Palliative care in inborn metabolic diseases - what does the pediatrician should know?

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Abstract

Inborn errors of metabolism correspond to a group of individually rare but collectively numerous diseases which affect the body's mechanisms of breakage and renewal through enzymes. According to the pathophysiological mechanism can be classified into 3 groups, which have heterogenous signs and symptoms that may be acute or chronic. The recognition of these findings favors the early diagnosis and consequently the appropriate therapeutic approach. However, because they are chronic health conditions threatening or limiting life, the inborn errors of metabolism fulfill criteria for the use of palliative care to the diagnostic suspicion.
Inborn errors of metabolism (IEM) comprise individually rare, but collectively frequent, heterogeneous disorders. Described in 1902 by Archibald Garrod and later compiled in the book: principles of Human Biochemical Genetics, IEM affect the body’s chemical reactions of breakage and renewal, mediated by the enzymes necessary for the conversion of a metabolite into energy.

IEM should be considered in parallel with any clinical condition; in situations where the symptoms persist or return even after the appropriate approach; in any unexplained neonatal death - especially those attributed to sepsis, and may be present at any age.

The signs and symptoms result from the deficiency of some catalytic protein or carrier. Thus, there is a transport deficiency of a metabolite from one compartment to another; a defect in the conversion of a metabolite into its substrate; an increased conversion of one metabolite to another due to its buildup; a defect in the interaction between apoenzyme and cofactor, and a decrease of inhibitory feedback from the conversion of one metabolite to another due to substrate deficiency, as shown in figure 1.

Among the main clinical findings to be considered for suspected IEM we can highlight coma and altered level of consciousness, early and difficult to control seizure spells, presumed sepsis without infectious markers, developmental involution, early liver failure, cyclic vomiting or short stature, biochemical changes (metabolic acidosis, pancytopenia, hypoglycemia, hyperammonemia, lactate increase), non-immune fetal hydrops, dilated or hypertrophic cardiomyopathy, atypical odor, early death or sudden death syndrome and parental inbreeding.

According to the pathophysiological mechanism, IEM can be divided into 3 groups, as presented in table 1. Group 1 corresponds to disorders that cause intoxication, affecting the intermediate metabolism, by the buildup of molecules proximal to the blockade. This group does not affect embryo-fetal development; therefore, dysplasia, dimorphisms and malformations are not seen. They have a period that they go symptom-free period free and without symptoms and signs of intoxication, which include vomiting, coma, liver failure and acute thromboembolic complications; and short stature, delayed neurospsychomotor development and chronic cardiomyopathy.

Group 1 involves defects of amino acid catabolism (Phenylketonuria, Syrup Urine Disease and Bordo), amino acid synthesis (serine, proline), organic acidurias (methylmalonic, propionic and isovaleric), urea cycle defects (ornithine transcarbamylase, citrullinemia), sugar intolerance (galactosemia), metal metabolism defects (Wilson’s disease, Menkes disease), neurotransmitter disorders, and porphyrias.

Group 2 comprises defects in energy metabolism, both of cytoplasmic and mitochondrial origin, affecting the production and use of energy in the liver, muscles, myocardium and brain. Among the mitochondrial energy metabolism disorders, we can highlight congenital lactic acidosis, respiratory chain disorders, fatty acid oxidation defects and ketone body defects. Clinically they present with hypoglycemia, generalized hypotonia, hyperlactatemia, hepatomegaly, myopathy, cardiomyopathy, and may progress to sudden death.

The above signs and symptoms may also be seen in disorders of cytoplasmic energy metabolism in a less severe form. In this case, glycolysis, glycogen, gluconeogenesis and hyperinsulinism disorders and disorders of creatine metabolism and the pentose phosphate pathway are highlighted.

Group 3 IEM involves cellular organelles such as lysosomes, peroxisomes, endoplasmic reticulum, Golgi and mitochondria in the synthesis, remodeling, recycling, and defects on the transit and catabolism of complex molecules.

