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REVIEW ARTICLE

Glutaric aciduria type I: A translational approach to an enigmatic disease

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Abstract:

Glutaric aciduria type I (GA-I) is an autosomal recessively inherited disorder of L-lysine, L-tryptophan and L-hydroxylysine metabolism which is biochemically characterized by the accumulation of putatively toxic glutaric and 3-hydroxyglutaric acids, and non-toxic glutarylcarnitine due to deficient activity of glutaryl-CoA dehydrogenase. The prognostic relevant event of this disease is the manifestation of a complex movement disorder with predominant dystonia superimposed on axial hypotonia. This movement disorder most often manifests during infancy or early childhood after the precipitation of acute encephalopathic crises by catabolic state but it may also develop insidiously without clinically apparent crises. Advances have been made in the description of the natural disease course and neuroradiological abnormalities demonstrating overlapping episodes of cerebral alterations including (reversible) maturational delay of the brain in utero, (irreversible) acute striatal injury during a vulnerable period of brain development and chronic progressive changes that may continue lifelong and involving extra-striatal brain regions. Neonatal identification of asymptomatic patients by tandem mass spectrometry allowing to start combined metabolic treatment in asymptomatic patients has significantly improved the neurological outcome in countries with such newborn screening programmes. In contrast, therapeutic concepts for symptomatic patients are much less effective. Post mortem studies and investigations in Gcdh-deficient mice, a transgenic mouse model for GA-I, have helped to unravel the pathomechanism. Evidence is increasing that some of the accumulating metabolites in GA-I patients are neurotoxic due to their interference with glutamatergic neurotransmission, inhibition of the 2-oxoglutarate dehydrogenase complex and impairment of the dicarboxylic acid shuttle between astrocytes and neurons. Strikingly, glutaric and 3-hydroxyglutaric acids massively accumulate in the brain of patients due to the low permeability of the blood brain barrier for dicarboxylic acids which may explain the selective neurological phenotype of GA-I. Current therapeutic concepts aim to reduce the cerebral concentrations of neurotoxic metabolites by modulating lysine influx to the brain and stimulating the formation of non-toxic glutarylcarnitine. Despite the outlined progress, the mechanism of current neuroprotective concepts is still quite hypothetical and lack a proof of principle. Our understanding has been hampered by the fact that in affected patients the biochemical effect of metabolic treatment could be determined only by using invasive methods (which would be unethical), whereas the concentrations of these biomarkers in body fluids are unlikely to correlate with the brain tissue. Therefore, a translational approach to this disease is indispensable to further unravel the mechanisms of neurologic disease and to elucidate the major principles of neuroprotective strategies.

Keywords: organic aciduria, newborn screening, striatum, dystonia, guideline

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Introduction

Glutaric aciduria type I (GA-I) is an autosomal recessively inherited disorder of L-lysine, L-hydroxylysine and L-tryptophan metabolism first described in 1975 [1]. It has an overall estimated incidence of approximately 1 in 100,000 newborns [2,3]. High-risk populations with an incidence of up to 1 in 300 newborns have been identified such as the Amish Community in Lancaster County, Pennsylvania, USA [4], the Oji-Cree in Western Ontario and Manitoba, Canada [5], the Lumbee in North Carolina, USA [6], and the Irish Travellers in Ireland and the United Kingdom [7]. Furthermore, newborn screening in Germany suggests a high frequency in migrating families with Turkish origin [3], however, the incidence of this disease in the Turkish population is not yet known.

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GA-I is caused by mutations in the *GCDH* gene which consists of 11 exons (7 kb) and is known to be located on 19p13.2 [8]. More than 200 disease-causing mutations have been identified so far [9,10]. Most patients are compound heterozygous for two different mutations. The most frequent mutations in Caucasians is p.R402W accounting for 10-20% of all alleles. Other mutations are predominantly or even exclusively found in certain populations such as p.A421V in the Amish Community as well as Southern parts of Germany and Switzerland, the original settlement area of the Amish, IVS1+5G>T in the Oji-Cree [11] 2002), p.P248L and p.E365K in Turkey [3], and p.R227P and p.V400M in Spain [10].

