Clinical and Biochemical Spectrum of Tyrosinemia Type 1 and outcome in patients from India and Pakistan

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Introduction : HT1 is an autosomal recessive disorder caused by deficiency of fumarylacetoacetate hydrolase (FAH), the last enzyme of tyrosine catabolism. It is characterized by liver failure, renal tubular dysfunction, rickets and coagulopathy. Incidence of the disease in population worldwide is 1/100000 live births[3]. However incidence in India and Pakistan is not clearly known.

Objective : To review clinical spectrum of the disease at the time of diagnosis and outcome in developing countries like India and Pakistan with limited resources.

Material & Method : We investigated 31 patients with tyrosinemia visiting our clinic from Jan 2000 to Jan 2014. Of these 31 patients we diagnosed 25 patients and 6 were referred to us after initiation of the treatment. We analyzed their clinical details and following tests were performed to confirm diagnosis of HT1 : Plasma Tyrosine, Phenylalanine and Methionine levels by UHPLC, blood SA level, urine SA quantitation by GC/MS (SIM Method), PBG synthase enzyme activity, serum AFP level, liver function tests, Renal function tests and USG and MRI of abdomen was done for prognosis of liver malignancy.

Result : Out of total 31 cases, 25 cases that we diagnosed with HT1 were untreated. Amongst them 32% (8/25) were females and 68% (17/25) males. Another 6 patients that we monitored had already been started treatment; of them 50% were males and 50% females. Average age at presentation was 20 months, minimum being 17 days and maximum 6.5 yrs. Of 25 patients (Untreated) we found mean values for following biochemical parameters at the time of diagnosis:

Parameters	Oberserved Values	Mean ± SD	Ref Ranges
Tyrosine	251. 12 - 970	528.46 ±199.59 uM/L	50 - 130
Methionine	14-625.12	204.91 ±165.95 uM/L	20 - 50
Urine SA	5.10 - 2965.61	425.35 ± 606.56 uM /mM Cr	0 - 2
PBG Synthase	0.002-0.43	0.14 ± 0.14 nkat/ gHb	0.58 - 1.25
AFP	506-412000	49,439.73 ± 89,892.52 ug m/L	< 12

In our cohort of 31 patients, 9 were lost for follow up, 16 are under treatment with NTBC and are regular in their follow up and 6 remained untreated and ultimately expired. Of 16 follow up patients, 2 patients with cirrhosis received LTx. Both of them were doing well immediately after transplant. Of another 2 patients who were on NTBC developed HCC, one was inoperable and expired. The other one received LTx was doing well immediately after transplant and stopped NTBC. We noticed slight increase in urine SA. (Fig.1)

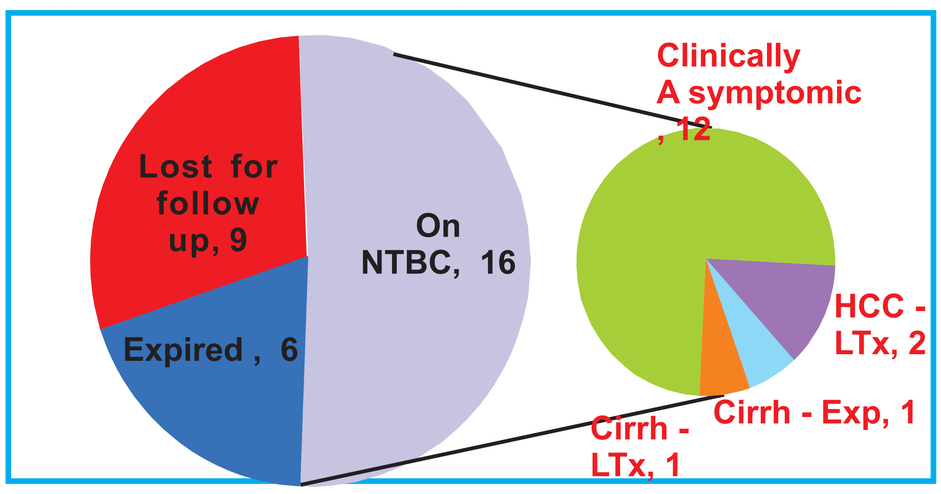

Fig.1 Diagrammatic representation of outcome of our cohort.

