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Citrin deficiency—The East-side story

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Abstract

Citrin deficiency (CD) is a complex metabolic condition due to defects in *SLC25A13* encoding citrin, an aspartate/glutamate carrier located in the mitochondrial inner membrane. The condition was first described in Japan and other East Asian countries in patients who were thought to suffer from classical citrullinemia type 1, and was therefore classified as a urea cycle disorder. With an improved understanding of its molecular basis, it became apparent that a defect of citrin is primarily affecting the malate–aspartate shuttle with however multiple secondary effects on many central metabolic pathways including glycolysis, gluconeogenesis, de novo lipogenesis and ureagenesis. In the meantime, it became also clear that CD must be considered as a global disease with patients identified in many parts of the world and affected by *SLC25A13* genotypes different from those known in East Asian populations. The present short review summarizes the (hi)story of this complex metabolic condition and tries to explain the relevance of including CD as a differential diagnosis in neonates and infants with cholestasis and in (not only adult) patients with hyperammonemia of unknown origin with subsequent impact on the emergency management.

KEYWORDS

fatty liver disease, cholestasis, adult citrullinemia, hypercitrullinemia, brain edema

1 | THE BEGINNING OF UNDERSTANDING A NEW DIFFERENTIAL DIAGNOSIS FOR CITRULLINEMIA

The title of this short review article is taken from a lecture held at the recent SSIEM Annual Symposium 2023 in Jerusalem. The organizers had scheduled this lecture on "Citrin deficiency – The East-side story" to allude to the fact that citrin deficiency (CD) was long considered as a condition prevalent and therefore relevant in East Asia, but of less importance to Western countries and its metabolic societies. This assumption probably was never true, but it is important to realize that it is not only not true but may even be dangerous. This short review summarizes the (hi)story of a metabolic condition that was described first in Japan and other East Asian countries, where knowledge on genetics, biochemistry and management was build long before the more recent perception of its global existence.

The condition now known as CD was first reported in adult patients with elevated plasma citrulline concentrations and signs of hepatic encephalopathy.[1] The primary suspicion of a defect in argininosuccinate synthetase

TABLE 1 Differential diagnoses of "citrullinemia."

Name	Type of condition	Gene name	OMIM	Usual plasma citrulline range (μmol/L)*	Characteristics
Citrullinemia type 1	Classical	*ASS1*	#215700	>2000	Early onset severe hyperammonemia
	mild	*ASS1*	#215700	Up to 800	Often identified through NBS, often asymptomatic
Argininosuccinate lyase deficiency		*ASL*	#207900	Up to 600	Cit remains elevated, but less severe than in citrullinemia type 1
Pyruvate carboxylase deficiency	Type B ("French phenotype")	*PC*	#266150	Up to 200	Patients may have severe hyperammonemia and lactic acidosis
Dihydrolipoamid dehydrogenase deficiency		*DLD*	#246900	Up to 400	Often only elevated cit during metabolic crises
Lysinuric protein intolerance		*SLC7A7*	#222700	Up to 150	Mildly elevated cit in NBS and later in life, mechanism not fully understood
Citrin deficiency	NICCD	*SLC25A13*	#605814	Up to 500	Not reliably elevated cit, often intrahepatic cholestasis, often spontaneous resolution
	FTTDCD	*SLC25A13*	–	Normal	Sometimes mild symptoms (fatigue, failure to thrive, hypoglycemia), often silent period
	AACD	*SLC25A13*	#603471	Up to 600	Mainly elevated cit in symptomatic patients, often self-selected protein- and lipid-rich and carbohydrate restricted diet

Abbreviations: AACD, adolescent and adult citrin deficiency (former CTLN2); cit, citrulline; FTTDCD, failure to thrive and dyslipidemia by citrin deficiency; NBS, newborn screening; NICCD, neonatal intrahepatic cholestasis by citrin deficiency.
*Plasma citrulline concentrations are approximations provided here as a guidance for clinical practice.

1 (ASS1), a well-known classical urea cycle disorder,[2] was initially seemingly supported by the findings of decreased hepatic argininosuccinate synthetase 1 (ASS1) activity with normal kinetic properties and heat stability.[3,4] However, this assumption was not confirmed since none of the patients had genetic variants in *ASS1*. In the first large patient cohort (>80 patients), there was a remarkable proportion of consanguinity of about 20%, which by far exceeded the expected rate of inbreeding in Japan of about 1%–2%.[5] This observation led to further investigations and identification of the true cause of this condition by the same group, when homozygosity mapping in 118 families, including 18 consanguineous pedigrees, identified the chromosomal region 7q21.3 and therein five different *SLC25A13* variants.[6] This finding ruled out ASS1 deficiency as the underlying cause but instead expanded the small group of differential diagnoses of "citrullinemias" by yet another member (Table 1).[7]

The product from this newly detected gene locus, named citrin, was later found to be a mitochondrial aspartate/glutamate carrier located in the mitochondrial inner membrane (AGC2),[8] and part also of the malate–aspartate shuttle. Citrin is highly expressed in liver mitochondria but also present in many other organs such as kidney, pancreas, and heart, and holds a prominent role relevant for several important biochemical pathways (Figure 1).[10,11]

The condition related to a defect in citrin is an autosomal recessive disorder and presents with highly variable age-dependent clinical manifestations[12–15] (Table 1). There have been recent review articles describing in detail the "clinical and therapeutic landscapes of citrin deficiency," and the reader is referred to these papers.[12,16] Importantly, to avoid a potentially fatal confusion with classical citrullinemia type 1 (caused by a defect in *ASS1*),[17] the former adult-onset type II citrullinemia (CTLN2, caused by a defect in *SLC25A13*) has been recently suggested to be re-named to "adolescent and adult citrin deficiency" (AACD).[12]

