Case Report

Long-Term Outcome of Living Donor Liver Transplantation in a Thai Boy with Hereditary Tyrosinemia Type I: A Case Report

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Hereditary tyrosinemia type I (HT-I) is an autosomal recessive inborn error of tyrosine metabolism, caused by mutation(s) in the gene encoding for fumarylacetoacetate hydrolase (FAH) enzyme. The authors report a Thai boy who presented at two months of age with liver failure. HT-I was diagnosed based on the presence of succinylacetone in urine and homozygous R237X mutations of FAH gene. He was started on tyrosine and phenylalanine restricted diet immediately. Due to a limitation of 2-(2-nitro-4-trifluoromethyl benzoyl)-1, 3-cyclohexanedione (NTBC) therapy in Thailand, it was commenced at eight months old and used as a bridging therapy before liver transplantation. He had a good response to NTBC therapy with an improvement in liver chemistries and synthetic functions. Subsequently, living donor liver transplantation (LDLT) was performed at 15 months old. Long-term follow-up for 6.3 years following LDLT revealed normal growth, good school performance, normal liver, renal tubular, and glomerular functions, and without urinary excretion of succinylacetone.
Conclusion: *Liver transplantation is a promising treatment for patients with HT-I when NTBC is unavailable, resulting in a good long-term outcome.*

Keywords: *Tyrosinemia, Hereditary tyrosinemia type I, Cholestatic jaundice, Cirrhosis, Liver failure, Liver transplantation, Living donor liver transplantation*

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Hereditary tyrosinemia type I (HT-I, OMIM 276700) is a rare autosomal recessive inborn error of metabolism caused by mutation(s) in the gene encoding for fumarylacetoacetate hydrolase (FAH) enzyme, located on chromosome 15q23-25[1]. Deficiency of FAH, the terminal enzyme in tyrosine metabolism results in an accumulation of toxic metabolites, fumarylacetoacetate, and maleylacetoacetate and their metabolites, succinylacetoacetate and succinylacetone (SA)[1,2]. These metabolites are responsible for pathologic changes in liver and kidney[1]. Manifestations include acute and chronic forms. The acute form usually presents in early infancy with liver failure, ascites and coagulopathy whereas hypophosphatemic rickets, cirrhosis, renal tubular dysfunction, cardiomyopathy and acute intermittent porphyria-like symptoms dominate the chronic form[2-4]. Death typically occurs within two years of age in the acute form, if untreated[2-4]. Children surviving beyond infancy are at considerable risks for developing hepatocellular carcinoma (HCC)[6,7]. Biochemical characteristics of this disorder include increased plasma levels of tyrosine, methionine, alpha-fetoprotein (AFP) and excessive urinary excretion of SA[1-4].

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Case Report

The patient was a 2-month-old Thai male infant who presented with fever, abdominal distension, and poor feeding for one day. He was the second child of a non-consanguineous couple and born at term

following an uneventful pregnancy with a birth weight of 3,320 g. Family history was unremarkable. Physical examination revealed BW of 4,900 g, T 38.5°C, slightly enlarged liver and spleen, and unremarkable findings of the remainder. Investigations for infectious diseases were all negative. Blood chemistries showed aspartate aminotransferase 50, alanine aminotransferase 53, gamma-glutamyltransferase 79, alkaline phosphatase 2,756 U/L, albumin 17.2 g/L, total bilirubin 1.0 and direct bilirubin 0.7 mg/dL and AFP > 60,500 ng/mL (N 323 $\pm$ 278 ng/mL). Coagulogram revealed prothrombin time 33 seconds (N 10-15 seconds) and INR 2.98 (N 0.85-1.10). Abdominal ultrasonography and computed tomography revealed regenerating nodules in the liver and mild splenomegaly. Urine organic acid analysis revealed excretion of SA and tyrosine metabolites (4-OH-phenylacetate and 4-OH-phenylpyruvate). Plasma amino acid profiles showed markedly increased tyrosine, methionine and phenylalanine levels at 561, 600 and 188 umoL/L, respectively. Urinalysis was normal. Skeletal x-ray showed no rickets. Polymerase chain reaction and sequencing of the entire coding segment of the FAH gene revealed that the patient had homozygous nucleotide substitution of T for C at nucleotide 709 in the exon 9, leading to a change from arginine to stop codon at position 237 (or R237X).

