Altered Plasma Biotinidase Enzyme Levels in Indian Patients with Hepatic Glycogen Storage Disorders

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Introduction
❖ Hepatic glycogen storage diseases are a set of inherited metabolic disorders caused by a lack of or reduced activity of a glycogen-degrading enzyme.
❖ Human carboxylases use biotin as a cofactor for gluconeogenesis, fatty acid synthesis, and branched-chain amino acid catabolism.
❖ Biotinidase is an enzyme that is primarily produced in the liver and catalyzes the hydrolysis of biotin from biocytin.
❖ Glycogen metabolism and biotinidase are not directly linked.
❖ Several investigations have found enhanced biotinidase levels in patients with hepatic GSDs, albeit the specific source of this increased biotinidase activity in GSD patients is still yet to be determined.

Objective
To evaluate the utility of biotinidase activity as a biomarker for screening of hepatic GSDs.

Methods
❖ From 2013 to 2017, a cohort of 59 patients with hepatic GSDs and 86 age-matched controls were recruited from the genetics and metabolic clinic.
❖ Patients were enrolled based on the clinical and biochemical suspicion of GSD and later on diagnosis was confirmed by the gene sequencing.
❖ The mean age of the patients and control was 39±25 months and 20±27 months with a M:F 37/22 and 53/33 respectively.
❖ Biotinidase enzymatic activity was determined in random plasma samples.
❖ The spectrophotometric approach was used to estimate biotinidase activity using biotinyl-p-aminobenzoate as a substrate.
❖ The statistical analysis was performed using the SPSS 22 statistical software.

Results

Figure 2: Distribution of patients across various GSDs

Figure 3: The area under the curve (AUC) for biotinidase levels collected from all confirmed patients and controls was 0.932 (95 percent CI=0.88-0.98) on the receiver operating characteristic curve (ROC).
Figure 4: Biotinidase level (nmol/min/mL) in (A) GSDs patients vs Control (B) Different forms of hepatic GSDs patients vs Control.

Table: Biotinidase activity in different groups of the cohort

- Patients may have another type of GSD; GSD VI, IX, # Patients have typical GSD characteristic (clinical and biochemical) but not confirmed on gene sequencing, Confidence Interval (CI); GSD (glycogen storage disorder)

Discussion

- The mean biotinidase level in the patients was 11.3 nmol/min/mL with 95 percent CI (10.9-11.8), while the mean in the control group was 7.7 with 95 percent CI (7.4-8.0).
- Between the two groups, there was a statistically significant difference (p=0.001). For confirmed hepatic GSDs, plasma BTD had 86 percent sensitivity, 87 percent specificity, 78 percent positive predictive value, and 93 percent negative predictive value.
- In GSDIII patients, biotinidase levels were unchanged following diet therapy (9±3 months)
- Increased BTD activity in GSDs could be due to up-regulated gluconeogenesis and fatty acid metabolism.
- Normal biotinidase activity could be attributed to the functional polymorphism c.1330G>C (p.As444His) in the BTD gene, which reduced BTD activity by 48%.
- Increased activity in three non-GSD patients with similar biochemical and clinical manifestations of GSD suggested that increased BTD activity may be associated with a specific liver metabolic derangement rather than the disease itself.

Conclusion

Our findings suggest that biotinidase activity could be used as a biomarker to screen hepatic GSDs in a resource-limited setting, whereas its normal activity cannot rule out the diagnosis of GSD. The levels are indistinguishable between different types of hepatic GSDs and are unaffected by dietary intervention.

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