ratio	< 0.06 mmol/l

Glucose requirements of each patient should be individually calculated. A single measurement of blood glucose is not very reliable due to the great variation during the day. It is best to use home capillary blood glucose monitoring for 48 hours, day and night. Measurement of lactate in urine or lactate/creatinine index gives more reliable information of lactate production.

degradation and the liberation of glucose to the blood[2]. In this chapter we will discuss the following clinical conditions (Fig. 3.1): a) Glycogenosis type I (glucose-6-phosphate deficiency); b) Glycogenosis type III (amylo-1-6-glycosidase or glucose debranching enzyme deficiency); c) Glycogenosis type VI (liver glycogen phosphorylase deficiency); and d) Glycogenosis type IX (phosphorylase-kinase deficiency).

The principal treatment for this group of diseases is to maintain blood glucose levels at optimum levels, and most importantly, to prevent hypoglucemia (Table 3.2). Indeed, hypoglucemia is responsible for the clinical and biochemical manifestations of these conditions, as well as for their complications[3]. To this end, a continuous source of exogenous glucose must be available both day and night by providing frequent meals (every 2-4 hours) rich in carbohydrates during the day, and a nocturnal glucose infusion through a nasal-gastric probe or preferably via gastrostomy. The administration of raw corn flour can also be used, especially for older children[2].

Glucose requirements of each patient should be individually calculated. A single measurement of blood glucose is not very reliable due to the great variation during the day. It is best to use home capillary blood glucose monitoring for 48 hours, day and night. Measurement of lactate in urine or lactate/creatinine index gives more reliable information of lactate production.

Glycogenosis type I

For infants, an intake of 8-9 mg/kg/min of glucose is necessary (blood glucose levels must be monitored to adjust treatment according to the requirements of each patient*). During the day, the infant should be fed every 2-3 hours. The same rate of feeding, every 2-3 hours, can be maintained at night or nasogastric feeding can be used. There is disagreement among doctors about the use of formulas without lactose and sacarose as some doctors contend they exacerbate hyperlactacidemia. If the intake of carbohydrates from the formula does not maintain adequate blood glucose levels, it can be enriched with glucose polymers (Maxijul®, Fantomalt®, Polycose®) depending on the requirements of the patient. After 4 months of age, precooked starches (rice and corn) should be added to the diet, gradually increasing the intake until it reaches 6% of the concentration of the formula, in order to prolong gastric emptying. The diversification of the diet during the first year will generally follow the same chronological sequence as a normal infant. The frequency of each meal can be reduced to intervals of 3 hours during the day and 4 hours during the night at an age of 6-12 months if the patient responds well.

Preschool and older children

The quantity of glucose administered should be gradually reduced to 5-7 mg/kg/min during the day and 5 mg/kg/min at night, as glucose requirements are lower at night. The administration of glucose should be monitored closely as excess glucose can induce a vulnerability to hypoglucemia while insufficient

levels can cause intense hyperlactacidemia and delay growth. An increase in the concentration of lactate to 5-6 mmol/l is permitted, as it serves as an alternative substrate, especially in the brain, when glucose concentrations are low. The diet should contain a composition of 60-70% carbohydrates, 10-15% proteins and the rest fats (20-30%). Meals rich in complex carbohydrates with slow or semi-slow absorption, such as rice, oats, pasta, legumes, etc. are recommended, while the intake of saccarose, fructose and lactose (no more than 0.5 l of milk per day) should be limited. As this diet provides limited amounts of calcium, ascorbic acid and other micro-nutrients, vitamin and mineral supplements should be gadded to ensure proper growth and development.

- Raw corn starch can be introduced safely after 2 years of age, as it is not digested well before this age. It is recommended because it contains a high concentration of branched glucose chains that are slowly hydrolyzed and released, allowing blood glucose levels to be maintained at normal levels for 6-8 hours. Indeed, it is even more effective than an equivalent intake of glucose every 3 hours. It can be used as supplement to the oral feedings during the day with nocturnal enteral feeding or it can be given every 4-6 hours around-the-clock without nocturnal feedings providing metabolism and growth are under control. The dose of corn starch can range between 1.5 and 2.5 g/kg[5-7] every 4-6 hours during or after meals. It should be prepared in cold water at a concentration of 1:2 (weight:volume). Unheated milk, pudding or yogurt may also be used, but it should not be mixed with sugars that are rapidly absorbed. Other starches, such as rice, tapioca or wheat, do not have the same desired results, nor does gofio (flour obtained from toasted cereals).
- Nocturnal enteral feeding is normally given over 12 hours in order to maintain adequate growth and to prevent nocturnal hypoglycemias. Once the infusion is finished, breakfast should be taken no more than 15 minutes later to avoid a rapid drop

in glucose levels. Approximately 30-35% of the daily energy intake should be in the form of formula, or in older children, as a solution of glucose polymers dissolved in water to avoid high caloric intake.

Adolescents and adults

Adolescents and adults require a nocturnal glucose infusion rate of less than 3-4 mg/kg/min. A meal rich in starch (1.5 g/kg cornstarch) at bedtime can provide adequate levels and can substitute nasogastric feeding once pubertal growth has finalized. Some authors recommend restricting the intake of saturated fat and increasing polyunsaturated fats to control hyperlipidemia[6].

Prevention of complications

Gout and the formation of kidney stones can be prevented with the administration of alopurinol (10-15 mg/kg/day). Treatment should begin when hyperuricemia persists (>7 mg/dl or 400 µmol). Additional measures include the administration of sodium bicarbonate to decrease urine acidity and the intake of large amounts of water. Liver adenomas are frequently produced in patients that are not treated adequately. In some cases a reduction in the size of the adenoma is reported once intense dietary treatment is begun.

Glycogenosis type III

In this form of glycogenosis, although glycogenolysis is reduced, glyconeogenesis is normal or even increased. A restriction on the intake of lactose or sacarose is not necessary as galactose and fructose can be normally converted to glucose. There is some controversy surrounding the treatment of these patients. Some doctors recommend treatment similar to that used in glycogenosis type I, but since the tendency for hypoglucemia is less severe, the treatment is normally less demanding (during the day frequent meals rich in carbohydrates that are slowly absorbed along with

one nocturnal enteral feeding or supplements of raw cornstarch). For a young patient, the daily dietary intake should consist of 50-55% carbohydrates, 25% proteins and 20-25% fats. Protein intake should not be restricted as the amino acids serve as a substrate for gluconeogenesis. It is thought that proteins play an important role in the treatment of miopathic forms of glycogenosis III.

In contrast, other authors[8] recommend a diet low in carbohydrates (45%) and with a high protein content (25%) that will serve as the substrate for gluconeogenesis to treat the hypoglucemia, impede the accumulation of glycogen in the liver and muscle tissue, improve protein synthesis in muscle tissue and reduce hypertriglyceridemia. The diet should include frequent high-protein low-carbohydrate meals during the day and high-protein enteral feeding at night for severe cases.

Glycogenosis type IV

The only treatment for this disease is a liver transplant. However, while waiting for a transplant, the hypoglucemia can be treated with continuous enteral nutrition and cornstarch, as in type I.

Glycogensosis types VI and IX

The clinical characteristics of these forms are similar to those found in types I and III, but with less severe metabolic abnormalities. There is slight hypoglucemia that normally does not require treatment, except during prolonged periods of fasting. Additional nocturnal feeding should be implemented during infectious processes.

3.2. INBORN ERRORS OF GALACTOSE METABOLISM

Galactose is a monosaccaride commonly found in foods, especially in milk, legumes, fruits and cereals. It is metabolized to galactose 1-P by the enzyme galactokinase (GALK) and then to uridyl-diphosphate- galatose (UDP-Gal) in a reaction catalyzed by

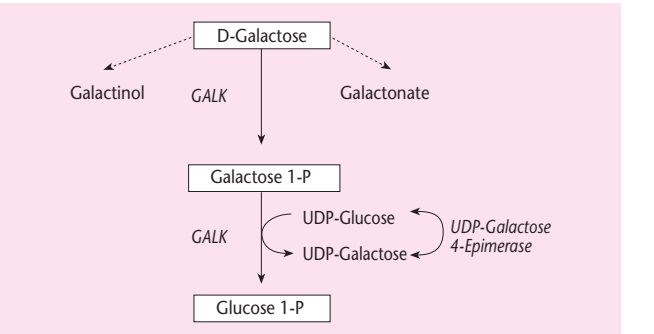

Figure 3.2. Galactose is mainly metabolized in the liver. Initially, it is phosphorylated by galactokinase (GALK) to galactose-1-phosphate (galactose-1-P), which interacts with the UDP glucose molecule by galactose-1-phosphate-uridyl transferase (GALT), releasing glucose-1-phosphate (Glucose 1-P) and producing UDP-galactose, by action of the UDP.

the enzyme galactose 1-P uridyltransferase (GALT). Glucose-1-P can enter the Kreb's cycle, while UDP-Gal can be used in the synthesis of glycoconjugates or, through the action of epimerase, be converted to UDPGlu and then to glycogen (Fig. 3.2).

The most frequent enzymatic deficiencies include GALK (1/60,000 newborns) and GALT (1/50,000 newborns). The only clinical manifestation of GALK deficiency is the appearance of bilateral cataracts, while GALT deficiency produces classical galactosemia. The pathogenesis of galactosemia is not fully known, but the increase in galactilyol and galactose-1-phosphate is thought to be responsible for the development of cataracts and the liver-kidney damage.

The first symptoms are usually observed after the first weeks of life and include vomiting, failure to thrive, lethargy, progressive ichtericia, which is confirmed by hepatic (increased transaminases, bilirubin) renal (proximal tubulopathy: hyperchloremic acidosis, glucosuria, albuminuria and amino aciduria) function testing, as well as glactosuria (Clinitest: reducing bodies +) (Table 3.3). The diagnosis can be verified by determining the enzyme deficit in

TABLE 3.3. IEM of carbohydrates. Galactosemia

Galactosemia[9] (↓ uridyl transferase galactose)	
Pathophysiological group	• Type II
Incidence (cases/NB)	• 1/50,000
Debut Age	• Neonatal • Early childhood
Clinical aspects	• Progressive • General toxic syndrome (vomiting, lethargy, rejects feedings, failure to thrive) • Cataracts • Hepatic failure • Proximal tubulopathy
Treatment	• Avoid galactose and lactose in diet • Calcium
Prognosis and complications	• Mental retardation • Ataxia • Gonadal dysfunction • Pubertal delay in girls

erythrocytes. However, if the patient has previously received a blood transfusion, other cells, such as fibroblasts, can be tested.

The patient's genetic mutation, and that of the immediate family should be determined wherever possible. The treatment of this disease requires the total suppression of lactose from the diet for the entire life of the patient, without exception. Mammalian milk and its derivatives is the main source of lactose, but it is also present in diverse medications, manufactured products and a wide variety of commercial products[4,9].

For newborns, correct treatment includes the use of a formula that is completely free of lactose, ideally based on soy products[10]. Formulas with hydrolyzed bovine proteins may contain lactose derived from the casein and serum albumin fractions. The problems to maintain a galactose-free diet begin with the introduction of complementary alimentation.

This is due to the current difficulty in obtaining information concerning the content of free or bound galactose in foods and the lack of knowledge concerning the ability of the organism to use α or β linked galactose chains. α-Linked galactose chains are present in animal organs (brain, kidney, liver, pancreas or spleen), in polysaccharides of plant origin such as raffinose, staquios and verbascose, very abundant in some cereals and legumes, and in some complex molecules such as galactopinitols, found in dry legumes. α-linked galactose chains are found as parts of complex molecules (arabinogalactons I and II, galactolipids, etc.) that are essential constituents of the cell walls of many fruits and legumes. In any case, from a practical point of view, these non-milk food products are all insignificant sources of galactose when compared to endogenous production and there is therefore no clinical evidence to support their exclusion from the diet.

Lactose is commonly found in the composition of many medications. This is generally indicated on the packaging and, in the case of doubt, it is relatively easy to obtain information from the manufacturer. Some products, such as calcium lactobionates, are sources of galactose in the intestine and cannot be used as calcium supplements in these patients.

It is, however, practically impossible to know the amount of free or bound galactose contained in the majority of home-made food products and all such foods that are not prepared at home should be avoided. Industrial manufacturers are also unreliable since current legislation regulating product labeling allows an indeterminate amount of galactose to go unperceived, especially in the form of artificial flavorings and sweeteners (Table 3.4).

It has been shown that if a child over three years of age follows a diet for children with galactosemia that is not specifically supplemented, adequate intake of calcium is not assured. For this reason, after this age oral Ca^{++} supplements must be included in the diet. The dose will depend on the dietary intake of each patient

TABLE 3.4. Guideline of foods for galactosemia

Foods to be freely used	Foods for use under control of Gal-1-P[a]	Foods not recommended*
Milk and derivates		
Soy formulas	Soy formulas with soy flour	Milk and derivatives (caramel custard, creams, yogurts, cheeses, etc.) Drinks with milk
Cereals		
Wheat, barley, oats, common rye, corn, rice All pastas manufactured without milk: noodles, macaroni, spaghetti, pancakes, popcorn without butter, etc.	Soy flour	All products made with milk
Pastry		
Sweet made of pumpkin and syrup, gelatine, All products made without milk.		All products made with forbidden elements
Eggs		
All		Recipes with milk
Fats		
Bacon / Fat Lard / Fat Margarine without milk Vegetable oils		Butter. Cream Margarine with milk Products with caseinate Peanut butter with milk
Vegetables		
Artichoke, asparagus, squash, beet, cauliflower, celery, cardoon, cabbage, lettuce, mushroom, parsley, radish, eggplant, carrot, onion, broccoli, white cabbage, cucumber, turnip, potatoes, spinach, green bean	Pumpkin, Brussels sprouts, peppers, leek, tomato	Peas
Sugars/sweetener		
Cane sugar Corn syrup Honey Jams of permitted fruits Maple syrup Saccharine	Fruit jams to control Cacao Yeast	Syrup and apple molasses Sweeteners with lactose Jams of forbidden fruits Toffee candies
Meats/fish/poultry		
Ox, chicken, veal, lamb, beef pork, ham, fish, shell fish		Canned food and cooked with milk Control sausages, cured ham, etc. Offal: brains, kidneys, liver, pancreas, spleen

TABLE 3.4. Continuation

Foods to be freely used	Foods for use under control of Gal-1-P[a]	Foods not recommended*
Legumes/Seeds		
Peanuts, walnuts, olives	Sunflower seeds	Chick peas, lentils, beans, peas, hazelnut
Fruits/Juices		
All juices without lactose, or non-forbidden fruits Apricot, avocado, cherry, melon, grape juice, lemon, clingstone peach, orange, apple, mango, banana, pear, peach, strawberry, grapefruit, grape	Plum, watermelon, kiwi	All conserves with lactose Dates, dried figs, prunes, caqui, raisins

[a]Galactose 1-P (Gal-1-P) is used as biochemical parameter for dietetic control (VN ≤ 4mg/dl).
**There is no unanimous agreement on the use of legumes. Probably, most of the patients can tolerate moderate amounts of these foods, but it is best not to abuse them in the daily diet.*

and if possible, calcium carbonate (Caosina®, 1 g supplies 400 mg of elemental Ca) or calcium pidolate (Ibercal®) for its reduced chelating effect (375 mg of calcium pidolate = 50 mg Ca^{++}. Oral solution: 10 ml = 135 mg of Ca^{++}, 1 envelope = 500 mg of Ca^{++}) should be used. Effervescent tablets are not indicated as they contain lactose.

In patients with GALK deficiency milk should be eliminated from the diet, but it appears that they can tolerate foods will lower galactose content such as milk derivatives, legumes, etc. In any case, and given the danger of developing cataracts, milk should be eliminated from the diet for the entire lifetime.

The peripheral forms of epimerase deficiency do not require treatment, but should be carefully monitored. Those suffering from more severe forms of epimerase deficiency must follow a galactose restricted diet for life. However, given that these patients are galacotose- dependent for UDP-galactose synthesis, it is difficult to obtain an adequate equilibrium between intake and necessity[4].

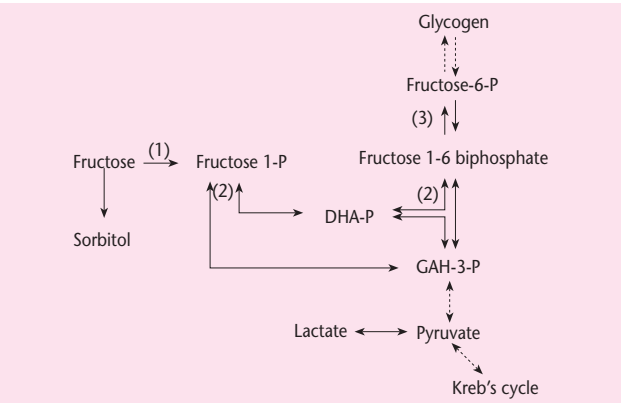

Figure 3.3. Metabolism of fructose in the liver. DHA: dihydroxyacetone; GAH: glyceraldehyde; P: phosphate. (1) fructokinase, (2) aldolase B, (3) fructose 1-6 biphosphatase.

3.3 INBORN ERRORS OF FRUCTOSE METABOLISM

There are two known genetic defects of fructose metabolism, essential or benign fructosuria due to deficit in fructokinase and hereditary fructose intolerance due to a deficit in aldolase B (Fig. 3.3). The first form is asymptomatic and benign, requiring no treatment. However, all sources of saccarose, fructose and sorbitol must be eliminated from the diet of those suffering from hereditary fructose intolerance.

For hereditary fructose intolerance the first symptoms become apparent when complementary foods containing fructose (fruit) and/or sacarose, which may be present in commercial infant cereals, begin to be introduced to the nursing infant's diet. Fructose- 1-phosphate-aldolase deficiency can result in liver and kidney damage (Table 3.5), very similar to what is seen in galactosemia. From a clinical point of view, the infant may suffer from ichtericia and, depending upon the amount of fructose or sacarose ingested, they may also suffer from hemorrhages, ascitis and abdominal distention, with the possibility of acute liver failure and the need for a liver

TABLE 3.5. IEM of carbohydrates, hereditary intolerance to fructose

Hereditary intolerance to fructose (↓ aldolase B)	
Pathophysiological group	• Type II
Incidence (cases/NB)	• 1/20,000
Debut Age	• Infant (with onset of fructose intake)
Clinical aspects	• Acute symptoms (vomiting, lethargy, dehydration, coma, acute hepatic failure, renal tubular dysfunction) • Chronic symptoms (isolated vomiting, eating difficulty, hepatomegaly, failure to thrive)
Treatment	• Eliminate fructose, sucrose and sorbitol from diet • Vitamin C • Folic acid
Prognosis and complications	• Good prognosis with strict diet

transplant. Clinical symptoms may include vomiting, lethargy and a failure to thrive with a less pronounced development[11].

In a clinical analysis these patients may suffer from hypoglucemia, increased transaminases, hypoalbuminemia, low cholesterol and alterations in vitamin K dependent coagulation tests. They also display symptoms compatible with Fanconi's tubulopathy. The definitive diagnosis can be made by determining the levels of enzyme in a liver biopsy of the patient. Genetic diagnosis of the most frequent genetic mutation in Caucasians (A149P) can be made with a sample of dry blood.