Dietary therapy with phenylalanine-tyrosine restriction was started immediately after the diagnosis. Treatment with 2-(2-nitro-4-trifluoromethyl benzoyl)-1,3-cyclohexanedione (NTBC) was not initially started due to unavailability of NTBC in Thailand. However, this medication, generously given free of charge by the Swedish Orphan AB, was commenced at the age of 8 months. He had a good response to NTBC therapy with an improvement in liver profiles and his coagulopathy improved significantly following 4 weeks of treatment. Due to the limited amount of donated NTBC and parents could not afford for the high cost of life-long NTBC therapy, living donor liver transplantation (LDLT) was subsequently performed at 15 months of age, using left lateral segment from his mother. The post-operative course was uneventful. Histopathology of explanted liver revealed cirrhosis and regenerate nodules without HCC. Liver profiles and AFP level became normal after liver transplantation (LT) (Table 1). Long-term follow-up for 6.3 years after LT, the patient has been in good physical condition with normal growth and normal liver functions. He has been on tacrolimus as a standard immunosuppression

Table 1. Liver profiles and coagulogram of the patient

Parameters (normal value)	Age (m)								
	3	5	6	8[d]	9	11	12	15[e]	18
ALP (U/L)[a]	2,276	699	1,740	1,793	760	550	533	474	470
AST (15-37 U/L)	50	77	82	129	367	19	149	177	44
ALT (30-65 U/L)	53	57	58	76	60	203	178	202	60
GGT (U/L)[b]	79	150	119	90	91	266	460	511	49
Albumin (34-50 g/L)	17	26	32	31	32	42	42	45	46
TB (0.2-1.0 mg/dL)	1.0	2.9	3.3	4.4	5.2	3.2	2.3	1.5	0.8
DB (0.0-0.7 mg/dL)	0.7	2.0	2.2	2.9	4.4	2.2	1.8	0.8	0.4
AFP (ng/mL)[c]	>60,500	>60,500	>60,500	>60,500	>60,500	NA	6,670	4,480	5.35
PT (10-15 sec)	37	42	32	26	17	13	13	13	12
INR (0.85-1.10)	3.3	3.7	2.9	2.28	1.5	1.1	1.1	1.1	1.0

m = month; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma-glutamyltransferase; TB = total bilirubin; DB = direct bilirubin; AFP = alpha-fetoprotein; PT = prothrombin time; NA = not available

[a] Normal values for children < 1 year, 185-555; 1-2 years, 185-520 U/L

[b] Normal values for children 1-2 months, 12-123; 2-4 months, 8-90; 4 months-10 years, 5-32 U/L

[c] Normal values for children 3 months, 88 $\pm$ 87; 5 months, 46.5 $\pm$ 19; 6 months, 12.5 $\pm$ 9.8; 8 months, 8.5 $\pm$ 5.5; > 12 months, 0-7 ng/mL

[d] Blood tests before NTBC therapy

[e] Blood tests before liver transplantation

protocol in Ramathibodi Hospital. Glomerular and tubular functions, evaluated at the age of 7 years, showed normal glomerular filtration rate (179 mL/min per 1.73 m^2) and normal tubular reabsorption of phosphate (TRP, 93%), normal calcium excretion (3.8 mg/kg/day), and absence of urinary SA. At the time of writing, the patient is 7.5 years old, weighs 20.6 kg with height of 120 cm and does well in school.

Discussion

HT-I is a rare but serious metabolic disease. Early diagnosis is of the utmost importance because prompt treatment can prevent death and morbidities. To the authors' knowledge, this is the first reported case of HT-I in Thailand who underwent liver transplantation with excellent long-term outcome.

Elevated plasma tyrosine, methionine, and phenylalanine levels, and presence of urinary SA are hallmarks of the disease. Confirmatory tests can be performed by the measurement of FAH in lymphocytes or cultured skin fibroblast or by mutation analysis[1,8]. Currently, 44 mutations have been reported in the Human Genome Mutation Database[9]. Common mutations and founder effect have been observed in US, Ashkenazi-Jewish, French-Canadian and Finnish populations[10]. The R237X mutation identified in the present patient has been described only once in a Dutch patient[11].

Since the introduction of NTBC in 1991, it has been established that this medication has enormously improved clinical outcome and quality of life[2,12,13]. Approximately 90% of infants presenting with acute liver failure respond to NTBC therapy with improving coagulopathy within 1 weeks[2,12]. NTBC is an inhibitor of 4-hydroxyphenylpyruvate dioxygenase and as such blocks the further catabolic pathway of tyrosine[2]. NTBC, in combination with dietary restriction of tyrosine and phenylalanine has become the first line treatment[1,2,14]. However, there are some limitations with long-term use of NTBC. Firstly, some patients do not respond to this drug and are still at risk for HCC[14,15] particularly in those whom NTBC was started after two years of age[12]. Secondly, there is compliance problem with the diet restriction[14]. Thirdly, cognitive impairment is common, probably due to chronic hypertyrosinemia[14]. Finally, the high cost of NTBC treatment has made it unaffordable and unavailable in many developing countries. Due to the effectiveness of NTBC and the potential morbidities-related to LT including life-long immunosuppression, LT is currently reserved for patients with NTBC non-responders, suspected HCC, poor quality of life related to dietary restriction, and unavailability of NTBC[1,12,18].