In this group the symptoms are permanent, progressive, independent of complications and are not related to food intake, being present in lysosomal storage diseases (Mucopolysaccharidoses, Gaucher disease), peroxisome disorders (Zellweger’s disease); defects on the transit

![Figure 1. Pathophysiology of IEM (Adapted from Clarke, 2005).](image-url)
Table 2. Main signs and symptoms of Inborn Errors of Metabolism.

<table>
<thead>
<tr>
<th>Group</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>This group does not affect unaffected embryo-fetal development. No dysplasia, dysmorphism and malformations are seen. They have a period free of symptoms and signs of intoxication, including vomiting, coma, liver failure, and acute thromboembolic complications; and stature-weight deficit, neuropsychomotor developmental delay and chronic cardiomyopathy. Amino acid catabolism defects include: (Phenylketonuria, Maple Syrup Urine Disease), amino acid synthesis (serine, proline), organic acidurias (methylmalonic, propionic and isovaleric), urea cycle defects ornithine transcarbamylase, citrullinemia), sugar intolerance (galactosmia), defects in metal metabolism (Wilson’s disease, Menkes disease), neurotransmitter disorders and porphyrias.</td>
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<tr>
<td>Group 2</td>
<td>Mitochondrial energy metabolism disorders: congenital lactic acidemia, respiratory chain disorders, fatty acid oxidation defects and ketone body defects. Clinical presentation: initial hypoglycemia, generalized hypotonia, hyperlactatemia, hepatomegaly, myopathy, and cardiomyopathy, may progress to sudden death. They may be observed in cytoplasmic energy metabolism disorders in a less severe form. In this case, glycolysis, glyconeogenesis, glutamine metabolism and hyperinsulin metabolism disorders, disorders of creatine metabolism and disorders of the pentose phosphate pathway deserve special mention.</td>
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<tr>
<td>Group 3</td>
<td>Symptoms are permanent, progressive, independent of adverse events and unrelated to food intake.</td>
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Table 3. Main treatment approaches or inborn errors of metabolism.

<table>
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<tr>
<th>Group</th>
<th>Treatment</th>
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<tr>
<td>Group 1</td>
<td>Restriction of the non-metabolized substrate. It occurs through diet and detoxification measures through &quot;cleansing drugs&quot; (penicillamine, sodium benzoate and carnitine) and extracorporeal (hemodialysis) procedures.</td>
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<tr>
<td>Group 2</td>
<td>Treatable diseases such as disorders of glycolysis, gluconeogenesis, glycogen metabolism and hyperinsulin metabolism through dietary measures. Partially treatable as Coenzyme Q10 defects, fatty acid oxidation defects, ketone body defects, and creatine metabolism disorders through defective cofactor replacement and prolonged fasting prevention. Diseases for which there is no treatment such as disorders of the pentose phosphate pathway, congenital lactic acidemia and mitochondrial respiratory chain disorders.</td>
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<tr>
<td>Group 3</td>
<td>The objective is to restore lysosomal activity through enzyme replacement therapy (Gaucher type I, Fabry, Pompe and Mucopolysaccharidoses types I, II, IV and VI). Transplantation of hematopoietic and bone marrow cells (Mucopolysaccharidoses type I, X-linked adrenoleukodystrophy, metachromatic Leukodystrophy and Krabbe’s disease). Gene therapy and chaperone protein therapy; and reduction of accumulated substrate biosynthesis (Gaucher disease).</td>
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of complex molecules (deficiency of alpha-1 antitrypsin) and defects in the synthesis, remodeling and recycling of complex lipids and fatty acids.1,3

Table 2 summarizes the main signs and symptoms present in inborn errors of metabolism according to their pathophysiological classification.

Concerning the treatment of inborn errors of metabolism, its division into these 3 groups elucidates the principles of therapeutic used in each of them, which are compiled in table 3.

