Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Editorial paper | Artykuł redakcyjny

Pediatr Endocrinol Diabetes Metab 2024; 30 (1): 1-2
DOI: https://doi.org/10.5114/pedm.2024.138665

redakcja@pediatricendocrinology.pl
www.pediatricendocrinology.pl
www.pteidd.pl

Inherited metabolic disorders… …do not miss treatable diseases…

Dziedziczne schorzenia metaboliczne... ...nie przeocz chorób uleczalnych...

Maria Giżewska

Department of Paediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age, Pomeranian Medical University in Szczecin, Poland

Key words: inherited metabolic disorders, inborn errors of metabolism, population newborn screening, intoxication syndrome.
Słowa kluczowe: dziedziczne schorzenia metaboliczne, wrodzone wady metabolizmu, populacyjne badania przesiewowe noworodków, zespół intoksykacji.

In the latest issue of *Pediatric Endocrinology, Diabetes and Metabolism*, readers will have the opportunity to read an interesting publication on the emotional and behavioral functioning of patients with tyrosinemia type 1. This prompted the need to recall information on the numerous inherited metabolic disorders (IMD).

The term IMD, formerly known as inborn errors of metabolism (IEM), was first introduced in 1908 by an English physician Archibald Garrod who analyzing the histories of families with alkaptonuria, linked abnormalities in biochemical reactions to hereditary phenomena. This group includes conditions in which primary alterations of biochemical pathways are related to specific biochemical, clinical and/or pathophysiological features.

The IMD forms a heterogeneous group of genetically determined disorders that are mostly inherited but can also arise from spontaneous mutations. Regarding this group, autosomal recessive inheritance is most common, but all other modes of inheritance, including mitochondrial, are possible. Environmental and epigenetic factors are also involved in their clinical presentation. Inherited metabolic disorders belong to rare conditions, i.e. diseases that occur at a frequency of less than 5×/10 000 births. Although individual ones may be described in only single families worldwide, collectively they occur frequently. According to one of the most recent IMD classifications (An International Classification of Inherited Metabolic Disorders – JIMD 2021 January; 44 (1): 164–177), the group of genetically determined metabolic disorders includes nearly 1,500 diseases assigned to one of 124 categories but new diseases are described almost every month.

In most of IMD, monogenic enzyme defects in the metabolism of carbohydrates, fats, proteins, purines and pyrimidines, steroids, metals, porphyrins, as well as disorders of renal tubular transport, metabolism of cofactors and minerals, or neurotransmission defects underlie their pathogenesis. In daily practice, the 2014 classification by Saudubray and Charpentier which divides IMD into disorders of complex molecules, intoxication disorders and energy deficiency, is especially useful. Approximately 50% of IMDs are already manifested in the neonatal period, while the remaining ones show symptoms in infancy, older children and adults, including very advanced age. Their clinical symptomatology is very broad with one or more tissues and organs involved.

A breakthrough in early diagnosis, which in many IMD allows for the early introduction of specific treatment, has been shown to be population-based newborn screening (NBS). First introduced in the early 1960s by Robert Guthrie, NBS is one of the most successful public health initiatives, thanks to which thousands of children worldwide avoid significant health and developmental disabilities or death. At the beginning of NBS, bacterial inhibition assay was developed to detect elevation of phenylalanine in dried blood spots collected on filter paper to diagnose phenylketonuria. In subsequent years, based on Wilson and Junger's criteria, more IMDs, endocrine disorders and other rare diseases were added to the NBS panel. In the past, each disease required a separate test which was changed at the turn of the 20th century when tandem mass spectrometry (MS/MS) was introduced. This method quantifies both amino acids and carnitine esters by using electrical and magnetic fields to separate and measure the mass of charged particles. MS/MS allows for a number of biochemical specimens to be tested in a single dried blood spot resulting in identification of numerous IMD including aminoacidopathies, urea cycle disor-

Received: 14.03 2024
Accepted: 16.03 2024
Conflict of interest: not declared.
Funding: no external funding.
Ethics approval: not applicable.

Maria Giżewska
Department of Paediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age, Pomeranian Medical University in Szczecin, Unii Lubelskiej 1, 71-242 Szczecin, Poland
e-mail: maria.gizewska@gmail.com

ders organic acidemias as well as disorders of fatty acid oxidation. This possibility has considerably changed the fate of children affected by multiple IMDs for which we can offer effective treatment nowadays. In many US states, the NBS screens all newborns for 50 diseases; in all states, screening procedure covers a core panel of 30 rare conditions, including many metabolic disorders. In European countries, NBS coverage varies. Poland with a list of 30 rare genetic diseases included in NBS panel, is among the leaders in the region. In recent years, new metabolic conditions, including lysosomal diseases, have been included in NBS pilot programs. Unfortunately, not all newborns can benefit from NBS. In many countries in the Middle East, Asia and Africa, babies are born with potentially treatable metabolic diseases and die or live with irreversible multi-organ damage. However, even the broadest NBS panel will not cover all possible IEMs, hence selective screening requires analysis of basic biochemical tests, urine organic acid profile tested by GCMS (gas chromatography coupled to mass spectrometry), assessment of amino acid in blood and cerebrospinal fluid. Many other tests, including genetic (next-generation sequencing – NGS) maybe needed. The scope of the tests can be determined by a metabolic pediatric specialist.

There are a few basic truths about IMD that pediatricians should understand and remember to save the lives and health of sick children. In neonates with metabolic disorders presenting with intoxication (aminoacidopathies, organic acidurias, disorders of sugar metabolism, congenital hyperammonemias), sudden symptoms may manifest in a seemingly healthy child with an uneventful family and perinatal history. After a short asymptomatic period (tens of hours or days needed for the toxins to accumulate), symptoms appear that may suggest generalized infection, perinatal trauma, endocrine or surgical conditions. Children do not respond to routine treatment, their condition may deteriorate very rapidly and even lead to sudden death. In such cases, it is essential to definitively exclude metabolic basis for a condition, also to perform a proper genetic counselling for the family. Similarly, in disorders of fatty acid oxidation, long-chain fatty acids (LCHADD, VLCADD), accumulation of toxic acylcarnitines can irreversibly damage the liver or heart muscle, while hypoglycaemia and hyperammonemia can impair functioning of central nervous system. For many of these conditions, effective treatments can be offered, including diet, supply of cofactors of blocked reactions, vitamins, enzyme therapies, transplantation procedures and, more recently, gene therapy. Also, one cannot overestimate proper prevention of metabolic decompensation, which can be induced by starvation, stress, hypermetabolism in infection. A prerequisite for effective treatment, however, is the earliest possible diagnosis. Not only to avoid a lengthy diagnostic odyssey, but above all (to quote Prof. Jean Marie Saudubray) – *not to miss treatable disorders...*