Dietary treatment of hereditary fructose intolerance includes exclusion of fructose, sucrose and sorbitol from the diet[4]. This diet must be strictly followed for life, without exception, since even small quantities of fructose can be harmful, causing abdominal pain, vomiting and possible growth retardation[11]. The total daily

intake of fructose from all sources should be 1-2 g, derived from free fructose, saccarose and sorbitol. Natural fructose is found in honey (20-40%), fruits, fruit juices (20-40%), vegetables (1-2%) and other plant foods. The quantity of fructose/saccarose in fruits and vegetables may vary according to the growth conditions of the plant. Storage after harvesting also affects the sugar content. For example, new potatoes have a higher content of fructose than old potatoes (0.6 g/100 g versus 0.25 g/100 g, respectively). Fructose is frequently used as a sweetener in foods and medications. Corn syrup is rich in fructose and is increasingly used as a sweetening agent in industrial food production. Crystallized fructose is recommended as an alternative to saccarose as it is sweeter than table sugar and less caloric. Many products for diabetics are sweetened with fructose or sorbitol.

Saccarose is found in the diet as sugar (white sugar, brown sugar, cane sugar, beet sugar, powdered sugar), syrups (including those used in medications), candy, desserts, soft drinks and as a natural ingredient of fruits (1-12%), fruit juices and many plants and vegetables (1-6%). Even some brands of toothpaste contain saccarose[8]. Sugar is the main ingredient in cakes, cookies, desserts and soft drinks, but it is also found in many other commercial foods such as canned meats, sauces, soups, crackers, foods for children and breakfast cereals, although it is less evident. In fact, very few commercial foods can be included in the diet of these patients. Artificial flavors are also a potential source of fructose and saccarose as these sugars are sometimes used as vehicles for the flavorings. Inverted sugar is obtained from the acidic hydrolysis of saccarose.

Sorbitol, found in fruit, vegetables and as a sweetener in diet foods, is another source of fructose. Raffinose and stachyose are complex carbohydrates that contain fructose and are found in legumes while small quantities can be found in grains, nuts, seeds and vegetables. However, due to the absence of a-galactosidase in the human intestine, appreciable quantities of fructose do not appear to be absorbed from these compounds. Fructose polymers

such as inulin are widely found in various plants, such as artichokes, but they are also not absorbed and undergo fermentation by bacteria in the colon.

Only those vegetables that predominantly contain starch, such as green leafy vegetables, can be included in the diet. As cooking results in the loss of free sugars, cooked vegetables are recommended over raw[12-14]. Sources of alternative carbohydrates to be included in the diet of these patients include glucose, lactose from milk and milk derivatives, and permitted starches. Glucose can be used as an alternative to sugar and can also constitute a useful source of energy.

It is important to supplement the diet with vitamin complexes containing vitamin C, given that all sources of this vitamin are excluded from the diet. The inclusion of folic acid is also recommended as it seems to increase the activity of glycolytic enzymes, including fructose-1-phospho aldolase. Saccarose, as well as fructose and sorbitol, are frequently used as excipients and coating for pills, as well as in syrups and suspensions for infants and children. Thus, the ingredients of all medications should be reviewed in detail with a pharmacist.

There is no unanimity with regards to the optimum diet for these patients (Table 3.6), especially with about permitted foods and the amount of fructose intake that is considered safe, as well as the relaxation of restrictions for older children and adolescents. Some authors suggest that after adolescence, at the end of the growth cycle, a greater number of vegetables can be included. However, the introduction of new foods must be closely controlled. Additionally, the aversion some patients have for foods that are harmful to them often impedes broadening the range of foods included in their diet.

During periods of fasting, the principal source of glucose is liver glycogen. Over the course of fasting, glycogen stores become depleted and glucose is synthesized by gluconeogenesis using substrates other than carbohydrates, that is, amino acids (alanine),

TABLE 3.6. Food guideline for Hereditary Intolerance to Fructose

Foods	Permitted	Not recommended
Milk and derivatives	Whole, semi-skimmed and skimmed milk Non-sweetened evaporated milk Powdered milk Milk fermented without added sugar Butter, margarine Natural yogurt Cheeses, cottage cheese Instant coffee, tea products	Condensed milk Milkshakes Ice creams Fruit, vanilla and flavored yogurts Liquid soy milk Infant formulas: Portagen, Isomil, Soylac, Alimentum Some cheese spreads or cheeses with added ingredients (e.g.. nuts)
Meats and fish	Veal, chicken, lamb, pork, rabbit, turkey, horse Offel Fish and shellfish Cured ham, bacon	Meats processed with added sugar, fructose or honey: meatloaf, Frankfurt hotdogs, raw cured sausage (salami, black pudding), liver pate, foie-gras, cooked ham
Eggs	All	None
Fruits	Avocado Lime juice Lemon or lemon juice	The remaining fruits and fruit products
Vegetables and legumes (cooked, discard cooking water)	Group 1(< 0.5g fructose/100g): broccoli, celery, artichokes, mushrooms, old potatoes, spinach, watercress, chard, curry endive, endives, lentils, mangetout Group 2 (0.5-1g fructose/100g): asparagus, cabbage, cauliflower, squash, green spotted zucchini, cucumber, leek, new potatoes, pumpkin, radishes, turnip, white beans, red beans, black beans, chickpeas	Beets, Brussel sprouts, carrot, onion, little onion, sweet potato, tomato, sweet corn, parsnip, green beans, canned vegetables with added sugar, mayonnaise or salad dressings Peas, soy, green beans with tomato

TABLE 3.6. Continuation

Foods	Permitted	Not recommended
Bread and cereals	Rice, wheat, rye, tapioca, semolina, (non-whole grain varieties) Corn flour, wheat, rice Pasta (preferably white): spaghettis, macaroni, noodle Unsweetened white bread Cream crackers, Matzo crackers, water crackers, Ryvita	Wheat bran, wheat germ All breads, cereals and cookies that contain sugar, wheat germ or wheat brand (whole gran varieties) Biscuits, deserts, pastry Pasta with tomato sauce Soy flour
Fats and oils	Vegetable oils Lard, fat	Commercial salad dressings Mayonnaise
Sugars and sweeteners	Glucose, glucose polymers, glucose syrups, glucose tablets, dextrose Lactose Starch, Maltose, maltodextrines, malta extract Saccharine, cyclamate	Sugar (cane, beet): white, brown, powdered Fruit sugar Fructose, levulose, sorbitol Lycasine, isomalt, hydrogenated glucose syrup Honey, jam, Jelly, desert sauces Caramel syrup, maple syrup, corn syrup, molasses Caramel, chocolates, toffees, gum, gum tablets

TABLE 3.6. Continuation

Foods	Permitted	Not recommended
Drinks	Tea, coffee, cacao Glucozade (not those of fruit flavors), soda water, mineral water Soft drinks sweetened only with saccharine or aspartame (without sugar or fruit flavorings)	Instant tea Drinking chocolate, malted milk drink Fruit and/or vegetable juices Soft drinks Drinks for diabetics that contain sorbitol or fructose
Others	Herbs and spices Vinegar, Bovril Salt, pepper Sesame seeds Sunflower and pumpkin seeds (maximum 10 g/day)	Vanilla flavouring Ketchup, commercial sauces, soup packages Remaining nuts (hazelnuts, almonds, chestnuts, peanuts, etc.), peanut butter

lactate, pyruvate and glycerol. In cases of fructose-1-6-biophosphatase deficiency (Fig. 3.3), the process of gluconeogenesis using these substrates, including fructose, is blocked and during periods of fasting patients may suffer from hypoglycemia and significant lactic acidosis accompanied by ketosis. In these cases there is an exclusive dependency on glucose (and galactose) intake and the degradation of liver glycogen to maintain normal blood glucose levels[12]. Therefore, the objectives of the dietary management of these patients are to prevent hypoglycemia, reduce the necessity of gluconeogenesis and promote large glycogen reserves. To achieve this, long periods of fasting must be avoided with frequent meals high in carbohydrates with slow absorption starches (70% of caloric intake), reduced fats (15-20%) and a protein intake of 10%. The intake of fructose, saccarose and sorbitol should be limited in small children and for all patients suffering from metabolic stress.

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4 Inborn errors of fat metabolism

4.1. ALTERATIONS IN BETA-OXIDATION OF FATTY ACIDS

During prolonged periods of fasting or in situations of high energy demand (e.g., intense exercise, infections, etc.), the oxidation of fatty acids constitutes the principle metabolic fuel since: a) they are a direct energy source for both skeletal and cardiac muscle; b) in the liver they give rise to ketone bodies, which are a supporting energy source for almost all tissues, including the brain, and c) they can supply sufficient energy for gluconeogenesis and ureagenesis in order to maintain adequate metabolic homeostasis during periods of fasting[1] (Fig. 4.1). Energy is obtained from β-oxidation of fatty acids (βOFA) through successive fragmentation of the fatty acid molecule into small molecules containing two carbons which, after being activated by CoA, form acetyl-CoA that then enters into the Kreb's cycle where it is further metabolized[2].

When β-oxidation is interrupted, the energy supply is blocked during periods of prolonged fasting resulting in metabolic decompensation characterized by hypoketotic hypoglycemia (an error in gluconeogenesis and the formation of ketone bodies) and hyperamoniemia (an error in ureagenesis). A dysfunction also occurs in the tissues which depend on lipid metabolism, which can explain the cardiomyopathies and myopathies that are frequently seen in patients with these disorders. This is most surely due to the potential toxicity of accumulated metabolites[3].

There is a broad spectrum of symptoms, leading to possible alteration in the βOFA in cases where hypoketotic hypoglycemia (in infrequent defects of ketonuria may appear in the case of

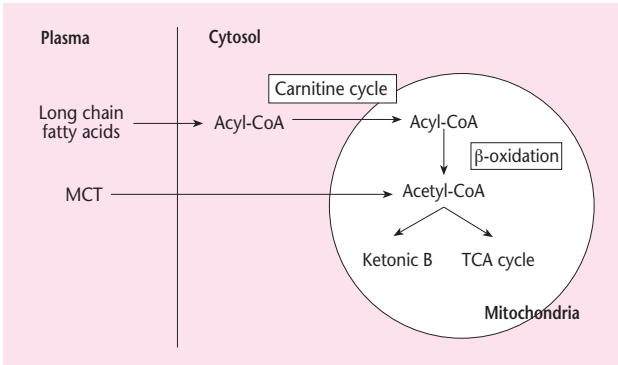

Figure 4.1. Fatty acid oxidation. Fatty acids of less than 10 carbon atoms freely enter the mitochondria through its membranes, while longer chain fatty acids need a transportation system called the carnitine cycle that includes 3 enzymes and carnitine. Previously, these have been activated to CoA esters by means of acyl-CoA ligase in the cytosol. MCT (medium chain fatty acids); Ketonic B (ketone bodies); TCA cycle (tricarboxylic acid cycle or Kreb's cycle).

infrequent defects in the β-oxidation of short chain fatty acids) is often a guiding symptom. The range of clinical symptoms can include liver failure, Reye-like syndrome, skeletal myopathy (hypotonia, muscular pain, rabdomiolysis), dilated myocardiopathy, arrhythmias, cyclic vomiting and sudden death syndrome. This wide range is due to the fact that the deficiency in each enzyme acting in different cycles and metabolic chains can be expressed more intensely in specific organs or systems. Depending on the degree of deficiency, these can appear at any age or in any situation (exertion, fasting, pregnancy, etc.).

Diagnosis is based on the above mentioned symptoms in addition to hypoglycemia, with the possible presence of acidosis and increased ammonium, lactic acid, transaminases and/or muscle enzymes (CPK). The diagnosis is confirmed by the analysis of: a) blood: decreased carnitine (in alterations of β-oxidation of short

TABLE 4.1. IEM of fats. Long and very long chain fatty acids beta-oxidation disorders

Beta-oxidation disorders[1-3] (↓ Acyl CoA of long and very long chain fatty acids)	
Pathophysiological group	• Type III
Incidence (cases/NB)	• 1/50,000
Debut Age	• Infant • Late
Clinical aspects	• Hypoglycemia • Reye-like syndrome • Muscle involvement • Cardiac disease
Treatment	• Diet: present fasting periods • MCT • DHA if low levels. Walnut oil • Liver transplant • Carnitine • Creatine: 130 mg/kg/day
Prognosis and complications	• Regular with frequent relapses with intercurrent conditions (viral disease, etc.) • 25% with residual neurological damage

chain fatty acids this is normal); increase in free fatty acids; increase in carnitine esters (acylcarnitines), which are altered in periods of decompensation and between crises, and b) urine: acylglycines and dicarboxylic acids. Given the different patterns in some of the illnesses, the final diagnosis should be done by enzymatic testing in fibroblasts and accompanied by genetic analysis. A summary of the clinical characteristics of these conditions is provided in tables 4.1 and 4.2.

Treatment of these alterations is based on decreasing the dependency on this metabolic pathway. This is accomplished by:

1. Avoiding fasting.
2. Controlling lipolysis by introducing a diet rich in slow absorption carbohydrates.

TABLE 4.2. IEM of the fats. Medium chain fatty acid beta-oxidation disorders

Beta-oxidation disorders (↓ Acyl CoA of medium chain fatty acids)	
Pathophysiological group	• Type III
Incidence (cases/NB)	• 1/10,000
Debut Age	• Infant > 2 years • Late forms
Clinical aspects	• Hypoglycemic coma • Hepatopathy (Reye-like) • Sudden infant death syndrome • Neurological disease • Possibility of late and monosymptomatic forms
Treatment	• Diet similar to those of long chain disorders • Do not administer MCT
Prognosis and complications	• Similar to long chain disorders

The diet should be characterized by[4]:

- Frequent meals that contain starch and/or slo absorption carbohydrates to obtain a slow release of glucose and maintain the blood glucose at normal levels. In infants less than 6 months of age, nightly feedings are required to avoid periods of fasting longer than 4 hours. These can be gradually increased according to the individual tolerance of each patient and by monitoring blood glucose levels. This will result in periods of approximately 6 hours between 6-24 months of age, 8 hours for children between 2-6 years and less than 12 hours for those over 6 years. Given that fatty acid oxidation increases as the period of fasting in prolonged, it is essential that a snack is taken during the night and that breakfast is not omitted. The diet should be balanced to provide an intake of carbohydrates between 60-65%, fats 30-35% and proteins 10-20%.

- At the age of 8-10 months (or even 2 years according to some authors) raw corn starch can be introduced into the diet at a dose of 1-2 g/kg/day.
- During situations of stress with poor oral tolerance and risk of hypoglycemia such as infections, fever or periods of prolonged physical exercise an emergency regime should be introduced[5] including frequent intake of fluids with high concentrations of sugar or glucose polymers (Fantomalt®, Maxijul®, Polycose®) both day and night and according to age.
- For cases of intermediate chain fatty acid disorders (ICFD), foods rich in intermediate chain fatty acids (ICF), such as coconut and particularly coconut oil, and infant formulas rich in ICF, must be avoided. In contrast, for long chain fatty acid disorders (LCFAD) when the intake of long chain fatty acids is limited to 40-60% of the total fat intake, ICF oil should be incorporated into the diet in a proportion of 40-60% of the total fat intake (1-1.5 g/kg)[7]. ICF oils can be used for cooking in substitution of common oils or fats. They will provide an additional energy source, and improve the taste of the diet. However, they should always be introduced slowly into the patient's diet. Extra care should be taken when cooking with these oils as they have a lower smoking point than other oils and may burn easily. When overheated these oils acquire a bitter flavor and disagreeable smell.
- Patients suffering from LCFA deficits are at risk of essential fatty acid (EFA) deficiency. It is necessary to monitor their levels and maintain an appropriate linoleic:linolenic acids level ratio (5:1-10:1). Although 1-2% of the total fat intake is in the form of EFA, docosahexaenoic acid (DHA) levels may be low and may need to be supplemented in some cases.
- Oral supplement with L-carnitine[8]: In most β-oxidation disorders plasma carnitne levels are low due to accumulation

TABLE 4.3. IEM of fats. Smith-Lemli-Opitz syndrome

Smith-Lemli-Opitz (SLO) syndrome (↓ 7-dihydrocholesterol reductase)	
Pathophysiological group	• Type I
Incidence (cases/NB)	• 1/20,000-40,000
Debut Age	• Neonatal
Clinical aspects	• Polymalformation syndrome • Serious mental retardation • Microcephalia • Gothic palate, palatal fissure • Failure to thrive • Heart disease • Eyelid ptosis • Cataracts • Genital abnormalities • Syndactylia 2-3 toes
Treatment	• Saturated fat rich diet • Cholesterol 1,200 mg/day • Cholesterol Module® • Ursodeoxycholic acid
Prognosis and complications	• Mild improvements in psychomotor development and no progression of the clinical picture with cholesterol treatment • Bad prognosis

of acylcarnitine. For patients with intermediate and short chain fatty acid deficits, total carnitine levels may be very low due to urinary loss. The administration of L-carnitine at a dose of 50-100 mg/kg/day is effective in compensating this urinary loss. Patients with long chain fatty acid deficiency should only be treated with L-carnitine if their plasma carnitine levels are low, as a possible increase in toxic long chain acylcarnitines levels can be harmful. Treatment with creatine at a dose of 150 mg/kg/day has also been proposed[9].

4.2. SMITH-LEMLI-OPITZ SYNDROME

Smith-Lemli-Opitz Syndrome (SLO) is the most frequent inborn error of cholesterol metabolism. The most obvious clinical symptoms include syndactily between the 2nd and 3rd toes, microcephaly, mental retardation, micrognathia and cleft palate. Other symptoms may include genital alterations, growth retardation, and malformation of other organs (kidney, lungs, liver, etc.). (Table 4.3).

Since 1994, when the relationship between SLO and cholesterol metabolism was demonstrated[10], treatment has been based on the addition of exogenous cholesterol to the diet. This can be provided by foods which are naturally rich in cholesterol (eggs, offal, cream and meats) at a dose of 50-300 mg/kg/day, or with pure cholesterol specifically formulated for pharmaceutical use that can be added to the child's diet[11]. A new pharmaceutical product, Cholesterol Module®, has been developed that permits an exact dosage of cholesterol to be administered. The treatment can also include the addition of biliary acids (ursodesoxycolic acid). This treatment has resulted in improved growth and decreased irritability of SLO patients.

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5 Inborn errors of amino acid and protein metabolism

5.1. GENERAL ASPECTS OF AMINO ACID DISORDERS

Of the 20 amino acids required for protein synthesis some include carbon chains that cannot be synthesized in the body (essential or indispensable amino acids), while the carbon skeleton of others can be synthesized from common intermediate products of metabolism (non essential or dispensable amino acids). The nutritional requirements of proteins refers to the need for essential amino acids, as well as a source of nitrogen for the synthesis of non-essential amino acids. The majority of the nitrogen for this synthesis must come from amino groups of amino acids, since the body has limited capacity to incorporate inorganic nitrogen (ammonium, NH^3 and NH_4^+) into amino acids. For humans, essential amino acids include leucine, isoleucine, valine, lysine, threonine, tryptophan, phenylalanine, methionine and histadine. Thyrosine and cysteine are considered semi-essential amino acids as they can only be synthesized from essential amino acids (phenylalanine and methionine, respectively). Generally, the intake of proteins in the diet supplies the 20 amino acids, but the organism can adjust the proportions by transferring nitrogen to the carbon backbone of the non-essential amino acids and catabolizing excess amino acids.