Inherited deficiency of glutaryl-CoA dehydrogenase, a mitochondrial flavoprotein which catalyzes the dehydrogenation and decarboxylation of glutaryl-CoA to crotonyl-CoA in the catabolic pathways of L-lysine, L-tryptophan and L-hydroxylysine, causes accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA) and glutarylcarnitine (C5DC). These metabolites can be detected in body fluids by quantitative gas chromatography/mass spectrometry (GA, 3-OH-GA) or tandem mass spectrometry (C5DC). In some countries, C5DC screening has been included to tandem mass spectrometry-based newborn screening allowing to identify patients with GA-I before the onset of symptoms [2,12-14]. Quantitative analysis of urinary GA and 3-OH-GA excretion has identified two biochemical subgroups termed high and low excretors [15]. In high excretors who show a (near) loss of GCDH activity high concentrations of GA (above 100 mmol/mol creatinine) are found, whereas in the low excreting patients due to a GCDH residual activity of up to 30% GA excretion is below 100 mmol/mol creatinine and in some patients is (intermittently) normal. The excretion of 3-OH-GA in both groups is less variable. In analogy to GA, C5DC concentrations of low excretors may be low in dried blood spots used for tandem mass-spectrometry based newborn screening. Therefore, low excretors are at an increased risk to be missed by newborn screening or selective metabolic screening [11,16].

Increased GA is also found in patients with glutaric aciduria type II (multiple acyl-CoA dehydrogenase deficiency) and type III but elevated C5DC is only found in glutaric aciduria type II [17]. Urinary GA and C5DC in dried blood spots can also be elevated

in patients with renal failure, and elevated GA is often found in patients with mitochondrial diseases. 3-OH-GA is not increased in the above mentioned conditions but is increased in ketotic patients [18] and in patients with short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency [19]. Pseudoglutarylcarnitinemia was reported in patients with medium-chain acyl-CoA dehydrogenase deficiency [20]. Thus, presence of GA, 3-OH-GA and C5DC is not pathognomonic for GA-I but should also consider the mentioned differential diagnoses.

The variable natural disease course

In the newborn period, 75% of newborns affected with GA-I show macrocephaly which may progress during infancy [3,21,22]. Additionally, unspecific clinical signs, such as mild axial hypotonia, irritability and slight motor delay may appear. Cranial magnetic resonance imaging (MRI) in newborns and young infants has identified temporal hypoplasia, subependymal pseudocysts, immature gyration pattern and delayed myelination [23]. Some of these changes may be visible in the last trimester of pregnancy suggesting prenatal onset of neuropathology [24,25]. However, the mentioned neuroradiological abnormalities may improve or even normalize postnatally if treatment is started in the newborn period and – based on this – the onset of irreversible neurological symptoms is prevented. If patients remain undiagnosed and thus untreated, the majority of them during infancy or early childhood develops a complex movement disorder best described as predominating dystonia superimposed on axial hypotonia [7,12,21,26]. With increasing age dystonia may be more fixed, and patients may develop spasticity or akinetic-rigid parkinsonism in addition. Choreatic movements may be also observed [27,28]. Chronic epilepsy is thought to be rare in GA-I [29] but dystonic spasms may be mistaken for seizures [30]. Mild to severe neurologic disease leaves the affected children permanently incapacitated with variable degrees of impaired mobility, feeding problems and respiratory problems. Life expectancy of those symptomatic children is significantly reduced [26,27]. The impact on the cognitive development remains to be elucidated [23,31].

