Outcome in tyrosinaemia type II

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Abstract

Tyrosinaemia type II was diagnosed in a boy with failure to thrive and in his sister on neonatal screening. On diet the outcome, at 12 and 10 years respectively, has been excellent in respect of oculocutaneous sequelae, growth, and psychomotor development, contrasting with the generally unfavourable outcome in most reported cases.

Oculocutaneous tyrosinaemia (first described as the Richner-Hanhart syndrome) and now designated tyrosinaemia type II is due to deficiency of hepatic cytosolic tyrosine aminotransferase. The gene defect has recently been localised to chromosome 16. Clinically there is a variable combination of hyperkeratotic skin lesions, keratoconjunctivitis, and mental retardation.¹

This report documents clinical and biochemical findings in two further cases under long term follow up, in whom serious sequelae appear to have been avoided by early institution of a low tyrosine diet.

Case reports

DIAGNOSIS

The index case (case 1) was the first child of unrelated Scottish parents, male, born at term, with a birth weight of 3700 g. At 3 months of age, after difficulties in breast feeding, he was changed to formula feeds. His progress from 3 to 5 months was characterised by slow feeding, vomiting, irritability, drowsiness, and deterioration in weight from the 50th to the 3rd centile. A plasma tyrosine concentration of 1300 $\mu\text{mol/l}$ (reference range 30–100) and an increased urinary excretion of tyrosine were the only abnormalities found. At 8 months of age a low tyrosine diet was instituted and within days the infant improved.

The second child (case 2) of the same parents was female, full term, and weighed 4000 g. On breast feeding at 4 days of age plasma tyrosine concentration was 705 $\mu\text{mol/l}$, rising to 1340 $\mu\text{mol/l}$ at 18 days, and a low tyrosine diet was commenced.

At presentation both children had normal liver function tests, normal plasma methionine, and no generalised aminoaciduria. On restricted diet with plasma tyrosine concentrations of 400–800 $\mu\text{mol/l}$ both children had abnormal urinary excretion of p-hydroxyphenyllactic, p-hydroxyphenylpyruvic, and p-hydroxyphenylacetic acids. N-acetyl tyrosine was identified by gas chromatography-mass spectrometry. Succinyl acetone and delta amino laevulinic acid excretion in urine were within normal limits.

Ascorbic acid, used in transient neonatal tyrosinaemia,¹ was tried in a dose of 200 mg

three times a day on case 1 at the age of 2 years with no effect on plasma tyrosine. Pyridoxine, the cofactor of tyrosine aminotransferase,¹ in a dose of 50 mg three times a day, was also ineffective.

DIET

The protein substitute has been a low phenylalanine/tyrosine free amino acid mixture (Code 114, Scientific Hospital Supplies) supplemented with Ketovite liquid and tablets (Paines and Byrne) and metabolic mineral mixture (Scientific Hospital Supplies). Protein was given as 1g exchanges at mealtimes. With age the number of exchanges has gradually increased from four to 12 and has been titrated against the plasma tyrosine response. When the diet was introduced plasma phenylalanine concentration fell to <25 $\mu\text{mol/l}$. Increasing the number of protein exchanges resulted in plasma tyrosine concentrations of greater than 1000 $\mu\text{mol/l}$. Acceptable phenylalanine concentration without undue hypertyrosinaemia was achieved by giving daily supplements of 500–800 mg phenylalanine. Protein free or low protein foods have been allowed freely.

PROGRESS

In the early years both children had repeated episodes of photophobia with eye pain, redness and watering, often triggered by intercurrent infection and usually with plasma tyrosine concentrations in excess of 800 $\mu\text{mol/l}$. During acute episodes ophthalmological examination showed that both children had bilateral keratopathy resembling dendritic ulceration due to herpes simplex infection. The number of protein exchanges in the diet was cut by up to 50% at the earliest sign of eye discomfort.

Biochemical monitoring of tyrosine concentrations (figure) shows fluctuating control in the range 300–800 $\mu\text{mol/l}$ with occasional peaks of up to 1000 $\mu\text{mol/l}$.

At 12 years case 1 was on the 50th centile for height and weight. His eye symptoms had become less frequent and less severe with no overall change in plasma tyrosine concentrations. On psychometric testing using the Wechsler intelligence scale for children, standardised for Scotland (WISC-RS), he showed overall average ability scoring 98 (45th centile) on the full scale, with a discrepancy (significant at the 5% level) between the verbal scale score 85 (16th centile) and the performance scale score 115 (84th centile).

At 10 years case 2 was on the 75th centile in height and the 97th centile in weight. Bouts of mild conjunctivitis continued to occur every three to six months and responded to temporary further reduction in tyrosine intake. She was

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Plasma tyrosine concentrations when diet was controlled; d and p indicate introduction of diet and phenylalanine supplementation respectively.

within the average range of ability in the WISC-RS scoring 92 (27th centile) on the full scale, with a verbal scale score of 96 (40th centile) and a performance scale score of 89 (23rd centile).

Both children have normal visual acuity, no significant refractive error, and only minimal scarring from the previous pseudodendritic ulcers.

They are making normal progress in mainstream education at a level consistent with parental ability. The father is self employed as a graphic designer and the mother is a housewife and part time secretary.

Discussion

The clinical and biochemical findings are consistent with tyrosinaemia type II. Diagnostic liver biopsy was not justified. Attempts to identify a point mutation at the tyrosine aminotransferase locus² in this family are currently being undertaken (G Scherer, personal communication).

Buist *et al* estimated that about 80% of cases have skin lesions, 75% eye disease, and 60% intellectual retardation.³ Age at presentation varied from the newborn to adult. Our index

case was diagnosed as the result of investigation of failure to thrive in infancy at a time when he had none of the characteristic clinical features.

Typically, bullous cutaneous lesions develop on the extremities and crusting leads to hyperkeratotic patches. These painful lesions clear up rapidly on controlling the hypertyrosinaemia. Our cases have never developed any cutaneous stigmata.

Eye lesions are extremely distressing with photophobia, intense burning pain, inflamed conjunctivae, and herpetic-like corneal ulceration. Residual damage can occur with dense corneal scarring, neovascularisation, and visual impairment. In our patients on diet episodes of keratoconjunctivitis occurred at times of intercurrent infection and usually, but not invariably, with plasma tyrosine concentrations of >800 $\mu\text{mol/l}$. Symptoms responded rapidly to further temporary restriction of tyrosine intake and no significant corneal damage has resulted.

The mechanism of brain damage is not known. A range of neurological outcome is reported from normality, through defects in fine coordination and language skills, to microcephaly, self mutilation, and gross retardation. The incidence of mental defect may partly reflect ascertainment bias in the selection of cases studied. Maternal tyrosinaemia type II has been associated with normal³ and microcephalic⁴ progeny. Our patients at follow up show overall average ability in psychometric assessment.

Genetic heterogeneity in tyrosinaemia type II may be responsible for some of the variation in manifestations and prognosis, but in our cases there is a reasonable presumption that long term control of hypertyrosinaemia was responsible, at least in part, for the satisfactory outcome. Goldsmith and Laberge have emphasised the lack of information on the optimal timing of diet and the degree of control needed to achieve the best results.¹

Along with two cases reported by Halvorsen,⁵ our patients show that with early detection, effective diet, and careful biochemical surveillance, this form of tyrosinaemia can have a good prognosis.

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