Tyrosinaemia — treatment and outcome

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Summary: Tyrosinaemia type I is, untreated, a fatal disease: in the acute form from liver failure, in the chronic form often from hepatocellular carcinoma. Acute neurological crisis is also a cause of death. Traditionally the treatment has been with diet, but for a decade liver transplantation has been the ultimate treatment. The continuous production of the pathological metabolites in the kidneys after transplantation appears to be without significance. Introduction of the enzyme inhibitor NTBC in the treatment of tyrosinaemia has reduced the need for liver transplants. Neonatal screening may be justified as efficient treatment has become available. The complex phenotype of lethal albino mice, with severe alterations in gene expression, has been shown to be caused by fumarylacetoacetase deficiency. Prolonged hypoglycaemia in otherwise adequately treated tyrosinaemia patients may result from depressed expression of genes coding for enzymes in gluconeogenesis, as seen in the mouse model. Self-induced genetic correction in liver tissue that occurs in many tyrosinaemia patients may reduce the risk of liver failure in some patients.

Tyrosinaemia type I is a classical inborn error of metabolism. The clinical and biochemical features of the disorder, as well as the treatment strategies, illustrate many characteristic aspects of inborn errors of metabolism.

The primary defect of tyrosinaemia is in fumarylacetoacetase (FAH), the last enzyme of tyrosine degradation. Owing to the enzyme block the alkylating metabolites fumaryl- and maleylacetoacetate accumulate and are presumed to cause the liver and kidney damage of tyrosinaemia. The primary metabolites are converted to succinylacetone, which is found in increased amounts in body fluids of the patients. Inhibition of haem synthesis by succinylacetone (and possibly fumarylacetoacetate) is presumed to be the basis of the life-threatening porphyria-like neurological crises in tyrosinaemia.

Tyrosinaemia patients may die from liver failure in infancy or show a protracted course resulting in development of hepatocellular carcinoma.

The workshop on tyrosinaemia at the 1994 SSIEM meeting contained overviews of neonatal screening for tyrosinaemia, risk assessment, experiences with liver transplantation, discussion of unexpected prolonged hypoglycaemia, the extent of the self-induced genetic correction in liver tissue, and, as the main lecture, an update of the results from the NTBC study supported by a report of NTBC treatment for neurological crisis in tyrosinaemia. The main NTBC study is separately reported elsewhere in this journal.
DELAYED CORRECTION OF HYPOGLYCAEMIA ON ADEQUATE TREATMENT — A REFLECTION OF PATHOGENETIC FACTORS?

Bergman and colleagues (1994) reported a patient who was treated from 3 months of age with protein restriction and NTBC, in addition to supportive measures. Despite adequate clinical response, normalization of liver function tests and electrolytes, fasting hypoglycaemia lasted for several months. Fasting tolerance gradually improved to 16h at age 9 months.

Recently the phenotype of a lethal albino mouse with a 3.8 Mb deletion of chromosome 7 was shown to be due to lack of FAH mapping within the deletion (Kelsey et al 1993; Grompe et al 1993). The lethal albino mice die within hours after birth, presumably from hypoglycaemia. The liver shows a widespread derangement of gene expression; mRNA of many proteins, among these importance enzymes in gluconeogenesis, such as glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, is severely depressed. The complex phenotype of lethal albino mice is completely corrected in deletion-homozygous mice expressing transgenic FAH (Kelsey et al 1993). The link between the tyrosine metabolites and the deranged gene expression is obscure and presumably complex. The correction of the glucose homeostasis in mice rescued by FAH transgenes is, however, correlated to the level of FAH expression, presumably reflecting the metabolite level (Kelsey et al 1993). Although not yet shown, the molecular effects of FAH deficiency in humans may, at least in some respects, compare to the mouse model. Possibly a delayed correction of glucose homeostasis in otherwise adequately treated tyrosinaemia patients may reflect a protracted effect on development or expression of certain genes, perhaps exaggerated by a persistent low level of the alkylating metabolites.

RISK ASSESSMENT AND LIVER TRANSPLANTATION VERSUS NTBC TREATMENT

Van Spronsen and colleagues (1994) evaluated 108 tyrosinaemia cases with regard to outcome in relation to symptoms and age of presentation. Their study indicates that age at presentation rather than symptoms predicts the outcome, and the presenting age should be the main factor on which treatment strategy is based. The study further confirmed that porphyria-like crisis, in addition to liver failure and hepatocellular carcinoma, is a common cause of death (10%). Liver transplantation in tyrosinaemia was discussed by Wijburg and colleagues (1994). In Groningen 9 patients have been transplanted at mean age 2 years (range 4 months to 4 years), with 100% survival and only one retransplantation. Similar results were reported by Perez-Cerda and colleagues (1994); 8 of 9 Spanish patients transplanted at mean age 2.3 years (range 7 months to 4 years) survived.

The Groningen group also reported the follow-up of kidney function after retransplantation, which is important. As the genetic defect is retained in the kidneys after liver transplantation and the patients continue to excrete succinylacetone presumably produced in the kidneys, deterioration of kidney function after liver transplantation is possible. The Groningen study did not indicate a deterioration of renal function, which could not be attributed to the cyclosporin medication in their 6-year follow-up. All the patients had normal tubular function assessed by \( \beta_2 \)-microglobulin and lysozyme clearance. Results from the lethal albino mice expressing transgenic FAH only in the liver, with no detectable