Title: Commentary: "Galactosemia Diagnosis by Whole Exome Sequencing later in life"

Running title: Galactosemia in Adult with Cerebral Palsy

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Main Text

Precise molecular diagnosis of individuals with developmental delay is important to guide management and future prognostication. Lucas-Del-Pozo and colleagues describe a patient with cerebral palsy(CP) diagnosed in adulthood with galactosemia highlighting the power of genomic sequencing to identify previously unsuspected metabolic disorders.[1]

Classic galactosemia is an inborn error of metabolism leading to toxic accumulation of galactose and derived metabolites. This condition usually presents within days of ingesting milk with failure to thrive, hypoglycemia, bleeding diathesis, and jaundice. Left untreated, complications including liver failure and sepsis resulting in neonatal fatality occur.[2] Early institution of lactose-restricted diet may eliminate these systemic features, though children remain at risk for developmental motor and speech delays, cataracts, poor growth, female reproductive abnormalities, impaired intellectual functioning and motor deficits including ataxia and extrapyramidal abnormalities.[2] Many of these features are evident in retrospect in this case.

Clues in adulthood to potential metabolic disorder include a history of early neonatal difficulties and hyperbilirubinemia improved with dietary manipulation as well as later onset progression of symptoms associated with evolution of brain MRI findings. Additionally, this patient, diagnosed previously with CP, displays an ataxic phenotype. Though acquired etiology is reported, underlying genetic etiology is frequent for this CP sub-type.

Appropriate evaluation including metabolic screening identified abnormal sialotransferrins suggesting a congenital disorder of glycosylation (CDG). Galactosemia, though not a primary disorder of glycosylation, shares many clinical characteristics with CDG. Though the exact pathogenic mechanisms are not fully understood, the toxic buildup of galactose intermediates or shortage of metabolic end products is hypothesized to interfere with glycosylation.[3,4] Persistent

defects in glycosylation are thought to contribute to poor neurologic outcomes despite dietary galactose restriction. Better understanding of the links between these two pathways and the persistence of glycolytic abnormalities in galactosemia patients may lead to development of improved therapeutic approaches in the future.[3]

Author Roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

JF: 3A

SL-D-P: 3B

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Daniel M-M: 3B

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Disclosures

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Ethical Compliance Statement

The authors confirm that neither informed patient consent nor the approval of an institutional review board was necessary for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Video 1. Full video from the 2020 Video Challenge discussion of this case.