Free amino acid pool (Fig. 5.1) is the term used to describe amino acids that exist in a free form within the organism and to differentiate them from those forming part of peptides, polypeptides and proteins. The size of this pool in the human being is approximately 150 g and the daily flux of dietary amino acids flowing through this pool is between 400 to 500 g per day. The most important sources of amino acids are: 1) the digestion of

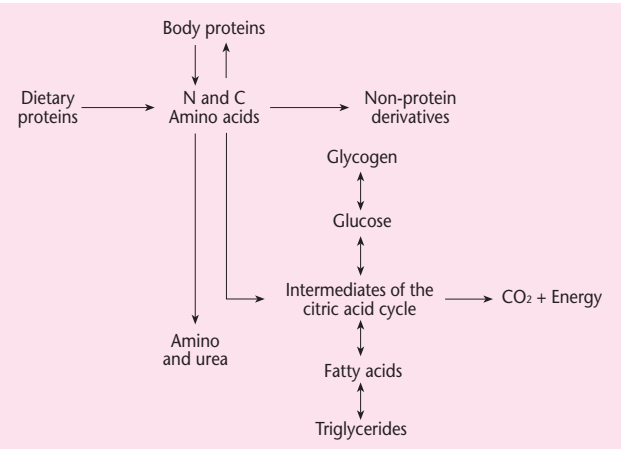

Figure 5.1. General view of metabolism of proteins and amino acids. The destination of most of the amino acids that move through the amino acid pool is protein synthesis or catabolism with the use of carbonated skeletons (C) as an energy source. Nitrogen (N) is fundamentally eliminated as urea and ammonium.

endogenous proteins and secreted proteins in the gastrointestinal tract and their subsequent absorption into the circulation (approximately 70 g per day); 2) proteins derived from the diet after their digestion and absorption (approximately 100 g per day, depending on the diet), and 3) the renovation or degradation of intracellular proteins (approximately 230 g per day). The most important metabolic destinations of these amino acids include: 1)their use in protein synthesis; 2) their catabolism, where the nitrogen is excreted and the carbon backbone is used as an energy source, and 3) their use as precursors for the synthesis of a large number of non-protein nitrogen compounds (purine and pyrimidine bases, neurotransmittors, and non-protein hormones). Destinations 1 and 2 represent the majority of the flow to the free amino acid pool.

Every amino acid has one or more individual metabolic pathway, although there is a common pathway for amino acid catabolism,

transamination. This reaction, catalyzed by aminotransferases, consists in the transfer of an amino group of an amino acid to a ketoacid to form another amino acid. α-keto-glutarate is widely used as a receptor of amino groups in transamination reactions.

There are a limited number of reactions in the organism that are capable of liberating the amino group in the form of ammonium and form a ketoacid via desamination. The most important reaction by glutamate deshydrogenase that catalizes the conversion of glutamate to α-keto-glutarate and ammonium. The final destination of the ammonium produced is tissue specific. In the liver, it is incorporated as urea, in the kidney it is excreted as urinary ammonium while it is incorporated into glutamine in the brain.

The carbon skeleton of the majority of ketoacids is metabolized Into intermediate substrates of the citric acid cycle or the glucolytic pathway, so they can be used for gluconeogenesis. Once they have entered into the main metabolic pathways, they can be oxidized to obtain energy or used to synthesize other compounds such as non-essential amino acids, glucose and glycogen, cholesterol, triglycerides and small quantities of ketone bodies[1].

Diseases of amino acid metabolism

In general, pathologically expressed diseases of amino acid metabolism are caused by in catabolism and tend to result in the accumulation of toxic substances that affect mainly the brain, liver and kidney. The symptoms of a specific enzymatic defect depend upon the specific toxicity of the accumulated metabolites, the deficiency of the product, the severity of the enzymatic deficit and especially, protein intake or the liberation of endogenous amino acids by protein catabolism. Therefore, the objectives of dietary treatment include[2,3]:

1. Limiting the intake of the affected amino acid or acids to the minimum required adequate growth and development. The intake of amino acids must be strictly adjusted to the patient's requirements. Inadequate intake, especially of essential amino

acids, can be dangerous, as can excess consumption of these precursors of metabolic toxins.

2. On some occasions it may be necessary to supplement the diet with different amino acids due to defective synthesis, excess consumption or loss in urine or the intestine.

The requirement of individual amino acids is difficult to determine as optimum growth and development can be obtained with a broad spectrum of combinations of intake. A low-protein diet must provide the minimum protein, nitrogen and essential amino acids required for adequate growth. The most widely used recommendations for protein intake are from FAO/WHO that are based on the intake of foods with proteins of high biological value (milk and eggs) and that are 100% digested to assure sufficient intake of essential amino acids. These recommendations are calculated to meet the requirements of 97% of the general population, often indicating a higher consumption than necessary, even in patients with inborn errors of metabolism. In previous reviews[4,5], based on an intake/growth analysis and studies of nitrogen balance, it was seen that protein requirements in neonates and children are 27-35% and 17-20%, respectively, below the FAO/WHO estimations (Table 5.1). It should be noted that the minimum protein intake necessary to sustain life may be much lower than that required for maximum genetic growth potential.

Dietary management includes[3]:

- Individual limits on the amount of protein ingested depending on the age, growth and residual enzyme activity. In the most severe cases, the patient may not tolerate more than 0.75 g/kg of natural protein. The individual tolerance must be determined according to plasma levels and the elimination of corresponding organic acid, the acid-base equilibrium and ammonium and ketone bodies levels. Protein tolerance will depend on the residual enzyme activity of the specific disorder, growth, age and sex.

  Limits on protein intake will require:

TABLE 5.1. Protein requirements according to age, expressed in g/kg/day

Age	Safe level FAO/WHO/UN 1985	Safe levels -revised (Dewey et al. 1996)
Months		
0-1	–	2.69
1-2	–	2.04
2-3	–	1.53
3-4	1.86	1.37
4-5	1.86	1.25
5-6	1.86	1.19
6-9	1.65	1.09
9-12	1.48	1.02
Years		
1-1.5	1.26	1.0
1.5-2	1.17	0.94
2-3	1.13	0.92
3-4	1.09	0.9
4-5	1.06	0.88
5-6	1.02	0.86
6-7	1.01	0.86
7-8	1.01	0.86
8-9	1.01	0.86
9-10	0.99	0.86
Girls		
10-11	1.0	0.87
11-12	0.98	0.86
12-13	0.96	0.85
13-14	0.94	0.84
14-15	0.9	0.81
15-16	0.87	0.81
16-17	0.83	0.78
17-18	0.8	0.77
Boys		
10-11	0.99	0.86
11-12	0.98	0.86
12-13	1.0	0.88
13-14	0.97	0.86
14-15	0.96	0.86
15-16	0.92	0.84
16-17	0.9	0.83
17-18	0.86	0.81

- An increase in the caloric intake to obtain maximum protein protection, to prevent their use as an energy source. It is therefore also important to avoid long periods of fasting. Low-

protein diets may be energy deficient due to the dietary restrictions of the patient. This situation must be avoided since inadequate energy intake will result in poor growth and poor metabolic control, with an increase in endogenous protein catabolism resulting in increased production of toxic metabolites. Energy requirements should be satisfied through natural foods with low or no protein content, manufactured foods with low protein content (e.g., pasta, bread, special crackers or cookies) and energy supplements derived from glucose polymers and/or fat emulsions.

- Where possible, an increase in the proportion of protein with high biological value up to 70% of total intake. In low protein diets, the main source of proteins should have a high biological value, although this is not always possible since more food with more calories per gram of protein can be given if foods low biological value of protein are used. It is important to ensure that the diet is as varied as possible (potatoes, legumes, cereals, pasta, rice), providing all essential amino acids and not limiting protein synthesis. If the patient has a high protein-tolerance, proteins of high biological value can be given to improve the quality of the diet.
- Monitoring possible side effects associated with limited protein intake, especially with deficiencies in specific vitamins (B_{12}, niacin, folic acid), minerals (calcium, zinc, iron, selenium) and long-chain polyunsaturated fatty acids, in case supplements are necessary[6]. Vitamin and mineral supplements are essential when protein intake is severely limited, especially for iron, copper, zinc, calcium and the B vitamins. Sufficient intake of vitamins A and C can be obtained through fruits and vegetables. The diet and supplements must provide the RDA of vitamins and minerals. Pediatric Maxivit® is a good supplement and can be added to the bottle of formula at the required dose and in older children it can be given using a spoon. It can be flavored with honey, marmalade, or pureed

fruit and given with liquids afterwards in order to dilute the hyperosmotic mixture. Periodic analysis of plasma vitamin, mineral and trace element levels should be performed. Fluoride supplements should also be given as the majority of these diets have a high sugar content.

- Periodic tests should be conducted to detect deficiencies, including: serum levels of proteins with a short half-life (prealbumin, retinal binding protein), nitrogen balance, and examination of typical clinical symptoms (growth, alterations of the skin and mucous membranes, etc.). This should be performed in a clinic (examining hair and skin looking for signs of protein deficiency such as eczema) and include an anthropometric examination, biochemical evaluation (analysis of amino acids, electrolytes and albumin) and regular evaluation of the diet.
- At times it is necessary to supplement protein intake with special preparations available for each disease containing all essential amino acids except those whose metabolic pathway is affected. These industrial dietetic products are designed to help in the therapeutic management of these disorders and to prevent the accumulation of toxic substances. As these industrial products lack specific essential amino acids they alone cannot provide the substrates for anabolism, therefore they must always be used in combination with other products or natural food that contains those essential amino acids that are lacking. For the same reason, they should not be used as the sole protein source in situations of acute imbalance associated with hyperammoniemia since they become a toxic source of nitrogen. These products are especially useful during early lactation when protein requirements per kilogram of weight are highest and where a diet lacking in natural proteins may not cover nitrogen needs. However, protein requirements are increasingly met with maternal milk or commercial formulas with the addition of caloric supplements. For children older than 1-3 years of age, these supplements are often unnecessary.

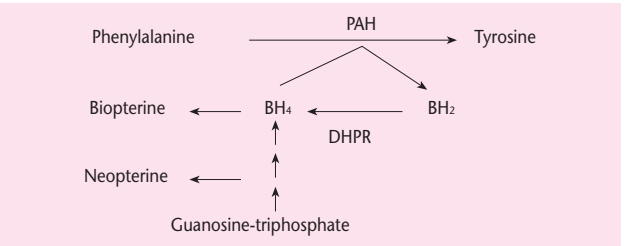

Figure 5.2. Metabolism of phenylalanine (PAH: phenylalanine hydroxylase. DHPR: dihydropteridine reductase. BH4: tetrahydrobiopterin. BH2: dihydrobiopterine).

5.2. HYPER PHENYLALANINEMIAS. PHENYLKETONURIA

Phenylalanine (Phe) is an essential amino acid that by action of phenylalanine hydroxylase (PAH) is metabolized to tyrosine. This reaction requires the cofactor tetrahydrobiopterine (BH4) that is converted into dihydrobiopterine (BH2). Cofactor BH4 is regeneration by action of the enzyme dihydrobiopterine reductase (DHPR) and various enzymes are required for its synthesis from guanosine triphosphate (Fig. 5.2).

A deficiency of PAH or the enzymes required for synthesis and regeneration of BH4 results in hyperphenylalaninemia, which indicates persistent blood concentrations higher than 150 µmol/l (2.5 mg/dl). From a clinical point of view, hyperphenylalaninemias are arbitrarily classified according to Phe concentrations and clinical tolerance, that is, the amount of dietary Phe that maintains concentrations within acceptable limits. Three different forms have been identified:

- Classical phenylketonuria (PKU): Plasma concentrations at diagnosis are >1,200 µmol/l (>20 mg/dl). Tolerance to this amino acid is less than 350-400 mg/day. Residual activity of PAH is less than 5%.
- Moderate hyperphenylalaninemia: Initial concentrations of Phe are between 360 and 1,2000 µmol/L (6-20 mg/dl). Dietary tolerance is 350-600 mg/day. Residual activity of PAH is 10%.

- Benign hyperphenylalaninemia: Initial concentrations of Phe are <360 µmol/L (<6 mg/dl) and do not require dietary restriction of Phe. Residual activity of PAH is between 10 and 35%.

This classification is useful, but any patient requiring a restrictive diet is considered PKU while those that do not, have benign hyperphenylalaninemia. At present, with the ability to determine genetic mutations each patient is classified as having a specific type of hyperphenylalaninemia.

PKU is an autosomal recessive disease with an incidence of 1/15,000 newborns. The incidence of hyperphenylalaninemia is somewhat higher in the Mediterranean area (1/12,000 newborns). This disease has all of the characteristics to be included in screening programs for all newborns. Indeed, in Spain this analysis became standard for all newborns 25 years ago.

The classic case of an undiagnosed form of this disease is a normal newborn developing favorably until 6-8 months when signs of delayed psychomotor skills begin to appear, becoming worse over time and developing into convulsions (West syndrome), hyperactivity and psychotic behavior that includes aggressiveness, destructive tendencies and self-mutilation. If a patient has been diagnosed and treated, but abandons the diet for a period greater than 4-6 years, the clinical manifestations are not as severe although these patients present alterations in behavior, psychomotor skills and sleep patterns, an intellectual quotient inferior to that of their siblings, and alterations in their EEG and MRI. Patients with benign phenylalaninemia are asymptomatic, although it is currently suggested that they may have a higher incidence of sleep and attention problems with a lower intellectual quotient than normal. Moreover, women with hyperphenylalaninemia could have children with slight cerebral dysfunction given that the Phe gradient in the placenta is double on the fetal side. Fetal concentrations of 12-14 mg/dl may be harmful (Table 5.2)[3,7].

TABLE 5.2. IEM of amino acids and proteins. Phenylketonuria

Hyperphenylalanimemias (phenylketonuria)[3, 7] (↓ phenylalanine hydroxylase)	
Pathophysiological group	• Type II
Incidence (cases/NB)	• 1/15,000-20,000
Debut Age	• Neonatal screening: presymptomatic diagnosis • Spontaneous symptoms : 6-8 months
Clinical aspects	• Serious mental retardation • Microcephaly • Epilepsy • Eczema • Hyperactivity • Psychotic traits
Treatment	• Low phenylalanine diet • Tyrosine supplement
Prognosis and complications	• Fetopathy in pregnant mothers with phenylketonuria • Important that neonatal screening be universal

This disease is diagnosed by testing amino acids levels after 3 days of a non-restricted diet. In addition to the increase in Phe, these patients have reduced tyrosine concentrations with normal levels of other amino acids. In urine, Phe concentrations are high, as are its derived organic acids phenylpyruvic acid, phenylacetic acid, etc. Defects in the cofactor BH4 are detected by DHPR testing (whole blood spotted on filter paper) and determining the concentrations of biopterine and neopternins, and their ratios, in urine. These defects constitute between 1 and 3% of all PKU hyperphenylalaninemias. Given that PAH can only be determined by a liver biopsy, a genetic analysis is performed directly.

High levels of phenylalanine are neurotoxic and can cause mental and motor retardation. Early diagnosis and treatment are necessary to avoid mental retardation. In Spain, early detection

TABLE 5.3. Recommendations for the treatment of phenylketonuria. Units in µmol/l (mg/dl)

Recommendations	English Group, 1993	German Group, 1999	American Group, 2001
Onset of treatment*	Phe > 400 (>6,6)	Phe ≥ 600 (≥ 10)	Phe 420-600 (7-10)
Desired Phe levels			
Preschool-age (0-5 years)	120-360 (2-6)	40-240 (0,7-4)	120-360 (2-6)
School-age (5-10 years)	120-480 (2-8)	40-240 (0,7-4)	120-360 (2-6)
Adolescents	120-700 (2-11,6)	40-900 (0,7-15)	120-600 (2-10)
Adults	120-900 (2-15)	≤1.200 (20)	120-900 (2-15)
Pregnant women	60-250 (1-4)	60-250 (1-4)	120-360 (2-6)
Frequency of monitoring of Phe levels	0-4 years: e/week 4-10 years: e/2 weeks 10 years: e/month	0-1 year: e/1-2 week 1-9 years: e/2-4 week 10-15 years: e/month > 15 years: e/2-3 months	0-1 year: e/week 1-12 years: e/2 wks > 12 years: e/mo.

** Treatment should be initiated as soon as possible (in the first 7-20 days of life)*

programs were initiated in 1968 and currently covers approximately 99% of all newborns[8].

For newborns who, with a protein intake of 2-3 g/kg/day, have plasma Phe levels capable of inducing CNS lesions should receive dietary treatment as soon as possible (normal levels 40-100 µmol/l [0.6-1.6 mg/dl]). However, there is no unanimous agreement on the level at which dietary treatment should be implemented, nor the optimum Phe level at different ages[9]. Table 5.3 presents the recommendations of different groups[10-13].

Infants with Phe levels below the treatment threshold should be monitored to ensure that their Phe levels do not significantly increase as the protein content of their diet increases, especially when complementary foods are introduced:

- Phe levels <100 µmol/l (1.6 mg/dl): high.
- Phe levels > 100 µmol/l (1.6 mg/dl):repeat test when foods other than maternal milk are introduced:
  – >150 µmol/l (2.5 mg/dl) should be tested regularly.
  – > 360 µmol/l (6 mg/dl) dietary intervention is recommended.

Women with benign hyperphenylalaninemia should be closely monitored while pregnant as high Phe levels could be harmful to the fetus.

Initial dietary management

The objective of this treatment is to reduce Phe levels to within a safe range (120-360 µmol/l; 2.6 mg/dl) as rapidly as possible. The dietary plan should be developed taking the initial Phe levels into consideration. A Phe-free period is usually required (Table 5.4) and formulas free of phenylalanine (XP Analog®, XP Analog LCP®, Phenyl-free®) can be used with an estimated initial quantity of 150 ml/kg/day.

As Phe is an essential amino acid required for normal growth and development, after a period using the phenylalanine free formula (Phe free F), specific quantities of Phe must be added to the diet to maintain plasma Phe levels within a safe range. The

TABLE 5.4. Dietary plan to reduce the initial levels of phenylalanine

Initial levels of Phe, µmol/l (mg/dl)	Number of days without Phe	Volume of Phe free formula
> 2,500 (41.6)	5	60 ml x 5
2,000-2,500 (33.3-41.6)	4	60 ml x 5
1,500-2,000 (25-33.3)	3	45 x 5
1,000-1,500 (16.6-25)	2	45 x 5
500-1,000 (8.3-16.6)	1	30 x 5
360-500 (6-8.3)	0	30 x 5

The plasma levels of Phe decrease at a rhythm of approximately 400 µmol/l/day (5-10 mg/day).

source of this Phe should be maternal milk or a commercial formula.

1. Newborns receiving maternal milk:

Nurse 5 times per day:

1. The measured quantity of phenylalanine free formula (Table 5.3), followed by.
2. Nursing on demand. Child nursing should be unlimited and on demand.

2. Newborns receiving commercial formulas:

At the start of treatment 200 mg of Phe (50-70 mg/kg/day) should be introduced using a type I baby formula (the majority contain 20 mg of Phe per scoop), and adjusted according to the individual tolerance. If the child weighs less than 3 kg, start with 50 mg/dg/day. This quantity is normally divided into 5 feedings that should be given as follows:

1. The measured quantity of formula I, followed by:
2. Phe free formula on demand.

Five feedings will ensure that the infant receives the necessary quantity of Phe. Phe free formula should be given for any additional feedings.

Subsequent management

Control of plasma Phe levels

The objective of these controls is to maintain plasma Phe levels within safe limits (Table 5.3) to avoid mental retardation due to the toxicity of elevated phenylalanine while avoiding growth retardation due to a deficiency in phenylalanine.

Newly diagnosed patients

1. Breastfed infants:

- Phe < 120 µmol/l (<2 mg/dl): =↓ 75ml/day of Phe free formula (15 ml x 5).
- Phe 120-360 µmol/l (2-6 mg/dl): no change
- Phe > 360 µmol/l (>6 mg/dl): ↑ 75 ml/day of Phe free formula (15 ml x 5).

  An increase in the intake of Phe free formula will reduce the intake of maternal milk, thus reducing phenylalanine intake. A reduction in Phe free formula, will result in increased maternal milk and phenylalanine intake.

