BIOMARKERS IN LYSOSOMAL STORAGE DISEASE: LABORATORY APPROACH

Eser Yıldırım Sözmen
Ege University Faculty of Medicine, Department of Medical Biochemistry, İzmir

Lysosomal storage diseases which are related to deficiency of specific lysosomal hydrolases resulted to clinical aspects due to accumulation of substrates in different tissues. Since Dried Blood Spot (DBS) is non-invasive, low-cost, easy transportable, acceptable enzyme stability compared to leucocyte and/or fibroblast culture, it's recommended as a first screening test. As enzyme replacement therapies are available currently, early diagnosis of these diseases is crucial nowadays. The gold standard for diagnosis is determination of enzyme activity in DBS and/or plasma and/or leucocyte samples. Disease diagnosis is verified by determination of genetic mutation in gene of enzyme protein which is specific for LSD. However, a variety of problems such as low accuracy of enzyme activity methods, unknown genetic mutations, high ratio of false positive diagnosis due to methods, complicate the correct diagnosis of these patients. Therefore, clinicians need new biomarkers other than enzyme activity to diagnose and monitor of enzyme replacement therapy of the patients. Recently two types biomarker have been suggested for LSD. 1) Primer biomarkers which are metabolites accumulated in tissue due to enzyme deficiency, found in plasma and/or urine, e.g. glycosaminoglycan in urine of patients with mucopolysaccharidosis, tetrasaccharide in urine of patients with Pompe disease. 2) Secondary biomarkers which are non-specific, increase in serum/urine resulted from damaging of other tissues due to disease, e.g. biomarkers of liver damage and renal damage. Some biomarkers in this group are partially specific to disease, e.g. chitiniotriase which is a macrophage activation marker, increases in blood of patients with Gaucher disease, Niemann Pick disease. Currently, LAMP-1 LAMP-2, some interleukins, saposins and cathepsins as further biomarkers are focus of investigations.

BIOMARKERS FOR LYSOSOMAL STORAGE DISORDERS: CLINICAL APPROACH

Sema Kalkan Uçar
Ege University Faculty of Medicine Children Metabolism Laboratory, İzmir

Lysosomal storage disorders (LSD) are group of diseases with metabolic defects associated primarily with a disruption in the catabolism and/or transport of by-products of cellular turnover, coupled with the secondary consequences of the accumulation of incompletely metabolized substrates within particular cell types. Initially, the individual disorders were grouped according to the chemical composition of the storage material, e.g. sphingolipidoses (Gaucher, Fabry, Niemann-Pick A/B/C, Metachromatic leukodystrophy, Krabbe disease, Tay-Sachs/Sandhoff disease, GM1-gangliosidosis), mucopolysaccharidoses (Hurler/Scheie, Hunter, Sanfilippo, Morquio, Maroteaux-Lamy, Sly, Natowicz) oligosaccharidoses (Mannosidosis, Sialidosis, Fucosidosis, Aspartylglucosaminuria ) etc. More recently, these disorders have been clustered according to their biochemical or molecular basis. To date, the LSDs encompass at least 250 different clinical entities. LSDs are pernicious, multi-systemic and under diagnosed disorders, frequently with a (sub) clinical onset at pediatric age. Their phenotype is heterogeneous in age of onset, rate of progression and involved organs. Several clinical manifestations, such as hepatosplenomegaly, coarse facial features and skeletal dysplasia, can serve as an important clue for LSD. On presentation, especially in a young child, the diagnosis can be missed, particularly when the family history is uninformative. Therefore, identification of the biomarkers that can serve as a surrogate for or indicator of disease severity, in terms of either overall disease burden or involvement of a particular organ or system is very important. Diagnostic confirmation necessitates biochemical and/or molecular genetic testing. Ideally biomarkers should be easily and cheaply measurable in readily obtained samples (urine/blood) and moreover, their concentration or activity should be found to be greatly elevated in disease states, without overlap in values between affected and healthy subjects, and should change rapidly in response to specific treatment outcomes that are clinically meaningful. The main known markers for LSD are chitiniotriase-CCL18-PARC-ACE-TRAP (Gaucher), globotriaosylceramide (lysoGb3)-uramodulin (Fabry) and urinary Glc4-plasma Hex4 (Pompe).