The heart of the treatment of group 1 IEM is the restriction of the non-metabolized substrate. It occurs through diet and detoxification measures, using "cleansing drugs" (penicillamine, sodium benzoate and carnitine) and extracorporeal (hemodialysis) procedures.1,5

Group 2 of the IEM comprises treatable diseases such as disorders of glycolysis, gluconeogenesis, glycogen metabolism and hyperinsulin metabolism through dietary measures; partially treatable as Coenzyme Q10 defects, fatty acid oxidation defects, ketone body defects, and creatine metabolism disorders by replacing the deficient cofactor and preventing prolonged fasting; and those for whom there is no treatment such as disorders of the pentose phosphate pathway, congenital lactic acidemia and mitochondrial respiratory chain disorders.1,3,5

In the inborn errors of complex molecules, therapeutic measures can be approached with the objective of restoring lysosomal activity through enzyme replacement therapy (Gaucher type I, Fabry, Pompe and Mucopolysaccharidoses types I, II, IV and VI), cell transplantation
heterogeneous and bone marrow (Mucopolysaccharidosis type I, X-linked adrenoleukodystrophy, leukodystrophy, or Krabbe disease), gene therapy and chaperone protein therapy; and reduction of accumulated substrate biosynthesis (Gaucher disease). In parallel to the support measures mentioned above in each of the IEM groups, it is necessary to have a multidisciplinary approach and an active participation of the caregivers in the management of patients with a diagnosis of hereditary metabolic disease. Being rare, multisystem diseases of unlikely early parental experience, IEMs require an explanation of the diagnosis (or suspected diagnosis), the pattern of treatment and care, the course of the disease and outcome, emergencies and emergency treatments, and the monitoring of the treatment for proper patient follow-up. Given the need for a multi- and interdisciplinary approach, the chronicity and multisystem involvement of hereditary metabolic conditions, we can classify them as complex chronic health conditions. Complex chronic health conditions are those that can last for at least 12 months (unless death occurs) and involve multiple systems of organs or organ systems severely enough to require special pediatric care, and probably some period of hospitalization in a facility. Around 12,000 children die each year due to complex chronic health conditions, and about 600,000 to 1,600,000 of those under the age of 18 are living with a limiting or life-threatening condition. Life-limiting conditions are those for which there is no possible cure and the likelihood of death is real. Some cause progressive deterioration and increase the child’s dependence on their parents and caregivers. Life-threatening conditions are those for which curative treatment may be feasible, but may fail. From these definitions, the complex chronic limiting and life-threatening conditions in children can be divided into 4 groups, which correspond to indications of pediatric palliative care. Group 1 contains life-threatening conditions which treatments may fail, such as cancer, congenital heart disease and diseases with indication of transplantation, the latter being represented by inborn errors in the metabolism of complex molecules that can be transplanted into the hematopoietic system and bone marrow. Group 2 responds for conditions which cure is not possible and premature death is inevitable, but treatments are directed to the pathophysiology of the disease as a way to prolong life and the quality of life. In this group, cystic fibrosis, Duchenne muscular dystrophy, and inborn errors of metabolism, lysosomal deposition disorders such as Mucopolysaccharidoses, Gaucher’s Disease and Fabry’s disease are highlighted. Most of the inborn errors, especially those of intermediate and energy metabolism, are allocated to group 3, that is, progressive chronic conditions with no curative treatment options, which focus on the treatment of manifestations of the disease such as seizures, nutrition, pain and secondary osteopenia. The last group of complex chronic conditions in pediatrics comprises irreversible non-progressive conditions causing severe impairment and leading to susceptibility to health complications and the likelihood of premature death, such as hypoxic-ischemic brain lesions and central nervous system malformations. Considering the natural history of inborn errors of metabolism, the signs and symptoms manifest themselves mainly in the neonatal period, childhood and adolescence/adulthood. The prenatal period in hereditary metabolic diseases generally does not present problems, considering the supply of fetal metabolism by the maternal metabolism, being the signs and symptoms observed from birth. In the neonatal period, we can highlight the IEM of the intermediate and energy metabolism. Under these conditions, supportive treatment (diet, hemodialysis and co-factors) is employed in parallel to the treatment of symptoms. In this group of diseases, the patient care approach should consider the acute (intoxication) condition of a life-threatening disease in a previously healthy child. Stability periods are punctuated by acute decline of health and recovery, often with a new plateau, which becomes the new state of “normality” for the patient. The introduction of palliative care in this context occurs at the time of diagnosis of a complex chronic disease and comprises a physical approach to symptom control; psychological support to parents in the context of a child in need of complex intensive care amidst feelings of anxiety, depression, and guilt; as a form of respect for the parents’ beliefs; and social aspects considering the environment in which this patient is inserted, and prevention measures to be taken outside the hospital environment. After this period and from an adequate management of symptoms and metabolic block, some patients may progress to the period of childhood, in which complex molecule disorders are also present. In childhood, the approach to supportive care and symptom control are also in line. When a child develops an illness, it may occur suddenly or gradually. In addition, the interval between initial concerns and the definitive diagnosis of a limiting or life-threatening condition ranges from hours to months or years or, a lack of diagnostic definition is not uncommon. Inborn errors of intermediate and energy metabolism can be allocated in a sudden onset. Generally, children with adequate prenatal history, born at full term in
uneventful deliveries, and who eventually present clinical signs of intoxication - vomiting, coma and liver failure - especially after the introduction of diet or hypotonia and recurrent hypoglycemia.

