Liver Transplantation for Hereditary Tyrosinaemia Type 1 in the United Kingdom

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Abstract

Fourteen children have undergone liver transplantation for hereditary tyrosinaemia type 1 (HT1) at Birmingham Children's hospital (BCH) since 1989; six were treated prior to the availability of Nitisinone in 1993 and eight in the post Nitisinone era. Prior to 1993 essentially all children with HT1 were referred for transplantation. In the Nitisinone era only those with unresponsive liver failure or suspected malignancy were considered for transplantation. Those who were treated pre-emptively following newborn screening have no evidence of liver disease and none have required transplantation.

Absolute patient survival is 86% for the whole group and 100% in the Nitisinone era. There has been a functional correction of the metabolic defect in all cases allowing a normal diet. Persistent renal succinylacetone production was universal but did not appear to have any clinical consequence. Renal function appeared better, and hypertension less common in those treated in the Nitisinone era.

Outcome was poorer for those four children with established malignancy; one was unfit for transplantation and another developed a pulmonary metastasis, which was successfully resected.

Keywords

Tyrosinemia type I • Liver transplantation • Inherited metabolic disease • Hepatocellular carcinoma • Nitisinone treatment

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Abbreviations

AFP	Alpha-fetoprotein
cGFR	Calculated glomerular filtration rate

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HB	Hepatoblastoma
HCC	Hepatocellular carcinoma
HT1	Hereditary tyrosinaemia type 1
PCR	Protein:creatinine ratio
SA	Succinylacetone
TRP	Tubular reabsorption of phosphate

7.1 Introduction

Liver transplantation for hereditary tyrosinaemia type 1 (HT1) was first undertaken in 1976 by Professor Starzl in a 9-year-old girl who had developed hepatocellular carcinoma (HCC) (Fisch et al. 1978). Although she died 3 months later from infective complications, her metabolic defect was corrected. Since that time more than 150 liver transplants have been undertaken for HT1 with greater than 80% long term survival (Bartlett et al. 2014; Mayorandan et al. 2014). The metabolic effect has been consistent with an immediate functional correction of the systemic defect allowing a normal diet in all cases. Fourteen children have undergone Liver transplantation for HT1 at Birmingham Children's hospital (BCH) since 1989.

The outcome for children with HT1 continues to improve era on era (Mayorandan et al. 2014). This is multifactorial and encompasses progress in medical management, the possibility of pre-emptive treatment following newborn screening, the availability of more palatable dietary products and in the management of liver transplantation and immunosuppression.

Liver transplantation in children for metabolic disease is a highly successful treatment with an expected 1 year survival following elective transplantation of greater than 95% in experienced centres (Mazariegos et al. 2014). Children surviving more than 1 year can confidently expect long-term survival (McKiernan 2010). Follow up studies are consistent in showing that correction of the metabolic defect is lifelong, and that quality-of-life for children and their families are excellent for the great majority.

7.1.1 Indications for Transplantation

As with any hepatic based inborn error of metabolism whether and not liver transplant is appropriate will depend on the interaction of current clinical status, success and availability of liver transplantation and the effectiveness and tolerability of alternative treatments. Traditionally the major indication for transplantation in HT1 has been to prevent the development of hepatocellular carcinoma (HCC). This was based on a "not if but when"philosophy. In practice all children with HT1 were candidates for transplantation and the exact timing of listing was determined on local criterion. These ranged from either arbitrary size or age criterion to some individual biological marker suggesting increased risk of HCC (Mohan et al. 1999; Sokal et al. 1992). These latter included rising alpha-fetoprotein (AFP), histological evidence of hepatocyte dysplasia or radiological features such as the development of new nodules or progression of established ones.

The availability of Nitisinone from 1993 transformed this approach. From this time all were treated with Nitisinone and a more expectant approach taken (McKiernan 2013). Indications for transplantation became failure of Nitisinone and suspected (or proven) HCC. As shown in Table 7.1, referral for transplantation became the exception rather than the rule. Only one child was transplanted because of liver failure

Table 7.1 Referral for transplantation at Birmingham Children's Hospital in two eras

	Pre-nitisinone (1989–1992)	Post-nitisinone (1993–2015)	P value
No. referred for transplantation	6/7	9[a]/34	<0.05
Age at transplant months (range)	61 (19–126)	53 (5–173)	0.94
Time on nitisinone prior to transplantation (months)		39 (2–161)	
Median age starting nitisinone treatment (days)		OLT 428	0.03
		No OLT 52	

