Tyrosinemia Type I in Japan: A Report of Five Cases

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Abstract

Tyrosinemia type I in Japan was reported for the first time in 1957 by Sakai et al. (Jikei Med J 2:1–10, 1957) and Kitagawa et al. (Proc Jpn Acad Ser B 88:192–200, 1957). Five cases of patients with tyrosinemia type I were reported to be definitively diagnosed in Japan. The first case was reported by Sakai et al. and Kitagawa et al. To the best of our knowledge, this was the first definite report in the world. The second and third cases were those of a brother and a sister who underwent liver transplantation and who were the children of a Japanese-descent migrant worker; the fourth case was that of a girl who underwent liver transplantation after 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) treatment, which was reported by Hata et al.; and the fifth case was that of a patient who was administered NTBC, which was reported by Ito et al. These were of the subacute type, wherein residual activity was considerably present. When combined therapy with a low phenylalanine and tyrosine diet and NTBC administration is started after early diagnosis, patients can survive without liver transplantation. Development of liver cancer is not found in the cases in Japan, but performing liver transplantation without delay is necessary when liver cancer is found.

Keywords

HT1 Japan • NTBC

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Abbreviations

AFP	alpha-fœtoprotein
ALP	alkaline phosphatase
APPT	activated partial thromboplastin time
FAH	fumarylacetoacetate hydrolase
HPT	heptoplastin T
γ-GTP	γ-glutamyl transferase

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Tyrosinemia type I in Japan was reported for the first time in 1957 by Sakai et al. (1957) and and Kitagawa et al (1957). Five cases of patients with tyrosinemia type I were reported to be definitively diagnosed in Japan. The first case was reported by Sakai et al. and Kitagawa et al. To the best of our knowledge, this was the first definite report in the world. The second and third cases were those of a brother and a sister who underwent liver transplantation and who were the children of a Japanese-descent migrant worker; the fourth case was that of a girl who underwent liver transplantation after 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) treatment, which was reported by Hata et al.; and the fifth case was that of a patient who was administered NTBC, which was reported by Ito et al. These were of the subacute type, wherein residual activity was considerably present. When combined therapy with a low phenylalanine and tyrosine diet and NTBC administration is started after early diagnosis, patients can survive without liver transplantation. Development of liver cancer is not found in the cases in Japan, but performing liver transplantation without delay is necessary when liver cancer is found.

12.1 Case 1: The First Tyrosinemia Type I Report

The initial case reported that occurred in Japan in 1955 was that of a 2-year-old boy. Based on the report by Sakai and Kitagawa (1957), he was born of a consanguineous marriage, and his birth weight was 3900 g. He had normal growth and development during infancy, but appetite loss and abdominal distension were noticed at the age of 2 years. Medical examination revealed that the spleen and liver were 5 cm and 4 cm upon palpation, respectively. A significant increase in urinary 4-hydroxyphenyllactate was shown after hospitalization. The child had diarrhea and weight loss and presented with hypophosphatemia, suggesting Fanconi rickets. Hepatosplenomegaly and appetite loss worsened, and he developed hepatic coma and subsequently died at 5 years of age. Pathological examination showed cirrhosis and liver cancer. From these courses, this case is thought to be the first report of tyrosinemia type I in the world.

12.2 Cases 2 and 3: Children of a Japanese-Descent Migrant Worker (Ueda et al. 2005)

The son of a Japanese-Brazilian father and a Brazilian mother was diagnosed with tyrosinemia type I, and underwent live donor liver transplant 5 months after birth. His younger sister was born weighing 4130 g and underwent blood amino acid analysis because her brother had tyrosinemia type I. The tyrosine and phenylalanine blood levels were 645.7 nmol/ml and 65.5 nmol/ml, respectively. She was treated with phenylalanine- and tyrosine-removed milk, but hypoproteinemia and abnormality of the coagulation system were found (Table 12.1) subsequently. The mother became a donor for the older brother, while the father had difficulty becoming a liver transplant donor because of his disease. The girl was offered the use of NTBC from abroad, which was not commercially available at that time. NTBC administration started 2 months after birth. Eruption, anemia, hypoproteinemia, and

Table 12.1 Clinical examination in administration

WBC 10.2x10^3 /μl	Alb 4.1 g/dl	PT 14.8 sec
RBC 4.67x10^6 /μl	UA 3.6 mg/dl	APTT 44.3 sec
Hb 13.4 g/ dl	BUN 5 mg/dl	HPT 24.8%
Ht 39.3%	Cr 0.3 mg/dl	Factor II 33.6%
Plt 15.1x10^4 /μl	Na 137 mEq/L	FactorV 105.0%
AST 42 IU/L	K 4.7 mEq/L	Factor VII 35.5%
Alt 26 IU/L	Cl 104 mEq/L	Factor VIII 120%
LDH 480 IU/L	Ca 9.8 mg/dl	Factor IX 39.9%
T-Bil 0.3 mg/dl	P 5.5 mg/dl	Factor X 43.2%
ALP 1154 IU/L g-	Mg 2.4 mg/dl	Factor XI 53.2%
GTP 101 IU/L	CRP 0.04 mg/ dl	Factor XII 19.3%
TBA 153.1 μmol/L	IgG 818 mg/dl	Factor XIII >70%
T-Cho 161 mg/ dl	IgA 32 mg/dl	Serum tyrosine
TG 111 mg/ dl	IgM 99 mg/dl	350 μmol/L
TP 6.6 g/ dl	AFP 46,072 ng/ml	

liver function improved dramatically after starting NTBC. She was offered liver donation from an aunt on her mother's side at 1 year 9 months of age and underwent live donor liver transplant. Hypertyrosinemia was not observed after NTBC discontinuation after the liver transplantation.