In Thailand, NTBC was not available and treatment option for HT-I was LT. However, LT for a small infant has high potential morbidities[19]. NTBC, donated by the Swedish Orphan AB, was given as a bridging therapy until his general condition was suitable for LT. LT was subsequently performed at 15 months of age. Since the organ donation in Thailand was low resulting in a high waiting-list mortality, the authors decided to perform LDLT in the presented case.

Although LT cures the liver disease in HT-I, as the transplant liver retain the normal FAH enzyme activity, renal tubular defects are not completely resolved due to persistent enzyme defect in the kidney[17,18,20]. Urinary excretion of SA in HT-I patients following LT has been reported[17,18]. Pierik et al reported a long-term follow-up following LT in nine patients with HT-I with the mean duration of 11 years (range 6 months to 14.5 years)[20]. Urinary SA excretion was found in all patients and tubular dysfunction developed in five of these patients[20]. Although long-term use of calcineurin inhibitor (cyclosporine and tacrolimus) can cause renal dysfunction, its effect is mainly on glomerular function[21]. Herzog et al reported mean pre-LT glomerular filtration rate in 27 children with HT-I was below normal but stable post LT during median follow-up duration of six years[22]. In the presented case, glomerular and tubular functions evaluated at five years nine months following LT were normal with undetectable urinary SA. Up to present, the patient is on a regular diet and doing well in a mainstream school, and has good quality of life. However, continuing follow-up is required for precise conclusion about the long-term outcome.

In conclusion, HT-I is a rare but serious metabolic disease. Early diagnosis and early treatment is important to ensure the good outcome. NTBC with diet restriction therapy is the first line of treatment. Liver transplantation is indicated for NTBC non-responders or when the medication is unavailable. Liver transplantation provides a good long-term outcome.

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Potential conflicts of interest

None.

References

1. Ashorn M, Pitkanen S, Salo MK, Heikinheimo M. Current strategies for the treatment of hereditary tyrosinemia type I. Paediatr Drugs 2006; 8: 47-54.
2. Holme E, Lindstedt S. Nontransplant treatment of tyrosinemia. Clin Liver Dis 2000; 4: 805-14.
3. Kvittingen EA. Tyrosinaemia—treatment and outcome. J Inherit Metab Dis 1995; 18: 375-9.
4. Russo PA, Mitchell GA, Tanguay RM. Tyrosinemia: a review. Pediatr Dev Pathol 2001; 4: 212-21.
5. Mitchell G, Larochelle J, Lambert M, Michaud J, Grenier A, Ogier H, et al. Neurologic crises in hereditary tyrosinemia. N Engl J Med 1990; 322: 432-7.
6. Buyukpamukcu M, Varan A, Haberal M, Buyukpamukcu N, Koksal Y, Coskun T, et al. The efficacy of liver transplantation in malignant liver tumors associated with tyrosinemia: clinical and laboratory findings of five cases. Pediatr Transplant 2006; 10: 517-20.
7. Kim SZ, Kupke KG, Ierardi-Curto L, Holme E, Greter J, Tanguay RM, et al. Hepatocellular carcinoma despite long-term survival in chronic tyrosinaemia I. J Inherit Metab Dis 2000; 23: 791-804.
8. Mustonen A, Ploos van Amstel HK, Berger R, Salo MK, Viinikka L, Simola KO. Mutation analysis for prenatal diagnosis of hereditary tyrosinaemia type 1. Prenat Diagn 1997; 17: 964-6.
9. Cassiman D, Zeevaert R, Holme E, Kvittingen EA, Jaeken J. A novel mutation causing mild, atypical fumarylacetoacetase deficiency (Tyrosinemia type I): a case report. Orphanet J Rare Dis 2009; 4: 28.
10. Sniderman KL, Trahms C, Scott CR. Tyrosinemia type 1. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews [database on the Internet]. Seattle, WA: University of Washington; 1993 [updated 2008 Oct 21; cited 2011 May 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1515/
11. Ploos van Amstel JK, Bergman AJ, van Beurden EA, Roijers JF, Peelen T, van den Berg IE, et al. Hereditary tyrosinemia type 1: novel missense, nonsense and splice consensus mutations in the human fumarylacetoacetate hydrolase gene; variability of the genotype-phenotype relationship. Hum Genet 1996; 97: 51-9.
12. McKiernan PJ. Nitisinone in the treatment of hereditary tyrosinaemia type 1. Drugs 2006; 66: 743-50.
13. Santra S, Preece MA, Hulton SA, McKiernan PJ. Renal tubular function in children with tyrosinaemia type I treated with nitisinone. J Inherit Metab Dis 2008; 31: 399-402.
14. Masurel-Paulet A, Poggi-Bach J, Rolland MO, Bernard O, Guffon N, Dobbelaere D, et al. NTBC treatment in tyrosinaemia type I: long-term outcome in French patients. J Inherit Metab Dis 2008; 31: 81-7.
15. van Spronsen FJ, Bijleveld CM, van Maldegem BT, Wijburg FA. Hepatocellular carcinoma in hereditary tyrosinemia type I despite 2-(2 nitro-4-3 trifluoro- methylbenzoyl)-1, 3-cyclohexanedione treatment. J Pediatr Gastroenterol Nutr 2005; 40: 90-3.
16. Freese DK, Tuchman M, Schwarzenberg SJ, Sharp HL, Rank JM, Bloomer JR, et al. Early liver transplantation is indicated for tyrosinemia type I. J Pediatr Gastroenterol Nutr 1991; 13: 10-5.
17. Perez-Cerda C, Merinero B, Sanz P, Castro M, Gangoiti J, Garcia MJ, et al. Liver transplantation in nine Spanish patients with tyrosinaemia type I. J Inherit Metab Dis 1995; 18: 119-22.
18. Mohan N, McKiernan P, Preece MA, Green A, Buckels J, Mayer AD, et al. Indications and outcome of liver transplantation in tyrosinaemia type 1. Eur J Pediatr 1999; 158 (Suppl 2): S49-54.
19. Noujaim HM, Mayer DA, Buckles JA, Beath SV, Kelly DA, McKiernan PJ, et al. Techniques for and outcome of liver transplantation in neonates and infants weighing up to 5 kilograms. J Pediatr Surg 2002; 37: 159-64.
20. Pierik LJ, van Spronsen FJ, Bijleveld CM, van Dael CM. Renal function in tyrosinaemia type I after liver transplantation: a long-term follow-up. J Inherit Metab Dis 2005; 28: 871-6.
21. Fine RN. Renal function following liver transplantation in children. Pediatr Transplant 2005; 9: 680-4.
22. Herzog D, Martin S, Turpin S, Alvarez F. Normal glomerular filtration rate in long-term follow-up of children after orthotopic liver transplantation. Transplantation 2006; 81: 672-7.