[a]Only eight underwent transplantation

Table 7.2 Radiological findings and alpha-fetoprotein (AFP) evolution in eight children treated with Nitisinone referred for liver transplantation for suspected malignancy at Birmingham Children's Hospital 1993–2015

	AFP evolution	Radiological appearance
Proven malignancy (3)	Persistent elevation 1	Dominant nodule 3
	Initial fall and secondary decrease 2	Extrahepatic spread (1)
Hepatic adenoma (1)	Fell to normal	Dominant nodule
Suspected malignancy (4)	Initial fall but never normalised	Non dominant nodules 3
		Dominant nodule 1

despite Nitisinone. Eight children were referred for transplantation because of proven or suspected malignancy. Interestingly the age at transplantation was similar in both eras.

Of the eight children referred with suspected malignancy following Nitisinone treatment this was confirmed in three. Two children had developed HCC and one developed hepatoblastoma (HB). One other child proved to have an adenoma, which has not been reported in HT1 before, but in the context was probably a premalignant lesion. The AFP patterns and radiological appearances in the referred children are summarised in Table 7.2. All children had abnormal cross-sectional radiology, which showed a multinodular appearance. In the cases with proven malignancy there was a dominant nodule in combination with an abnormal evolution of AFP. In contrast, the four children without proven malignancy showed a logarithmic decease in AFP, but which failed to completely normalise. Only one of these four had a dominant nodule on imaging.

This demonstrates how difficult management decisions can be in individual cases. Given the risk of irreversible consequences from established malignancy and the excellent results of transplantation; where there is genuine diagnostic doubt, transplantation will usually be indicated.

Unfortunately the one child with HB had evidence of extrahepatic disease with extensive splanchnic vascular thrombosis when the tumour was recognised. There was no meaningful response to chemotherapy and the tumour proved rapidly fatal. There have been two previous reports of hepatoblastoma in HT1 (Buyukpamukcu et al. 2006; Nobili et al. 2010), which suggests that it is not a coincidental association. However the very different aetiological spectrums of HCC and HB make a mechanistic link difficult to explain at this time.

It is also important to highlight the impact of age when Nitisinone was commenced. Of the 34 children treated at BCH since 1993, 12 were treated pre-emptively following detection by newborn screening. This cohort remains well with normal AFP and hepatic imaging at median age of 9 years (McKiernan et al. 2015) and other centres have reported similar experience (Larochelle et al., 2012). None of this cohort have been considered for transplantation and it seems unlikely they ever will be. Going forward, the indications for liver transplantation in HT1 will continue to be unresponsive liver failure and where hepatic malignancy is suspected in patients who initially presented symptomatically.

7.1.2 Management of Transplantation

All children received orthotopic transplants from cadaveric donors. Immunosuppression management was according to the contemporaneous protocol, with some minor modifications. Prior to 2000, immunosuppression consisted of lifelong Cyclosporin in combination with Prednisolone for 3 months and Azathioprine in the first year. Following 2000, Tacrolimus was substituted for Cyclosporin and Azathioprine. Since 2004 anti IL-2 induction and mycophenolate mofetil were added in tandem with lower Tacrolimus target levels with the aim of preventing nephrotoxicity.

7.1.3 Post Transplant Monitoring

Conventional monitoring of renal function, liver function and immunosuppression was as according to the contemporaneous protocol. Renal function (calculated glomerular filtration rate, cGFR) was evaluated using the Schwartz formula for height:creatinine ratio expressed in ml/min/1.73m^2 and calculated as (height in cm × 40)/plasma creatinine (Schwartz et al. 1987). cGFR was classified using the National Kidney

Foundation stages of chronic kidney disease classification (National Kidney Foundation 2002). Tubular function was assessed by tubular reabsorption of phosphate (TRP) and urinary protein:creatinine ratio (PCR). Normal TRP was considered to be >80% and normal PCR <20 mg/mmol. Formal measures of glomerular filtration rate were undertaken at least every 5 years. In those transplanted for malignancy, or where malignancy was discovered in the explanted liver, AFP was repeated every 3 months for 1 year and subsequently annually. The extent of the residual metabolic defect was assessed by annual measures of urinary and plasma succinylacetone (SA) and plasma amino acids.

