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Glutaric aciduria type 1 and neonatal screening: time to proceed—with caution

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Abstract The new technology of tandem mass spectrometry is having a significant impact on the diagnostics of inborn metabolic errors. One of the most important aspects of this new technology is the possibility of recognising a whole class of disorders within a single analytical step. Shall this powerful technology be applied to the screening of newborn babies? Careful evaluation of every single disorder that could potentially be identified is needed. In the following, I will present some considerations that concern glutaric aciduria type 1 (MIM 231670; glutaryl-CoA dehydrogenase deficiency).

Keywords Glutaric aciduria type 1 · Newborn screening · Tandem mass spectrometry

Abbreviations *GADH* glutaryl-CoA dehydrogenase · *GAI* glutaric aciduria type 1 · *TMS* tandem mass spectrometry

The natural course of glutaric aciduria type 1

The clinical manifestations of glutaric aciduria type 1 (GA1) have been reviewed by several authors [2, 3, 6, 9, 11, 28]. Essentially, the majority of individuals homozygous for pathogenic mutations in the glutaryl-CoA dehydrogenase (*GADH*) gene will develop neurological disease, either acutely following an encephalopathic crisis, or, less frequently, with an insidious course. The neurological disease in GA1 consists of an extrapyramidal movement disorder of varying degree; most individuals who have had an encephalopathic crisis have severe dystonia with marked disability. Intelligence

usually remains intact. Some individuals are known to have no neurological disease in spite of proven enzyme deficiency and/or *GADH* mutations; they are, however, the exception rather than the rule.

What is the pathogenesis of brain injury in glutaric aciduria type 1?

It appears that two distinct pathogenetic moments should be distinguished [28]. Frontotemporal atrophy of variable degree, often with arachnoid cysts, develops before birth and probably during some months after birth [1, 5, 7, 13, 20, 21, 22, 26, 31, 34]. The pathogenetic mechanism is not understood. Interestingly, there is no close correlation between the degree of frontotemporal atrophy in an infant and subsequent neurological impairment; often there is frank discordance. Subdural haematoma is a common complication and may lead to suspected child abuse.

Degeneration of basal ganglia, in particular of the corpus striatum, is clinically more relevant. As discussed, this can occur in an insidious way or acutely following an encephalopathic crisis. Clinical circumstantial evidence has pointed to a concurrence of several factors in the pathogenesis of basal ganglia degeneration [28]: carnitine depletion, excitotoxic mechanisms, and, during an acute crisis, hyperthermia with increased energy requirements and infection with cytokine release. Moreover, a developmental profile of one or more neuronal receptor(s) has been advocated to explain the susceptibility window to acute crises (beyond the age of 4 years or so, acute crises become rare and there is a tendency to stabilisation of the neurological findings – again, with exceptions). Experiments with neuronal cell cultures have confirmed that metabolites accumulating in GA1 may elicit excitotoxic and apoptotic pathways [14, 15, 17, 18, 32] but concentrations used in the studies have been higher than those observed in body fluids and these studies fail to explain the lack of correlation between the concentration of glutaric acid metabolites in

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body fluids and the severity of neurological disease. Although promising, the studies in cell culture have not yet thrown conclusive light on the exact mechanisms triggering neuronal degeneration nor provided avenues to pharmacological prevention.

Can we prevent the natural course of the disease?

Yes, we can. There is abundant, although indirect, evidence indicating that once the diagnosis of GA1 has been made, the risk for acute encephalopathy and basal ganglia degeneration is significantly reduced [2, 10, 12, 23]. Unfortunately, no case-control or prospective study is available, and these conclusions, although accepted by most experts, are based solely on the retrospective case collection study of Georg Hoffman and coworkers as well as on observations on single families. Opinions differ as to what component of our therapeutic arsenal is more effective. Replenishment of carnitine stores, usually depleted by the time of diagnosis, may be the single most effective factor. Avoidance of prolonged hyperthermia and catabolism with anti-inflammatory medication, hydration, and caloric supply also plays a role. Current dietary management includes restriction of protein intake but not to a degree requiring supplementation with amino acid mixture. No concrete study has ever shown the efficacy of such an approach; and the risk of amino acid imbalance is present [25]. The use of neuroprotective drugs during episodes of fever and catabolism makes sense and has been advocated, but no rigorous studies have been conducted and *in vitro* evidence is equally lacking. Contrary to early reports, riboflavin has not proven to be helpful [4].