ผลการติดตามระยะยาวหลังการปลูกถ่ายตับโดยผู้บริจาคมีชีวิต ในเด็กชายไทยโรค Hereditary Tyrosinemia Type I: รายงานผู้ป่วย 1 ราย

สุทธิรักษ์ จิตรารัชช์, สุพร ตรีพงษ์กรุณา, สุเมธ ธีรรัตน์กุล, ดวงฤดี วัฒนศิริชัยกุล, สุรศักดิ์ ลีลาอุดมปิติ, พัฒนา ศรมยุรา, สมชาย เวียงธีรวัฒน์, สุทัศน์ ศรีพจนารถ

Hereditary tyrosinemia type I (HT-I) เป็นโรคทางพันธุกรรมที่ถ่ายทอดแบบ autosomal recessive ที่มีความผิดปกติในเมแทบอลิสมของไทโรซีน สาเหตุเกิดจากการกลายพันธุ์ของยีนควบคุมเอนไซม์ fumarylacetoacetate hydrolase (FAH) ผู้นิพนธ์รายงานผู้ป่วยเด็ก 1 ราย ที่มาด้วยอาการตับวายตั้งแต่อายุ 2 เดือน และได้รับการวินิจฉัยว่าเป็นโรค HT-I โดยการตรวจพบ succinylacetone ในปัสสาวะและตรวจพบการกลายพันธุ์ของยีน FAH ผู้ป่วยได้รับการรักษาโดยงดอาหารที่มีไทโรซีนและเฟนิลอะลานีนทันทีที่วินิจฉัยและได้ยา 2-(2-nitro-4-trifluoromethyl benzoyl)-1, 3-cyclohexanedione (NTBC) เมื่ออายุ 8 เดือน ผู้ป่วยมีการตอบสนองดีต่อยา NTBC โดยที่การทำงานของตับดีขึ้น แต่มีขีดจำกัดในการใช้ยา NTBC จึงใช้ยานี้เพียงชั่วคราว ผู้ป่วยได้รับการรักษาโดยปลูกถ่ายตับโดยใช้ผู้บริจาคที่มีชีวิตเมื่ออายุ 15 เดือน การติดตามระยะยาวเป็นเวลา 6.3 ปี ภายหลังการปลูกถ่ายตับ พบว่าผู้ป่วยมีการเจริญเติบโตและการเรียนปกติ การทำงานของตับและไตปกติ ตรวจไม่พบ succinylacetone ในปัสสาวะ

***สรุป**: การปลูกถ่ายตับเป็นการรักษาผู้ป่วยโรค HT-I ในกรณีที่ไม่สามารถรักษาด้วยยา NTBC และให้ผลดีในระยะยาว*