

Laboratory diagnostics of emergency conditions associated with inborn errors of metabolism

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ABSTRACT

Inborn errors of metabolism are a growing group of monogenic hereditary diseases whose pathogenesis may be accounted for by biochemical disorders. The great majority of these diseases may occur as a metabolic crisis at any period of life. For their adequate treatment, fast recognition of the cause of the metabolic disorder is necessary, as well as good collaboration of all health professionals involved in immediate patient healthcare. On the path to final diagnosis, it is advisable to consult specialised centres in order to select appropriate diagnostic tests and procedures.

Key words: inborn errors of metabolism, metabolic crises, laboratory tests

Introduction

Inborn errors of metabolism (IEMs) are a consequence of biochemical alterations originating in genes that result in the alteration of a protein. As the possibility of mutations is extremely high, a variety of changes at the biochemical level is understandable, as well as a high variability of clinical data. Taken individually, IEMs are highly infrequent but, taken as a whole, IEMs (of which over 550 have been described to date) can affect 1/500 newborn babies. The field of inborn errors of metabolism has been developing very fast over the past few years. New diseases have been detected, new diagnostic tests developed and novel treatment opportunities have been found. (1) Although IEMs have usually been considered as paediatric diseases, the fact that they can be present at any age represents a special challenge in general and paediatric practice. They are frequently characterised by acute,

life-threatening crises that require an immediate and specific intervention. The development and prognosis of affected patients may depend on rapid and effective treatment, but the large number of genetic defects in various metabolic pathways makes it difficult to be familiar with all diagnostic strategies and specific therapies. (2)

The diagnostic approach

The fact that treatment is becoming available for an ever-increasing number of disorders from this group of diseases imposes the need for their early clinical recognition and for adequate laboratory diagnostics. Given their individual infrequency, most physicians and laboratory professionals have limited experience in dealing with these diseases, so that their collaboration is of utmost importance.

IEMs that occur with increased frequency in certain populations and are curable (but cannot be clinically recognised at an early stage), are included in newborn screening programmes (e.g. phenylketonuria, congenital hypothyroidism, leucinoses, homocystinuria, fatty acid

beta-oxidation disorders, etc.). The technology of tandem mass spectrometry currently enables the diagnosis of more than 50 inherited metabolic diseases as early as in the newborn period (dried blood spot). Regrettably, most of these diseases are not treatable at present; and since diseases in the pre-symptomatic phase are also being detected, such an approach to diagnostics opens a number of ethical doubts that each community must solve. (3)

Another approach to the diagnostics of these rare diseases implies the laboratory management of symptomatic patients (so-called selective screening). The majority of diseases are detected in this process in the manner that the possibility of an inherited metabolic disorder is suspected on the basis of typical data from the patient's medical history, status and basic laboratory test results. Subsequently, certain specific metabolic analyses are performed in suspected patients in order to confirm/reject the suspicion as soon as possible.

Metabolic crises

The clinical symptoms of the most

important metabolic diseases can be classified according to their pathophysiological background as being of "intoxication type, energy deficiency type, diseases due to limited intolerance of starvation, neurotransmission disorders, and other acute metabolic disorders". A large number of these diseases manifest themselves with suddenly occurring life-threatening conditions, or so-called metabolic crises. Metabolic crises frequently occur as early as in the first days of life and may also be explained as newborn sepsis. Circumstances that can provoke acute metabolic attacks include prolonged starvation, stressful situations, fever, intercurrent illness, and these may even manifest for the first time at an adult age. (4)

In order to provide urgent and adequate treatment of patients with a metabolic crisis, inborn errors of metabolism should be suspected and assessed (based on metabolic test results) in order to be classified among one of the above-mentioned groups of disorders.

Disorders that give rise to intoxication lead to an acute or progressive intoxication from the accumulation of toxic compounds proximal to the metabolic block. This group consists of IEMs of amino acid catabolism (leucinosys, tyrosinemia, etc.), most organic acidurias (methylmalonic, propionic, isovaleric, etc.), congenital urea cycle defects, glucose intolerances (galactosemia, hereditary fructose intolerance), metal intoxication and porphyrias. All the conditions in this group are characterised by a symptom-free interval and clinical signs of "intoxication", which may be acute (vomiting, coma, liver failure, thromboembolic complications, etc.) or chronic (failure to thrive, developmental delay, ectopia lentis, cardiomyopathy, etc.). Most of these disorders are treatable and require the emergency removal of the toxin by special diets, extracorporeal procedures or "cleansing" drugs (carnitine, sodium benzoate, penicillamine, etc.).