2. Formula fed infants:

- Phe <60 µmol/l (<1 mg/dl): ↑ 50-100 mg Phe/day.
- Phe 60-120 µmol/l (1-2 mg/dl): ↑ 50 mg Phe/day.
- Phe 120-360 µmol/l (2-6 mg/dl): no change.
- Phe 360-600 µmol/l (6-10 mg/dl): ↓ 50 mg Phe/day.
- Phe > 600 µmol/l (> 10 mg/dl): ↓ 50-100 mg Phe/day.

  Once Phe levels have been controlled it is not necessary to alter the diet if isolated tests indicate that Phe levels are either too high or low. These tests should be repeated one week later and if they are still outside of the accepted range, appropriate adjustments to the diet should be made.

3. Patients with established PKU. In these patients, Phe levels should be interpreted considering occasional illnesses, weight gain or loss, caloric intake and protein supplements free of amino acids. While infants are exclusively feed only breast milk

or formulas their diets can be adjusted as described above; however, once they begin to ingest phenylalanine through solid food the following guidelines should be used:

- Phe <60 µmol/l (<1 mg/dl): ↑ 50-100 mg Phe/day.
- Phe 60-120 µmol/l (1-2 mg/dl): ↑ 50 mg Phe/day.
- Phe 120-360 µmol/l (2-6 mg/dl): no change.
- Phe > acceptable range for age: ↓ 25-50 mg Phe/day.

Introduction of solid foods

Complementary alimentation is recommended from 4-6 months of age. Following the same basic principles for the introduction of foods in a normal infant, this should be done gradually and progressively until the normal diet of an adult is reached. The caloric distribution of the macronutrients, as well as the vitamin and mineral requirements of these children, do not differ from those of children not suffering from PKU.

Given that the majority of foods contain diverse quantities and qualities of proteins, and therefore of phenylalanine, the intake of natural proteins must be restricted but contain the quantity of phenylalanine necessary for growth and development. The amount of Phe in the diet is calculated using specific quantities of foods with moderate protein content, such as cereals, potatoes and vegetables. These quantities are calculated using an exchange system, so that one food can be substituted for another with the same quantity of phenylalanine. Some countries use exchanges of 50 mg of Phe (e.g., United Kingdom), while others use 15 mg exchanges, where the Phe content is calculated for the majority of foods in the diet. Another alternative is to calculate every milligram of Phe that is administered in the diet. Each system has its limitations and there are no studies comparing the success of different dietary regimens[14,15].

Diet should be considered like a traffic light where red represents those foods that should not be eaten, yellow those foods that should be eaten in limited quantities (e.g., quantity

TABLE 5.5. Food guide for phenylketonuria

RED LIST – STOP! *(Foods not permitted - high phenylalanine content)*	**YELLOW LIST - BE CAREFUL!** *(Foods that contain phenylalanine in moderate amounts. They should be eaten with caution and in controlled and weighed quantities)*	**GREEN LIST – GO AHEAD** *(Foods that contain small amounts of phenylalanine. They can be eaten in normal quantities, but never in excess)*
Meat: all types (Veal, lamb, pork, ham, bacon, chicken, duck, pheasant, goose, rabbit, offel, hotdogs, canned meat, chopped meat and any meat containing product)	**Lactic:** milk, milk cream, cream, yogurt	**Fruits:** most (strawberry, canned, fresh or in syrup): apples, pears, oranges, tangerines, nectarines, kiwis, pineapple, grapes, peaches (not dry), fresh or dried apricot, fresh raspberry, cherries, blueberries, figs (fresh, not dried), plums, guava, melon, watermelon, papaya, mango, lichis, raisins, lemons, lime
Fish: all types (fresh, frozen, canned) including shell fish	**Vegetables, root vegetables and legumes:** potatoes, sweet potatoes, broccoli, Brussels sprouts, spinach, asparagus, peas, corn (corn on the cob or canned sweet corn)	**Vegetables:** chard, chicoria, artichokes, celery, garlic, green spotted zucchini (squash), eggplant, watercress, onion, cabbage, cauliflower, endives, green beans, lettuce, cucumber, leek, pepper, radish, tomato, parsley and aromatic herbs
Eggs: all types	**Cereals and rice**	**Cereals:** corn starch, tapioca, custard powder (not instant)
Cheeses: all, including spreads	**Fruits:** avocado, banana, maracuya (passion fruit)	**Fats:** butter, margarine (not those containing milk), fat, lard, vegetable fats and oils
Nuts		**Drinks:** water, mineral water, soda, lemon drink, fruit drinks, tea, Coca-Cola, black coffee and fruit juices. Many of the light varieties of soft drinks contain aspartame.
Bread, flours, biscuits, normal cookies		**Miscellaneous:** sugar (white, brown, powdered), glucose, jam, honey, syrup, maple syrup, essences and colorants (vanilla, mint, almond, cochineal) Salt, pepper, vinegar, mustard, mint sauce, cream, tartar, powdered curry, herbs and spices, bicarbonate, powdered yeast, crystal candy, cotton candy
Soy: all products made with soy		
Aspartamo: artificial sweetener that contains phenylalanine (foods and drinks that contain them have the following in their composition: artificial sweetener, aspartame or artificial sweetener E951)		

of food or interchange that has 50 mg of phenylalanine) and green for foods that can be eaten in normal quantities, but not to excess. Further detail of these three groups can be found in table 5.5.

When introducing complementary alimentation to an infant one should begin with foods low in Phe content. These should be given after the Phe free formula and breastfeeding. Once they have begun ingesting foods low in Phe, breastfeedings or feedings with normal formula should begin to be substituted with solids containing Phe.

As the intake of proteins of high biological quality is limited, phenylalanine-free commercial formulas containing a mixture of amino acids should be used. There are products on the market with varied content of amino acids, vitamins and minerals per 100 g of product, in order to adjust intake according to age and condition. These protein supplements are an integral part of the correct treatment of PKU, supplying close to 75-85% of the protein requirements (except Phe) of the patient[16,17].

The following is a list of the different products according to composition[14]:

1. Hydrolyzed protein in powder.
2. Amino acids in powder: with or without carbohydrates and without vitamins or minerals.
3. Amino acids in powder: with carbohydrates added, with our without fats, vitamins and minerals.
4. Amino acid capsules or tablets: without carbohydrates, vitamins or minerals added.
5. Bars of amino acids: without vitamins or minerals.

It is important to offer the patient different possibilities, but there are no criteria to define the ideal composition and little data exist, comparing the effect of the different presentations on plasma Phe levels, growth, biochemical parameters, appetite, nutrient intake and general acceptability. The protein substitutes with carbohydrates added, with or without fats, vitamin and minerals

tend to be those of choice. They are easy to prepare and ensure adequate intake of vitamins and minerals. However, they are voluminous and hypercaloric and large amounts are needed to meet the amino acid requirements while modular amino acid substitutes are less caloric and easier to ingest[18], but they are not enriched with vitamins and minerals, which must then be administered.

It is essential to ensure adequate intake of proteins (protein supplements free of Phe plus natural food proteins). Protein requirements of these patients are greater than that recommended for the normal population (although some authors suggest that children with PKU have the same requirements as healthy children)[19]. This is due to the synthetic character of the protein supplements, which diminishes their bioavailability and increases their escape from protein catabolism. It has been demonstrated that after protein supplement intake, plasma concentrations of amino acids rise higher and faster, followed by a more rapid decline compared to dietary protein intake. This results in a greater loss of amino acids and it is recommended that protein supplements are divided into at least 3 daily doses combined with natural protein intake.

Commercially available foods low in proteins (bread, pasta, flour, cookies, egg substitutes) can be freely eaten and supply variety and energy to the diet (they are not financed by the National or Autonomic Health Systems in Spain).

Management during occasional illnesses

In situations where food intake is reduced or there is an increase in energy requirements (acute illness, surgical intervention, reduced appetite, etc.) the Phe levels from endogenous catabolism may be increased. During these periods, a diet rich in calories and low in Phe is necessary to avoid an excessive increase in plasma Phe concentrations. The following measures should be adopted in these cases:

- Decrease natural protein intake. The amount of infant formula ingested can be reduced by substituting it with Phe free formula. In older children it may be necessary to reduce the normal number of Phe exchanges in their diet, that will be increased again once the patient has improved and recuperates their appetite.
- Continue with the protein free supplement to promote protein synthesis, but without force feedings as this could provoke refusal of the preparation, including even after the patient recovers.
- Increase energy intake by adding glucose polymers to their liquids, including the phenylalanine free formula. For example, during an episode of gastroenteritis oral rehydration may be necessary for 12-24 hours. In this case glucose polymers can be added at the following doses: children less than one year 10 g of glucose polymers can be added to 200 ml of oral rehydration solution (10% carbohydrate solution) and in children older than 1 year of age 20 g of glucose polymers in 200 ml of oral rehydration solution (15% carbohydrate solution) can be used.
- Make sure that liquid intake is abundant.
- Offer food only when asked for. Do not force feed.

Maternal phenylketonuria

Strict control of Phe levels is necessary both before and during pregnancy to prevent the risk of fetal damage or embryopathies (intrauterine growth retardation, microcephaly, psychomotor retardation, congenital cardiopathies) as a result of maternal phenylketonuria and the teratogenic effects of phenylalanine. There is a positive transplacental maternal-fetal amino acid gradient causing the fetus to be exposed to higher concentrations of phenylalanine than the mother.

Mothers with PKU should know the risks associated with pregnancy and the need for careful planning[20,21] with strict control

TABLE 5.6. Recommendations of the AAP on maternal PKU

1. All the child-bearing aged women who have elevated levels of phenylalanine, including those suffering PKU and mild forms of hyperphenylalaninemia, should be identified and advised on the risks that maternal phenylketonuria has on the fetus when the phenylalanine levels are not controlled during pregnancy
2. Women with hyperphenylalaninemia who are incapable or do not wish to maintain Phe levels in the optimum range (1-4 mg/dl) for pregnancy should be advised on safe contraceptive methods, including tubal ligation if demanded
3. Women with hyperphenylalaninemia who conceive with Phe blood levels greater than 4-6 mg/dl should be informed on the risks for the fetus and undergo a selective echography to detect fetal abnormalities (intrauterine growth restriction, microcephaly, heart disease). Interruption of the pregnancy should be considered in those women who conceive with levels considered to be associated to high fetal risk (> 15 mg/dl; > 900 mmol/l)
4. Hyperphenylalaninemia should be ruled out in women who give birth to children with characteristics of fetopathy due to maternal phenylketonuria without known cause

from the very early stages. Phenylalanine levels should be analysed 1-2 times per week to maintain Phe levels between 60 and 240 µmol/l (1-4 mg/dl) for at least 3 months prior to conception, and then throughout the entire pregnancy. The recent recommendations concerning maternal phenylketonuria from the Committee of Genetics of the American Academy of Pediatrics are shown in table 5.6[22]. Depending on the previous tolerance, the patient should be started with an initial diet supplying 250-500 mg of phenylalanine (6 mg phe/kg/day) to be adjusted according to Phe levels. During the second half of pregnancy, phenylalanine tolerance increases due to the rapid growth of the fetus and phenylalanine metabolism by the fetus and increased protein synthesis. This will allow Phe intake to be increased and result in a decrease in the amount of protein supplement required. The phenylalanine free protein supplement used should contain all

necessary vitamins and minerals so that additional supplements are not required. At times, the amount of supplement has to be increased upon pregnancy in order to obtain a protein intake (natural proteins + phe free protein supplement) of approximately 70 g per day.

During the early stages of pregnancy appetite disorders may exist, for example nausea. Energy supplements may be required to maintain an adequate caloric intake and to prevent weight loss. If tyrosine concentrations fall below normal range (<40 µmol/l) during the pregnancy, L-tyrosine supplements will be necessary, starting with 3 g per day added to the phenylalanine free protein supplement.

5.3. TYROSINEMIAS

Tyrosine is considered a semi-essential amino acid as its synthesis depends on the presence of its precursor, phenyalalanine. Catabolism of phenylalanine and tyrosine takes place in the liver, with the conversion of phenylalanine to tyrosine being the first step in the degradation of phenylalanine, as well as the step that allows phenylalanine to serve as the dietetic precursor of tyrosine. The latter is also a precursor of catecholamine, melanin and thyroid hormone synthesis[1].

Tyrosinemia is an inborn error of metabolism caused by a deficiency in fumaryl-acetoacetate hydrolase. Deficiency in this enzyme produces an accumulation of precursor products such as maleyl and fumaryl-acetoacetate, which are hepatotoxic, and succinylacetone that has systemic effects (Fig. 5.3). This condition is autosomal recessive, with an incidence of 1/100,000 newborns.

There are two types: type 1a tyrosinemia (Franco-Canadian) with acute onset, hepato-renal failure and rapid deterioration, and type 1b (Scandinavian) with chronic onset, renal dysfunction, cirrhosis, and hepatocellular carcinoma. Type 1a can manifest itself during the first year of life.

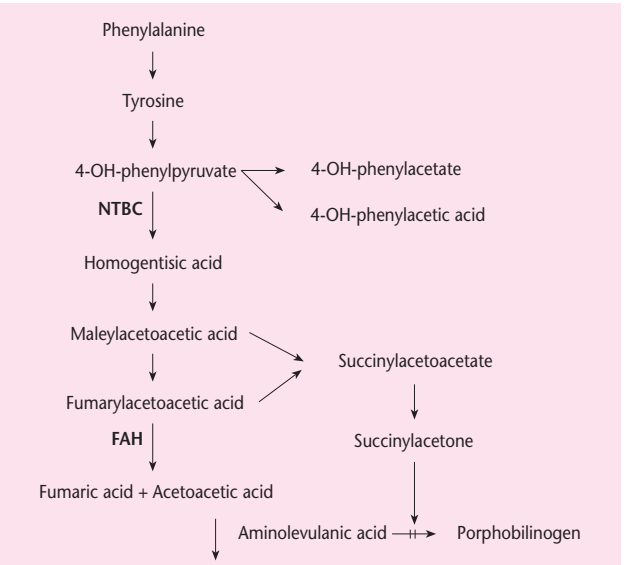

Figure 5.3. Metabolism of tyrosine (FAH: Fumaryl Acetoacetate Hydrolase. NTBC: 2-nitro-4-trifluoromethylbenzoyl) -1,3-cyclohexanedione).

The classic symptoms are: a) Liver failure, including hepatomegaly, alterations in coagulation with gastrointestinal bleeding, hypertransaminasemia and an increase in α-fetoprotein. The chronic form is characterized by cirrhosis and a very high risk of hepatocellular carcinoma. b) Renal dysfunction that can range from mild to kidney failure, most frequently being tubulopathy that produces hypophosphatemic rickets. c) Neurological symptoms are less frequent and, although they can be very severe, they are most commonly acute peripheral neuropathies. Symptoms similar to porphyria may also appear (Table 5.7). Diagnosis can be made when a highly elevated plasma tyrosine concentration is demonstrated, initially this increase may be discrete even though the suggestive symptoms are severe. Hyperphenylalaninemia is common as is the presence of succinylacetone in the plasma and

TABLA 5.7. IEM of amino acids and proteins.Tyrosinemia

Tyrosinemia[23-26] (↓ fumaryl acetoacetate hydrolase)	
Pathophysiological group	• Type II
Incidence (cases/NB)	• 1/100,000
Debut Age	• Acute: infant • Chronic: > 6 months
Clinical aspects	• Acute: failure to thrive, lethargy, hepatomegaly, jaundice, ascites, bleeding, nephromegaly, renal tubular dysfunction • Chronic: renal dysfunction, cirrhosis, hepatocellular carcinoma
Treatment	• Diet low in tyrosine and phenylalanine • NTBC: (2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) • Hepatic transplant
Prognosis and complications	• Treatment with NTBC has greatly improved the prognosis • Complications: hepatic carcinoma and renal failure

urine, as well as the metabolites OH-phenylacetic acid and OH-phenyl-lactic acid.

Treatment of this disease includes[23-26]:

- Diet: Dietary treatment requires a low intake of phenylalanine and tyrosine in order to maintain plasma tyrosine levels between 200-400 µmol/l (normal range 30-120 µmol/l) and phenylalanine between 30-70 µmol/l to minimize the formation of toxic metabolites. Proteins should be restricted with the intake of natural proteins oscillating between 0.5-1 g/kg/day, depending on the plasma levels of tyrosine and growth[23-26]. The remaining protein intake, in order to meet daily requirements, is in the form of protein supplements free of phenylalanine or tyrosine. These should be administered throughout the day with the same considerations as those for

phenylketonuria. In order to obtain an adequate energy intake and dietary variety, the same commercial products low in protein as those used in the phenylketonuria can be employed. Strict dietary treatment can prevent and repair renal tubular damage and improve growth, but does not prevent the progression of liver disease and the development of hepatocellular carcinoma[27].

- NTBC (2-(2-nitro-4-trifluromethybenzoil)-1-3-cyclohexanedione): This triacetone has herbicide activity and acts as a potent inhibitor of the enzymatic activity of 4-hydroxiphenylpiruvate dioxigenase, thereby blocking the degradation of tyrosine and the formation of hepato- and nephro-toxic metabolites[28,29]. The initial dose is 1 mg/kg/day divided into two doses and then modified depending on the response of the patient. A diet low in phenylalanine and tyrosine should be maintained given that plasma concentrations of tyrosine will increase (they should not exceed 500 µmol/l), although it has been reported that the tolerance of natural proteins is greater[27].
- Liver transplant: This was the treatment of choice before NTBC treatment became available as it normalizes the metabolic disturbances and liver function with normal protein intake. Currently this treatment is reserved only for critically ill patients that do not respond to NTBC treatment or those with hepatocellular carcinoma.
- Others: In a transitory manner and in the initial stages of treatment the use of liposoluble vitamins, calcium, phosphorus and 1,25-dihydroxycolecalciferol supplements may be required.

Type II tyrosinemia (Richner-Hanhart syndrome)

This infrequent autosomal recessive disease is due to a deficit in cytosolic tyrosine aminotransferase resulting in intracellular tyrosine crystals and inflammation. The principal clinical symptoms include cheratitis with herpetiform corneal ulcers and erosions and palmoplantar hypercheratosis. Moderate mental retardation and

incidences of self-mutilation may occur. Liver and renal function are normal.

Treatment of this condition includes a diet low in phenylalanine and tyrosine, following the same guidelines as those for type I tyrosinemia, but in these cases tolerance to tyrosine and phenylalanine is higher. With early implementation of the restrictive diet the clinical symptoms rapidly disappear and mental retardation can be prevented.

5.4. HOMOCYSTINURIA

This term encompasses those inborn errors of metabolism characterized by increased concentrations of total homocystine in plasma or serum. Total homocystine (tHcy) includes homocystine and the group of dysulphide derivatives found in plasma. Normal tHcy levels are <15 µmol/l. The congenital causes of hyperhomocystinemia (Fig. 5.4), all of which are autosomal recessive, include: cystationine β-synthase (CBS) deficiency in the transulfuration pathway, deficiency in 5,10 methylene-tetrahydrofolate reductase (MTHFR) in the remethylation pathway, or defects in the metabolism of cobalamine that interferes with the remethylation of homocystine to methionine either due to a defect in the synthesis of the coenzyme (methylcobalamine) or of the enzyme methionine synthetase (MS)[30,31].

