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Minireview

The unsolved puzzle of neuropathogenesis in glutaric aciduria type I

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ABSTRACT

Glutaric aciduria type I (GA-I) is a cerebral organic aciduria caused by deficiency of glutaryl-Co-A dehydrogenase (GCDH). GCDH deficiency leads to accumulation of glutaric acid (GA) and 3-hydroxyglutaric acid (3-OHGA), two metabolites that are believed to be neurotoxic, in brain and body fluids. The disorder usually becomes clinically manifest during a catabolic state (e.g. intercurrent illness) with an acute encephalopathic crisis that results in striatal necrosis and in a permanent dystonic–dyskinetic movement disorder. The results of numerous *in vitro* and *in vivo* studies have pointed to three main mechanisms involved in the metabolite-mediated neuronal damage: excitotoxicity, impairment of energy metabolism and oxidative stress. There is evidence that during a metabolic crisis GA and its metabolites are produced endogenously in the CNS and accumulate because of limiting transport mechanisms across the blood–brain barrier. Despite extensive experimental work, the relative contribution of the proposed pathogenic mechanisms remains unclear and specific therapeutic approaches have yet to be developed. Here, we review the experimental evidence and try to delineate possible pathogenetic models and approaches for future studies.

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Abbreviations: 3-OHGA, 3-hydroxyglutaric acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APV, D-2-amino-5-phophonovalerate; BBB, blood–brain barrier; BCB, blood–cerebrospinal fluid barrier; CAT, catalase; CHO, Chinese hamster ovary; CK, creatine kinase; CNS, central nervous system; Cr, creatine; DCFH-DA, 2′,7′-dichlorofluorescein diacetate; DNQX, 6,7-dinitroquinoxaline-2,3dion; Glu, glutamate; GA, glutaric acid; GA-I, glutaric aciduria type1; GCDH, glutaryl-CoA dehydrogenase; GPx, glutathione peroxidase; GSH, glutathione; i.p., intra peritoneal; i.v., intra venous; IL-1β, interleukin-1β; IFN-γ, interferon-γ; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; NaDC3, Na^+-dependent dicarboxylate transporter; NA, not applicable; NMDA, N-methyl-D-aspartate; NMG, N-methyl-D-glutamine; NO, nitric oxide; NR2B, N-methyl-d-aspartate receptor subunit 2B; OAT, organic anion transporter; OCT, organic cation transporter; PCr, phosphocreatine; PDC, L-trans-pyrrolidine-2,4dicarboxylate; PDH, pyruvate dehydrogenase; QA, quinolinic acid; ROS, reactive oxygen species; RNS, reactive nitrogen species; s.c., sub cutaneous; SDH, succinate dehydrogenase; SOD, superoxide dismutase; TAR, total antioxidant reactivity; TCA, tricarboxylic acid cycle; TRAP, total radical-trapping antioxidant potential; VEGF, vascular endothelial growth factor.

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1. Introduction: the puzzling faces of glutaric aciduria type I

Glutaric aciduria type I (GA-I, OMIM #231670) is an autosomal recessive neurometabolic disease caused by deficiency of glutaryl-CoA dehydrogenase (EC 1.3.99.7; GCDH) [1]. GA-I was first reported in 1975 [2] and has an estimated prevalence of 1:100,000 newborns [3,4]. Different cohorts with an increased prevalence for GA-I have been identified: the Amish Community [5], Canadian Oji-Cree Indians [6], Irish Travelers [7] and black South Africans [8]. In many patients macrocephaly is present at or shortly after birth and precedes the neurological manifestation. Affected babies often present additional subtle neurological symptoms like hypotonia, irritability and feeding difficulties. Neuroimaging in the so-called "presymptomatic period" shows a pattern of frontotemporal atrophy in the majority of affected children, accompanied by delayed myelination and high-signal intensity in the pallidum [9,10]. GA-I patients are prone to acute subdural hemorrhages including retinal hemorrhages after minor head trauma [11]. Such hemorrhages often happen around the first birthday when the children start to walk, and may be mistaken as signs of child abuse [12]. While most untreated patients with GA-I are asymptomatic in the first months of life, about three-fourths of patients present with an encephalopathic crisis, often associated with a respiratory or gastrointestinal infection. The presenting encephalopathic crisis occurs usually between the 6th and the 18th month of life; 87% of encephalopathic crises have occurred by the age of 24 months. During an encephalopathic crisis the child often loses neurological functions like the ability to sit, head control or suck and swallow reflexes. The infant presents with profound axial hypotonia and athetoid movements of hands and feet. Generalized seizures can also occur. Unfortunately, most infants and toddlers do not recover from such a crisis. This results in an irreversible dystonic–dyskinetic movement disorder with well preserved intellectual functions. If undiagnosed and not treated, additional cerebral areas are progressively affected leading to generalized brain atrophy, pyramidal tract signs and mental retardation. Secondary to impaired chewing and swallowing in combination with a high energy demand due to increased muscle tone, affected children often show failure to thrive and malnutrition. Aspiration, intercurrent pneumonia and respiratory failure can lead to early death. A minority of patients present with developmental delay from birth and progressive dystonic cerebral palsy ("insidious onset"). This presentation of the disease is more frequent in the Spanish population (about 20% of patients) in comparison to the general Caucasian population [13]. Rare cases of adult onset [14] or individuals without neurological symptoms have been reported.

