Clinical Brief

Tyrosinemia Type I : A Clinico-Laboratory Case Report

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Abstract. Progressive hepatocellular dysfunction in a neonate, resulting in elevated serum α-fetoprotein together with raised blood levels of tyrosine and methionine, a generalized amino aciduria and the absence of urinary δ-aminolevulinic acid and succinylacetone, suggests a diagnosis of tyrosinemia type Ib. Classical tyrosinemia type I arises from a deficiency of fumarylacetoacetate hydrolase while the variant tyrosinemia type Ib results from a deficiency of maleylacetoacetate isomerase.
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Tyrosinemia type I is a disease inherited in an autosomal recessive manner and manifests when the enzyme fumarylacetoacetate hydrolase (FAAH) is deficient.[1] It is a common disorder of tyrosine metabolism with over 30 different mutations identified in the FAAH gene.[2] It is found world-wide with a high prevalence in Quebec, Northern France and Scandinavia.[3] The disease presents as two extreme clinical phenotypes, acute (severe, early onset and death) and chronic (delayed onset and slow course).[4] Genetic heterogeneity does not however explain the clinical heterogeneity of the disease and it is postulated that epigenetic and other factors modify the phenotype of this disorder.

Tyrosinemia type I, a hepato-renal disease, with all 5 enzymes involved in tyrosine degradation found only in the liver and renal proximal tubules,[5] features elevated levels of tyrosine and its metabolites in blood and urine (Fig 1). High levels of tyrosine would appear unusual in a disorder where the enzyme deficiency is downstream in the catabolic pathway and result from a secondary inhibition of the early steps in tyrosine metabolism and not from the absence of FAAH.[5] FAAH deficiency also leads to the formation of blood and urinary succinylacetoacetate and succinylacetone, metabolites of the accumulating maleylacetoacetate.[1] Succinylacetoacetate and succinylacetone are inhibitors of d-aminolevulinic acid dehydratase, the first step in heme biosynthesis, which accounts for the neurologic crisis resembling acute intermittent porphyria frequently seen in Tyrosinemia Type I.[6] Fumarylacetoacetate that accumulates in Tyrosinemia type I as a result of FAAH deficiency, is toxic to liver and kidney, leading to raised a-fetoprotein early in the disease.[1,5]

The laboratory diagnosis of Tyrosinemia type I is based on a tissue deficiency of fumarylacetoacetate hydrolase and / or presence of urinary succinylacetone.[5] However, typical laboratory findings of raised plasma α-fetoprotein, tyrosine, methionine, proline, alanine and increased urinary excretion of tyrosine and its metabolites, as well as methionine, proline, glycine, alanine and lysine are strongly indicative of the disorder.

Tyrosinemia type I has not been reported from India and a case is presented suggesting the disorder in a new born child based on the clinical description, serum amino acid profile and elevated α-fetoprotein levels.

CASE REPORT

Baby girl P, was admitted at 38 hours of age with a history of poor feeding and respiratory distress of 6 hours duration. She was the product of a consanguineous marriage and was born by assisted breech delivery at term with a weight of 2630 gm to a primigravida mother with no antenatal complications. She cried well at birth and there were no risk factors for sepsis. On admission the baby was tachypneic with a respiratory rate of 82 /min. The heart rate was 148/min and peripheral perfusion was poor. There were no dysmorphic markers and systemic examination was normal.

She was admitted with an initial differential diagnosis of pneumonia, septicemia or an inborn error of metabolism. She was started on IV fluids, IV antibiotics after blood culture and kept nil oral. Complete blood counts, blood sugar, serum calcium, electrolytes and chest X-ray were normal. Arterial blood gas showed severe metabolic acidosis with an anion gap of 28, which was corrected with intravenous infusion of soda bicarbonate. Intravenous antibiotics were discontinued after 7 days when blood culture and CRP reports were found to be normal. On the 7th day, the baby was found to be icteric with hepatosplenomegaly and serum direct