7.1.4 Outcome of Liver Transplantation for HT1

Fourteen children underwent transplantation at a median age of 5 years (4 months–13 years) of whom 12 survive, currently aged 23 (2–34) at a median of 17 years (2–26) post transplantation. Six underwent transplantation prior to the availability of Nitisinone and eight had received Nitisinone prior to transplantation (Fig. 7.1). There were two deaths in the early cohort giving an absolute patient survival of 86%. One patient developed hepatic artery thrombosis with chronic rejection and had a re-graft 11 months later. He developed the same complications in the second graft and died 5 months later. A second patient from the early era developed primary non-function and died 10 days later despite urgent re-transplantation.

All eight patients undergoing transplant in the second cohort are alive and well. Two have required repeat transplantation giving an absolute graft survival of 71%. One patient underwent transplant for proven HCC aged 13 and received a second transplant 8 months later for chronic rejection. Another patient who underwent first transplant age 4 months required repeat transplantation due to a combination of vascular outflow obstruction and biliary fibrosis 12 years later.

7.1.5 Outcome of Transplantation for Established HCC

Three children had established HCC at the time of transplant. In two cases this had been detected preoperatively and was the primary indication for transplantation while in the other it was an incidental finding in the explanted liver. One child had presented with chronic liver disease aged 20 months, which responded well to Nitisinone. At age 13 routine monitoring simultaneously detected a new hepatic nodule and a rapidly rising AFP. He underwent transplant 2 months later and by then there was evidence of vascular invasion. Due to the high risk of recurrence his

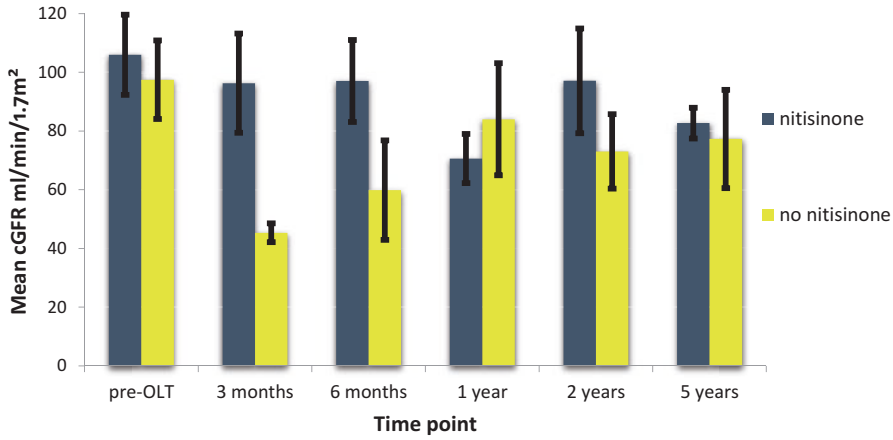

Fig. 7.1 Change in cGFR following liver transplantation in pre and post Nitisinone eras

immunosuppression was minimised but he developed chronic rejection requiring repeat transplant 8 months later. Two years after the original transplant routine monitoring showed an acute rise in AFP and chest radiology revealed a pulmonary metastasis. Abdominal imaging showed no recurrence and the pulmonary metastasis was fully resected. He remains well without evidence of further recurrence 9 years later.

The second case was asymptomatic until presentation with abdominal distension aged 4 months. A large hepatic mass was found with grossly raised AFP. Histology was suggestive of a hepatoblastoma and she received appropriate chemotherapy. Although the mass showed some response it was never resectable. Further investigation of persistent coagulopathy confirmed she had HT1 and Nitisinone was commenced. She underwent liver transplant aged 7 months and remains well 3 years later. Histology of the explant confirmed the tumour to be HCC. She did not receive any further chemotherapy.

The final case was treated in the pre-Nitisinone era. He underwent liver transplantation aged 5 because of established hepatocyte dysplasia. The explant was found to contain an established HCC without vascular invasion. He developed chronic rejection, which recurred following repeat transplantation and he died 16 months after original transplantation. There was no evidence of tumour recurrence at any time.

This experience demonstrates that liver transplantation in children with HT1 and established malignancy has an acceptable outcome, even when vascular invasion has been shown. However the morbidity is higher compared to those where malignancy was suspected rather than proven prior to transplantation. An additional child with malignancy had already developed extrahepatic metastases by the time malignancy was recognised and hence was never suitable for transplantation. There is an ongoing need for close monitoring for malignancy in children with HT1 who present clinically and a need for improved methods for early detection (Baumann et al. 2006).

