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Glycogen Storage Diseases: Next-Generation Medicine

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Glucose is an important energy source for the body, stored in the form of glycogen and released into the circulation when necessary. Numerous enzymes and transporters intervene in the synthesis and degradation of glycogen, and deficiencies of virtually all of these can cause different types of glycogen storage disease (GSD), inducing aberrant storage and/or utilization of glycogen. The different GSDs are denoted by a roman numeral that reflects the historical sequence of their discovery, by the deficient enzyme, or by the name of the author of the first description. The clinical features of the GSDs depend on the organ of abnormal glycogen metabolism and primarily involve the liver and/or muscle, but rare neurological phenotypes are recognized.[1,2] Hepatic and muscle GSDs are the most well-known categories and their clinical and biochemical phenotypes are extremely heterogeneous.

In general, hepatic GSDs present with failure to thrive, hepatomegaly, and/or fasting intolerance–induced (hypo- or hyperketotic) hypoglycemia.[1,2] Glycogen storage diseases presenting principally with hypoglycemia are GSD I (glucose-6-phosphatase deficiency), GSD III (debranching enzyme deficiency), GSD 0 (hepatic glycogen synthase deficiency), and GSD XI (Glut-2 deficiency). Glycogen storage diseases presenting mostly with isolated hepatomegaly are GSD VI (phosphorylase deficiency), GSD IX (phosphorylase kinase deficiency) and GSD IV (hepatic branching enzyme deficiency). Muscle/cardiac GSDs fall into 3 clinical groups. Glycogen storage diseases presenting with exercise intolerance often followed by rhabdomyolysis are type V (muscle phosphorylase deficiency) and type VII (phosphofructokinase deficiency). Glycogen storage diseases X, XII, and XIII also belong to this group, but these are extremely rare. Glycogen storage diseases presenting with myopathy/cardiomyopathy are type IIa (lysosomal acid maltase deficiency) and type IIb (lysosomal-associated membrane protein 2 deficiency). The extremely rare myopathic forms of GSD 0 and glycogenin 1 deficiency also fit in this category. Unlike the other forms of GSD, GSD IIIa and GSD IXb are the only types that affect both the liver and muscle.

The aim of this *Journal of Inborn Errors of Metabolism and Screening* special issue is to present new fields of research in hepatic GSDs and to improve understanding of the complexity of the treatments and the differences in the approaches considering the different realities (country, people, and cultures). The hepatic GSDs have been amongst the oldest inborn errors of metabolism since the first patient reports in the late 1920s. After major achievements in dietary management, both patients and professionals emphasized the importance of uniform evidence-based (as fare as possible for ultrarare disorders, however) treatments. Management guidelines have been designed by genetic and/or metabolic centers that are dedicated to the medical care and cure of patients with GSD. The (international) collaborative cohort studies (eg, the European Study on GSD I,[3,4] the International Study on GSD III,[5] and the American College of Medical Genetics and Genomics[6,7]) have defined the traditional phenotype from a *cohort* point of view and/or formulated guidelines for GSD I and GSD III. For decades, the field of inherited metabolic diseases has been acknowledged for its personalized medicine approach and dietary management has been the cornerstone. In the next generation, our field will direct toward additional treatments and precision medicine thanks to new methodologies and improved understanding of differences between *individual* patients with GSD.[8]

Generally, inborn errors of metabolism do not stop at borders between countries or continents, and in the area of ultrarare disorders, global collaboration is crucial. Related to developing countries, we believe that there is much space for approximation of information (1) to improve the therapeutic behavior of people with hepatic GSD, (2) to improve quality of life, and (3) to avoid extreme unnecessary procedures and treatments, like—in most cases—liver biopsies or liver transplants.

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Recognized clinical expertise, secure eHealth applications, databases and patient registries, active patient participation, and transparent governance structures including academias, publishers, politics, industries, and health-care insurances will be crucial conditions to improve transborder transfer of knowledge, care, and cure between professionals and patients in all possible directions.

Declaration of Conflicting Interests

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