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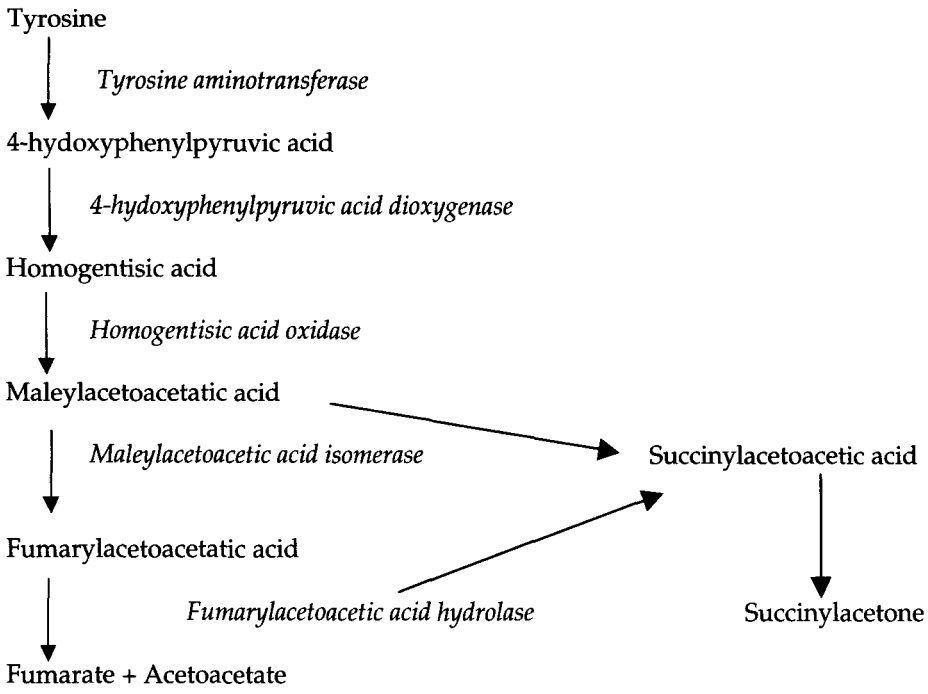

Fig 1. Tyrosine catabolism

hyperbilirubinemia (Table 1). The TORCH titers were negative, ultrasound of abdomen was normal, urine was negative for galactose, reducing substances and ketones. Plasma ammonia and serum lactate were mildly elevated and serum a-fetoprotein was >3300 IU/ml (normal < 5 IU/ml). Blood urea was normal.

Serum and urine were analyzed for amino acids by high performance liquid chromatography on a strong cation exchanger. Blood tyrosine (1160 uM) and glutamate (980 uM) were highly elevated and methionine, proline and alanine high. Generalized amino aciduria was noted with excessive excretion of tyrosine, proline, glycine, alanine and methinone (Table 2). Urinary organic acids detected on thin layer chromatography,[7] were of a catabolic state with glutaric acid, pyruvic acid, succinic acid and β-hydroxy butyric acid.

δ-aminolevulinic acid, estimated with Ehrlich's reagent, was not detected in the urine. The urine did not inhibit erythrocyte δ-aminolevulinic acid dehydrataseas, assayed as given by Grenier *et al*,[8] indicating an absence of succinylacetone.

After initial stabilization, feeds were started on the 8th day, along with alkali solution and therapeutic doses of Vitamin B_{12}, pyridoxine, riboflavin, thiamine and carnitine. Serial blood gas estimations were subsequently normal and she was discharged after 2 weeks. She was followed up till 5 months of age when she weighed 3000 gms and continued to be icteric with direct hyperbilirubinemia. She was then lost to follow up.

DISCUSSION

The differential diagnoses in a neonate with an inherited metabolic disease presenting as hepatocellular dysfunction in the newborn period would include galactosenia, tyrosinemia, a_1 anti trypsin deficiency, neonatal hemochromatosis and type IV glycogen storage disease. The absence of reducing sugars and galactose in the urine ruled out galactosemia. The markedly elevated serum α-fetoprotein level in this baby favours a diagnosis of tyrosinemia. Although raised a-fetoprotein can occur in liver disease, there are only a few conditions in which extremely high levels are seen. These include hepatoblastoma, neonatal hemochromatosis and resolving viral hepatitis. The ultra sound of the abdomen ruled out hepatoblastoma, viral titers were negative and neonatal hemochromatosis, which has a fulminant course, was unlikely as most neonates with this disorder die in the early weeks of life.

In this neonate, the blood amino acid profile of elevated tyrosine and methionine, a generalized amino aciduria with excessive excretion of tyrosine, methionine, proline and alanine, the absence of a specific organic aciduria and the elevated levels of α-fetoprotein, are suggestive of tyrosinemia type I. The very high blood levels of tyrosine and the progresive liver abnormality (Table 1) support an inborn error of metabolism rather than a transient hypertyrosinemia. High levels of methionine probably result from the inhibition of S-adenosylmethionine synthetase by the metabolites of tyrosine breakdown, fumarylacetoacetic acid, maleylacetoacetic acid, fumarylacetone and fumarylacetone glutathione.[9]

Liver, kidney and peripheral nerves are the main organs affected in tyrosinemia type 1. This can present as

Table 1. Serial Liver Function Tests of Baby P

Month	Bilirubin		Total Protein	Serum Albumin	SGOT	SGPT	Alkaline phosphatase
	Total (mg %)	Direct (mg %)	(g %)	(g%)	(U/L)	(U/L)	(U/L)
1st	17.1	13.2	4.3	2.9	88	55	343
2nd	19.8	15.9	4.1	2.9	159	69	673
4th	15.0	10.6	5.7	3.9	600	190	1620
Normal	0.2–1.0	0.12–0.5	5.1–7.3	3.8–5.4	15–60	13–45	25–125

