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EDITORIAL

INHERITED METABOLIC DISORDERS: A CENTURY OF EVOLUTION

DOENÇAS HEREDITÁRIAS DO METABOLISMO: UM SÉCULO DE EVOLUÇÃO

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Inherited metabolic disorders (IMD) constitue a vast and complex group of pathologies increasingly relevant in the 21st century.[1]

The term "inborn error of metabolism" (IEM) was first enunciated in 1908 by Sir Archibald Garrod in reference to four diseases: alkaptonuria, pentosuria, cystinuria, and albinism. The first book on this subject was published in 1960 and included 80 diseases, but more than 1000 diseases are currently described, with ongoing discoveries.[2,3]

Indeed, IMDs are at the forefront of medical progress, with new methods on metabolomics and genomics identifying the molecular basis of an increasing number of previously unknown pathological conditions and syndromes. Metabolomics is the culmination of a century of biochemical diagnoses as the fundamental basis of IEM approach. Biochemical profiling allows laboratory assessment of the chemical fingerprint of multiple metabolites and their metabolic pathways in body tissues and fluids, usually with small samples and high speed. Although this technology is not yet ready to replace the classic biochemical diagnostic methods, it is highly likely that its influence will increase as we move forward in this century. Genomics, or clinical exome sequencing, the cornerstone of genetic diagnosis and standard of care for unexplained genetic or metabolic changes, will be replaced in the future by clinical genome sequencing resulting from evolution of algorithms underlying bioinformatic analysis and use of artificial intelligence for diagnostic purposes.[3,4]

The approach provided by these new tools allows for diagnoses not previously suspected and for acknowledging new classes of metabolic defects (e.g. defects in synthesis and remodeling of complex lipids, including phospholipids, sphingolipids, and complex fatty acids) and widening of their clinical phenotypic spectrum.[3]

Along with this enormous multidisciplinary diagnostic capacity, these emerging technologies enable to link clinical, biochemical, and molecular characteristics of metabolic diseases and provide a basis for therapeutic intervention.

In the therapeutic field, classic approaches aiming to reduce toxic metabolites, include dietary restrictions, establish alternative ways to promote elimination of potentially toxic metabolites (eg. medications and dialysis in diseases of the urea cycle or organic acidurias), and use substrate reduction therapies (e.g. eliglustat and miglustat for Gaucher disease) are being monitored and/or replaced by treatment options designed to more directly correct the underlying metabolic defect. This last group includes replacement therapy with recombinant enzymes, use of coenzymes and chaperons as modifiers, and cell/organ-transplantation. Other promising treatments include therapeutic mRNA and gene therapy using viral vector systems or gene editing. Many of these new therapies are currently in clinical trial phase, with evidence regarding diagnosis still largely outpacing evidence regarding new therapies.[3-5]

Early and adequate therapy, before the onset of irreversible sequelae, is a reality and a prerequisite for a significant number of diseases associated with good prognosis. Systematic neonatal screening plays a very important role in this setting. The use of tandem mass spectrometry – currently employed in the analysis of dried blood spotss on paper (Guthrie's test) – increased the number of treatable diseases capable of being simultaneously detected through metabolic disease identification. Also in this setting, new diagnostic methods associated with novel therapeutic approaches foresee inclusion of different diseases in the screening.[4]

Moreover, in this vast group of individually rare and complex genetic diseases initially considered to be pediatric diseases, an increasing number of patients present or are diagnosed in adulthood, as the result of a sometimes surprising phenotic variability or influence of other

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variables, as epigenetics or modifier genes that can confer risk for a particular disease or alter its severity and natural history.[3,6] Exponential knowledge of disease, metabolic fingerprints, and their underlying genetic basis is to be expected and clinicians will need to be more open-minded than ever before.

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