When properly treated, these IEM may evolve and present with chronic manifestations such as developmental delays and stature/weight deficits. Together with disorders of complex molecules they present a gradual entry into the disease process and consequently into the process of palliative care.

Differently from palliative care (PC) in adults, PC in children encompasses a variety of conditions, of which ⅔ correspond to genetic, congenital and neurodegenerative diseases; causing inaccurate prognosis definition and its introduction is based more on the needs of the patient than on the diagnosis.

Along the path of an illness, care is patient-centered, based on the patient’s needs and focused on the family. It is in this period that the support for decision-making is addressed; management, control and prevention of symptoms; coordination and integration of services; healthcare, social and psychological support.13

The end of palliative care occurs for a short period (until a new period of worsening) or for an extended period (transplanted patients).13 In this context, the parents are in a duality of feelings of joy and concern, and the uncertainty of when the new flare up event will occur.12

Parallel to the focus of this paper, errors of the intermediate and energy metabolism can evolve to death with each new episode of decompensation or after an appropriate clinical approach, determining a new plateau of normality for the child. The same is true for deposition diseases, but insidiously, despite enzyme replacement therapies or transplants.

Care for a child with complex chronic limiting or life-threatening condition demands time and is rather costly to parents. In relation to time, one of the caregivers usually abdicates from their place in the labor market to stay at home and care for the child’s demands. This decision also reflects a loss in costs, considering that these are conditions that require expensive medications, supplies, special equipment - wheelchairs and respirators - and modifications in the home and vehicles.

Parents of children with limiting/life-threatening illnesses present a variety of needs, both conscious and unconscious. Among the latter, we can highlight concerns about the child’s funeral and life after his/her death.15

These parents suffer from multiple losses, because of the chronic health condition that affects their child, among them, loss of lifestyle, loss of income, loss of friends, loss of privacy and loss of control. Thus, with the principles of palliative care in mind, the family environment must be supported in all spheres of care: physical, psychological, social and spiritual. This guarantees the maintenance of the quality of life of the caregiver and, consequently, of the patient.15

As for many IEM, healing is not possible, families need time to process diagnosis and prognosis, experience several stages of mourning at the same time; they present spiritual stress questioning their own beliefs; need support in news communication and live in conflict with themselves and others.16

Thus, due to the prolonged survival of the patients mentioned above, their clinical characteristics, medications and technologies demanded, complexity and chronicity of the pathologies has indicated an early introduction of palliative care in their lives with the disease.

REFERENCES