The most common etiologic cause for neurological deterioration is the development of an *acute*

encephalopathic crisis precipitated by infectious diseases, vaccinations and surgery. Most of these crises occur from age three months to three years, only a few crises have been reported between age three and six years, whereas there is no report about a crisis beyond six years of life [12,26]. This pattern suggests a ‘window of vulnerability’ during brain development for the manifestation of such crises. The neuroradiological correlate of complex movement disorders following encephalopathic crises is acute striatal injury [32]. Using diffusion-weighted MRI three stages of acute striatal injury have been delineated: 1) an acute stage, within 24 h of motor regression, characterized by cytotoxic oedema within the basal ganglia, cerebral oligemia, and rapid transit of blood throughout gray matter; 2) a sub-acute stage, 4-5 days after the onset of clinical signs, characterized by reduced striatal perfusion and glucose uptake, and supervening vasogenic edema; and 3) a chronic stage of striatal atrophy [33]. Within the striatum, neuronal loss spreads in a dorsoventral direction and mostly affects GABAergic medium-spiny neurons [34]. Medium-spiny neurons which are highly susceptible to various neurotoxins are of enormous functional importance for the striatum which receives major input from the cortex and thalamus. Striatal neurons cause pallidal GABAergic neurons, which fire at steady rates in the absence of input, to pause thereby modulating the pallidal inhibition of target regions. Loss of striatal input to the internal globus pallidus via the direct and/or indirect pathway results in uninhibited tonic inhibition exerted by pallidal neurons and thus dystonia.

In some patients, striatal injury may occur without clinically apparent crisis. This has been termed *insidious-onset* GA-I [21,35]. It was doubted, however, that acute and insidious-onset of motor symptoms is mechanistically distinct. Apparent diffusion coefficient maps revealed that a few patients with insidious motor delay have suffered striatal injuries before or shortly after birth, followed by latent periods of several months before disability was apparent [33]. These authors concluded that acute and insidious presentations may occur by similar mechanisms, and differ only with regard to the timing of injury.

Late-onset GA-I has been reported in a few adolescents and adults presenting with a clinically

distinct symptomatology including cephalgy, vertigo, nausea, gait disturbances, and hand tremor. In these patients, T2-weighted images revealed intact basal ganglia but supratentorial white matter changes with variable severity. Accordingly, in all of these patients lysosomal storage defects and peroxisomal disorders have been suggested first [26,36,37]. Since white matter abnormalities have also been demonstrated in children – even in asymptomatic patients who have received metabolic treatment until the newborn period [23], it remains to be elucidated whether *late-onset* GA-I is clinically distinct. In fact, evidence increases that white matter changes and other extrastriatal abnormalities such as T2 hyperintensities in globus pallidus, dentate nuclei, substantia nigra, thalamus and tractus tegmentalis centralis are frequent in patients with and without preceding encephalopathic crises [23,38]. The neuropathological correlate of white matter abnormalities is spongiform myelinopathy due to intramyelinic vacuolation and splitting of the myelin sheath. This is somewhat similar to aspartoacylase deficiency (Canavan’s disease) – although less severe than in this disease [39,40]. The clinical relevance and progression of these extrastriatal abnormalities, however, is yet unknown.

There is no evidence that the genotype correlates with the clinical phenotype in GA-I owing to a high variation of the disease course among individuals [26]. A comparison of siblings sharing the same *GCDH* gene mutations and the same biochemical phenotype have confirmed a significant variations of the natural disease course even within families [3,7,12,41].

Pathophysiological concepts

The understanding of the mechanisms underlying the neuropathology of GA-I is still hampered by the enormous complexity of putatively relevant parameters and the variable clinical phenotype. At present, there is no unifying and generally accepted concept for the neuropathogenesis of GA-I. In analogy to other organic acidurias such as methylmalonic and propionic aciduria which like GA-I may present with stroke-like onset of neurodegenerative changes particularly affecting the basal ganglia, the term *metabolic stroke* has been introduced [42]. It has been suggested that basal ganglia lesions are induced by an accumulation of putatively toxic metabolites and that they cannot be

explained by hypoxemia or vascular insufficiency, nor do the lesions fit in a vascular distribution when detected on neuroimaging studies. A limitation of this concept is that it is purely descriptive and lacks a conclusive pathophysiological and neuroradiological definition.