GCDH, a mitochondrial matrix protein, is an enzyme of the catabolic pathway of tryptophan, lysine and hydroxylysine. Lysine is naturally more abundant in protein compared to tryptophan. Lysine breakdown is substantially increased during catabolic crisis [15]. In mice, GCDH is expressed mainly in liver, kidney and brain (Fig. 1). In brain, GCDH expression is limited to neurons [16,17]. The highest level of expression is seen in cerebellum; lower levels in striatum and cortex [18]. Deficient GCDH activity results in an accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OHGA) and to a lesser extent glutaconic acid and glutarylcarnitine in body fluids and brain [11,19,20]. A depletion of free carnitine occurs as a consequence of the formation of glutarylcarnitine. Residual activity of GCDH (2–30%) leads to low or undetectable excretion of GA in a subgroup of patients termed "low excretors". By contrast, "high excretors", with no residual GCDH activity, show the typical urinary metabolite pattern. Notably, despite a good correlation between genotype and biochemical phenotype, the genotype cannot predict the severity of neurological manifestations, which can be similar in low and high excretors [13,21–23]. Diagnosis of GA-I is made by organic acid analysis in urine (GA and 3-OHGA) and by acylcarnitine profile analysis in plasma by tandem mass spectrometry (glutarylcarnitine). Since low excretors could be missed by these methods, determination of GCDH activity in cultured fibroblasts and GCDH mutation analysis are considered as the only precise methods to establish the diagnosis of GA-I [24,25].

Early diagnosis of GA-I is very important, because start of treatment in presymptomatic infants results in better outcome. Dietary treatment (low lysine diet) in combination with carnitine and anticatabolic emergency treatment has been shown to be effective in preventing the neurological disease. Treatment in suspected GA-I patients should be started even before confirmation of diagnosis. The emergency treatment aims to prevent or reverse a catabolic state through high energy intake. This regime should be performed aggressively during febrile illness, surgery and immunization within the vulnerable period for acute encephalopathic crisis. Patients have the best chances for a good neurological outcome if the treatment is started in the newborn period [26,27]. However, one third of prospectively identified patients develop, despite close adherence to therapy, striatal injury leading to life-long disability [19]. Thus, GA-I is considered as a disorder for which newborn screening has an important impact on prognosis [27]. However, patients detected through newborn screening and treated early still may show subtle, but significant fine motor and speech deficits confirming the "chronic" toxicity in GA-I [28]. More than any other organic aciduria, a variety of changes in the structural development of the brain have been described in GA-I, occurring independently from encephalopathic crises: macrocephaly, hypoplasia or atrophy of the temporal and frontal lobes with widening of the Sylvain fissures, and the presence of subdural hygromas, white matter changes, acute subdural or retinal hemorrhage [10,29,30].

The observation of the clinical course in children with GA-I seems to indicate that at least three different mechanisms are involved in the neuropathogenesis of GA-I: 1. The presence of structural changes at birth and sometimes even in presymptomatic children indicates that they may be true developmental anomalies, thus relying on a pathomechanism with prenatal onset. The two other types of CNS lesions in children with GA-I develop postnatally: 2. An acute toxicity, the so-called encephalopathic crisis with striatal necrosis. The bilateral destruction of caudate nucleus and putamen leads to irreversible loss of neurological functions and dystonic–dyskinetic movement disorders [1,9,11,31]. 3. A chronic toxicity leading to progressive dystonic cerebral palsy in untreated patients ("insidious onset") and to fine motor and speech deficits in patients diagnosed and treated through newborn screening.

Several *in vivo* and *in vitro* studies have suggested different adjuvant therapies for GA-I such as administration of antioxidants [32,33], administration of homoarginine to compete with lysine uptake in CNS [16,34], and administration of anti IL-1β antibodies to modulate inflammation [35]. In one report, riboflavin responsiveness has been observed in a patient with 20% residual GCDH activity [36]. Although these treatments may appear as theoretically effective, there is no firm evidence that they are beneficial for the patients [27].