Tyrosinaemia Type I – an Update

E. A. Kvittingen

Institute of Clinical Biochemistry, Rikshospitalet, 0027 Oslo 1, Norway

Summary: Tyrosinaemia type I is a recessively inherited disorder caused by a deficiency of fumarylacetoacetase (FAH), the last enzyme in tyrosine degradation. The presumed toxic agents are fumaryl- and maleylacetoacetate which are converted to succinylacetone (SA), a metabolite found in increased amounts in urine and plasma of the patients. The major clinical features are progressive liver damage and renal tubular defects with hypophosphataemic rickets. Renal tubular dysfunctions with secondary rickets may be lacking altogether, even in chronic patients. Hepatocellular carcinoma is a major cause of death in the chronic form. Diagnosis of the disorder is made by assay of SA in urine and serum and by determination of FAH in lymphocytes or fibroblasts. Prenatal diagnosis is performed by SA assay in amniotic fluid supernatant and FAH analysis in cultured amniotic fluid cells or chorionic villus material. Presence of a 'pseudodeficiency' gene for FAH prevents prenatal diagnosis by enzyme analysis in some families, and this gene also precludes identification of heterozygotes outside tyrosinaemia families. Immunoblot analyses show that acute patients and some chronic patients lack immunoreactive FAH protein. cDNA probes for FAH have been developed and several polymorphisms related to the FAH gene have been reported, which may allow prenatal diagnosis in families with complex genotypes. The gene for FAH has been mapped to chromosome 15 q23-q25. Liver transplantation is the ultimate treatment; most patients continue to excrete SA in urine after liver transplantation and therefore there is a possibility of kidney disease after transplantation.

The hallmarks of tyrosinaemia type I, elevated blood tyrosine, liver cirrhosis and renal tubular defects, are found in a number of liver diseases in childhood. Before the identification of succinylacetone (SA), no specific laboratory parameters were associated with tyrosinaemia, and a number of patients have presumably been erroneously diagnosed as having tyrosinaemia type I. The discovery of SA in tyrosinaemia patients and the suggestion that fumarylacetoacetase (FAH) was the primary defect in tyrosinaemia was a breakthrough in the understanding of the disorder (Lindblad et al., 1977). Deficiency of FAH in tyrosinaemia patients was soon confirmed by several groups.

The essential biochemistry of tyrosinaemia is illustrated in Figure 1. A deficiency of FAH leads to accumulation of fumaryl- and possibly maleylacetoacetate, which are presumed to be converted to SA by reduction and decarboxylation. An important
feature of SA is the strong inhibitory effect on the enzyme $\delta$-aminolevulinate dehydratase ($\delta$-ALA DH), which explains the elevated levels of $\delta$-ALA found in tyrosinaemia patients. Fumarylacetoacetate also inhibits $\delta$-ALA DH and this compound furthermore inhibits adenosylmethionine synthase, which may explain the elevation of methionine found in many patients (Berger et al., 1983). Tyrosinaemia patients have low levels of $p$-hydroxy-phenylpyruvate dioxygenase in liver tissue resulting in hypertyrosinaemia and increased excretion of phenolic acids. Fumarylacetoacetate and SA have not been found to inhibit the dioxygenase directly (Berger et al., 1983). It is still plausible that this enzyme is depressed through some mechanisms secondary to the primary block at the FAH level.

The disorder occurs worldwide with the highest frequency in Quebec, Canada, where in some regions 1 child in 700 is born with the disease (Goldsmith and Laberge, 1989).

\[ \text{phenylalanine} \]
\[ \text{TYROSINE} \]
\[ \text{p-OH-phenylpyruvate} \quad \text{p-OH-phenyllactate} \]
\[ \text{homogentisate} \]
\[ \text{maleylacetoacetate} \]
\[ \text{succinylacetoacetate} \quad \text{fumarylacetoacetate} \]
\[ \text{succinylacetone} \quad \text{FAH} \]
\[ \text{fumarate + acetoacetocetate} \]
\[ \text{\(\delta\)-aminolevulinate} \quad \text{phorphobilinogen} \]

\[ \text{Figure 1} \] The primary enzyme defect in tyrosinaemia type I is at the fumarylacetoacetase (FAH) step of tyrosine degradation. Due to the enzyme block fumaryl- and possibly maleylacetoacetate accumulate, being reduced and decarboxylated to succinylacetone, a potent inhibitor of the enzyme $\delta$-aminolevulinate dehydratase (2). This enzyme is also inhibited by fumarylacetoacetate which furthermore inhibits adenosylmethionine synthase (1). Fumarylacetoacetate and succinylacetone have not been shown to directly inhibit $p$-hydroxy-phenylpyruvate dioxygenase (3), which has low activity in liver tissue from tyrosinaemia patients, but presumably the enzyme is depressed due to some mechanisms secondary to the primary defect.

\[ J. \text{Inher. Metab. Dis.} \text{ 14 (1991)} \]