

TYROSINEMIA TYPE II: REPORT OF THE FIRST FOUR CASES IN SAUDI ARABIA

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Tyrosinemia type II (oculocutaneous tyrosinemia) is an autosomal recessive disorder due to deficiency of tyrosine aminotransferase, an enzyme involved in the metabolism of tyrosine.¹ More than 50 cases have been reported to date. Most of the patients are Italian, German, French, Swedish, Spanish, Norwegian, American, Canadian, Australian, and Turkish Ashkenazi Jews.²⁻⁵ Almost half of the patients that have been reported are from Italy.⁶ Our files contain four patients under clinical follow-up with confirmed biochemical diagnosis for tyrosinemia type II.

The aim of this study is to increase the awareness of the scientific and medical community, particularly in the Kingdom of Saudi Arabia, of the clinical progression of this disease, the ability to make a diagnosis through tandem mass spectrometry (MS/MS) and the rewarding clinical response and prevention of complications by use of dietary therapy.

Patients and Methods

The clinical and biochemical data of four tyrosinemia 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 center for metabolic diseases in the Kingdom of Saudi Arabia. All of the patients had the typical clinical presentation, with mild mental retardation, progressive painful nonpruritic and hyperkeratotic plaques on the soles and palms. An experienced physician assessed their IQ, and the eye examination was performed by an ophthalmologist. The diagnosis of the disease was established by the findings of high-plasma tyrosine and normal plasma phenylalanine levels through plasma high-pressure liquid chromatography (HPLC) and tandem mass spectrometry (MS/MS) (Figure 1).⁷

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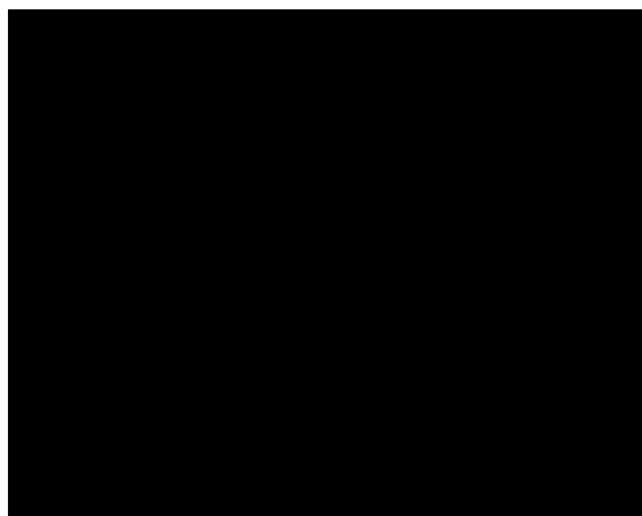


FIGURE 1. (Top) Electrospray tandem mass spectrometry (ESI-MS/MS) analysis of blood spot from a patient with tyrosinemia type II, showing a high tyrosine level. (Bottom) ESI-MS/MS analysis of blood spot from a control.

Results

The tyrosinemia type II patients reviewed at KFSH&RC were from the Western part of Saudi Arabia, and came from the same tribe. They included three women aged between 25 and 30 years, and a boy of seven years. They were all mildly mentally retarded and had painful nonpruritic and hyperkeratotic plaques on the soles and palms. No eye signs or symptoms could be demonstrated. The treatment consisted of dietary restriction of tyrosine and phenylalanine to a degree sufficient to achieve a resolution of the clinical symptoms. The patients were compliant with the dietary therapy, and six weeks later, the hyperkeratotic plaques on the soles and palms had completely healed (Figure 2). Before the initiation of therapy, the tyrosine values were above 1000 $\mu\text{mol/L}$ (normal 30-90 $\mu\text{mol/L}$) in all of the patients. There was a drop of between 15%-20% in the tyrosine levels after the dietary therapy (Figure 3). This drop was accompanied by a parallel improvement in the clinical status of the patients.

Discussion

Tyrosinemia type II (oculocutaneous tyrosinemia) is an autosomal recessive disorder due to deficiency of tyrosine aminotransferase (TAT). Skin, eye, and neurological signs are the cardinal features of this disease. Richner in 1938⁸ and Hanhart in 1947⁹ independently described this clinical syndrome.

Skin manifestation of the disease usually begins after the first year of life, but may begin as early as one month of age. The patients usually suffer from progressive painful, nonpruritic, and hyperkeratotic plaques on the soles and palms. Hypothenar and thenar eminences are areas of predilection. Hyperhidrosis may be associated with hyperkeratosis.¹⁰ Leukokeratosis of the tongue has been reported.¹¹ The pain in the soles may be severe enough to prevent ambulation.

