1. INTRODUCTION

Dihydropyrimidinase (DHP, EC 3.5.2.2) catalyzes the second step in the degradation of uracil and thymine. The first step is catalyzed by dihydropyrimidine dehydrogenase (DPD, EC 1.3.1.2), the third step by β-ureidopropionase (UP, EC 3.5.1.6) and the fourth step is catalyzed by three transaminases (R)-(−)-β-aminoisobutyrate pyruvate aminotransferase (BAIBPAT, EC 2.6.1.40), β-alanine-pyruvate aminotransferase (BAPAT, EC 2.6.1.18) and β-alanine-α-ketoglutarate aminotransferase (BAKAT, EC 2.6.1.19). The first three steps of the catabolism of uracil and thymine are controlled by enzymes shared by both pathways and result in the production of the neurotransmitter acid β-alanine from uracil and the non-functional (R)-β-aminoisobutyrate from thymine. The thymine analogue 5-fluorouracil is degraded by the same pathway to fluoro-β-alanine. In contrast to DPD deficiency of which 50 cases have been reported only six cases have been described with DHP deficiency and none with UP deficiency, although secondary UP deficiency has been reported in patients with propionic acidemia. The reason for this difference may be a lesser frequency of DHP compared to DPD deficient individuals, but another possibility may be that patients with DHP deficiency are overlooked. Therefore, we will focus on the clinical presentation and biochemical detection of patients with DHP deficiency.
2. CLINICAL ASPECTS

Symptomatology of DHP deficient individuals seems to be as variable as in DPD deficiency. Epileptic or convulsive attacks were mentioned in three\textsuperscript{3,5,8} mental retardation, motor retardation and microcephaly in two of these individuals.\textsuperscript{5,8} Dysmorphic features and growth retardation were seen in one case.\textsuperscript{8} One patient suffered from intractable diarrhoea due to congenital microvillous atrophy, but had no other symptoms.\textsuperscript{9} Two individuals are healthy; they were detected by mass-screening in Japan.\textsuperscript{6,7} The clinical picture varies from severe to completely healthy. Inheritance is autosomal recessive.

3. BIOCHEMICAL ASPECTS

3.1. Metabolism

In DHP deficient patients dihydrothymine and dihydrouracil accumulate and because of the reversibility of the first step of pyrimidine degradation also thymine and uracil accumulate. These metabolites will appear in elevated concentrations in the body fluids. In contrast, the concentrations of the $N$-carbamyl-$\beta$-amino acids are low or absent. The reduced concentration of the neurotransmitter $\beta$-alanine may be of relevance with respect to the cerebral dysfunction and for this reason treatment with $\beta$-alanine supplementation is under investigation. Exposure of the nervous system to high concentrations of dihydropyrimidines and pyrimidine bases may be a contributing factor. Although not yet reported, increased sensitivity to fluorouracil toxicity can also be expected in individuals with (partial) DHP deficiency.

3.2. Detection and Diagnosis

The preferential material for the screening of DHP deficiency and the other pyrimidine degradation defects is urine, as all waste products accumulate in this body fluid. If urine is not available blood and cerebrospinal fluid can be used for screening, but the accumulation of abnormal metabolites in these body fluids is less prominent. DHP deficiency can be detected by procedures which are widely used for the screening of inborn errors of metabolism such as GC-MS analysis of urinary organic acid extracts\textsuperscript{5} and amino acid analysis of urine before and after acid hydrolysis.\textsuperscript{11} Quantification requires sophisticated methods such as HPLC with detection at various wavelengths in off- or on-line prepared fractions,\textsuperscript{12} isolation of dihydropyrimidines followed by acid hydrolysis and amino acid analysis of the resulting $\beta$-amino acids\textsuperscript{11} or proton NMR spectroscopy.\textsuperscript{13} Concentrations of the relevant metabolites in urines from the individuals with DHP deficiency are shown in Table 1. As can be seen dihydrothymine and dihydrouracil are strongly elevated, thymine and uracil are moderately elevated in all cases. This pattern is highly characteristic for DHP deficiency, but the diagnosis can be missed if the urine is contaminated by bacteria e.g. due to urinary tract infection.\textsuperscript{11} Except for uracil, which was found to be below the detection limit, increased concentrations for these metabolites were reported in CSF from two cases:\textsuperscript{9,13} thymine 10 and 3, dihydrouracil 79 and 117, dihydrothymine 46 and 179 $\mu$mol/L, respectively.

3.3. Molecular Aspects

The diagnosis of DHP can only be confirmed by analysis of the enzyme activity in liver, because the enzyme is not expressed in other more accessible tissues. The enzyme