Does early diagnosis matter?

Making the diagnosis of GA1 matters at any time in life. Even in individuals with advanced basal ganglia injury, carnitine repletion makes them less vulnerable to further damage and to hypoglycaemic episodes. Early diagnosis, following the diagnosis in older affected sibs or because of macrocephaly or arachnoid cysts, can result in at least partial prevention of subsequent neurological deterioration. Early diagnosis allows, of course, for adequate genetic counselling before the onset of further pregnancies.

What have we learnt from current screening programmes?

Neonatal screening programmes for GA1 have been going on for several years in selected regions of the United States and Canada [8, 24], and for 2 to 4 years in large provinces in Germany (A. Muntau, G. Hoffmann, and A. Roscher, personal communications; and discussion on *Metab-L*). Without reviewing the details, the

following issues are addressed: (1) the incidence of GA1 in the general population of Europe and North America appears to be lower than the 1:40,000 extrapolated from preliminary studies approximately 10 years ago (this does not apply to selected geographic areas with known higher incidence of GA1); (2) the timing of blood sampling may play a role (samples taken too early may give false negative results); (3) determining the correct threshold for glutarylcarnitine in the dried blood samples appears to be problematic; several GA1 cases have been missed in screening programmes, but lowering the threshold for glutarylcarnitine would lead to unacceptably high recall rates; (4) neonatal diagnosis followed by treatment with carnitine, dietary advice, and emergency management does not necessarily prevent the onset of neurological disease; some children have developed encephalopathic crises with neurological damage in spite of early diagnosis and treatment [8, 16].

Should glutaric aciduria type 1 be included in neonatal mass screening programmes?

The criteria of Wilson and Jungner [33], long considered the golden rule for the inclusion in mass screening programmes, are clearly not fulfilled by GA1 [29, 33]. In particular, although the morbidity of the disease is sufficiently high to justify screening, the incidence of the disorder remains unknown and treatment may not prevent disease manifestations in all cases, thereby raising thorny questions on the ethical acceptability. Finally, the more frequently used screening method (tandem mass spectrometry (TMS) of acylcarnitines in dried blood spots) might not detect 100% of cases. It is clear that both the medical aspects of GA1 treatment and the technical issues (timing of the blood sampling, refining of cutoff criteria on TMS analysis) need our full attention.

On the other hand, we should not remain captive to preset criteria. There are several excellent reasons to proceed with neonatal screening for GA1, some of which are precisely the reverse of those quoted above: (1) screening might be the only way to obtain a correct estimation of the incidence; (2) screening would allow for the implementation of prospective studies (e.g. comparing the incidence of neurological disease in a cohort of early-diagnosed patients with that occurring “naturally” in non-screened populations); (3) the additional costs would be limited, as GA1 would be part of a “package” of diseases detectable by TMS.

Screening comes of age

The time has come to abandon the concept of “perfect” screening, namely full sensitivity and complete treatability, as an ‘Allmachtsphantasie’: we know this does not hold true even for phenylketonuria or galactosaemia. We should depart from this all-or-none mentality

and instead learn to measure the impact of our preventive and therapeutic measures using more objective instruments such as burden of disease, quality of life adjusted years and disability-adjusted quality of life-years [19, 30]. This approach may also prove helpful in increasing the economic resources allocated to neonatal screening programmes [27].

Paediatricians involved in the care of children with genetic disorders can rarely boast of a complete cure for their patients, and learn instead to appreciate even small advances in the quality of life. If we translate this to GA1, being fully aware of the fact that we might not help each and every patient, we should not miss the chance of an early diagnosis – that is the best a baby with GA1 can hope for.

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