Discussion : Infants with HT1 present at an early age with the symptoms of failure to thrive, vomiting, diarrhea, fever, recurrent bleeding, acute liver failure and abdominal distention. Some of the patients present at a later age with severe form of liver complication due to unavailability of newborn screening in India. NTBC along with tyrosine restricted special diet at early stage drastically improves the course of HT1. NTBC administration is beneficial in late diagnosed patients but risk of developing HCC remains a concern[3]. We had a patient who started on NTBC at 18 months of age and developed large nodule of around 10cm x 10cm seen in MRI at the age of 3 yrs which was too late to operate and he expired. Urine SA and AFP levels must be monitored during NTBC treatment to detect the development of HCC. The indications for LTx include unresponsiveness to NTBC, acute liver failure and malignancy. LTx does not completely cure the enzymatic deficiency, since renal FAH deficiency is not corrected by LTx[1]. One of our patients with HT1 was on NTBC treatment, started developing HCC and thus posted for LTx. Urine SA level was normal before and immediately after transplant but he stopped NTBC intake and started showing slight increase in Urine SA. (Fig.2)

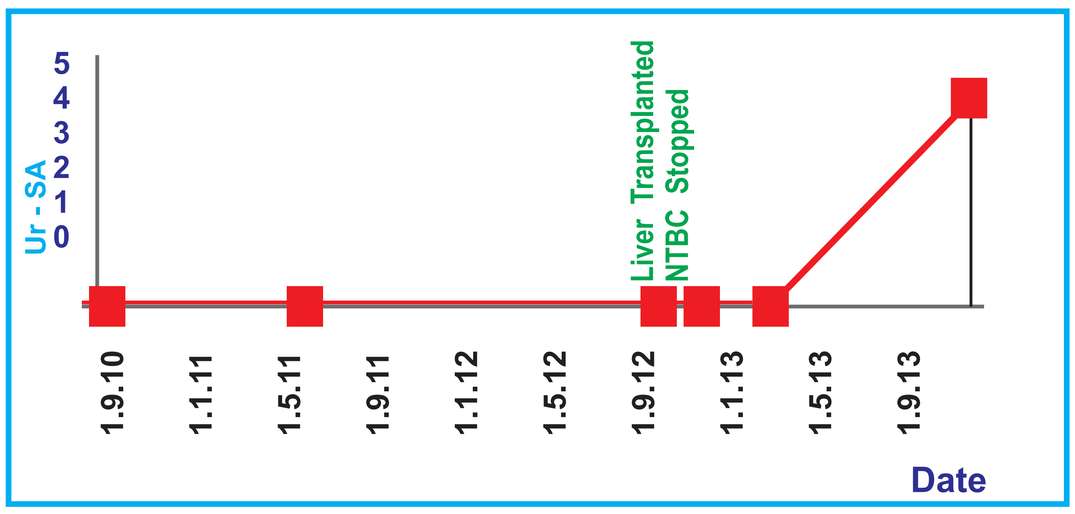

Fig.2 Patient showing increased Ur-SA after LTx

Conclusion : In our cohort mortality rate is 22.58% (7/31), Survival rate is 38.70% (12/31), Malignancy rate is 6.45% (2/31) and patients lost for follow up were 29.03% (9/31).

The prognosis has improved dramatically under combined dietary and Nitisinone therapy for HT1 patients. NTBC does not reduce development of malignancy if started at later age. None of our patient had started NTBC before 2 Months of age. This may be due to late diagnosis as there is unavailability of newborn screening in India and Pakistan. One of our patients showed slight elevation of SA in urine (Fig. 2) after LTx which may be of renal origin. There are many incidences of SA secretion after transplant[2, 3] Transplant recipients may benefit from low - dose NTCB therapy to prevent continued renal tubular and glomerular dysfunction resulting from the succinylacetone generated in renal tissue[4].

Abbreviations : **HT1** - Hepatorenal Tyrosinemia Type I, **SIM** - Selected Ion Monitoring, **GC/MS** – Gas Chromatography Mass Spectrometry, **UHPLC** – Ultra High Performance Liquid Chromatography, **PBG** - Porphobilinogen, **AFP** - Alpha Feto Protein, **SA** - Succinylacetone, **HCC** - Hepatocellular Carcinoma, **LTx** - Liver Transplant, **NTBC** - 2 - [2-nitro4 (trifluoromethyl) benzoyl] cyclohexane - 1, 3 - dione

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