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NMR-based Urinalysis for Symptomatic IEM Patients

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Introduction

Inborn errors of metabolisms (IEM) are heterogeneous (>300 different conditions) involving disorders of synthesis, catabolism/anabolism, transport, and storage of metabolites. Individual IEM condition is quite rare, but they are collectively common. The incidence of IEM in this locality was estimated to be at least 1 per 4122 live births. Because many of these conditions can be rapidly fatal and have non-specific signs and symptoms, the diagnosis of IEM is largely relied on laboratory which provide biochemical and genetic analysis of IEM.

Objectives

A rapid diagnosis can lead to specific treatment and ultimately prevent complications and mortality. Unfortunately, conventional laboratory analysis of IEM was largely relied on gas chromatography-mass spectrometry (GC-MS) for urine organic acid analysis which involved complex sample preparation steps and long incubation time. Here, we propose the use of Nuclear Magnetic Resonance (NMR)-based urinalysis as a complementary tool for GC-MS for the study of IEM. The sample preparation steps for NMR-based urinalysis is simple and the overall analytical time for a full proton NMR urine spectrum 200 human metabolites and >100 IEMs can be identified by NMR spectroscopy. In addition, NMR spectroscopy is able to solve complex and novel IEM conditions because of its ability to resolve unknown metabolites through de novo assembly.

Methodology

Urine samples were analysed using ¹H-NMR spectroscopy, including samples from patients with beta-ketothiolase deficiency (BKD), beta-ureidopropionase deficiency (UPD), citrin deficiency, fructose 1,6 bisphosphatase (FBP1) deficiency, holocarboxylase synthase deficiency (HLCS), 3-hydroxyisobutyric aciduria, hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, methylmalonic aciduria (MMA), propionic academia (PA) and succinic semialdehyde dehydrogenase (SSADH) deficiency, and controls without IEM.

Result

Disease-associated biomarkers were identified in all patients with IEM: butanone in

BKD; beta-ureidoisobutyric and beta-ureidopropionic acids in UPD; galactitol in citrin deficiency, glycerol in FBP1 deficiency, 3-hydroxyisovaleric acid and other markers in HLCS, 3-hydroxyisobutyrate in 3-hydroxyisobutyric aciduria, orotic acid in HHH syndrome, methylmalonic acid in MMA, 3-hydroxypropionic acid in PA, and 4-hydroxybutyric acid in SSADH deficiency, and these biomarkers were not found in excess in controls.

The workflow of NMR-based urinalysis is simple with a fast analytical time. Sample preparation is a two-step procedure which can be easily completed in <15 minutes. Unlike conventional GC-MS analysis which often requires a long sample preparation time and derivatization steps. We envisage NMR-based urinalysis will play a crucial role in acute IEM care and will become more available in modern hospital laboratories.