However, this concept has highlighted for the first time that accumulating pathological metabolites may contribute to the manifestation of neurological disease in organic acidurias in general and GA-I in particular and thus has become the backbone of recent pathophysiological concepts involving excitotoxic cell damage and mitochondrial dysfunction caused by mechanistic synergism of accumulating GA, 3-OH-GA and glutaryl-CoA [43-46]. Specifically, it was shown that accumulating metabolites weakly induce activation of NMDA receptors [44], inhibition of glutamate uptake from the synaptic cleft [47], depletion of the intracellular creatine phosphate pool [43], inhibition of the glutamate decarboxylase, the key enzyme of GABA synthesis [48], inhibition of the 2-oxoglutarate dehydrogenase complex, the rate-limiting enzyme of the TCA cycle [45], disturbance of the dicarboxylate shuttle between astrocytes and neurons [49,50], and dysfunction and cell death of microvessel endothelial cells [51] and oligodendroglial precursors [52]. A major argument against the relevance of the toxic metabolite hypothesis for GA-I, however, has been based on the lack of any known correlation between the biochemical and the clinical phenotype [26,53] and the striking discrepancy between the near-normal to normal urinary excretion of GA and 3-OH-GA in some patients with a severe neurologic disease [11].

A likely explanation for this apparent discrepancy was found in post mortem studies [34,54,55] and in Gcdh-deficient mice, a transgenic mouse model for GA-I resembling the high excretor phenotype [46,56,57]. These studies have highlighted that GA and 3-OH-GA acids strongly accumulate in brain tissue of GA-I patients and Gcdh-deficient mice, and are found at similar concentrations in both high and low excreting patients. In the terms of the toxic metabolite hypothesis, similar cerebral concentrations of putatively neurotoxic GA and 3-OH-GA in high and low excretors are expected to result in a similar risk of all patients for the manifestation of neurologic disease which in fact is supported by the clinical experience [26,53]. The high intracerebral

accumulation of GA and 3-OH-GA was explained by intracerebral *de novo* synthesis and subsequent accumulation due to a very limited efflux from brain to blood [34,57]. The physiological base of this observation is a very low permeability of the blood-brain barrier (BBB) for dicarboxylic acids such as GA and 3-OH-GA [57,58]. Although organic anion transporter (OAT) 3 (and 1) is expressed in brain capillary endothelial cells and mediates the efflux transport of dicarboxylic acids across the blood-brain barrier [59], the efflux transport capacity of endothelial OATs for dicarboxylic is very low [60]. Besides a weak expression of OATs, the low efficacy of dicarboxylic acid transport at the BBB can be explained by the lack of functional coupling between OATs and sodium-dependent dicarboxylic acid transporter (NaDCs) since NaDCs are not expressed at the BBB [60]. In contrast to the BBB, functional coupling of OATs and NaCs at the proximal tubular epithelium results in an effective renal clearance of GA and 3-OH-GA [61]. Furthermore, GA and 3-OH-GA are thought to be transported along the dicarboxylate shuttle between astrocytes and neurons which is mediated by NaDC2 and NaDC3 expressed on neurons and astrocytes and thereby impairing the physiologic flux of dicarboxylic intermediates of the tricarboxylic acid cycle [49,50].

The correlation between the lysine influx to the brain and cerebral GA and 3-OH-GA concentrations was demonstrated by oral lysine loading in Gcdh-deficient mice resulting in increased GA concentrations and the induction of cerebral injury similar to acute encephalopathic crises in human patients [46]. The manifestation of cerebral injury was prevented by treatment with homoarginine, which limits the lysine influx into the brain, and glucose, which prevents catabolism, both resulting in reduced intracerebral accumulation of GA [62]. In line with this, postem mortem investigations in two high-excreting patients having received low lysine diet showed near-normalisation of cerebral GA and 3-OH-GA concentrations [63,64]. Therefore, evidence is increasing that the BBB despite shielding the brain from toxic substances, facilitating transport of acquired nutrients and thus ensuring proper function of the brain is an integral part of the mechanisms underlying GA-I neuropathology. This has been formulated in the so-called trapping hypothesis [57,65].

