CITRIN DEFICIENCY

Citrin Foundation

Pathophysiology: Citrin deficiency (CD) is an inherited liver metabolic condition caused by mutations in the SLC25A13 gene encoding for citrin. Citrin is a mitochondrial transporter that moves aspartate from the mitochondria to the cytosol where it participates in the urea cycle to convert ammonia into urea. Citrin is also a key component of the malate-aspartate shuttle (MAS) that functions to transfer reducing equivalents (NADH) from the cytosol into the mitochondria to maintain redox balance. Citrin deficiency affects multiple metabolic pathways such as glycolysis, gluconeogenesis, de novo lipogenesis, beta-oxidation, and the TCA cycle that collectively contribute to an energy deficit in the liver. If the condition is not well managed, it may also lead to hyperammonemia due to impairment of the urea cycle.

Symptoms: CD has four distinct age-dependent phenotypes. Frequently observed symptoms are indicated in bold.

Age	Phenotype	Clinical Symptoms
Infants (< 1 year old)	Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD)	• **Prolonged jaundice** • **Cholestasis** • **Elevated blood citrulline** • Failure to thrive • Enlarged liver
> 1 year old	Silent / adaptation phase	• **Strong preference for protein/fat-rich foods** • **Aversion to carbohydrate/sugar-rich foods** • Fatigue • Hypoglycemia • Occasional stomachaches
	Failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD)	• **Strong preference for protein/fat-rich foods** • **Aversion to carbohydrate/sugar-rich foods** • Fatigue • Hypoglycemia • Low BMI & stunted growth • Fatty liver & dyslipidemia • Frequent stomachaches
Adolescence / adult	Adolescence and adult citrin deficiency (AACD)*	• **Strong preference for protein/fat-rich foods** • **Aversion to carbohydrate/sugar-rich foods** • **Fatigue** • **Hypoglycemia** • **Low BMI** • **Fatty liver & dyslipidemia** • **Elevated blood ammonia (may lead to psychiatric symptoms)** • **Elevated blood citrulline** • Pancreatitis • Hepatoma

* Previously termed as CTLN2

Dietary management: Dietary management is the front-line therapy for CD patients. The recommended protein:fat:carbohydrate (PFC) ratio for patients is 15-25%: 40-50%: 30-40%. Patients should be allowed to self-select their diets and are encouraged to snack in between meals to maintain adequate energy levels. Patients should avoid consuming alcohol as it can trigger the onset of AACD.

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Treatment: Medium-chain triglycerides (MCT) has been shown to improve or resolve most symptoms associated with CD as it can rapidly supply energy to the liver. The recommended daily dose for MCT is 1g/kg/day with a maximum daily dose of 40g. It is recommended to take MCT in divided portions throughout the day together with meals.

Population frequency: CD has an incidence rate of 1 in 17,000 in Japan. Carrier rates vary across Asia but may range from 1 in 65 in Japan to as high as 1 in 31 in Vietnam. Although originally reported as an East Asian condition, new cases of CD are being reported worldwide and includes individuals of non-Asian descent, underscoring the global nature of the condition.

Diagnosis: In newborns, CD may be detected through newborn screening, particularly for elevated citrulline levels, and is followed by confirmatory genetic testing of SLC25A13. Beyond the newborn phase, a hallmark symptom in children and adult CD patients is a strong food preference for foods high in protein and fats, whilst being averse to foods high in carbohydrates and sugars. Consumption of excess carbohydrates and/or sugars often causes patients to feel ill. Other reported symptoms in children and adults may include stunted growth, low BMI, episodes of hypoglycemia, elevated blood lipids and the presence of fatty liver. Some CD patients have been misdiagnosed as having a restrictive eating disorder due to the nature of their unique food preferences.

Labs that perform testing:

- Prevention Genetics
- Fulgent Genetics
- GeneDx

Register with the Citrin Foundation: If you have patients with CD, we strongly encourage them to register with us through our website, which contains useful information about CD, tips on how to manage the condition, and opportunities to connect with our growing community of patients.