Tyrosinaemia type II: an easily diagnosed metabolic disorder with a rewarding therapeutic response

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SUMMARY We retrospectively reviewed clinical and biochemical data of four patients diagnosed with tyrosinaemia type II. Diagnosis was established by high plasma tyrosine and normal plasma phenylalanine levels using plasma high-pressure liquid chromatography and tandem mass spectrometry. All patients were mildly mentally retarded and had painful non-pruritic and hyperkeratotic plaques on the soles and palms. There were no ophthalmic symptoms. The patients dramatically responded clinically and biochemically to a diet restricted in tyrosine and phenylalanine.

Introduction

Tyrosinaemia type II (oculocutaneous tyrosinaemia) is an autosomal recessive disorder affecting the eyes, skin and central nervous system. It is due to a deficiency of tyrosine aminotransferase, an enzyme involved in the metabolism of tyrosine [*1*]. The majority of reported cases are found among Italian, German, French, Swedish, Spanish, Norwegian, American, Canadian, Australian, and Turkish Ashkenazi Jewish populations [*2–5*], with almost half of these coming from Italy [*6*]. Our files contain four patients under clinical follow-up, with confirmed biochemical diagnosis for tyrosinaemia type II.

We aimed to increase awareness of the medical community (particularly in Saudi Arabia) of the clinical progression of this disease, and of the rewarding clinical response and prevention of complications through dietary therapy. A further aim was to enhance the ability of the medical community to make a diagnosis of tyrosinaemia type II using tandem mass spectrometry (MS/MS).

Patients and methods

The clinical and biochemical data of four tyrosinaemia type II patients were reviewed retrospectively. They were diagnosed by the Inborn Errors of Metabolism Section at King Faisal Specialist Hospital and Research Centre (KFSH&RC), a tertiary referral centre for metabolic diseases in Saudi Arabia.

All patients had typical clinical presentation, mild mental retardation and progressive painful non-pruritic and hyperkeratotic plaques on the soles and palms. An experienced neuropsychiatrist assessed their in-

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telligence quotient. Eye examination was performed by an ophthalmologist. Diagnosis of the disease was established by the findings of high plasma tyrosine and normal plasma phenylalanine levels using plasma high-pressure liquid chromatography and MS/MS [7].

Results

The four patients diagnosed as tyrosinaemia type II at KFSH&RC were all from the same tribe from the western region of Saudi Arabia. They included three women (age range: 25–30 years) and a boy (age 7 years). They were all mildly mentally retarded and had painful non-pruritic and hyperkeratotic plaques on the soles and palms. No eye signs or symptoms could be demonstrated.

Treatment consists of dietary restriction of tyrosine and phenylalanine to a degree sufficient to achieve a resolution of the clinical symptoms. Patients were compliant with the dietary therapy, and 6 weeks later the lesions on the soles and palms were completely healed. Before the initiation of therapy, the tyrosine values were above 1000 mmol/L (normal 30–90 mmol/L) in all the patients. A 15%–20% drop in tyrosine levels followed dietary therapy. This drop was accompanied by a parallel improvement in the clinical status of the patients.

Discussion

Tyrosinaemia type II (oculocutaneous tyrosinaemia) is an autosomal recessive disorder resulting from a deficiency in tyrosine aminotransferase (TAT). Skin, eye and neurological signs are the cardinal features of this disease [3]. Skin manifestation usually begins after the first year of life, but may begin as early as 1 month of age. Patients generally suffer from progressive, painful, non-pruritic and hyperkeratotic plaques on the soles and palms. Hypothenar and thenar eminences are areas of predilection. Hyperhidrosis may be associated with hyperkeratosis [8]. Leucokeratosis of the tongue has also been reported [9]. The pain in the soles may be severe enough to prevent walking.

Eye symptoms include photophobia, redness, lachrymation and pain. An eye examination usually reveals conjunctivitis and neovascularization. Central dendritic corneal erosions are also prevalent, which, if not treated, may progress to corneal opacities, cornea plana, stigmatism, strabismus, and glaucoma, and hence decreased visual acuity. In our patients, the lack of eye lesions is not unexpected since some patients may only have their first ophthalmic manifestation in their forties [5]. Moreover, the manifestations may be confined to the skin [4,10,11] as in our patients, or to the eyes [12–14].

Mental retardation may be variable, occurring in less than 50% of patients [2,6,15]. There is no relationship between age of diagnosis and mental retardation. However, the degree of mental retardation may be related to higher values of plasma tyrosine [6].

The diagnosis can easily be established by high plasma levels of tyrosine, with other plasma amino acid levels being normal [8,15]. Tyrosine is the only amino acid increased in the urine of these patients. TAT activity is reduced or absent in the supernatant of liver homogenates [16]. It is rarely necessary to perform a liver biopsy for TAT assay. Preclinical detection and treatment

should be possible in areas where neonatal screening for hypertyrosinaemia is in place.