Classic homocystinuria

This condition is due to a deficit in CBS and is the most frequent cause of homocystinuria. It is also the most frequently treated amino acid pathology after phenylketonuria. This condition is included in neonatal screening programs in some countries, even though methionine plasma levels may not be significantly elevated in newborns affected with homocystinuria. Thus, a percentage of these patients will only be diagnosed only after clinical symptoms appear. The most important clinical symptoms

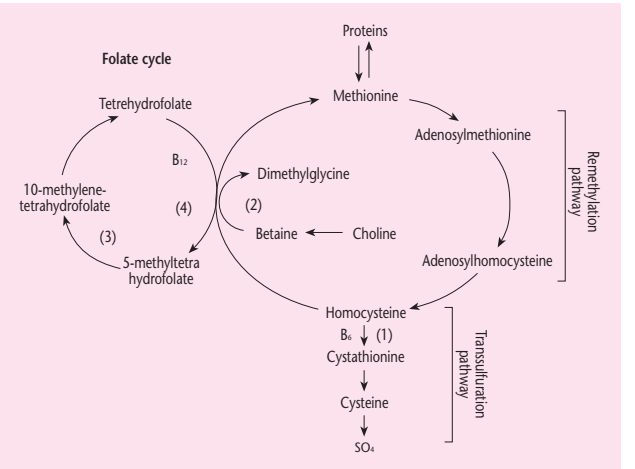

Figura 5.4. Metabolism of methionine. There are 2 main pathways: 1) Transsulfuration pathway: conversion of methionine into cysteine and its sulfurated derivatives. The cystathionine β-synthase enzyme (1) dependent of the pyridoxal phosphate cofactor is the only reaction that removes homocysteine from the methionine cycle. The irreversible character of this reaction explains the unidirectional flow from methionine to cysteine and that the animal cells cannot synthesize homocysteine from cysteine; 2) Transmethylation pathway: the homocysteine formed is remethylated to methionine by 2 reactions: one in which the betaine-homocysteine methyltransferase enzyme (2) uses betaine as donor of the methyl-group and the other in which the 5-methyltetrahydrofolate, which has been formed from 5,10 methyltetrahydrofolate by the 5,10 methylentetrahydrofolate reductase (3), donates it methyl-group and is converted into tetrahydrofolate by the Methionine synthetase enzyme (4) that uses methylcobalamine as cofactor.

associated with this disease are ectopy of the lens, thromboembolic phenomena, osteoporosis and mental retardation. The complications of this disease are directly related to an increase in homocysteine plasma levels and its disulfide derivatives. Therefore, the main objective of treatment is to decrease the accumulation of these metabolites.

The following strategies are recommended[32]:

TABLE 5.8. IEM of the amino acids and proteins. Homocystinuria

Homocystinuria[23,30] (↓ cystathionine- beta- synthetase)	
Pathophysiological group	• Type II
Incidence (cases/NB)	• 1/335,000
Debut Age	• > 2 years
Clinical aspects	• Progressive • Ectopia lentis, rapid progression of myopia • Mental retardation, seizures • Marfanoid habit, arachnodactyly • Osteoporosis, scoliosis • Vascular occlusions
Treatment	• Methionine low diet • Vitamin B_6 • Folic acid • Betaine
Prognosis and complications	• Thromboembolism • Osteoporosis

1. Increase the residual enzymatic activity: pyridoxine

The activity of the enzyme CBS depends on pyridoxine phosphate (Fig. 5.4), that forms part of pyridoxine or vitamin B6. A significant number of patients are sensitive to pharmacological doses of pyridoxine, showing both clinical and biochemical improvement with the possibility of even normalizing their plasma homocyteine and methionine levels. Other patients may only partially respond to this treatment. The mutation G307S (Celta mutation) provokes the most severe phenotype that is insensitive to pyridoxine, while the mutation 1278T appears to confer sensitivity to pyroxidine. In any case, subjects that have been diagnosed as having classic homocystinuria should start treatment with pyridoxal hydroclorate. The optimum dose is that which maintains the lowest concentrations of homocysteine. In general, the doses employed are:

- Newborns: 150 mg/day, every 8 hours.
- Children: 300-500 mg/day, every 8 hours.

- Adults: 500 to 1,200 mg/day, every 8 hours (doses ≥ 1,000 mg/day may provoke sensorial neuropathies).

The dose should be maintained over several weeks so that the response to the treatment can be evaluated[32-36]. Folic acid (5 mg/day) should also be given due to greater requirements resulting from increased passage through the remethylation cycle. If not administered, the lack of sufficient folate would impede an optimal response to the pyridoxine. The levels of vitamin B_{12}, a cofactor of folate metabolism, should also be monitored. In those patients that respond to pyroxidine deterioration, except for advanced ocular disease, can be prevented. Treatment should be maintained even for patients who do not respond.

2. Decrease the substrate available in the affected pathway and supplement the deficient products: a diet low in methionine and supplements of amino acids

For patients who do not respond to pyridoxine, the objective of the dietary treatment is (Table 5.9): reduce plasma homocysteine and methionine levels and augment cysteine levels (this becomes an essential amino acid in cases of CBS deficit as its endogenous synthesis is blocked).

To reduce methionine intake the amount of natural proteins eaten must be limited (Table 5.10). A system of interchanges similar to that for phenylketonuria can be used (interchanges equivalent to 20 or 25 mg of methionine, which is equivalent to 1 g of natural protein). The amount of methionine tolerated daily in order to obtain good metabolic control may vary (150-900 mg/day, with a mean of 200 mg/day), but once determined it remains relatively constant for life. To meet daily protein requirements, the diet must be complemented with essential amino acid supplements free of methionine and supplemented with cysteine, vitamins, minerals and trace elements. The supplement dosage should be divided amongst the main meals and ingested with natural proteins.

TABLE 5.9. Biochemical objective of classical homocystinuria treatment

	Plasma methionine	Plasma cysteine	Free plasma homocysteine	Total plasma homocysteine
Responders to B_6	Normal range	Normal range	< 10 µmol/l	< 50 µmol/l
Non-responders to B_0. Dietary treatment	Normal range	Normal range*	< 10 µmol/l	< 50 µmol/l
Non-responders to B_6. Betaine treatment.	High (up to 1,000 µmol/l)	Normal range*	< 10 µmol/l	< 50 µmol/l

**The subjects treated with a low protein diet and protein supplement free of methionine sometimes have low levels of cysteine even though the supplement is enriched with it. This could be due to the low solubility of cysteine that may be stuck to the drinking glass used. It is sometimes necessary to supply a supplement of L-cystine at a dose of 100-200 mg/kg/day.*

The objective of the concentration of free plasma homocysteine varies from some authors to others (5-20 µmol/l)[25,26,28]

Modified from Disorders of amino acid metabolism, organic acidaemia and urea cycle defects. In: Schaw V and Lawson M (eds.). Clinical Paediatric Dietetics. 2nd ed. Oxford, Blackwell Scientific Publications 2001. p. 267-73.

TABLE 5.10. Food guide for homocystinuria

RED LIST – STOP! *(Foods not permitted - high methionine content)*	**YELLOW LIST - BE CAREFUL** *(Foods that contain methionine in moderate amounts. They should be eaten with caution and in controlled and weighed quantities)*	**GREEN LIST – GO AHEAD** *(Foods that contain small amounts of methionine. They can be eaten in normal quantities, but never in excess)*
Meat: all types (Veal, lamb, pork, ham, bacon, chicken, duck, pheasant, goose, rabbit, offel, hotdogs, canned meat, chopped meat and any meat containing product)	**Lactic:** milk, milk cream, cream, yogurt	**Fruits:** most (strawberry, canned, fresh or in syrup): apples, pears, oranges, tangerines, nectarines, kiwis, pineapple, grapes, peaches (not dry), fresh or dried apricot, fresh raspberry, cherries, blueberries, figs (fresh, not dried), plums, guava, melon, watermelon, papaya, mango, lichis, raisins, lemons, lime
Fishes: all types (fresh, frozen, canned) including shell fish	**Vegetables, root vegetable and legumes:** potatoes, sweet potatoes, broccoli, Brussels sprouts, spinach, asparagus, peas, corn (corn on the cob or canned sweet corn)	**Vegetables:** chard, chicoria, artichokes, celery, garlic, green spotted zucchini (squash), eggplant, watercress, onion, cabbage, cauliflower, endives, green beans, lettuce, cucumber, leek, pepper, radish, tomato, parsley and aromatic herbs
Eggs: all types	**Cereals and rice**	**Cereals:** corn starch, tapioca
Cheeses: all, including spreads	**Fruits:** avocado, banana, peaches, nectarines, raisins, sultanas, dried figs, dried dates, dried apricots	**Fats:** butter, margarine (not those containing milk), fat, lard, vegetable fats and oils
Nuts		**Drinks:** water, mineral water, soda, lemon drink, fruit drinks, tea, Coca-Cola, black coffee and fruit juices
Bread, flours, biscuits, normal cookies		**Miscellaneous:** sugar (white, brown, powdered), glucose, jam, honey, syrup, maple syrup, essences and colorants (vanilla, mint, almond, cochineal) Salt, pepper, vinegar, mustard, mint sauce, cream, tartar, powdered curry, herbs and spices, bicarbonate, powdered yeast, crystal candy, cotton candy
Legumes: lentils, white beans, soy and derivatives		
Others: Jelly, caramels, chocolate, licorice, cacao		

Adequate energy intake is important to prevent protein catabolism and for normal growth and development. For this, special commercial products low in protein should be used in conjunction with natural foods.

3. Use of alternative pathways: oral betaine

Betaine acts as a donor of methyl groups, inducing the remethylation of homocysteine to methionine through the enzyme betaine homocysteine methyltransferase (Fig. 5.4). This results in an increase in methionine levels that could reach 1,000 µmol/l and decreases the levels of homocysteine. It is not clear whether the increase in methionine plasma levels can be used as a parameter for measuring the compliance with treatment since this increase does not occur in all patients. Adverse effects due to the increase in plasma methionine levels have not been described, but the majority of physicians decrease the betaine dose when methionine levels are >1,000 µmol/l. The recommended dose is 6-9 g/day of oral betaine anhydride (not available in Spain, although Cystadane® from Orphan is available for compassive use) divided into 2 or 3 doses, or betaine citrate (foreign drug) at a dose of 12-18 g/day. This drug is useful for patients who are not sensitive to vitamin B6, are not disciplined in following their diet (adolescents, adults or patients with a late diagnosis) and/or as an addition to the diet, although it is difficult to ensure that the patients take it regularly[32]. Some authors have analyzed the use of choline, that is converted to betaine in the liver, but the experience has been limited and it does not appear to have advantages over betaine.

5.5. ORGANIC ACIDEMIAS

Leucine, isoleucine and valine are branched chain amino acids (BCAA) and constitute close to 40% of the essential amino acids. In contrast to other amino acids very little metabolism of the BCAA occurs in the intestine or liver, with the majority of their metabolism

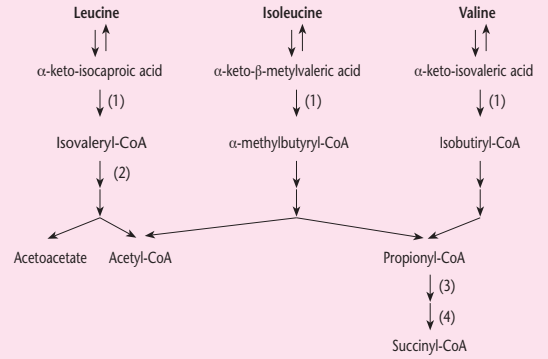

Figure 5.5. Metabolic pathways of the branched amino acids (1: Multienzymatic dehydrogenase complex. Maple syrup urine disease. 2: Isovaleryl-CoA dehydrogenase. Isovaleric acidemia. 3: Propionyl-CoA carboxylase. Propionic acidemia. 4: Methylmalonyl-CoA mutase. Methylmalonic acidemia).

taking place in the peripheral tissues such as skeletal muscle, heart, adipose tissue and kidney. For this reason, their plasma concentrations increase considerably after eating. The principal metabolic pathway is the incorporation into body proteins (close to 80%) and the remaining 20% is irreversibly degraded through the catabolic pathway (Fig. 5.5)[1,37].

The organic acidemias constitute a group of diseases due to congenital enzymatic defects that affect the catabolism of branched amino acids. The most frequent are maple sugar urine disease (MSUD), isovaleric acidemia (IVA), 3-methyl-crotonyl-glycinuria (3-MCG), propionic acidemia (PA) and methylmalonic acidemia (MA) (Fig. 5.5). They are characterized by an accumulation of carboxylic acids that can be detected in urine by gas chromatography and/or mass spectroscopy, while terminal amino academia includes amino groups that are detected by other analytical methods (ninhydrate reaction). The mitochondrial accumulation of CoA metabolites is an important pathogenic

TABLE 5.11. Organic acidemias. MSUD

MSUD[38-41] (↓ dehydrogenase complex of branched ketoacids)	
Pathophysiological group	• Type II
Incidence (cases/NB)	• 1/357,000
Debut Age	• Three types: Neonatal • Infant • Late
Clinical aspects	• Neonatal: toxic syndrome, hypotonia, coma, ketoacidosis • Intermediate: failure to thrive, psychomotor retardation, ataxia, seizures • Adult: no usual symptoms. Ataxia episode, seizures and ketoacidosis with intercurrent infections
Treatment	• Acute form: peritoneal dialysis, hemodialysis or hemofiltration; parenteral nutrition • Diet low in leucine, isoleucine and valine • Thiamine • Hepatic transplant
Prognosis and complications	• Good prognosis if treatment is early and diet strict

characteristic of many organic acidemias, which have some clinical and biochemical characteristics in common. It may be present as a severe neonatal form or intoxication, a chronic form that is intermittent and appears late; or a slow progressive form with hypotonia, leading to psychomotor failure and failure to thrive.

Maple Syrup Urine Disease, MSUD

MSUD is an aminoacidopathy produced by a deficiency in the branched-chain alpha-keto acid dehydrogenase (BCKD) complex, resulting in the accumulation of these ketoacids and their precursors the branched chain amino acids leucine, isoleucine and valine (step 1 in figure 5.5). Its incidence is 1/250,000 newborns and is inherited in a autosomal recessive manner.

The clinical presentation of MSUD varies from severe neonatal forms to the more mild variants and is classified by indirect parameters such as the onset of symptoms, tolerance to leucine and residual cellular activity of the deficient enzyme BCKD. There are 5 different clinical and biochemical phenotypes: classic, intermediate, intermittent, thiamine sensitive and dihydrolipoil deshydrogenase deficiency (E3 component of the BCKD multienzyme complex)[38-40].

Three clinical forms have been recognised: severe neonatal onset, late onset with intermittent symptomatology and a chronic progressive form. Recent advances in diagnostic techniques have permitted the identification of rarer forms of the disease.

The neonatal or classic form is characterized by an asymptomatic period after birth that can last from one to two weeks, depending on the degree of enzymatic deficiency and not necessarily on the quantity of proteins ingested. The clinical presentation then begins with weak suction, food refusal and lethargy that intensify progressively. The characteristic sweet smell of the urine, bradycardia and bradypnea begin to appear. There may be hypotony of the trunk with hypertony of the extremities, boxing or peddling movements and opistotono posture. This leads to coma and death if not treated early. Dehydration is infrequent. The most frequent neurological symptoms are ketosis (rarely with acidosis) with normal levels of lactic acid and ammonium. The residual enzymatic activity is 0-2% of normal.

The chronic progressive form may occur from 5-6 months up to 6-7 years of age with progressive neurological symptoms including psychomotor delay, convulsions and ataxia. Residual enzymatic activity in this form is between 3-30%. The intermittent form may appear at any age and is characterized by intoxication-type neurological symptoms similar to those seen in the classic form that are usually set-off by catabolic situations such as infections, burns or surgical interventions. The residual activity of this form varies between 5 and 20%. Forms sensitive to pharmacological

doses of thiamine have been described, but there are no uniform criteria for the diagnosis of this rare form. There are also very infrequent forms resulting from a deficiency of dehydrolipoil deshydrogenase (E3), one of the components of the branched ketoacid deshydrogenase multienzymatic complex.

It is diagnosed by testing the serum branched amino acid levels. In the classic form, leucine levels may be higher than 2,000 µmol /l (normal 80-200 µmol /l), with the characteristic presence of aloisoleucine, a compound resulting from the non-enzymatic racemation of isoleucine. The diagnosis is confirmed by verifying the descarboxylation deficiency of branched amino acids in fibroblasts or lymphoblasts.

In the acute phase of this disease, treatment must rapidly normalize BCAA levels, especially leucine, the most neurotoxic. This is followed by treatment that includes a diet to maintain adequate growth and development of the patient while avoiding a significant increase in BCAA levels[40,41].

Acute phase

Treatment should begin immediately due to the danger of irreversible neurological damage and possible death. There are two options for rapidly reducing high serum concentrations of BCAA:

- Extracorporal techniques: Due to the low renal clearance of BCAA, even when plasma concentrations are extremely high, extracorporal techniques are necessary for their elimination. The possibilities include peritoneal dialysis, hemodialysis, hemofiltration and exchange transfusion. Hemodialysis/hemofiltration results in a significant and rapid reduction in BCAA levels that is maintained, but requires a complex infrastructure and vascular access that is difficult for newborns and infants. Thus, the technique chosen will depend on the availability and experience of hospital staff.
- Induction of anabolism and protein synthesis through aggressive nutritional treatment using parenteral feeding and/or

continuous enteral feeding. Parenteral feeding uses a BCAA mixture of amino acids (not available in Spain) and a high energy content with glucose and insulin if necessary, as well as lipids. Another efficient treatment is to start continuous enteral feeding with BCAA free formula at a rate to obtain a protein intake of 2-3 g/kg/day (depending on age), and at least the normal energy requirements according to age[42]. This may be difficult during the first few days, and it may be necessary to start with a diluted formula that is supplemented with glucose polymers at a final concentration of 10% carbohydrates, or combine the enteral feeding with intravenous glucose and insulin (if necessary) to obtain a high energy intake and avoid catabolism. If the plasma concentrations of valine and isoleucine drop below 100 µmol /l a supplement (100-200 mg/day) should be given to maintain plasma levels between 100-400 µmol /l. Leucine should be given at a rate of 50-100 mg/day when its plasma levels drop below 800 µmol/l. If needed, this dose can be increased in order to maintain leucine plasma levels between 200-700 µmol/l[7,8].

- The combination of these two techniques, extracorporal techniques and nutritional support, is the most rapid manner to reduce plasma leucine levels, providing significant results in a period of 11-24 hours[9].

Maintenance phase

The objective of this treatment phase is to maintain BCAA concentrations slightly above normal to obtain adequate protein synthesis, while preventing protein deficiency (Table 5.12). The leucine concentrations should be maintained, if possible, close to the lowest recommended level.

As leucine is the most neurotoxic amino acid with generally higher levels than isoleucine and valine, the diet is based on leucine intake. Intake is adjusted according to plasma leucine levels. As BCAA requirements are not precisely known, decrease with age

TABLE 5.12. Recommendations for BCAA in MSUD

	Objetive, µmol/l (mg/dl)
Leucine	200-700 (2.6-9.2)
Isoleucine	100-400 (1.3-5.2)
Valine	100-400 (1.1-4.4)

TABLE 5.13. Vegetables and fruits with lower content in leucine

Vegetables with < 50 mg leucine/100 g[a]	Egg plant, beets, carrots, celery, chicory, green spotted zucchini (squash), cucumber, onion, peppers, radishes, sweet potatoes, tomato, pumpkin, cabbage
Fruits with < 30 mg leucine/100 g[b]	Apple, apple juice, apricot, cherries, oranges, orange juice, grapefruit, tangerine, lemons, grapes, guava, peach, plums, strawberries, pears, passion fruit, melon, raspberry, blueberry

[a]The protein content ranges from 0.5-1 g/100 g. The new varieties, in general, contain less leucine than the old ones. [b]The protein content ranges from 0.3-1 g/100 g.

and tend to vary widely in individuals, intake must be adjusted for each individual based on their plasma BCAA levels. Leucine requirements oscillate between 100- 110 mg/dg/day during the first 2-3 months of life, decreasing during the first year to 40-50 mg/kg/day. The majority of children suffering from MSUD have a leucine intake between 400- 600 mg/day.