12.3 Case 4: A Girl Reported by Hata and Shigematsu (2012)

A girl was born at 38 weeks gestational age at 2740 g without problem during the perinatal period or neonatal mass screening. Her sibling was normal. Poor weight gain was observed 1 month after birth, and epistaxis was noted 3 months after birth. Abdominal distension and edema occasionally developed 4 months after birth. Hypoproteinemia, coagulation system abnormality, and slight transaminase level increase were found in a blood examination. Alphafetoprotein (AFP) and tyrosine on amino acid analysis of the filter paper was 77,000 ng/ml and 540 nmol/ml, respectively. Urine organic acid analysis showed significant increase of succinylacetone level at 143 mmol/mol Cr. She was diagnosed with tyrosinemia type I because of elevation of AFP, tyrosine, and succinylacetone levels. She was administered phenylalanine- and tyrosine-removed milk and NTBC. She underwent partial liver transplantation from a live donor mother 5 months after birth.

12.4 Case 5: A Boy Reported by Ito et al. 2005

A boy was born without abnormality at 39 weeks and 4 days of gestation at 4074 g birth weight to parents without consanguineous marriage. Asphyxia or jaundice was not observed. No abnormality was found in his two siblings. The neonatal mass screening performed 5 days after birth was normal. He was administered vitamin K because the result of the hepaplastin test (HPT) 6 days after birth was 24%. The low level of HPT (14.5%) continued, and he was followed up as a case of congenital factor VII deficiency because the factor VII was found to be 8%. He was admitted to the hospital for examination because hepatosplenomegaly was found at 4 months of age. He was suspected to have tyrosinemia type I because of significant hepatosplenomegaly, mild liver dysfunction, high AFP level at 79,274 ng/ml, decreased coagulation factor, and increased urinary tyrosine excretion. He was transferred to a different hospital for close medical examination and treatment 6 months after birth. Bulbar conjunctiva did not show the jaundice, and heart and lung abnormality was not found upon admission. The abdomen was distended, and the liver and spleen were palpated to be 5.5 cm and 2.5 cm, respectively. No abnormal neurological finding was found.

12.5 Laboratory Findings

The laboratory findings at admission are shown in Table 12.1. A platelet count of 15.1×10^4/μl decreased slightly. Biochemical examination of the blood revealed that alkaline phosphatase (ALP), γ-glutamyl transferase (γ-GTP), total bile acids, and AFP were 1154I U/L, 101I U/L, 153.1 μmol/l, and 46,072 ng/ml, respectively. Coagulation factors II, VII, IX, X, XI, and XII were low; prothrombin time (PT) and activated partial thromboplastin time (APTT) were prolonged; and HPT was low. Tyrosine level was high at 403 nmol/ml by blood amino acid analysis. Urinary organic acid analysis (Fig. 12.1) showed significantly increased excretion of tyrosine metabolites, such as 4-hydroxyphenylpyruvic acid, 4-hydroxyphenyl lactic acid, 4-hydroxyphenyl acetic acid, and significant succinylacetone level increase, and the patient was diagnosed with tyrosinemia type I. Fumarylacetoacetate hydrolase (FAH) activity of the liver biopsy specimen was 2.93 μmol/min/mg protein compared with FAH activity (5.14 μmol/min/mg protein) in the liver of patients with cirrhosis, and he was diagnosed with tyrosinemia type I. The pathological diagnosis of the liver biopsy specimen was cirrhosis.

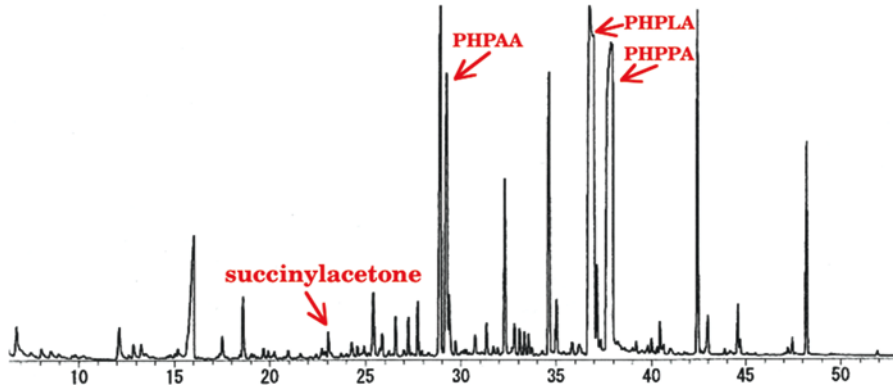

Fig. 12.1 Urinary organic acid analysis in case 5. Urinary organic acid analysis revealed elevation of succinylacetone, PHPAA, PHPLA and PHPPA