Table 2. Amino Acid Levels in Serum and Urine of Baby P

Amino acid	SERUM μM		URINE μmoles/g creatinine	
	Normal* 0-30 days	Baby P	Normal* 0-30 days	Baby P
Taurine	74-216	310	1521-6922	3333
Aspartate	0-17	BD	78-172	BD
Serine	94-243	200	80-1096	2100
Glutamate	0-50	980	34-363	BD
Proline	107-117	1210	74-537	23667
Glycine	224-514	740	1423-7143	30000
Alanine	236-410	4200	403-715	17667
Valine	80-246	340	18-314	153
Methionine	9-41	115	15-71	420
Isoleucine	27-53	48	43-179	BD
Leucine	46-109	238	17-72	BD
Tyrosine	42-99	1160	27-97	2333
Phenylalanine	42-110	BD	39-156	BD
β-amino isobutyric acid	-	-	0-111	6067
Histidine	49-114	295	148-721	6333
Lysine	114-269	104	74-1282	3933
Tryptophan	17-71	ND	0-106	ND
Arginine	22-88	-	50-73	-

Courtery : BD-Below detection; ND - Not detected
Textbook of Pediatrics 14th Edition (Editor : WB Nelson)

hepatic failure in the first year of life, as seen in this child, or as cirrhosis in older children and young adults. Renal tubular dysfunction, with rickets as the principal clinical manifestation, or glomerular dysfunction can also occur in tyrosinemia type 1.[10] Neurologic crisis in the disorder manifests as two phases (a) an active period with painful paresthesias, autonomic signs like hypertension, tachycardia and progressive paralysis and (b) a period of recuperation. This is attributed to d-aminolevulinic acid toxicity, from an inhibition of δ-aminolevulinic acid dehydratase by succinylacetone, manifesting in a severe porphyria-like condition.[5] No neurologic crisis was noted during the 5 month follow-up of the child in this report, suggesting an absence of succinylacetone.

The inability to detect urinary δ-aminolevulinic acid and succinylacetone may indicate that the case is not a classical tyrosinemia type I of fumarylacetoacetate hydrolase deficiency. In the absence of succinylacetone, the amino acid profile especially of elevated methionine suggesting inhibition of S-adenosylmethionine synthetase and the high serum levels of α-fetoprotein that could arise from hepatotoxicity of maleylacetoacetate, may reflect a deficiency of maleylacetoacetate isomerase in the metabolism of tyrosine. These findings have been reported earlier in tyrosinemia type I and the variant termed tyrosinemia type Ib.[11] However no mutations have been detected in the maleylacetoacetate isomerase gene and hence the disorder has not been confirmed at the molecular level. Fumarylacetoacetate hydrolase metabolizes succinylacetoacetate, which may account for the inability to detect succinylacetone in the urine. A definite diagnosis of Tyrosinemia Type Ia or b can only be made with enzyme studies, by DNA linkage analysis or by direct mutation detection. This case report highlights the usefulness of serum and urine amino acid profiles in children with unexplained liver disease as a screen for tyrosinemia.

Treatment options now available for tyrosinemia are diet therapy, liver and kidney transplantation. A short to medium term treatment of choice is use of 2(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione (NTBC), a potent inhibitor of 4-hydroxyphenylpyruvic acid dioxygenase (Fig 1) preventing formation of toxic downstream metabolites.[5,12] Prenatal diagnosis of tyrosinemia is possible by assay of succinylacetone in amniotic fluid, and by assay of fumarylacetoacetate

hydrolase and molecular analysis in amniocytes or chorionic villi.

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In our special supplement—Book of Abstracts on 8th Asian & Oceanian Congress of Child Neurology the following corrections are to be made:

Corrigendum

In the abstract *Newborn Screening for Hypothyroidism – A Pilot Study* by Veena Kalra, Madhulika Kabra, Atul Ahuja, Suman Vashisht, Arvind Sailly, AK Dutta, Rajiv Aggarwal, AK Deorari, S. Gulati, NK Arora, *PK Chaturvedi appeared on page 17 in the **Plenary Lectures** section, the last misprinted name *NK Arora should be corrected as ***Anand Kumar**. The error is regretted.

Addendum

On page 164 in the abstract 31 of the 10th October 2004 **Poster Presentations** section, the name **K. Chauhan** should be included as given below.

31 Leigh's syndrome and Renal Tubular Acidosis – In Interesting Association
M. Das, H. Goyal, A. Bajpai, **K. Chauhan,** S. Gulati, S. Hari, T. Shah, M. Kabra, A. Bagga, V. Kalra