The diet excludes all foods with proteins of high biological value (meats, fish, eggs and milk and its derivatives) due to their high leucine content. Leucine is obtained from foods with protein of a lower biological value such as potatoes, cereals and rice, as well as vegetables and fruits. Food options are limited due to the lack of leucine analysis of many foods, especially industrial products. Protein content cannot be used as an indicator of leucine content as this is extremely variable and thus not reliable. Table 5.13 lists the fruits and vegetables with the lowest leucine content.

Given that isoleucine and valine levels in foods are always lower than that of leucine and their daily requirements are also lower, leucine restricted diets normally contain sufficient quantities of isoleucine and valine. However, if a significant decline in their levels is observed in periodic testing, diet supplements must be included so that insufficient levels of these amino acids do not limit protein synthesis.

A starting dose of 50-100 mg/day diluted in water is normally used. This should be divided into 2-3 daily doses to be taken and can be increased depending on plasma levels.

The drastic limitation of natural proteins in the diet requires BCAA free protein supplements to ensure adequate protein intake to sustain adequate growth and development. The majority of these preparations contain vitamins and minerals that meet the patient's daily requirements according to age. A thiamine supplement of 5 mg/kg/day is recommended for all forms of this disease as it can improve the tolerance to BCAA in some patients[43]. Forms that are sensitive to thiamine require a dose of between 10-1000 mg/day.

Metabolic decompensation crisis

During intercurrent infections or other processes that increase energy demands, a rapid increase in BCAA levels is seen, especially of leucine levels. Thus, it is necessary to suppress the intake of foods containing protein and start an emergency dietary plan including glucose polymers in conjunction with BCAA free protein preparations in order to stimulate protein synthesis and supply adequate caloric intake.

Isovaleric acidemia (IVA)- Propionic acidemia (PPA). Methylmalonic acidemia (MMA)

The deficiency of enzymes employed at distinct steps in the metabolism of branched amino acids (Fig. 5.5) result in organic acidemias, of which the most frequent are:

- Isovaleric acidemia (IVA): This condition is caused by a deficiency in isovaleryl-CoA deshydrogenase (step 2 in figure 5.5).
- Propionic acidemia (PPA): This disease is caused by a deficiency in propionyl-CoA carboxylase, a biotin-dependent mitochondrial enzyme necessary for the metabolism of propionyl-CoA (step 3 in figure 5.5).
- Methylmalonic acidemia (MMA): This is a result of a deficiency in the mitochondrial enzyme methylmalonyl-CoA mutase, which requires the cofactor adenosyl-cobalamine and catalizes the step of methyl-malonyl-CoA to succinyl-CoA (step 4 in figure 5.5).

There are other acidemias caused by deficiencies in enzymes required for the metabolism of leucine (methylcrotonylglycinuria, type I and IV methylglutaconic, mevalonic, etc.), of valine (deficiencies of isobutiryl-CoA-DH, 3-OH-isobutiryl-CoA desacylase, etc.), as well as multiple carboxylase deficiencies. The three most frequent acidemias, IVA, PPA and MMA, are inherited in an autosomal recessive manner and have the common characteristics of intense acidosis (pH <7.25, bicarbonate <15), ketonemia and ketonuria, hyperammonemia of varying intensity, with normal or high glucemia and lactate. They tend to have an increased anion gap and pancytopenia.

The most frequent form of presentation is the severe neonatal form, where after a symptom-free period, the patient begins with an intoxication-type neurological picture including food refusal, vomiting, rapid dehydration, hypotonia, convulsions, apnea crises, coma and death. In IVA there is a characteristic smell of sweaty feet.

Less frequently there may be a a late onset form (even in the adult) characterized by acute recurrent symptoms that may be the result of a precipitating factor (fasting, intercurrent diseases) and a chronic progressive form where symptoms tend to be intense anorexia, failure to thrive and vomiting in conjunction with neurological signs (pyramidal and extrapyramidal, psychomotor delay). There may be clinical complications such as pancreatitis,

TABLE 5.14. IEM of amino acids and proteins. Organic acidemias. Isovaleric

Isovaleric aciduria (IVA)[41,44,45] (↓ Isovaleryl- CoA- dehydrogenase)	
Pathophysiological group	• Type II
Incidence (cases/NB)	• Unknown as it is not in neonatal screening programs and is underdiagnosed
Debut Age	• Neonatal • Late infancy
Clinical aspects	• Neonatal: general toxic syndrome • Late infancy: development and mental retardation, acidosis during decompensations, pancytopenia
Treatment	• Diet low in proteins and leucine • L-glycine and carnitine supplements
Prognosis and complications	• Good prognosis with early diagnosis and treatment • Poor prognosis with later diagnosis in neonatal forms

myocardiopathy, cutaneous lesions, progressive renal dysfunction, etc. (Tables 5.14 and 5.15).

The diagnosis is made by testing for organic acids in biological fluids using gas chromatography/mass spectrometry, where the diagnostic metabolites of each acidemia can be identified. Fibroblasts can be used to determine the corresponding enzymatic deficiency. In the following two tables a summary of these clinical entities is shown. In one table IVA is presented, while PPA and MMA are present together in the other table due to their clinical similarities. Treatment of the organic acidemias IVA, PPA and MMA have many common elements, for this reason they are present together[41].

Acute initial phase

This generally effects newborns suffering from acute and severe intoxication-type clinical symptoms where the treatment priorities will be[45-48]:

TABLE 5.15. IEM of amino acids and proteins. Organic acidemias

Methylmalonic acidemia (MMA) and propionic acidemia (PPA)[41,44,45] (↓ Methylmalonyl-CoA- mutase) (↓ Propionyl-CoA carboxylase)	
Pathophysiological group	• Type II
Incidence (cases/NB)	• 1/50,000 (methylmalonic)
Debut Age	• Neonatal • Infant • Late
Clinical aspects	• Metabolic acidosis • Hyperammonemia • Neutropenia • Failure to thrive • Anorexia, vomiting • Tendency to dehydrate • Adult (Corea and dementia) • Renal dysfunction • Myocardiopathy
Treatment	• Acute form: peritoneal dialysis or hemodialysis; correction of dehydration and acidosis; parenteral nutrition • Ammonium chelants • Carnitine, vitamin B_{12}, biotin at pharmacological doses • Diet low in methionine, valine, threonine and isoleucine • Metronidazole • Decrease in soluble fiber • Sufficient calorie supply
Prognosis and complications	• Good prognosis if the treatment is early and diet strict • Anorexia • Mental retardation • Osteoporosis • Renal failure

- Maintain the vital signs and rapidly eliminate the toxic substrate:
  - Admission and monitoring in the ICU.
  - Correction of the severe acidosis.

- Maintain good hydration and force diuresis with intravenous solutions during the first 24 hours, with or without diuretics. This is one of the most useful treatments in MMA due to the high renal clearance rate of methylmalonic acid.
- Extrarenal depuration: These techniques such as exchange transfusion, hemodialysis or peritoneal dialysis are useful especially in PPA given the very low urinary excretion of propionic acid and that alternative effective detoxification pathways are not available.
- Physiological detoxification: Carnitine at pharmacological dosis (200-400 mg/kg/day) can be used. In IVA the administration of L-glycine at a dose of 250-600 mg/day in conjunction with carnitine is a specific and effective means for the elimination of isovaleryl-CoA as isovalerylglycine and isovalerylcarnitine, two non-toxic compounds that are rapidly cleared by the kidney.
- Avoid *denovo* production of substrate and catabolism: Promote anabolism through increased nutritional intake of protein-free and hypercaloric products (glucose polymers with or without fats, plus electrolytes) for a maximum of 48 hours and preferentially by continuous enteral feeding (if not possible, by parenteral feeding). Proteins should then be introduced progressively (once the ammonium levels reach 100 µmol /l) beginning with a dose of 0.25-0.5 g/kg/day.
- Limit the production of propionate by intestinal bacteria using antibiotics such as metronidazol that inhibits the flora of the colon (20 mg/kg/day during 15 days followed by 10 mg/kg/day over longer periods of time).

Specific diagnosis phase

The objectives of treatment in this phase are to achieve normal nutrition and growth while avoiding the production of toxic metabolites. It is also important to prevent metabolic decompensation that has an increased risk in these patients under specific situations. To acheive these objectives it is necessary to:

- Limit protein intake: This is fundamental. The individual tolerance limit of each patient must be determined (the maximum quantity of proteins that can be ingested without altering their gasometry results or ammonium levels) and ensure the intake of the minimum protein required for adequate growth and development. Some authors use valine intake as a guide in PPA and MMA as it is one of the most direct precursors of propionyl-CoA. The initial intake of valine should be between 20-25 mg per day, increasing the dose depending on the individual tolerance of each patient. In general, a child will tolerate between 300-500 mg/day, which represents an intake of natural proteins of 5.5-7.5 g/day. In cases of IVA, the quantity of natural proteins can be adjusted according to the leucine requirements. During the first year of life, the quantity of leucine ingested should be increased progressively up to 800 mg/day (which represents approximately 8 g/day of natural proteins). The majority of children reach a tolerance of between 20-30 g of protein/day.
- Special amino acid supplements: When the limitation of proteins is at or below the minimum protein requirements, protein supplements free of the amino acid precursors valine, isoleucine, thrionine and metionine in PPA and MMA and of leucine in IVA, should be employed. These supplements should be given in conjunction with natural foods in order to promote anabolism and to complete the established protein requirements according to the patient's age. However, some authors disagree with their use, especially in children with a high protein tolerance arguing that they can obtain good metabolic control and adequate nutrition and growth without them. Additionally, these supplements are difficult to administer to children due to their flavor and texture.

  These compounds should not be given alone in cases of decompensation as in catabolic phases they can be converted into a source of ammonium production.

- Patients with PPA and MMA almost always suffer from anorexia and appetite problems, such that nasogastric or gastrostomy alimentation is necessary to ensure adequate food intake and prevent metabolic decompensation. With nocturnal gastroclysis not only is optimum nutrition obtained, but catabolism associated with fasting is reduced and thus the liberation of uneven branched chain fatty acids from fat deposits (another source of propionate).
- The caloric intake should be sufficient to avoid catabolism and the mobilization of endogenous proteins. Some authors suggest hypercaloric intake, while others have observed that children with organic acidemias require a relatively low energy intake to obtain normal growth[49].
- The liquid requirements of these patients may be increased due to a certain degree of polyuria as a result of the increased urinary excretion of organic acids.
- Supplements of vitamins, minerals and oligoelements may be necessary if the restrictive diet is composed only of natural foods, as the special amino acid supplements are usually the main source of vitamins, minerals and oligoelements.
- Use of cofactors and detoxifying agents: Pharmacological doses of biotin (10-20 mg/kg/day v.o.) for PPA and hydroxy-B12 (1-5 mg/week i.m.) for MMA are effective in the vitamin sensitive forms of these organic acidemias (they tend to be the delayed forms). They are not useful in the most common forms (vitamin insensitive). In IVA, treatment should be continued with L-glycine at a continued dose of 150-250 mg/kg/day. Carnitine should also be given for the secondary deficit that is produced, although at a low doses of between 30-50 mg/kg/day.
- Other treatments[50]: To reduce the production of intestinal propionate, metronidazol at a dose of 10 mg/kg/day can be given. Sodium bicarbonate is useful especially in MMA due to the defect in acidification as a result of the renal complications. Sodium benzoate can be used to reduce plasma ammonium

and glycine levels. Growth hormone and alanine have been used, but with inconclusive results. Although liver transplant may improve the quality of life, it is not a cure and the risk of complications continues. N-carbamylglutamate at normal doses (Table 2.6) can also be used.

Acute decompensations

Treatment should be started as soon as possible.

- Slight-moderate decompensation (bicarbonate < 14 mEq/l and ammonium < 150 mg/dl): Prohibit the intake of natural protein for 24 hours and special protein intake for 72 hours. Adequate hydration should be assured followed by forced diuresis. The emergency regimen of caloric intake, if possible by enteral feeding, should be implemented. The amount of carnitine ingested should be increased (100-200 mg/dg/day), and in IVA that of glycine.

Type I Glutaric aciduria (GAI)

This disease is autosomal recessive (McKusick 231670) and caused by a deficiency in the enzyme glutaryl-CoA deshydrogenase (Fig. 5.6). The clinical symptoms appear between 6-18 months of age when a nonspecific illness such as a respiratory or gastrointestinal infection or a vaccination gives rise to an acute encephalopathy crisis that, if not treated rapidly, causes acute necrosis of the basal ganglia (caudate and putamen). The consequence is a dystonic-dyskinetic disorder similar to brain paralysis and oscillates from extreme hypotonia to coreoatetosis and rigidity with spasticity.

The main objective of treatment is to prevent encephalopathy crises and neurological deterioration (90% of children treated do not suffer brain damage, while 90% of those not treated develop severe neurological damage)[51-54]. Diagnosis and early treatment in asymptomatic children is essential, given that treatment has little effect in children with neurological damage[53], although some

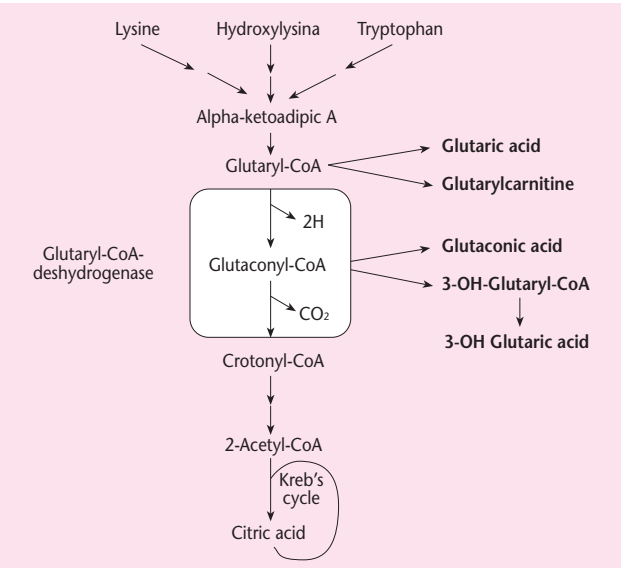

Figure 5.6. Catabolic pathway of glutaric acid. Glutaryl-CoA dehydrogenase is a mitochondrial enzyme that catalizes dehydrogenation and decarboxylation of glutaryl-CoA to crotonyl CoA. In patients with type I glutaric aciduria, both steps are blocked, which gives rise to an accumulation of glutaric acid, 3-hydroxyglutaric acid and glutaconic acid, as well as glutarylcarnitine.

authors suggest that further brain damage can be prevented. Some patients remain asymptomatic with little or no treatment (Table 5.16).

Treatment includes:

Carnitine supplements

All patients with GAI should receive carnitine to prevent carnitine deficiency and ensure mitochondrial homeostasis (the depletion of carnitine observed in the majority of these patients is due to urinary loss of glutaryl-carnitine that exceeds the capacity of endogenous synthesis). The normal dose is 30-100 mg/kg/day

TABLE 5.16. IEM of amino acids and proteins. Type I glutaric aciduria

Type I glutaric aciduria (GA)[41,45,51-53] (↓ Glutaryl- Co A deshydrogenase)	
Pathophysiological group	• Type II
Incidence (cases/NB)	• 1/30,000
Debut Age	• Infants • 6-8 months
Clinical aspects	• Encephalopathic crisis: Reye-like syndrome, hypoglycemia, metabolic acidosis) • Acute metabolic crisis • Progressive subclinical picture: neurological deterioration that progresses to paralysis)
Treatment	• Diet low in proteins and low in lysine and tryptophan • Carnitine: 30-100 mg/kg/day • Riboflavin • Baclofen
Prognosis and complications	• Good prognosis with early diagnosis + treatment • Poor prognosis with late diagnosis

and should be adjusted to maintain plasma free carnitine levels in the normal range. No patient receiving carnitine supplements has died of an encephalopathic crisis.

Dietary treatment

Although effective in other organic acidemias, a diet low in proteins, lysine and tryptophan has not been demonstrated to be beneficial to these patients. There are also no useful biochemical markers to evaluate the response to said diet. Moreover, dietary treatment alone is not sufficient to prevent metabolic decompensation. However, a long-term beneficial effect on psychomotor development cannot be excluded and many centers recommend that children with GAI maintain a diet low in lysine and tryptophan during the first years of life. The restriction of natural proteins is completed with

synthetic protein preparations low in lysine, hydroxylysine and tryptophan[55]. Amino acid mixtures without tryptophan should be avoided as tryptophan deficiency has contributed to patient deaths. In older children, foods rich in protein (fish, meat, chicken, nuts) should be restricted with the protein intake not exceeding 1.5 g/kg/day. Care should be taken that energy, as well as vitamin and mineral, intake is sufficient.

Some authors recommend a moderate reduction in protein so that special amino acid supplements are not necessary[56]. Maintaining good nutrition for severely affected patients is very important and affects long-term morbimortality. These patients are normally malnourished due to difficulties in chewing and swallowing, in addition to high energy expenditure as a result of their high muscle tone, dystonic movements and alterations in temperature control. At times adequate caloric intake can only be achieved by gastrostomy and many children only begin to gain weight after employment of nocturnal gastroclysis. It appears that when the nutritional state improves, there is a slight improvement in the dystonia.

Riboflavin

As riboflavin is a cofactor of glutaryl-CoA deshydrogenase, it is used to augment its enzymatic activity. An initial dose of 100 mg/day should be tried. The response is evaluated by measuring glutaric acid levels in various urine samples both before and after treatment. If there is no improvement the treatment should be suspended.

Medication

Different medications have been used to deter the neurological problems of these patients, but none are universally recommended.

- Baclophen: 1-2 mg/kg/day. It may cause severe hypotonia of the trunk and worsen the neurological symptoms in some patients.

- Benzodiacepines: diacepam 0.1-1 mg/kg/day.
- Others: vigabatrine, etosuximide, L-dopa + carbidopa, valproic acid (this can compete with glutaric acid for esterification, and should therefore be avoided).

Emergency management during intercurrent illnesses

It is very important that metabolic equilibrium is maintained during intercurrent illnesses, vaccinations and other situations that can provoke a catabolic state, especially during the preschool ages. This includes fever, diarrhea, vomiting, pain, trauma, poor food intake and poor general status. As soon as the first symptoms of illness appear one should:

- Suspend the intake of natural proteins.
- Caloric intake of at least 1.5 times the basal requirements (>60 Kcal/kg/day in neonates and preschool children) using liquids rich in carbohydrates should be given (see the emergency regimen).
- Liquid intake should exceed 1.5 times the basal requirements. In the case of gastroenteritis, the oral rehydration solutions should be enriched with glucose polymers.
- Double the dose of carnitine (200 mg/kg/day).
- Proteins should be reintroduced gradually no more than 24 hours later.
- If there is no improvement in 24 hours the patient should be admitted to the hospital. The early signs of a encephalopathic crisis include irritability, lethargy and hypotonia that may progress to stupor and hypotonia in hours.

Emergency management during metabolic descompensation

It is essential to correct the metabolic descompensation as soon as possible in order to prevent irreversible brain damage. Severe brain dysfunction may occur, at times even without biochemical alterations. Initial laboratory determinations should include pH and gases, electrolytes, glucemia, liver and kidney

function and ammonium levels. Metabolic acidosis, hypoglucemia and hyperammoniemia are normally absent until the later stages of the illness. It is necessary to use i.v. perfusion with a high concentration of glucose, as well as lipids, and to correct the acidemia. Treatment should include carnitine (i.v., 100-200 mg/kg in 4 doses) and sedation with diacepam (0.25 mg/kg every 6 hours). The use of dextrometorfan may be beneficial for neuroprotection, although its value has not been proven. Riboflavin (100 mg/kg) can be used if necessary. Hyperpyrexia is a common problem in children with GAI and post- encephalopathic brain damage. Clormetiazol has been found to be useful in severe cases.

