CLINICAL LANDSCAPE OF CITRIN DEFICIENCY: A GLOBAL PERSPECTIVE ON A MULTIFACETED CONDITION

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Citrin deficiency is caused by mutations in the SLC25A13 gene, which encodes for a mitochondrial protein called citrin. Citrin is important in maintaining normal bodily functions, such as deriving energy from food sources such as carbohydrates and proper functioning of the urea cycle.

Global Distribution, Genetic Variants and Prevalence

- Although initially identified in Japan, citrin deficiency has now been reported across East Asia, Europe, North America, and the Middle East.
- The prevalence of citrin deficiency is high in East Asian populations. For example, carrier frequencies are 1:31 in Vietnam and 1:47 in China.
- In Japan, about 1 in 17,000 people are affected based on a carrier frequency of 1:65.

A recommendation has been made to avoid the use of the term "citrullinemia type 2" (CTLN2) to prevent confusion with other urea cycle disorders, and to use "adolescent and adult citrin deficiency" (AACD) instead.

Clinical Manifestations and Diagnosis

Citrin deficiency presents in three age-dependent phases: NICCD (< 2 years), post-NICCD (including FTTDCD) (2-18 years), and AACD (> 18 years).

- Symptoms of NICCD include low birth weight, liver issues, hypoglycemia, and stunted growth. These symptoms often resolve by age one.
- Post-NICCD phase includes mild symptoms like dietary preferences and hypoglycemia. Some patients in this phase may develop FTTDCD with more pronounced symptoms such as hypoglycemia, stunted growth, stomach aches and dyslipidemia.
- AACD is marked by more severe symptoms such as hyperammonemia, neuropsychiatric symptoms, dyslipidemia, fatty liver, pancreatitis, and low BMI.

Efforts to improve the diagnosis and prognosis of citrin deficiency have led to its inclusion in new-born screening (NBS) programs, especially in East Asia. Traditional screening methods using citrulline levels in dried blood spots (DBS) have low sensitivity and specificity. A new method using thresholds for multiple amino acids and acylcarnitines has improved detection rates, with no additional costs to existing programs.

Citrin deficiency in Europe, the Experience From the UK

The largest European study of citrin deficiency was conducted in the UK, identifying over 30 patients. A significant number of these patients were of South Asian, Pakistani background. About a third of the cohort were diagnosed as infants (NICCD), another third was identified through family history, and the remaining were diagnosed during childhood or adolescence in the FTTDCD phase. Only two patients progressed to AACD.

Common symptoms reported in the UK cohort included liver disease and abdominal pain, with one patient requiring a liver transplant. Although less than half of the patients were specifically prescribed a low-carbohydrate, high-protein, high-fat diet, most tended to self-select a diet that was lower in carbohydrates and higher in proteins and fats. During episodes of metabolic crises, some patients were prescribed an "emergency regimen" consisting of whole milk or soya milk with added medium-chain triglycerides (MCT) and/or protein powder.

At diagnosis, many patients were underweight and short, but their growth improved with treatment, although they remained shorter than the population average. Even among patients with the same mutations, the severity of symptoms varied widely. Only a small number of patients showed liver disease, while over half experienced issues with low blood sugar (hypoglycemia). One patient succumbed from AACD.

Global Effort and Future Directions

- Recent studies, especially from East Asia, have provided significant insights into citrin deficiency.
- There is a push to create a global network for better understanding and management of the condition.
- Japan's guidelines for diagnosing and treating citrin deficiency could serve as a model for global standards.
- Patient registries are essential for tracking the disease and preparing for new treatments. Japan is developing a specific registry for citrin deficiency.

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