Besides the blood-brain barrier and the toxic effects of GA, 3-OH-GA and glutaryl-CoA, evidence is increasing that the regulation of the cerebral blood flow is also disturbed in GA-I patients. A recent MRI study has identified disturbed cerebral hemodynamics in GA-I patients [66], and it was reported that 3-OH-GA at high concentrations induced dysfunction and cell death of microvessel endothelial cells in vitro [50]. After Roy and Sherrington have published their groundbreaking paper on the regulation of blood supply of the brain in 1890, it has been confirmed in many ways that neuronal activity, brain energy metabolism and cerebral blood flow are directly coupled [67]. A disturbance of this coupling increases the risk for an insufficient cerebral supply with nutrients and oxygen in affected patients synergizing with the adverse effects of neurotoxic GA, 3-OH-GA and glutaryl-CoA on brain energy metabolism.

Neuroprotective concepts

An evidence-based guideline proposal for the treatment and management of GA-I patients has been published recently [68]. Accordingly, the therapeutical management of GA-I consists of the following three building blocks: 1) an age-adapted low lysine diet with adequate intake of essential nutrients and calories aiming to reduce the accumulation of neurotoxic metabolites, GA, 3-OH-GA and glutaryl-CoA, deriving from the major precursor amino acid, L-lysine; 2) carnitine supplementation to prevent secondary carnitine depletion, facilitate the production of non-toxic C5DC and replenish the intracellular free coenzyme A pool; and 3) prevention or rapid reversal of catabolic state by low- or no-protein and high-calorie diet which may be induced by infectious disease, surgery, and inflammatory response to vaccinations in order to prevent the onset of acute striatal injury. The combination of low lysine diet and carnitine supplementation is usually termed *basic metabolic treatment*, whereas therapeutic means aiming to prevent catabolic state are termed *emergency treatment*. This combined regime significantly improves the outcome in neonatally diagnosed children preventing the manifestation of acute encephalopathic crises and irreversible movement disorders in 65-95% of these children [3,12,14,21], whereas it is much less effective in patients in whom treatment starts after the onset of irreversible

neurological symptoms [22]. Therefore, neonatal identification which is preferentially performed by newborn mass screening or high-risk screening of families with known index patients or populations with known high carrier frequency and incidence for GA-I is the prerequisite for effective treatment and a favourable disease course. It has been demonstrated in Gcdh-deficient mice that low lysine diet and increased glucose intake reduce the accumulation of putatively toxic metabolites providing the first biochemical proof principle for basic and emergency treatment [62,69].

Since basic metabolic treatment and emergency treatment are usually administered in combination, the benefit of the single components of current therapy for GA-I patients is not yet very well understood. Basic metabolic treatment alone, however, is not thought to be sufficient to prevent the manifestation of irreversible striatal injury. Therefore, emergency treatment is considered as the most important neuroprotective principle if it is started before the onset of neurological symptoms during putatively threatening episodes [21,33,70]. A cross-sectional study on 279 patients and a prospective follow-up study in 52 neonatally diagnosed patients have demonstrated that low lysine diet alone or in combination with carnitine supplementation reduces the risk of patients for the manifestation of movement disorders [26,71]. The therapeutic benefit of patients from carnitine supplementation alone is less clear – in analogy to inborn errors of metabolism in general [72]. However, carnitine supplementation has been associated with a low mortality in symptomatic patients [26]. In contrast to low lysine diet, carnitine supplementation and emergency treatment the administration of riboflavin, a cofactor of GCDH, is less effective [26]. A likely explanation is that riboflavin responsiveness is a rare condition in GA-I [73].

Despite undoubted progress in the prevention of irreversible neurologic disease in GA-I patients, the mechanisms how neuroprotection is achieved are not very well understood. In particular, studies on the biochemical effects of metabolic treatment on cerebral lysine metabolism are hampered by the fact that GA and 3-OH-GA concentrations cannot be determined by MR spectroscopy, and CSF, plasma

and urine concentrations of these metabolites do not correlate with brain concentrations. Mechanistic knowledge of treatment is still based on post mortem studies and investigations in Gcdh-deficient mice and in vitro studies. Therefore, a translational approach to unravel the pathophysiology of GA-I and to understand and optimize current treatment strategies is indispensable.

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