During the last decade the dietary treatment and that of emergency crisis treatment, as well as the employment of carnitine, has prevented the appearance of acute encephalopathic crises in children with an early diagnosis[57]. However, a case was recently published of a patient suffering from acute encephalopathy with high excretion of glutaric acid and 3-hydroxyglutaric acid in spite of correct treatment[58]. The authors conclude that high excretion of these two acids provokes neuronal damage and makes these patients more susceptible to cerebral damage compared to those that secrete low quantities of glutaric acid and 3-hydroxyglutaric acid, even with proper treatment.

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6 Inborn errors of metabolism of specific cycles

6.1. DISEASES OF THE UREA CYCLE (DUC)

Nitrogen atoms found in food are only used in biosynthetic processes for growth or tissue repair. Excess nitrogen in the diet must be eliminated as there are no storage processes for this element, and moreover it is potentially toxic for the human being. To avoid this problem, mammals (ureotelic animals) have developed a pathway to excrete excess nitrogen through the formation of urea[1] (Fig. 6.1). The formation of urea or the complete urea cycle takes place in the liver and constitutes an essential biochemical pathway to eliminate surplus nitrogen. It is a system comprised of 6 metabolic reactions in which 2 moles of toxic ammonium is eliminated in the form of one molecule of urea (hydrosoluble and non-toxic) in every complete cycle (Fig. 6.2). Urea is the most important vehicle for the excretion of nitrogen and its production increases in conjunction with that of protein intake. Ammonium is also trapped by other compounds such as glutamate, pyruvate and aspartate and can also be used in the synthesis of compounds that contain nitrogen (glycine and pyrimadines including orotic acid). Blockage of this pathway can be caused by an enzymatic deficiency [carbomylphosphate synthetase (CPS), ornitintranscarbamylase (OTC), N-acetyl glutamate synthetase (NAGS), arginosuccynico synthetase (AS), arginosuccinate liase (AL) or arginase (A)], or by depletion of an essential amino acid necessary for normal functioning of the cycle. This is due to a defect in a transporter, as occurs in HHH syndrome or in protein intolerance with lysinuria[2]. When blockage of ureagenesis occurs two things happen, the synthesis of urea is inadequate and more importantly ammonium, which is toxic especially to the brain, accumulates in all cells of the organism.

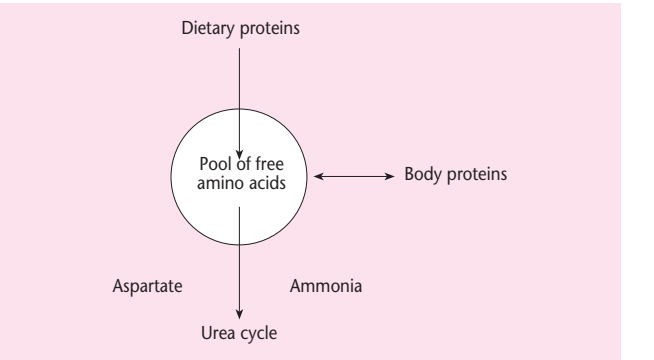

Figure 6.1. Relationships between dietary proteins, body proteins and urea synthesis. Nitrogen from the diet that is not used for growth or tissue repair should be excreted, since there is no physiological way of storing it. Mammals eliminate it by synthesis and excretion of urea. Only the nitrogen atoms contained in the ammonium (that are derived from different amino acids) and aspartate (from the oxalacetate and glutamate transamination) are destined to the production of urea and thus are called waste nitrogen atoms. Any drug agent that sequesters the free pool of amino acids will decrease urea synthesis requirements.

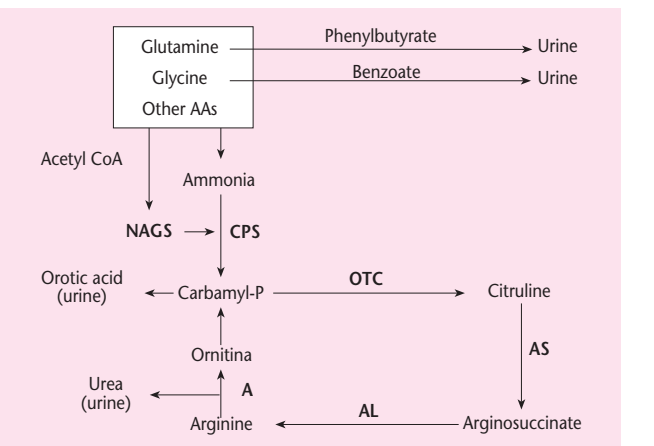

Figure 6.2. Urea cycle (CPS: Carbamoyl phosphate synthetase. OTC: ornithine transcarbamylase. AS: argininosuccinate synthetase. AL: arginosuccinate lyase. A: arginase. NAGS: N - acetylglutamate synthetase).

Additionally, other compounds, especially glutamine and glycine, are formed to transport the excess nitrogen and ease the toxic effects.

As there is no other effective system for the secondary elimination of ammonium, this compound and other precursor metabolites rapidly increase giving rise to acute cerebral edema with severe neurological effects that can lead to death. In general, deficiencies in enzymes at the beginning of the cycle produce hyperammoniemias that are more severe and more resistant to treatment (deficiencies in CPS and OTC are the most severe), although there is a wide variation depending on the degree of enzymatic deficiency.

The liver is the only organ where this cycle is complete. As a group, defects in the urea cycle are frequent, occurring in approximately 1/25,000 newborns, although it is suspected that there are undiagnosed cases and that the real incidence may be closer to 1/15,000 newborns. These conditions are inherited in an autosomal recessive manner, except for OTC deficiency that has an X-linked inheritance (however, currently many cases are being diagnosed in females, which could indicate de novo mutations). The pathogenesis is not well known, but it appears to be due to the increase in ammonium and amino acids (glutamine, glycine, alanine) that results in osmolarity changes (cerebral edema) and can cause acute or chronic encephalopathy, as well as alterations in neurotransmitters.

There are two forms of clinical presentation:

a. Acute neonatal onset (classic form): After a symptom free period, 24-48 hours after the initiation of feeding an intoxication type clinical picture begins that rapidly evolves to generalized convulsions. If the ammonium is >250 µmol/l they may go into coma that could result in death.
b. Chronic late onset form: This is set off by environmental factors (infections, high protein intake, etc.). An insidious clinical picture that is potentially grave appears. It can range from vomiting

TABLE 6.1. IEM of amino acids and proteins. Urea cycle diseases

Diseases of the urea cycle[3-6] (diverse enzymatic deficits)	
Pathophysiological group	• Type II
Incidence (cases/NB)	• 1/15,000 (OTC deficit)
Debut Age	• Neonatal (24-72 hours of life) • Late forms
Clinical aspects	• Neurological symptoms, intoxication type: weak suction, hypotony, vomiting, somnolence, coma, abnormal EEG • Paucistymptomatic forms
Treatment	• Hypercaloric diet supplemented with arginine and citrulline • Acute phase: ammonium chelates (benzoate, phenylbutyrate, phenylacetate), hemodialysis, hemofiltration or peritoneal dialysis • Hepatic transplant
Prognosis and complications	• Good prognosis with early diagnosis + treatment • Poor prognosis with late diagnosis

and somnolence, to convulsions and coma and improves with fasting. At times unexplainable hypertransaminasemia is found.

Older children, adolescents and adults have different neurological (migraines, disartria, ataxia) or psychiatric (hallucinations) symptoms (Table 6.1)[3-6]. The clinical picture is variable and there are paucisyntomatic forms that are underdiagnosed.

When confronted with a suggestive clinical picture, including repetitive undiagnosed neurological crises, DUC should be suspected. Diagnosis is based on hyperammoniemia (>150 µmol/l during the neonatal period and >80 µmol/l thereafter), with normal glucemia, negative ketonuria and normal lactic acid. There is usually respiratory alkalosis or mixed respiratory alkalosis and moderate liver affectation in the acute phases or during decompensation.

The definitive diagnosis is made with amino acid testing. The most frequent defects are those at the beginning of the cycle, deficiencies in OTC and CPS, with low citruline and can be differentiated by the urinary elimination of orotic acid in OTC deficiency (that can be confirmed by an alopurinol tolerance test). The cytoplasmic enzyme deficiencies are characterized by an increase in citruline, with this being much higher (>250 µmol/l) in AS deficiencies (citrulinemia) than in AL (arginosuccynic aciduria; 100-250 µmol/l). Deficiency in A (argininemia) shows very high levels of citruline and arginine and discrete hyperammonemia. The definitive diagnosis is made by genetic studies.

The treatment of these patients includes:

1. Restrict protein intake in order to reduce the need to excrete nitrogen. The protein tolerance depends on the degree of enzymatic deficit and the age of the child. As always, the maximum protein tolerance should be determined (that which allows adequate growth without metabolic destabilization). After birth, the objective is to provide a protein intake of 1.5 g/kg/day[3] beginning with quantities of 0.5-0.7 g/kg/day augmented gradually to avoid hyperammoniemia (the gradual increments should not be greater than 10% each time). The protein requirements of newborns change during the first months of life, with a «honeymoon» period where high levels of protein can be tolerated. After 6 months, the requirements per kilogram of bodyweight decrease. To confirm that adequate protein intake, clinical (growth, phenomena in the skin, hair and nails, etc.) and biochemical parameters should be tested including plasma determinations of ammonium, essential amino acids, glutamine, hemoglobin, hematocrit, albumin, prealbumin, transferrin and total proteins. Table 6.2 illustrates the biochemical objectives for adequate patient management[7]. Although it is necessary to ensure the minimum protein requirements, in cases of severe enzymatic deficiency, extreme protein restriction may not meet minimum protein needs. In

TABLE 6.2. Biochemical objectives for optimum control of the UCDs

- Plasma ammonium < 40 µmol/l (other authors < 80 µmol/l)
- Plasma glutamine < 1,000 µmol/l
- Normal plasma levels of alanine, glycine, lysine and arginine (except in arginase deficiency)
- Amino acid concentrations in low limit of normality
- Normal excretion of urinary orotate (< 3 µmol/mmol creatinine)
- Normal concentration of plasma proteins (albumin, prealbumin, transferrin, total proteins)

These objectives are sometimes not reachable and treatment should always be individualized.
Of all these laboratory tests, plasma ammonium and quantification of amino acids are useful. Ammonium levels are subject to many factors (protein intake, time of last meal, etc.), as well as artifacts in the collection of the samples. Thus, it may not be a good index of long term control and plasma glutamine is used as a better guide. Elevated levels of glutamine and ammonium may indicate that the body ammonium is elevated due to elevated protein intake, but the possibility of insufficient intake of proteins and calories must also be considered.
Urinary excretion of orotate is useful in OTC deficit.

both groups a specific amount of protein (between 25-50%) can be replaced by a commercial mixture of essential amino acids added to the formula in neonates and in older children as a drink or paste. One should start with a quantity of 0.2-0.5 g/kg/day, up to a maximum of 0.7 g/kg/day divided between 2-3 meals. In this way, the essential amino acid requirements can be met with the advantage that these have a lower density of nitrogen and, as the intake of non-essential amino acids is limited, excess nitrogen is used for their synthesis. Together this helps to limit the flux of nitrogen into the urea cycle. When the patients are clinically stable, including in severe forms, the amount of proteins that can be ingested is relatively flexible without provoking an increase in the levels of ammonium and glutamine. This is not possible in patients with poor control as their metabolic status would deteriorate rapidly.

Although the significant protein restriction can give rise to a deficit in essential amino acids, there is probably a greater risk in micronutrient deficiency, especially of iron and zinc. For this reason vitamin and mineral supplements are necessary.

Adequate caloric intake must also be ensured in order to avoid mobilization of endogenous proteins, obtained by ingesting foods with a very low protein content. The limited quantity of proteins that can be ingested should never be considered as a source of calories, but exclusively anabolic. Ingesting more energy than necessary will not reduce protein catabolism further, but only increase the possibility of being overweight.

2. Employment of medicines that use alternative pathways for the excretion of nitrogen. These are compounds that conjugate with amino acids and are rapidly excreted. These medications are used because nitrogen is excreted as a compound different from urea, such that the amount of nitrogen that enters the urea cycle is decreased. Sodium benzoate (250 mg/kg/day, every 6-8 hours), which is conjugated with glycine to form hypurate and is rapidly excreted, can be used. For every mole of benzoate a mole of nitrogen is excreted. The most common side effects include nausea, vomiting and irritability.

   Phenylbuterate is oxidized in the liver to phenylacetate and this is conjugated with glutamine to form phenylacetylglutamine. For every mole of phenylbuterate two moles of nitrogen are excreted. The dose used is 200-600 mg/kg/day, depending on whether it is used in combination with benzoate or alone. The excretion of hypurate and phenylacetylglutamine increases the amount of potassium lost in the urine, which can lead to hypopotassemia and metabolic alkalosis. Excessive doses of these compounds lead to symptoms similar to hyperammoniemic crisis including agitation, confusion and hyperventilation[8].
3. Correct nutrient deficiency: Arginine is an non-essential amino acid because it is synthesized in the urea cycle. In patients with defects in the urea cycle, except those with arginase deficiency,

arginine becomes a semi- or essential amino acid as a result of the metabolic blockage, making its intake necessary. The dose employed is between 100-170 mg/kg/day, although patients with citrulinemia and arginosuccynic aciduria require greater amounts (400-700 mg/kg/day) due to the important loss of ornitine in the urine, which should be reestablished. Plasma arginine levels should be maintained between 50-200 µmol/l. Commercial preparations are usually in the form of clorohydrates (oral or i.v.) and the tendency to produce hypercloremic acidosis should be monitored. The levels of citruline and arginosuccynic acid may be increased, as they eliminate nitrogen through urine. On occasions, and in variants with severe deficiencies of carbamylphosphate synthetase and ornitine carbamyl transferase, arginine can be substituted for citruline at a dose of 170 mg/kg/day with which the supplementary elimination of the nitrogen from the aspartate is obtained.

Other supplements: citrate. Citrate reduces the postprandial elevation in ammonium and could play an important role in controlling the arginosuccynic aciduria by correcting the deficit in aspartate, but its long-term effect is unknown. Carnitine: During hyperammoniemic descompensation crises, carnitine levels may be depleted and some authors recommend its administration during said crises (100 mg/kg/day).

In table 6.3 the treatments for DUC are summarized.

EMERGENCY TREATMENT OF INITIAL HYPERAMMONIEMIC COMA AND ACUTE DESCOMPENSATION

The hyperammoniemic coma is a medical emergency in which aggressive treatment should be started immediately to prevent or minimize irreversible brain damage[9-12]. Plasma ammonium levels of 100-200 µmol/l are associated with clinical symptoms of lethargy, confusion and vomiting while higher levels can result in coma. In OTC deficits (the most frequent DUC), more than half of surviving

TABLE 6.3. Chronic treatment of UCD

Disease	Proteins (g/kg/day)	Essential amino acids (g/kg/day)	Sodium phenylbutyrate (g/kg/day)	Arginine (g/kg/day) (g/m²/d)	Citrulline (g/kg/day) (g/m²/d)
OTC or CPS deficiency	0.7	0.7	0.4-0.6 in <20 kg 9.9-13 g/m²/d >20 kg	–	0.17 (3.8)
AS deficiency	1.5-2	–	0.4-0.6 in <20 kg 9.9-13 g/m²/d >20 kg	0.4-07 (8.8-15.4)	–
AL deficiency	1.5-2	–	It may not be necessary	0.4-0.7 (8.8-15.4)	–
Arginase deficiency	0.7	0.7	0.4-0,6 in <20 kg 9.9-13 g/m²/d >20 kg	–	–
NAGS deficiency*	1.5-2	–	Effective treatment is with N-carbamylglutamate at a dose of 100-300 mg/kg/day.		

- Modified by Berry GT and Steiner RD. Long term management of patients with urea cycle disorders. J Pediatr 2001; 138 (Suppl): 56-61.

patients suffer from severe neurological damage, with plasma ammonium levels at diagnosis being the only predictive factor of neurological prognosis[11,12].

The following steps should be taken[13-15]:

- Establish the airway passage: assisted ventilation (hyperventilation). These patients initially suffer from respiratory alkalosis.
- Intravenous perfusion: Good hydration of the patient should be obtained (being careful of cerebral edema) and non-protein glucose solutions (8-10 mg/kg/min) and lipid emulsions administered for a caloric intake of >80 kcal/kg/day and minimize endogenous proteolysis.
- Total suppression of protein intake during 24-48 hours. If the patient can tolerate oral food intake, enteral alimentation via a feeding tube with solutions of carbohydrates and lipids should be started.
- Elimination of accumulated ammonium: The most rapid method is dialysis and most effective systems include oxigenation with an external membrane connected to a hemodialysis machine (ECMO/HD) and hemofiltration[13]. Replacement transfusion is not effective. Dialysis should be suspended when ammonium levels fall below 200 µmol/l.
- The second line of treatment includes drugs that use alternative pathways for the elimination of ammonium. Table 6.4 depicts the treatment and doses to be used during the phase prior to definite diagnosis depending on the enzymatic defect involved[13]. The recommended arginine dosage has been increased as it appears that its rapid infusion has a significant impact on AS and AL deficiencies and it is relatively safe in patients with deficits in OTC, CPS and NAGS. It should be diluted in a solution of glucose and since 1 g of sodium benzoate contains 160 mg of sodium and 1 g of phenylacetate contains 147 mg of sodium, no additional sodium is needed. However, additional potassium is need due to its secondary depletion as a result of these drugs. The required i.v. dosage

TABLE 6.4. Recommended drug dose in severe hyperammonemia

Patient's age	Components of infusion solution			Dose		
	SB/SF Perfusion, 10%	Arginine HCL Perfusion, 10%	Dextrose perfusion, 10%	Sodium benzoate	Sodium phenylacetate	Arginine HCL
NEWBORNS/INFANTS/YOUNG CHILDREN						
			Prospective treatment pending final diagnosis of UCD			
Loading dose	2.5 ml/kg	6 ml/kg	~25 ml/kg	250 mg/kg	250 mg/kg	600 mg/kg
Maint. dose	2.5 ml/kg	6 ml/kg	~25 ml/kg	250 mg/kg	250 mg/kg	600 mg/kg
			OTC or CPS Deficiency			
Loading dose	2.5 ml/kg	2 ml/kg	~25 ml/kg	250 mg/kg	250 mg/kg	200 mg/kg
Maint. dose	2.5 ml/kg	2 ml/kg	~25 ml/kg	250 mg/kg	250 mg/kg	200 mg/kg
			AS or AL Deficiency			
Loading dose	2.5 ml/kg	6 ml/kg	~25 ml/kg	250 mg/kg	250 mg/kg	600 mg/kg
Maint. dose	2.5 ml/kg	6 ml/kg	~25 ml/kg	250 mg/kg	250 mg/kg	600 mg/kg
OLDER CHILDREN AND ADULTS						
			OTC or CPS Deficiency			
Loading dose	55 ml/m^2	2 ml/kg	~25 ml/kg	5.5 g/m^2	5.5 g/m^2	200 mg/kg
Maint. dose	55 ml/m^2	2 ml/kg	~25 ml/kg	5.5 g/m^2	5.5 g/m^2	200 mg/kg
			AS or AL Deficiency			
Loading dose	55 ml/m^2	6 ml/kg	~25 ml/kg	5.5 g/m^2	5.5 g/m^2	600 mg/kg
Maint. dose	55 ml/m^2	6 ml/kg	~25 ml/kg	5.5 g/m^2	5.5 g/m^2	600 mg/kg

SB: sodium benzoate; SF: sodium phenylacetate.
Taken from Sumar M. Current strategies for the management of neonatal urea cycle disorders. J Pediatr 2001; 138 (Suppl): 30-9.

should be maintained until it can be administered orally once the patient is stabilized (ammonium levels 100-200 µmol/l) and food intake has been reestablished. These drugs can be used as the first line of treatment if ammonium levels are not very high and dialysis is not immediately available. They can be used in combination with dialysis as it their effects are enhanced. Occasionally, enteral citruline treatment (150-200 mg/kg/day) is used in newborns with OTC and CPS deficiencies as its use in combination with aspartate increases nitrogen clearance. This should not be administered in cases of AS and AL defects as these patients have excess levels of citruline. Valproic acid should not be used for the treatment of convulsions since it diminishes the activity of the urea cycle, worsening the hyperammoniemia.

