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*Short Communication*

# Early signs and course of disease of glutaryl-CoA dehydrogenase deficiency

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Glutaryl-CoA dehydrogenase deficiency (GDD; McKusick 231670) or glutaric aciduria type I is an inborn error of lysine, hydroxylysine and tryptophan catabolism due to deficiency of glutaryl-CoA dehydrogenase (EC 1.3.99.7). The mitochondrial flavin–adenine dinucleotide-requiring enzyme catalyses the dehydrogenation of glutaryl-CoA as well as the subsequent decarboxylation of glutaconyl-CoA to crotonyl-CoA. Clinical and biochemical characteristics of the disease, especially the course of disease, are distinct and different from other well-known disorders of amino acid catabolism (Amir et al 1989; Haworth et al 1991; Hoffmann et al 1991; Morton et al 1991; Kyllerman et al 1994).

Following a workshop in 1993, new data not previously published are presented in this report on more than 20 patients with GDD, revealing hitherto unreported details of the clinical presentation and the natural history of this probably still widely underdiagnosed neurometabolic disorder.

## RESULTS AND DISCUSSION

Clinical and neuroradiological findings and milestones in the natural course of the disease are summarized in Table 1. An important clue to early diagnosis is not so much the finding of gross macrocephaly at birth, but the observation of a pathologically increased head growth in infancy, crossing the centiles. Furthermore, affected babies often have additional 'soft' neurological symptoms of hypotonia, irritability, and jitteriness. Neuroimaging is often performed, revealing the characteristic findings of frontotemporal atrophy and delayed myelination; despite this, metabolic investigations are generally not undertaken.

**Table 1 Course of disease and clinical and neuroradiological findings in 21 symptomatic patients with glutaryl-CoA dehydrogenase deficiency**

| | |
|---|---|
| Onset of symptoms | |
| Encephalopathic crisis | 76% |
| Insidious onset of dystonia and psychomotor retardation | 24% |
| Age at encephalopathic crisis[a] ($n=16$) | 14 months (2–37 months) |
| Age at diagnosis[a] ($n=21$) | 36 months (3–170 months) |
| Clinical findings | |
| Dyskinesia | 100% |
| Dystonia | 100% |
| Hypotonia | 83% |
| Tetraplegia | 17% |
| Macrocephalus at birth | 43% |
| Macrocephalus in infancy | 67% |
| Profuse sweating | 35% |
| Hyperpyrexic crises | 10% |
| Neuroradiological findings | |
| Frontotemporal atrophy | 82% |
| Basal ganglia pathology | 71% |

[a]Mean age and ranges of patients

Additional neuroimaging findings in patients with GDD are transient germinaloid cysts of the caudothalamic pit. These have been observed by cerebral sonography or NMR imaging during the first 6 months of life. Chronic subdural effusions and haematomas have been rarely reported (Osaka et al 1993; Drigo et al 1993), but were observed in 20–30% of our patients. In three of our patients chronic subdural effusions and/or haematomas were the leading presenting symptom during infancy. Because these were detected following relatively mild traumas, the families were suspected of child abuse. One child had been taken into care. Paediatricians need to be aware that selective screening for GDD should be included in the diagnostic work-up of infants presenting with subdural effusions and haematomas.

During the second six months of life the 'soft' neurological signs slowly subside, and around their first birthday patients with GDD are mostly considered normal except for a slight delay of gross motor development. To parents and paediatricians the mild clinical abnormalities of these children during early infancy appear trivial compared to and unrelated to the severe movement disorder developing later. It is therefore not surprising that these aspects have not yet been emphasized. However, recognition of the early clinical symptoms of GDD with appropriate biochemical investigations at this time are, at present, the only way to the diagnosis of a higher proportion of patients with GDD during this 'presymptomatic' stage.

About 75% of patients suffer an acute encephalopathic crisis, mostly associated with an upper respiratory and/or gastrointestinal infection between the ages of 2 and 37 months (Table 1). The metabolic symptoms, such as hypoglycaemia and metabolic acidosis, are minimal. After recovery, the children have lost most motor skills and function at a 1–2 month old level. At this point the very distinctive clinical picture of a severe dystonic–dyskinetic syndrome in alert-looking children with relatively well-preserved intellectual functions and a prominent forehead may be recognized. If the

underlying metabolic disorder remains undiagnosed, cerebral atrophy develops; clinically, pyramidal tract signs and mental retardation. The severity of symptoms and final outcome can be quite variable even within families.

A subgroup of patients never suffer encephalopathic crises but present with subacute motor delay. These patients (24% in our series) show developmental delay from birth and a progressive dystonic 'cerebral palsy'. Whereas in most patients with GDD there is often remarkable discrepancy between the severe motor impairment and normal or near-normal intellectual functions until late in the disease process, children who never developed normally are more likely to be impaired mentally. In addition, the sequence of increased head growth in infancy and frontotemporal atrophy is not always observed. The pathogenetic basis for these discrepancies is at present unknown. There are no differences in the biochemical findings of metabolite levels in physiological fluids or in residual enzyme activity.

In neurologically symptomatic patients, treatment results in no or only slight clinical improvement. Nevertheless, in our experience, the combination of a low-protein diet with carnitine supplementation seems in most cases to prevent further deterioration. With time, dedicated support and training, patients may become able to cope with their disabilities to the point that, despite the unchanged (dys)hypotonic disorder, normal schooling can be initiated utilizing language computers for communication. As involuntary movements of orofacial muscles may be severe, feeding difficulties can become a major problem. In addition, increased muscular tension and sweating, a common finding in GDD, require a high intake of calories and fluid. Patients may benefit greatly from percutaneous gastrostomy (Kyllerman et al 1994).

Rational therapy for GDD is hampered by our lack of understanding of the natural history of the disease, especially the pathogenesis of encephalopathic crises. As the risk for encephalopathic crises declines after 3 years of age, patients with neurological disease should not be treated with severe protein restriction beyond this age. However, carnitine supplementation and emergency measures during intercurrent illnesses, especially gastrointestinal infections, need to continue as in other disorders of organic acid metabolism.

Despite many unanswered questions in the natural history, the course of disease of GDD can be altered by early recognition and treatment, especially if accomplished before the development of severe neurological symptoms as a result of irreversible damage to the basal ganglia. Improved recognition of the early symptoms and neuroimaging findings of GDD may lead to a better understanding of the course of the disease and its pathogenesis and to diagnosis and initiation of early therapy before the onset of acute, devastating encephalopathic crises.

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