Treatment consists of dietary restriction of tyrosine and phenylalanine to a degree sufficient to achieve a resolution of the clinical symptoms. There is no consensus about the optimal blood level of tyrosine, or at what age the diet should be started to prevent neurological impairment. A blood level of tyrosine of 600 µmol/L is suggested to be a reasonable goal.

Tyrosinaemia type II is a very labile disease. From our local experience at KFH, we have observed that a tyrosine level of 1000 mmol/L is the "biochemical threshold" above which the clinical manifestations start to appear. This probably explains in part why these patients dramatically improved when the tyrosine level was kept below this figure.

Low tyrosine and phenylalanine formulas are commercially available, to optimize growth and meet the nutritional requirements for these patients. The eye and skin lesions usually resolve after a few weeks of dietary therapy, but recur if the diet is stopped [*17,18*]. Since there is risk of mental retardation in TAT-deficient patients, careful dietary control of maternal plasma tyrosine levels should be considered during pregnancy [*3*]. Treatment with systemic steroids should be avoided, as the disease can worsen with this therapy [*19*].

References

1. Goldsmith LA. Tyrosinemia with plantar and palmar keratosis and keratitis. *Journal of pediatrics*, 1973, 83:798–805.
2. Goldsmith LA. Tyrosinemia and related disorders. In: Stanbury JB et al., eds. *The metabolic basis of inherited disease*, 5th ed. New York, McGraw–Hill, 1983:287–99.
3. Mitchell GA et al. In: Scriver CR et al, eds. *The metabolic and molecular bases of inherited disease*, 7th ed. New York, McGraw–Hill, 1995:1077–106.
4. Colditz PB et al. Tyrosinaemia II. *Medical journal of Australia*, 1984, 141:244–5.
5. Chitayat D et al. Hereditary tyrosinaemia type II in a consanguineous Ashkenazi Jewish family: intrafamilial variation in phenotype; absence of parental phenotype effects on the fetus. *Journal of inherited metabolic disease*, 1992, 15:198–203.
6. Fois A et al. Presentation of the data of the Italian registry for oculocutaneous tyrosinaemia. *Journal of inherited metabolic disease*, 1986, 9 (suppl.):262–3.
7. Rashed MS et al. Diagnosis of inborn errors of metabolism from blood spots by acylcarnitines and amino acids profiling using automated electrospray tandem mass spectrometry. *Pediatric research*, 1995, 38:324–31.
8. Hunziker N. Richner–Hanhart syndrome and tyrosinemia type II. *Dermatologica*, 1980, 160:180–9.
9. Larregue M et al. Syndrôme de Richner-Hanhart ou tyrosinose oculo-cutanée. A propos d'un cas. [Richner–Hanhart's syndrome or oculocutaneous tyrosinosis.] *Annales de dermatologie et de venereologie*, 1979, 106:53–62.
10. Rehak A et al. Richner–Hanhart syndrome (tyrosinaemia-II) (report of four

cases without ocular involvement). *British journal of dermatology*, 1981, 104:469–75.

11. Lestringant GC. Tyrosinemia type II with incomplete Richner–Hanhart's syndrome. *International journal of dermatology*, 1988, 27:43–4.

12. Gramet C, Lods F. Syndrôme de Richner-Hanart sans atteinte cutanée. [Richner–Hanart syndrome without skin involvement]. *Bulletin des Societes d' Ophtalmologie de France*, 1984, 84:129–30.

13. Heidemann DG et al. Early diagnosis of tyrosinemia type II. *American journal of ophthalmology*, 1989, 107:559–60.

14. Roussat B et al. A propos de deux cas de tyrosinose de type II (syndrôme de Richner- Hanhart). [2 cases of type II tyrosinosis (Richner–Hanhart syndrome)]. *Bulletin des Societes d' Ophtalmologie de France*, 1988, 88:751–7.

15. Balato N et al. Tyrosinemia type II in two cases previously reported as Richner–Hanhart syndrome. *Dermatologica*. 1986, 173:66–74.

16. Lemonnier F et al. Tyrosine aminotransferase isoenzyme deficiency. *Journal of pediatrics*, 1979, 94:931–2.

17. Al-Essa M et al. *An atlas of common metabolic and genetic diseases*. Riyadh, Saudi Arabia, King Faisal Specialist Hospital and Research Centre, 1997:111.

18. Al-Essa M and Ozand PT. *Manual of metabolic diseases*. Riyadh, Saudi Arabia. King Faisal Specialist Hospital and Research Centre, 1998:115.

19. Sayar RB et al. Clinical picture and problems of keratoplasty in Richner–Hanhart syndrome (tyrosinemia type II). *Ophthalmologica*, 1988, 197:1–6.