- Reintroduction of proteins: Once the plasma levels of ammonium have been stabilized (<100 µmol/l), an intake of 0.25-0.5 g/kg/day of protein can be started.

TREATMENT OF SPORADIC HYPERAMMONIUMIA

Any stressful situation such as an infection, prolonged fasting, surgery, etc., can trigger a crisis of hyperammoniemia. It is important that parents are instructed what to do in these situations of risk or in the case of a suspected decompensation. Protein intake should be reduced to half (at times suspended completely) and an emergency regime should be started (with glucose polymers and/or sugar solutions), while maintaining pharmacological treatment. If the patient does not tolerate oral liquids or the general state of health worsens, hospital admission is recommended.

OTHER TREATMENTS

- Liver transplant: This should be considered for patients who cannot follow the necessary restriction diet or who have

recurrent episodes of hyperammoniemia even when adequate medical treatment is followed. In the subgroup of patients with severe forms of OTC and CPS deficiencies, evaluation for the transplant program should be started early as these illnesses are difficult to control as they develop. In contrast, as the child grows, those affected with citrulinemia and arginosuccynate lisase deficiency have a greater tolerance to proteins and decreased frequency of hyperammoniemia crises. After liver transplant, ammonium levels are controlled rapidly and protein restriction or drug use is not necessary. As the enzyme defects of the urea cycle are not corrected in the rest of the body (intestine, kidneys), the deficiency in arginine biosynthesis persists such that supplements are necessary[14].

- Gene therapy: Treatments using adenovirus vectors are currently under investigation.

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7 Conclusion

«Each individual inborn error of metabolism is infrequent, but collectively they are numerous». This statement identifies the great challenge of the inborn errors of metabolism. Without a doubt we are dealing with a group of illnesses that we have only just begun to «understand» and that are being diagnosed with increasing frequency. In the years to come we will most likely see how diverse clinical pictures, which at the moment are unidentified, are explained etiologically and clinically as their metabolic bases are discovered.

While we wait for the possibility of genetic therapy, in most cases these diseases are treated using dietary control. The training of interdisciplinary teams of pediatricians and dietitians specialized in metabolism, and in collaboration with other professionals, constitutes the primary option for the diagnosis and treatment of these patients.

8 Appendix

APPENDIX 1.

APPENDIX. SUMMARY TABLES OF THE NUTRITIONAL TREATMENTS AND PRODUCTS TO BE USED IN IEM OF CARBOHYDRATES, FATS AND SOME AMINO ACID DISEASES

IEMS OF CARBOHYDRATES

Disease	Nutritional treatment	Products
Galactosemia	Galactose suppression (lactose) Supplement: Calcium	Formula and soy milks
Hereditary intolerance of fructose	Restriction of fructose (1-2 g/day infant) Supplement: Vitamin C, Folic acid	Fructose, sacarose and sorbitol free foods
Glucogenosis type I	↑ Slow absorption carbohydrate (50-60%) ↓ Fat (20%-30%) and cholesterol Protein (5%-10%) Limit lactose, fructose and sacarose intake Supplement: vitamin-mineral	Corn starch (Maicena®) glucose polymers: Fantomalt, Maxijul and Polycose
Glucogenosis type III	Or similar to type I or rich in proteins (20%-25% Proteins, 45%-50% carbohydrates, 20%-30% fats)	
Muscle glucogenosis	25% Proteins and 35%-40% of fats and carbohydrates	

Disease	Nutritional treatment	Products
Deficit of long and very long chain Acyl CoA	↑ Slow absorption carbohydrates ↓ Fat Avoid fasting Supplement: MCT, carnitine and DHA (only if levels are low)	Monogen Low fat module Maizena® Glucose polymers
Deficit of medium chain Acyl CoA	↓ Fat, NO MCT Avoid fasting Supplement: carnitine	
Smitz Smitz-Lemli-Opitz	Diet rich in saturated fats Cholesterol 1200 mg/day	Cholesterol module

IEMS OF AMINO ACIDS

Disease	Nutritional treatment	Products
Phenylketonuria	↓ Phenylalanine	XP Analog, XP Analog LCP XP Maxamaid XP Maxamun Anamix Gama PHLEXY-10 PHL EXI-VITS Easiphen GAMA P-AM Phenyl-free 1, Phenyl-free 2 HP PKU 1, PKU 1 mix with Milupan, PKU 2, PKU 3
Tyrosinemia	↓ Tyrosine and phenylalanine NTBC	XPHEN TYR Analog XPHEN TYR Maxamaid XPHEN TYR Maxamum XPHEN TYR Tyrosidon XPTM Analog XPTM Maxamaid XPTM Tyrosidon TYR 1, TYR 1 mix with Milupan, TYR 2 Tyros 1 and Tyros 2
Homocystinuria	↓ Methionine (y homocysteine) ↑ Cysteine Supplements, Vitamin B_6, folic acid, betaine	XMET Analog XMET Maxamaid XMET Maxamum XMET Homidon HOM 1, HOM 1 mix con Milupan, HOM 2

IEMS OF AMINO ACIDS AND UCD

Disease	Nutritional treatment	Products
Maple Syrup	↓ Valine, leucine, isoleucine Supplement: Thiamine	MSUD Analog MSUD Maxamaid MSUD Maxamum MSUD AID III MSUD 1 mix with Milupan MSUD 1 and MSUD 2 BCAD 1 and 2 PFD 1 and 2 Energivit
Glutaric Aciduria type 1	Restriction of proteins ↓ Lysine and tryptophan Supplement: carnitine, riboflavin (if patient is sensitive)	XLYS, low TRY Analog XLYS, low TRY Maxamaid XLYS, low TRY Maxamum XLYS, TRY Glutaridon GA 1 and GA 2
Glutaric Acidemia type II	↓ Fat ↓ Protein Supplement: carnitine riboflavin	
Isoveric Acidemia	Restriction of proteins ↓ Leucine Supplement: L-glycine, carnitine	XLEU Analog X LEU Maxamaid X LEU Maxamum LEU 1 and LEU 2 PFD 1 and 2 Energivit

IEMS OF AMINO ACIDS AND UCD (Continuation)

Disease	Nutritional treatment	Products
Methylmalonic Acidemia	↓ Methionine, valine, threonine and isoleucine Supplement: hydroxy- B_{12}, carnitine	XMTVI Analog XMTVI Maxamaid XMTVI Maxamum XMTVI Asadon OS 1 and OS 2 PFD 1 and 2 Energivit
Propionic Acidemia	↓ Methionine, valine, threonine and isoleucine Supplement: biotin, carnitines	XMTVI Analog XMTVI Maxamaid XMTVI Maxamum XMTVI Asadon OS 1 and OS 2 PFD 1 and 2 Energivit
Urea Cycle Disorder	↓ Protein Supplementation with essential AA Supplements: arginine, citrulline sodium benzoate, Phenylacetate Phenylbutyrate	Dialamine Essential Amino Acid Mix UCD 1 and UCD2 Energivit

APPENDIX 2.

EMERGENCY DIETARY REGIME

During prolonged fasting periods such as, for example, in intercurrent diseases, traumas, pre- and post-surgery, etc., the body enters into a situation of metabolic stress. Adaptation to this causes an increase in protein catabolism and mobilization of alternative energy substrates such as fatty acids and ketone bodies. In patients affected by congenital errors of intermediate metabolism, these metabolic decompensation periods give rise to the accumulation of potentially toxic substances that may place the subject's life at risk. Thus, an emergency dietary plan that totally or partially substitutes the usual diet of the child during a short period of time (24-48 hours) must be available to reduce protein catabolism and lipolysis. The standard emergency regime is, essentially, the same for all the diseases and is combined with specific therapy according to the type of disorder[32]. A glucose polymer solution is used as the main energy source because it is easy, pleasant to take and well tolerated. Fats decrease gastric emptying and may induce vomiting. Furthermore, they are contraindicated in some diseases such as fatty acid oxidation disorders. Feedings should be initiated orally, in the patient's home when the first signs of illness appear. The concentrations and volume of solution to be administered are shown in the following table. If there is danger of dehydration, an oral rehydration solution supplemented with glucose polymers should be given since alone they do not contain enough glucose. The solution is given in small and frequent sips, including 10 ml every 10 minutes if the patient has begun with occasional vomiting. It is important not to prolong fasting more than 4 hours at night. The parents should be taught how to use a nasogastric tube when the child does not want to drink. If the child continues to vomit and does not improve, then hospitalization is necessary to initiate i.v. perfusion with 10% glucose.

EMERGENCY REGIME - GLUCOSE POLYMERS AMOUNT AND CONCENTRATION REQUIRED ACCORDING TO AGE

Age	Glucose polymer concentration*	Dosage spoons of products per feeding	Daily volume	Feeding frequency
0-3 months	10%	1.5 (60 ml)	150-200 ml /kg	During the
3-6 months	10%	1 3/4 (75 ml)	150-200 ml/kg	Day: e/ 2 hours
6-12 months	10%	2 (90 ml)	120-150 ml/kg	
12-18 months	15%	3 (90 ml)	100 ml/kg	
18-24 months	15%	4 (120 ml)	100 ml/kg	During the
2-4 years	20%	5 (140 ml)	1200-1400 mls	night: e/3 hours
4-6 years	20%	6 (140 ml)	1400-1500 mls	
6-8 years	20%	7 (170 ml)	1500-1700 mls	
8-10 years	20%	8 (200 ml)	1700-2000 mls	
> 10 years	25%	10 (200 ml)	2000 mls	

Commercial preparations of powdered glucose polymers: Maxijul® (SHS), Fantomalt® (Nutricia), Polycose® (Abott). Use a 5 gram dosage spoon.

EMERGENCY REGIME - GLUCOSE POLYMERS AMOUNT AND CONCENTRATION REQUIRED ACCORDING TO AGE

Once the child has begun to recuperate, a normal diet should be gradually introduced. While the diet is being reintroduced, liquids rich in carbohydrates should continue to be administered until a normal diet is reached. In those patients on low protein diets, one should start with 1/4 of the normal intake, which is then increased to 1/2, then 3/4, until reaching the normal daily intake.

Oral rehydration solutions (Suerooral casen®, Suerooral hiposódico®, Miltina electrolit®, Isotonar®, etc.)

- 10% carbohydrate solution - 10 g (2 dosage spoons) of glucose polymers in 200 ml of oral rehydration solution.
- 15% carbohydrate solution - 20 g (4 dosage spoons) of glucosepolymers in 200 ml of oral rehydration solution.
- 20% carbohydrate solution - 30 g (6 dosage spoons) of glucosepolymers of oral rehydration solution.
- 25% carbohydrate solution - 40 g (8 dosage spoons) of glucosepolymers of oral rehydration solution.

Recommendations for hospital treatment

If the child is hypoglycemic and symptomatic, administer one i.v. glucose bolus in the amount of 200 mg/kg (2 ml/kg of 10% glucose) followed by a continuous perfusion of 5-10 mg/kg/min (3-6 ml/kg/h) of 10% glucose. Adjust infusion rhythm to maintain glucose levels at 4-8 mmol/l (70-140 mg/dl). Continue the perfusion until glucose levels remain stable and the child tolerates oral feedings.

If the child is asymptomatic and/or is normoglycemic when he/she reaches the hospital but does not tolerate oral feedings, an i.v. perfusion of glucose must be placed as mentioned above, but without the initial bolus.

APPENDIX 3.
CHART OF ALL THE DISEASES DESCRIBED

IEM of carbohydrates	Group	Incidence (Cases/NB)	Debut age	Clinical aspects	Treatment	Prognosis and complications
Glycogenesis (diverse enzyme deficits)	Type III	1/200,000	Infant Early childhood	Hypoglycemia, hepatomegalia Prominent abdomen Short height Doll face Muscle disorders (hypotony) Cardiac, renal involvement	Avoid hypoglycemia Biotin Hepatic transplant	Hepatic tumors Osteoporosis Renal failure
IEM of galactose (↓ of galactose uridyl transferase	Type II	1/50,000	Neonatal Early childhood	Progressive general toxic syndrome (vomiting, lethargy, rejection of feedings, failure to thrive) Cataracts Hepatic failure Proximal tubulopathy	Avoid galactose and lactose in diet Calcium	Mental retardation Ataxia Gonadal dysfunction Pubertal delay in girls
Fructosemia (↓ aldolase B)	Type II	1/20,000	Infancy (With initiation of fructose intake)	Acute symptoms (vomiting, lethargy, dehydration, coma, acute hepatic failure) Chronic symptoms (isolated vomiting, feeding difficulties, hepatomegalia, failure to thrive)	Eliminate fructose, sacarose and sorbitol from diet Vtamin C	Good prognosis with strict diet

IEM of fats	Group	Incidence (Cases/NB)	Debut age	Clinical aspects	Treatment	Prognosis and complications
Betaoxidation alterations (↓ Acyl CoA of long and very long chain Fatty Acids)	Type III	1/50,000	Infant Late	Hypoglycemia Reye-like syndrome Muscle involvement Cardiac involvement	Diet: prevent fasting periods MCT DHA if levels are low Hepatic transplant Carnitine	Regular with frequent relapses with intercurrent conditions (viral disease, etc.) 25% with residual neurologic damage
Betaoxidation alterations (↓ Acyl CoA of medium chain Fatty Acids)	Type III	1/10,000	Infant > 2 years Late forms	Hypoglycemic coma Hepatopathy (Reye-like) SIDS Neurologic disease Possibility of late and monosymptomatic forms	Diet similar to that of long chain Do not give MCT	Similar to long chain
Smith-Lemli-Opitz Syndrome (↓ 7-dihydrocholesterol reductase)	Type I	1/60,000	Neonatal	Polymalformation syndrome: Serious mental retardation Microcephalia Gothic palete, palatal fissure Failure to thrive Heart disease Eyelid ptosis Cataracts Genital abnormalities Syndactylia 2-3 toes	Diet rich in saturated fats Cholesterol 1,200 mg/day Ursodeoxycholic acid	Mild improvements and no progression of the clinical picture with cholesterol treatment psychomotor development

IEM of amino acids and proteins (1)	Group	Incidence (Cases/NB)	Debut age	Clinical aspects	Treatment	Prognosis and complications
Hyperphenylalaninemias (Phenylcetonuria) (↓ fphenylalanine hydroxylase)	Type II	1/21.740 (Catalonia)	Neonatal screening Spontaneous symptoms: 6-8 months	Serious mental retardation Microcephaly Epilepsy Eczema Hyperactivity Psychotic traits	Diet low in phenylalanine Tyrosine and carnitine supplement	Fetopathy in pregnant women with phenylketonuria
Tirosinemia (↓ fumaryl acetoacetate hydrolase)	Type II	1/100.000	Acute: infant: Chronic: > 6 months	Acute Failure to thrive, lethargy, hepatomegalia, jaundice, ascites, bleeding, nephromegaly, rickets Chonic Renal dysfunction, cirrhosis, hepatocellular carcinoma	Diet low in tyrosine and phenylalanine NTBC: (2-nitro-4-trifluoromethyl-benzoyl-1,3-cyclohexanedione) Hepatic transplant	Treatment with NTBC has greatly improved the prognosis Complications: hepatic carcinoma and renal failure
Homocistenuria (↓ cystathionine - beta- synthetase)	Type II	1/335.000	>2 years	Progressive Ectopia lentis Mental retardation, seizures Osteoporosis, scoliosis Arachnodactily Vascular occlusions	Diet low in methionine Vitamin B_6 Folic acid fólico Betaine	Thrumbus embolism Osteoporosis

IEM of amino acids and proteins (2)	Group	Incidence (Cases/NB)	Debut age	Clinical aspects	Treatment	Prognosis and complications
Maple syrup (↓ Branched-chain alpha-keto acid dehydrogenase complex)	Type II	1/257,000	Three types: Neonatal Infant Late	Neonatal: toxic syndrome, hypotonia, coma, ketoacidosis) Intermediate: failure to thrive, psychomotor retardation, ataxia, seizures Adult: no usual symptoms. Ataxia episode, seizures and ketoacidosis with intercurrent infections)	Acute form: peritoneal dialysis or hemodialysis, parenteral nutrition Diet low in leucine Thiamine Hepatic transplant	Good prognosis if treatment is early diet strict
Type I glutaric aciduria (↓ glutaryl-CoA-dehydrogenase)	Type II	1/30,000	Infancy	Encephalopathic crisis: Reye-like syndrome, hypoglycemia, metabolic acidosis Acute metabolic crisis progressive subclinical aspect: neurologic deterioration that progresses to paralysis	Diet low in proteins and low in lysine and triptophan Rivoflavin Baclofen ? Valproic acid? Vigabarin?	Good prognosis with early diagnosis + treatment Bad prognosis with later diagnosis
Isovaleric aciduria (↓ Isovaleryl- CoA-deshydrogenase)	Type II		Neonatal Infant late	Neonatal: general toxic syndrome. Late infancy: development and mental retardation, acidosis, pancytopenia	Diet low in proteins and leucine l-glycine and carnitine supplements	Good prognosis with early diagnosis + treatment Poor prognosis with late diagnosis

IEM of amino acids and proteins (3)	Group	Incidence (Cases/NB)	Debut age	Clinical aspects	Treatment	Prognosis and complications
Methylmalonic acidemia (↓ methylmatonyl-CoA mutase) And Propionic (↓ propionyl-CoA carboxylase)	Type II	1/50,000 (Methylmalonic)	Neonatal Infant Late	Metabolic acidosis Hyperammonemia Neutropenia Failure to thrive Anorexia, vomiting Tendency to dehydrate Adult (Corea and dementia) Renal dysfunction Myocardiopathy	Acute form: peritoneal dialysis, or hemodialysis, parenteral nutrition Ammonium chelants Carnitine, B12, or Biotin Diet low in methionine, valine, threonine and isoleucine Metronidazole Decrease in soluble fiber Sufficient calorie supply	Good prognosis if treatment is early and diet strict Anorexia Mental retardation Osteoporosis Renal failure
Urea cycle diseases urea (Several enzyme disorders)	Type II	1/15,000 (↓ OTC)	Neonatal (24-72 hours of life)	Neurological signs: weak suction, hypotonia, vomiting, somnolence, coma, altered EEG Late forms Paucisymptomatic forms	Hypoprotein diet: essential amino acids, arginine, citrulline Acute phase: ammonium chelants (benzoate, phenylbutyrate, phenylacetate), ICU support, hemodialysis, hemodiafiltration or peritoneal dialysis Hepatic transplant	Good prognosis with early diagnosis + treatment Poor prognosis with late diagnosis

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MET 86

SHS

Nutricia-SHS Spain
Ctra. Andalucía, km. 25,600
28343 Valdemoro (Madrid)
Phone: +34 900 444 800
Fax: +34 918 096 449