Renal Failure in Adult Patients with Hereditary Tyrosinaemia Type I

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Summary: An adult patient with hereditary tyrosinaemia type I who developed renal failure is reported. She received a renal transplant at the age of 23 years. In childhood her kidney disease was dominated by multiple tubular defects with resulting hypophosphataemic rickets. Metabolic acidosis was the most prominent feature in the years preceding the transplantation. Her kidneys were contracted to 40 g. The major morphological finding was that of a tubulointerstitial nephropathy. Liver biopsies taken at the ages of 5.5 and 23 years showed cirrhotic changes. Crystalloid inclusions in the liver mitochondriae were a prominent finding on electron microscopy. Fumarylacetoacetase was deficient in liver, kidneys, fibroblasts and lymphocytes. The typical biochemical parameters of tyrosinaemia, succinylacetone, p-hydroxyphenyllactate, p-hydroxyphenylpyruvate and serum tyrosine were only slightly elevated. A brief history of a second adult tyrosinaemia patient with decreasing renal function is also given.

INTRODUCTION

Hereditary tyrosinaemia type I (McKusick 27670) is due to a deficiency of fumarylacetoacetase (FAH) (EC 3.7.1.2). The enzyme defect results in accumulation of the metabolites maleyl- and fumarylacetoacetate which are converted to succinylacetone (SA), present in increased quantities in serum and urine of tyrosinaemia patients. The disorder occurs in acute and chronic forms. In the acute form the patients die of liver failure in early infancy. The chronic form is dominated by renal tubular defects with secondary hypophosphataemic rickets and development of liver cirrhosis. Hepatocellular carcinoma is frequently encountered (Weinberg et al., 1976). Although the renal tubular defects in tyrosinaemia may be secondary to the liver disease, production of toxic metabolites does occur in the kidneys and these metabolites are potentially toxic to the kidney cells (Kvittingen et al., 1986). Renal failure has not

MS received 20.3.90 Accepted 3.8.90
previously been reported in tyrosinaemia. We now report an adult Norwegian patient who developed renal failure and received a kidney transplant when 23 years old. She had very low levels of the typical tyrosinaemia metabolites, possibly indicating a variant form of tyrosinaemia. We also report another tyrosinaemia patient who had a decreasing glomerular filtration rate before she died at 21 years of age.

METHODS
Succinylacetone in serum and urine was determined by the \( \delta \)-aminolevulinate dehydratase inhibition assay described by Grenier and colleagues (1982) and/or by stable isotope dilution mass spectrometry (Jakobs et al., 1986). Authentic succinylacetone was purchased from US Biochemical Corporation (Cleveland, OH 44122). Erythrocyte \( \delta \)-ALA DH activity (blood collected in heparin) was determined by the method of Collier (1971) and \( p \)-hydroxyphenyllactate and \( p \)-hydroxyphenylpyruvate were quantitated according to the method of Gentz and colleagues (1969) with slight modifications as described previously (Kvittingen et al., 1986). FAH activity in lymphocytes, fibroblasts, liver and kidney tissue was assayed essentially as reported previously (Kvittingen et al., 1983), but the substrate (fumarylacetoacetate) concentration in the assay was reduced to 20 \( \mu \)mol/L and the liver enzyme preparation was gel filtered through a Sephadex G-25 (fine grade) column before enzyme analysis. All other analytical results were obtained using standard clinical chemistry methods.

Tissue specimens prepared for light microscopy (LM) were fixed in 4% buffered formaldehyde. The material prepared for transmission electron microscopy (TEM) was fixed in 2% buffered glutaraldehyde (pH 7.2) embedded in Epon 812, and was examined in a Jeol 100 B electron microscope.

CASE HISTORIES

AH, female, born 1962: She is the fourth child of a family of ten. All siblings are healthy and the parents are unrelated. The patient was first admitted to hospital at the age of 18 months due to a sideropenic anaemia, presumably of nutritional aetiology. In addition there were signs of rickets and she was given vitamin D supplementation. The patient was readmitted to hospital in 1968 with severe progressive rickets. She had multiple renal tubular defects, elevation of serum tyrosine and increased urinary excretion of \( p \)-hydroxyphenyllactate and \( p \)-hydroxyphenylpyruvate. Hereditary tyrosinaemia was suspected and an open liver biopsy was performed which revealed cirrhotic changes. A low tyrosine/phenylalanine diet was started at 5.5 years of age but the diet was inefficiently followed and was discontinued altogether after about two years.

Her renal function deteriorated progressively from the age of 10 years. At the age of 15 years her serum creatinine value was 200 \( \mu \)mol/L. She received treatment for lower urinary tract infections on several occasions but she never had episodes of acute pyelonephritis. Proximal renal tubular dysfunction, with resulting rickets, was severe all her life. The major problem during the years preceding the transplantation