7.1.6 Glomerular Function

Changes in cGFR pre- and post-OLT are shown in Fig. 7.1. Median pre-operative cGFR values for patients treated with Nitisinone (104 ml/min/1.73m^2, range 54–152) were similar to those of the early cohort (100 ml/min/1.73m^2, range 58–146). By 3 months after OLT, cGFR had significantly decreased in the early cohort (46 ml/min/1.73m^2 range 40–51, $p = 0.02$) but not in the Nitisinone treated cohort (90 ml/min/1.73m^2 range 51–172 $p = 0.5$). At later time points, median cGFR remained slightly below normal in those treated with Nitisinone equivalent to stage 1 or stage 2 (60–89 ml/min/1.73m^2) chronic kidney disease. In patients who had not received Nitisinone, median cGFR remained lower than those who had received Nitisinone. These were equivalent to stage 3A chronic kidney disease (45–59 ml/min/1.73m^2) for up to 6 months but later they improved to within the stage 2 category. However, there was no statistically significant difference between the two groups after 3 months. One patient who did not receive Nitisinone and had stage 2 chronic kidney disease prior to transplant (cGFR 64 ml/min/1.73 m^2) was the only patient whose renal function failed to improve following OLT. He developed renal failure and he underwent successful renal transplant 21 years post liver transplant.

7.1.7 Tubular Function

There was a trend towards higher TRP pre-OLT in the Nitisinone-treated group compared to those not treated with Nitisinone (93% range 91–98% vs. 82% range 50–88%, $p = 0.05$) although values were within the normal range for all except one patient in the non-nitisinone group who had a pre-OLT TRP of 50%. Following OLT, TRP remained normal in all patients in both groups up to 5 years with no significant difference between groups.

Urinary PCR was raised in about 50% of children pre-OLT with no significant difference between those who received Nitisinone and those who did not (median 25.7 range 14.0–32.2 vs.

median 19.0 range 13.5–32.0, p = 0.6). Following OLT urinary PCR remained elevated in the majority of children who did not receive Nitisinone and normal in the majority of children who did receive Nitisinone up to 5 years although these differences did not reach significance.

7.1.8 Hypertension

Following OLT, all four surviving patients (75 %) who did not receive Nitisinone are currently on antihypertensive medication with three patients requiring two or more agents and the third patient on a single agent. In the Nitisinone-treated group, only one of the seven patients (14.3%) is currently requiring antihypertensive treatment with a single agent.

7.1.9 Correction of the Metabolic Defect

All were allowed an unrestricted diet following transplantation. In the early era plasma amino acids normalised within 48 h of transplantation and remain normal during subsequent follow up. In those treated with Nitisinone prior to transplant, initial tyrosine levels were modestly elevated for the first month, which we attributed to the long half-life of Nitisinone. In all cases these subsequently became persistently normal.

An opposite pattern was seen with urinary and plasma SA. Those in the early era had high urinary SA prior to transplant, which fell rapidly to <5% of baseline, but still well above the normal range. Plasma SA levels were only available from >10 years post transplant and these were persistently raised at levels <5 % of that expected in an untreated patient with HT1 (Bartlett et al. 2013).

In those treated with Nitisinone prior to transplant, urinary and plasma SA were undetectable at the time of transplantation. Over the first 5 years following transplant plasma and urinary SA recurred and gradually rose to the persistent levels seen in the early cohort.

In both groups PBG synthase activity mirrored the plasma SA levels. PBG synthase levels were normal at the time of transplant in those treated with Nitisinone. In both groups PBG synthase fell to the low normal range by 5 years post transplantation.

The source of persistent SA is thought to be the kidney where FAH is also active (Tuchman et al. 1987) but the functional significance of this is still not fully understood. We did not detect any clinical consequence of these abnormalities and in particular there were no features of porphyria. There was no correlation between post transplant SA levels and any index of renal function.

It is known that tubular function normalises within 1 year in patients treated with Nitisinone and subsequently remains normal for more than 10 years (Santra et al. 2008). Continued Nitisinone treatment post-OLT has been suggested as a means of controlling the renal SA production and hence improving long term renal function (Pierik et al. 2005). We have not taken this approach for a number of reasons; there was no correlation of renal dysfunction with the extent of the SA production, renal dysfunction does not appear to be progressive; options for preventing and ameliorating immunosuppression associated nephropathy have increased. An additional factor to consider is that even low dose Nitisinone causes significantly raised tyrosine levels (Introne et al. 2011), raising the issue of whether reintroduction of dietary restriction would be necessary. This would likely have a significant negative impact on the quality of life for these transplant recipients.

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