12.1 Introduction

Hyperornithinemia-associated gyrate atrophy of the choroid and retina (HOGA) is caused by deficiency of ornithine-5-aminotransferase. HOGA is an autosomal recessive disorder characterized by progressive chorioretinal degeneration with myopia, night blindness, and loss of peripheral vision, starting late in the first decade, proceeding to tunnel vision and eventual blindness by the third and fourth decade. Plasma ornithine values range from 400 to 1400 µM. Permanent reduction of plasma ornithine to values < 200 µM slows or stops the chorioretinal degeneration. A small proportion of patients respond to pharmacological doses of vitamin B6 (Weleber et al. 1978). Additional therapeutic approaches to reduce ornithine are substrate deprivation by dietary arginine restriction (Kaiser Kupfer et al. 1991) and augmenting of renal losses by administration of pharmacological doses of L-lysine (Giordano et al. 1978; Peltola et al. 2000; Elpegleg and Korman 2001) or the nonmetabolizable amino acid α-aminoisobutyric acid (Valle et al. 1981). Combined treatment approaches appear to be necessary, since no form of therapy is unequivocally effective. Creatine administration improves the histological abnormalities in muscle (Heinanen et al. 1999), but does not halt the progress of chorioretinal degeneration.

Hyperlysinemia/saccharopinuria appears to be a rare “non-disease.” It is caused by deficiency of the bifunctional protein 2-aminoadipic semialdehyde synthase, the first enzyme of the main pathway of lysine degradation. The two functions of the enzyme, lysine:2-oxoglutarate reductase and saccharopine dehydrogenase, may be differently affected by mutations. In most cases, both activities are severely reduced, resulting predominantly in hyperlysinemia and hyperlysinuria, accompanied by relatively mild saccharopinuria (hyperlysineemia I). About half of the patients described were detected incidentally and are healthy (Dancis et al. 1979, 1983). Symptoms described to be associated with the disorder include psychomotor retardation, epilepsy, spasticity, ataxia, and short stature. Single patients were described with joint laxity and spherophakia, respectively. These observations suggest that it can be accounted for by sampling bias.

2-Aminoadipic and/or 2-oxoadipic aciduria may also have no clinical significance, but some patients are retarded and show variable neurological ab-
normalities. The metabolic profile is heterogeneous, with most patients showing elevations of 2-aminoadipic acid, 2-oxoadipic acid, and 2-hydroxyadipic acid, whereas some excrete 2-aminoadipic acid only. It can be assumed that isolated 2-aminoadipic aciduria without significant 2-oxoadipic aciduria is caused by a deficiency of 2-aminoadipate aminotransferase; whereas combined 2-aminoadipic/2-oxoadipic aciduria would be caused by a deficiency of the 2-oxoadipate dehydrogenase complex. However, the biochemical profile of the reported patients overlap, loading studies were inconclusive, and a deficiency of either enzyme has as yet not been shown directly.

Glutaric aciduria type I (GAI; synonyms: glutaric acidemia type I, glutaryl-CoA dehydrogenase deficiency) is an autosomal recessive inherited neuro-metabolic disease with an estimated incidence of 1:50,000 Caucasian newborns (Schulze et al. 2003). Early diagnosis and treatment of the asymptomatic child is essential, as current therapy has little effect upon the brain-injured child. In the natural course of the disease, 75% of undiagnosed and untreated children develop acute encephalopathic crises during infancy or early childhood (modal age 6–12 months) precipitated by febrile illnesses or routine vaccinations (Hoffmann et al. 1996; Bjugstad et al. 2000). These crises most often result in irreversible damage of vulnerable brain areas, in particular the striatum, and consequently in the development of a dystonic dyskinetic movement disorder. Restriction of protein and lysine, administration of l-carnitine, timely vigorous treatment during intercurrent illness and neuropharmaceutical agents during the first 6 years of life may completely prevent or at least halt the unfavorable course of the disease. There are, however, some high-risk patients in whom the disease progresses despite therapy (Kölker et al. 2001; Monavari et al. 2000). As GAI has become a treatable neurometabolic disorder, increased inclusion in neonatal screening programs to allow early detection and onset of therapy is the key to further progress. A deeper understanding of the pathological mechanisms will reveal additional therapeutic approaches, which will hopefully also prevent brain damage in those 20–30% of patients that suffer neurodegeneration under current therapeutic strategies (Strauss et al. 2003).