OUTCOME OF SYMPTOMATICALLY DIAGNOSED TYROSINEMIA TYPE I PATIENTS IN INDIA

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INTRODUCTION

Hereditary tyrosinemia type I (HT1) is an autosomal recessive disorder caused by deficiency of fumarylacetoacetate hydrolase (FAH). This study was undertaken to determine the outcome of symptomatically diagnosed patients with HTI in our cohort.

MATERIALS & METHODS

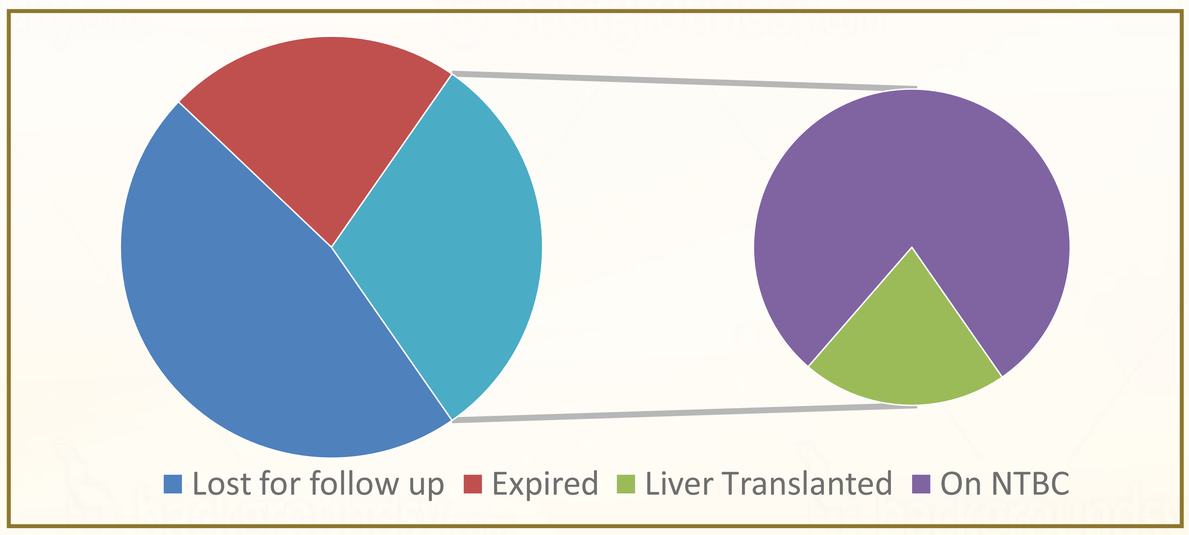
A retrospective study of HT1 patients diagnosed from the year 2002 to 2018 was carried out. We diagnosed 62 patients with HTI. The diagnosis of HT1 was confirmed by elevated levels of Succinylacetone in urine and blood. These patients were followed up regularly during the course of the study and following investigations were performed regularly: Plasma tyrosine methionine and phenylalanine were analysed by UHPLC (Agilent) , Blood Succinylacetone levels by LCMS-MS (Agilent), Urine Succinylacetone was quantified by GC/MS (SIM) (Agilent). Liver and renal function tests, coagulation profile and serum AFP were also monitored regularly. Blood NTBC levels were monitored in dried blood spots by LCMSMS (Agilent). USG abdomen was performed yearly and MRI abdomen in suspicious cases.

RESULTS

Among the total 62 patients that we studied over a period of 16 years, 14 (22%) expired and 29 patients (46%) were lost for follow- up. The remaining 24% (n= 15) are regular in their follow- up. 4 developed malignancy and they underwent liver transplant. Post liver transplant they are well controlled. One of the patients who expired had developed inoperable HCC and could not be saved.

All the 14 patients that we lost did not receive any NTBC. Mostly because they could not afford it or organize it in time because of non-availability in India. Patients who received NTBC (n=15) were all started on NTBC therapy after 3 months of age. They received NTBC in the dose of 0.7-1.0 mg/kg/day depending on the blood NTBC Levels. Those four children, who developed HCC, received NTBC after 1.5 yrs.of age and have been transplanted now. Overall survival with NTBC is good but it does not prevent development of HCC.

Outcome		n=62
Lost for follow up		29 (46.77 %)
Expired		14 (22.58 %)
Alive	Underwent liver transplant	04 (06.45%)
	On NTBC therapy	15 (24.20 %)



DISCUSSION

In absence of NBS programme, the diagnosis of HT1 is usually late and symptomatic in India. In our cohort of 62 patients with HT1, all were diagnosed when they were symptomatic. The most common clinical features of HT1 patients were - failure to thrive, irritability, lethargy, fever, vomiting, diarrhea, abdominal distension, hepatomegaly, edema, and coagulopathy. Due to the unavailability of new born screening in India, most of the patients are diagnosed only after the development of severe liver complications – usually with cirrhosis and liver failure.