Disorders involving energy metabolism comprise IEMs with symptoms due at

least partly to a deficiency in energy production or utilisation within the liver, myocardium, muscle, brain or other tissues. They encompass congenital lactic acidemias (defects of the pyruvate transporter, pyruvate carboxylase, pyruvate dehydrogenase and the Krebs cycle), mitochondrial respiratory chain disorders, fatty acid oxidation and ketone body defects, disorders of glycolysis and glycogen metabolism. Common symptoms in this group include hypoglycemia, hyperlactatemia, hepatomegaly, severe generalised hypotonia, myopathy, cardiomyopathy, failure to thrive, cardiac failure, circulatory collapse, sudden unexpected death in infancy and brain involvement.

Diseases caused by starvation intolerance (hepatic glycogenoses, gluconeogenesis disorders, some fatty acid beta-oxidation disorders, disorders of carnitine cycle, ketogenesis and ketolysis) are characterised by hypoglycemia after relatively brief starvation. The period of starvation necessary for symptoms to manifest varies depending on disease and a number of other factors.

Although pathophysiology is somewhat different from the inborn errors of neurotransmitter synthesis and catabolism (monoamines, GABA and glycine), the inborn errors of amino acid synthesis (serine, glutamine) can also be included in this group. These disorders manifest themselves as acute encephalopathy with epilepsy, with treatable convulsions. (5)

Emergency laboratory tests in an acute metabolic crisis

After clinically suspecting an IEM, samples for laboratory tests should be urgently collected, if possible during the metabolic crisis. Efforts should be made to perform sampling prior to infusion (of glucose, carnitine, etc.) because such samples provide the most information since they are often the only source of diagnostically significant metabolites.

In addition to basic laboratory tests (blood count, C-reactive protein, electrolytes, aminotransferases, creatine

kinase, urea, creatinine, urates, basic coagulation tests), basic metabolic tests should also be carried out (acid-base status, glucose, ammonium, lactate and methylketones). The results of these tests may indicate the presence of a metabolic disorder to a physician, yet they do not reveal the cause of the disorder. For a clinician, it is of utmost importance to receive the results of these tests as urgently as possible (within 60 minutes) in order to manage the patient before the basic cause of metabolic crisis is detected. (6,7)

The above-mentioned tests are part of the laboratory test panel of all general hospitals.

A further step in the search for the cause of the metabolic crisis is the interpretation of results of specific metabolic tests, i.e. amino acid concentration in plasma and/or cerebrospinal fluid, organic acids in urine, total and free carnitine in plasma and acyl-carnitine profile from a dried blood spot on filter paper and/or plasma.

These specific metabolic tests are available only in laboratories dealing with diagnostics of inborn errors of metabolism because specific equipment is needed for their implementation, as well as adequately educated medical biochemistry specialists. In a large number of cases, it is also necessary to perform a whole series of other specific tests on the pathway to a final diagnosis (e.g. biotinidase, galactose, homocysteine, creatine, neurotransmitters, free fatty acids, glutation, porphyrins, pyrimidines, etc.). Methods to perform these tests are often available only in specialist diagnostic centres. These tests should therefore be utilised economically after performing basic metabolic analyses, considering clinical data and providing specialist patient management. Due to a number of specificities that accompany the carrying out of most confirmation tests, it is advisable to consult specialist centres in order to additionally ensure correct sampling, storage and transport of adequate samples.

It is important to mention that in cases when a patient cannot be cured, every

effort should be made to collect and adequately store samples of plasma, urine and EDTA whole blood for DNA isolation, as well as to perform biopsy of the skin and, when necessary, other tissues. Only such an approach may enable the establishment of a post-mortem diagnosis and provide other members of the family of a patient

diagnosed with IEM with this information. (8)

Conclusion

However, although they are being increasingly recognised, IEM remain rare. They should be considered in parallel with other more common conditions and it should be remembered that an

IEM can be present at any age. Satisfactory care for acutely compromised IEM patients is only possible through teamwork that involves personnel in emergency admission wards, laboratories and centres specialised for IEM. In this regard, algorithms for procedures in certain situations that are prepared in advance may be of substantial aid.

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