The eye symptoms include photophobia, redness, lacrimation and pain. An eye examination usually reveals conjunctivitis and neovascularization. Also, central dendritic corneal erosions are prevalent. If the patient is not treated, these lesions may progress to corneal opacities, cornea plana, stigmatism, strabismus and glaucoma, and thus visual acuity decreases. In our patients (aged 7-30 years), the lack of eye lesions is not unexpected, since some patients may only have their first ophthalmic manifestation in their forties.⁵ Moreover, the presenting complaint and the manifestations may be confined only to the skin,^{4,12,13} as in our patients, or to the eyes.¹⁴⁻¹⁶

The mental retardation may be variable, and occurs in less than 50% of the patients.^{2,6,17} 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 In rare cases, convulsions, microcephaly⁶ and behavioral disorders¹⁸ have been reported. Their association with TAT deficiency is unclear. The diagnosis can easily be established by high plasma levels of tyrosine, with other plasma amino acid levels being normal.^{10,17} Tyrosine is the only amino acid increased in the urine of these patients. TAT activity is reduced or absent in supernatant of liver homogenates.^{19,20} 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 hyper-tyrosinemia is practiced. The 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 on the optimal blood level of tyrosine, or at what age the diet should be started to prevent neurologic impairment. A blood level of tyrosine of 600 $\mu\text{mol/L}$ is thought to be reasonable.

Restriction-fragment-length polymorphism has been applied for the human TAT gene,²¹ and seven pathogenic point mutations have been described.²²

Tyrosinemia type II is a very labile disease, and from our local experience at KFSH&RC, we have observed that

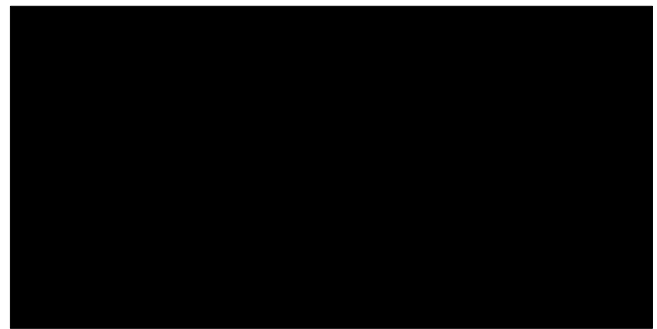


FIGURE 2A. A patient with tyrosinemia type II who suffered from painful progressive hyperkeratotic plaques before therapy.

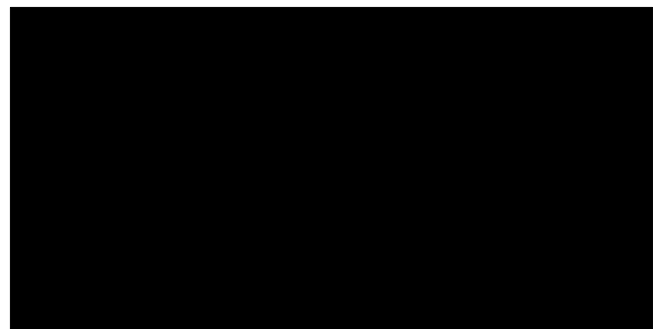


FIGURE 2B. The same patient after dietary treatment shows complete healing of the lesions six weeks later.

a tyrosine level of 1000 $\mu\text{mol/L}$ 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. Commercial low-tyrosine low-phenylalanine formulas are available to optimize growth and meet the nutritional requirements for these patients. The eye and skin lesions, as in our patients, usually resolve after a few weeks of dietary therapy, but recur if the diet is stopped. Oral retinoids can improve skin lesions without changing the tyrosine level.¹⁸ Since there is risk of mental retardation in TAT-deficient patients, careful dietary control of maternal plasma tyrosine level should be considered during pregnancy.²³ Treatment with systemic steroids should be avoided, as the disease can worsen with this therapy.²⁴

In a patient with painful and hyperkeratotic plaques on the soles and palms, the diagnosis of tyrosinemia type II should be suspected, and it can easily be confirmed by the high-plasma tyrosine level through blood tandem MS or amino acids profile. It is rarely necessary to perform a liver biopsy for the enzyme assay. Pre-clinical detection and treatment should be established, especially in areas where neonatal screening programs are practiced. Treatment of tyrosinemia type II is successful with dietary restriction of tyrosine and phenylalanine to a degree sufficient to achieve resolution of eye and skin symptoms. In order to optimize

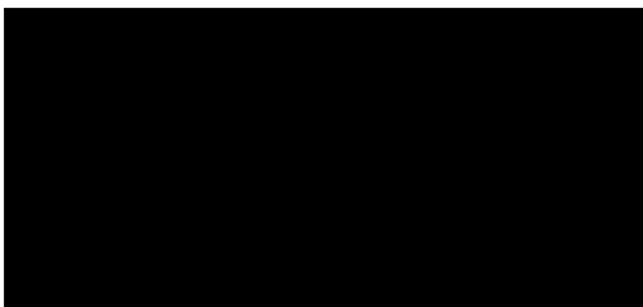


FIGURE 3. Tyrosine levels in the four patients before and after therapy.

growth and meet the nutritional requirements, commercial low-phenylalanine and low-tyrosine formulas are available for this purpose.

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