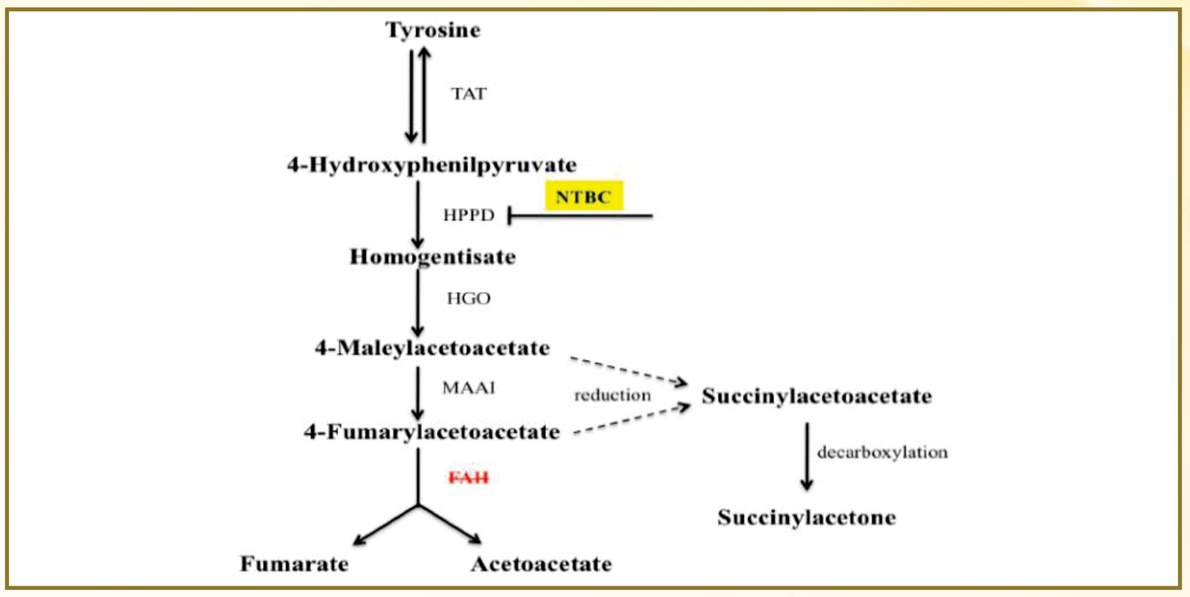


Fig. The five enzymatic steps of tyrosine catabolism and NTBC site of action. NTBC acts as a pharmacological inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPPD) and is used in therapy to avoid production of homogentisate. TAT, tyrosine aminotransferase; HGO, homogentisate dioxygenase; MAAI, maleylacetoacetate isomerase; FAH, fumarylacetocetate hydrolase.

NTBC treatment (usual dose 1mgm/kg/day) is known to dramatically improve the course of HT1. Our patients are well controlled with NTBC in the dose range of 0.7–1.0 mg/kg/day. They have maintained normal level of Succinylacetone in blood and urine and their neurological and physical development is within normal limits. However, NTBC is known to increase the level of tyrosine. One of our patients showed tyrosine level of 1,100 umol/L after starting NTBC. Hence, strict control over tyrosine intake is essential and has to be monitored on a regular basis. Our treatment goals are to maintain the blood Tyrosine levels between 300 – 500 umol/L and NTBC level in the therapeutic range of 30 – 60 umol/L.

In a Quebec study 71 patients with HT1 were studied for effect of NTBC on the course of HT1. According to this study, if NTBC is started before the age of 1 month, the chances of developing malignancy are reduced considerably[2]. Almost all of our patients received NTBC after 1 month of life as they were symptomatically diagnosed. In our study 21% (04/19) patients developed HCC. It would be very important for India to screen for HT1 and start NTBC + dietary treatment at the earliest. Interestingly 5 of our patients belong to a particular community in Gujarat and probably it will be more appropriate to initiate screening in this state.

NTBC is not easily available in India. NTBC cannot prevent malignancy is started late, beyond 3 months of life. Availability of good Liver transplant programmes in India was very helpful in timely treatment post HCC diagnosis. The outcome after OLT was very good. However one of the OLT recipients still shows slightly high excretion of Urinary Succinyl acetone (approximately 5 µmol/mmol Creatinine), but is asymptomatic and not on NTBC therapy.

CONCLUSION

HT1 is most of the times diagnosed symptomatically in India and thus treatment initiated with NTBC is late. With NTBC and dietary treatment, the results are excellent. Only 4 out of 19 developed malignancy and could be saved with timely Liver Transplant. If we develop a Newborn screening programme in India the chances of HCC will be reduced even further. We need to improve the follow-ups also, as 46% of the diagnosed patients were lost for follow-up. The role of primary physician cannot be over emphasised.

Conflict of Interest : None

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