2 | THE PRESENT GLOBAL SITUATION OF CITRIN DEFICIENCY AND WHY IT IS RELEVANT TO KNOW ABOUT THIS CONDITION

For many years, CD was exclusively described in East Asia, particularly in Japan,[18–20] with on overall incidence of 1 in 17 000 births[21] and carrier rates for *SLC25A13*

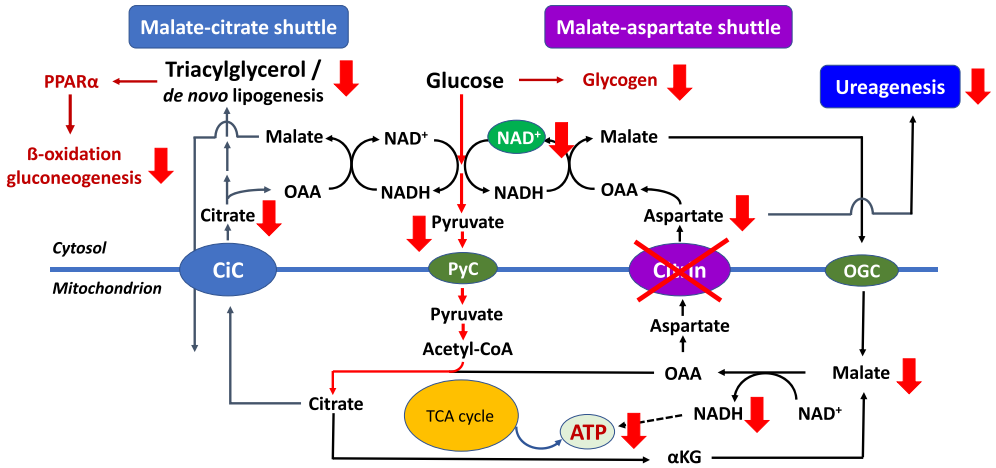

FIGURE 1 Role of citrin as part of the malate–aspartate shuttle in liver and related pathways. Simplified overview to illustrate the manifold interrelations of citrin, located at the inner mitochondrial membrane and being part of the malate–aspartate shuttle, with other metabolic pathways. Downward arrows (thick red) indicate possible impairment of the respective pathways and metabolites. CiC, citrate carrier; OAA, oxaloacetate; OGC, α-ketoglutarate-malate carrier; PPARα, peroxisome proliferator-activated receptor α; PyC, pyruvate carrier. *Source*: Figure adapted from Hayasaka and Numakura.[9]

variants up to 1/31 in Vietnam[22] and 1/41 in Singapore.[23] Besides the overall high prevalence of the disease, there are a few recurrent *SLC25A13* variants, which have been studied in detail regarding their migration pattern in East Asian countries.[24]

The global distribution of CD became apparent when not only immigrants from East Asia but also patients from other ethnicities were identified as suffering from any of the variable clinical phenotypes of the disease, and this is supported in the meantime by reports from many regions in the world.[17,25–36] Interestingly, almost all of the aforementioned referenced patients carry *SLC25A13* variants and genotypes different from those reported in East Asian patients. The only exception to this was reported by colleagues in Valencia, Spain, in a neonatal non-East-Asian patient from Romania, at that time only the ninth known Caucasian CD patient, who was affected by a *SLC25A13* variant prevalent in East Asia.[35] This suggests that the global distribution of CD is not the result of immigration of families from East Asia into other parts of the world, but primarily results from newly occurring genetic alterations in *SLC25A13*.

While due to the rarity of the condition, most metabolic specialists in Western countries may have never encountered a single patient with CD and may even never do so, there is still one important aspect that should be more widely considered. In an emergency situation due to hyperammonemia, the usual treatment for known as well as unknown patients includes a high dextrose infusion according to various guidelines.[37–39] However, this regime can be deleterious for CD patients, as reported in literature,[17] since high dextrose infusions may be toxic in their condition.

The danger of dextrose infusions in CD became apparent in an adult patient, who was included as No. 2 in a patient series of defects in the mitochondrial malate–aspartate shuttle and pyruvate carrier.[17] This patient had his first metabolic decompensation with somnolence at 37 years. When hyperammonemia (150 μmol/L, ref. < 50) was diagnosed, selective metabolic screening was added showing an increase of plasma citrulline (506 μmol/L, ref. 10–50). This led to the assumption of a late-onset citrullinemia type 1 and the respective emergency treatment for this condition. Unfortunately, the patient deteriorated under intensive care management, and only when the negative genetic investigation of *ASS1* became available, other differential diagnoses were considered. This finally led to the diagnosis of CD when the patient had already succumbed due to irreversible brain edema. Since this is not a singular event, levels of plasma citrulline only moderately elevated (Table 1) in (adult) patients with hyperammonemia of unknown origin should prompt to include CD as a differential diagnosis with subsequent careful implementation of dextrose infusions and emergency management. Due to the variable phenotypes known in this disease,[12] CD should in addition be considered in patients with cholestatic liver disease during infancy and early childhood, and in fatty liver disease of unknown origin in patients of all age groups.[30,40–42]

In summary, although the (hi)story of CD began as an "East-side story," it is now obvious that patients in all regions of the world and in all ethnicities may be affected.

A defect of citrin has multiple effects on human metabolism and in many pathways rendering this condition an area of interest and worth studying despite or possibly because of being a very complex disease. With our present understanding of CD, it serves as an excellent paradigmatic condition for the overall theme of the SSIEM Annual Symposium 2023, "where East meets West."

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CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest.

DATA AVAILABILITY STATEMENT

This manuscript includes all data analyzed during this review.

ETHICS STATEMENT

This manuscript does not involve any human data and thus, there was no need to involve the Ethics committee.

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