Table 12.2 Clinical examinations during NTBC administration

	Administration	Before	1 week	1 month	4 month	1 year	3 year	5 year	8 year
NTBC (mg/day)			9	9	10	15	15	20	30
Liver (cm)	5.5	5.0	5.0	4.5	3.0	2.5	2.0	2.0	0.5
Spleen (cm)	3.0	3.0	3.0	1.0	n.p.	n.p.	n.p.	n.p.	n.p.
Platelets ($\times 10^4/\mu l$)	15.1	25.0	27.3	46.6	33.3	23.6	24.1	20.1	23.4
HPT (%)	24.8	69.7	74.1	79.8	71.6	80.1	78.7	78.4	81.7
ɤ–GTP (IU/L)	101	128	113	97	32	18	17	15	15
TBA (μmol/l)	153.1	57.3	11.8	13.8	10.9	7.3	8.6	4.4	9.1
AFP (ng/ml)	46,072	2661	1475	463	91	8	5	4	4
Serum tyrosine (mg/dl)	7.30	0.82	1.06	0.32	4.70	5.60	8.91	8.11	6.33
EBC PBG synthase actibity (nkat/gHb)	–	0.030	0.900	1.070	0.850	0.830	0.720	–	–
Serum succinylacetone (mmol/l)	–	2.30	1.20	0.26	<0.10	0.12	<0.10	–	–
Urine 5–Aminolevulinic acid (mmol/mol Cr)	–	64.0	8.5	3.8	5.6	5.0	5.0	–	–
Urine Succinylacetone (mmol/mol Cr)	–	20.0	<1	<1	<1	<1	<1	–	–

n.p.: not palpable
(–): not evaluated

12.6 Clinical Course (Table 12.2)

NTBC therapy was administered after the chemical diagnosis by using organic acid analysis because the family consented. Professor Lindstedt from the Gotenberg University and Swedish Orphan Company provided NTBC. Before NTBC the administration, he was treated with a low tyrosine phenylalanine diet. PT, APTT, hepaplastin test, blood coagulation factors, and platelet count of $25.0 \times 10^4/\mu l$ improved after the diet therapy. Biochemical test showed that the total bile acids and AFP at 57.3 μmol/l and 2331 ng/dl, respectively, decreased; however, γ-GTP level of 128 IU/l remained high. Porphobilinogen (PBG) synthase activity in red blood cells was decreased at 0.03 nkat/g Hb (normal range, 0.58–1.25 nkat/g Hb), and plasma succinylacetone of 2.30

μmol/l (normal range, <0.1 μmol/l) increased. Urinary succinylacetone of 20.0 mmol/mol Cr (normal range, 1 or less) and urine aminolevulinic acid level of 64.0 mmol/mol Cr (normal range, 0–3) were high. One week after NTBC administration, PBG synthase activity in the blood was within the normal range, and urinary succinylacetone was lower than detection limit. Two months after NTBC administration, blood coagulation system examination, γ-GTP, plasma succinylacetone, and total bile acids were within the normal range. However, AFP levels became normal after 1 year (less than 10 ng/dl), and urine aminolevulinic acid decreased by 8.5 mmol/mol Cr after 1 week, but did not decrease to normal range (3.0 mmol/mol Cr). Hepatosplenomegaly gradually improved after NTBC administration, and the spleen was not palpated 1 month after NTBC administration, and the liver surface became smooth 8 months after, and hepatomegaly improved to approximately 2 cm beyond the rib bottom 1 year later. Abdominal MR imaging did not exhibit any neoplastic lesion in the liver. a special formula was used in addition to NTBC therapy to keep the patient's serum tyrosine concentration to 3–5 mg/dl. The NTBC dose is 0.6–1 mg/kg/day and does not show the adverse effects.

12.7 Newborn Screening of Tyrosinemia Type I

A pilot study of the newborn screening of tyrosinemia type I was conducted by Shigematsu et al. (2007). He measured tyrosine level from a filter paper sample. If the tyrosine level was 200 nmol/ml or more, succinylacetone of the filter paper was measured as the second testing. The cut-off value of succinylacetone was 5.0 nmol/ml. Of the 27,905 neonate samples, 499 (1.79%) were assayed for the second test because of high concentrations with tyrosine. No positive sample with succinylacetone concentrations level above the cut-off value was found. Further screening was continued, but no sample with high succinylacetone concentrations above the cut-off value was found after screening approximately 500,000 specimens. Therefore, the tyrosinemia type I incidence in Japan seemed to be extremely low, and newborn screening of tyrosinemia type I by measuring succinylacetone does not seem to be realistic.

12.8 Discussion

A total of 5 cases of tyrosinemia type I were found in Japan and were of the subacute type, wherein residual activity was considerably present. When combined therapy with a low phenylalanine and tyrosine diet and NTBC administration is started after early diagnosis, patients can survive without liver transplantation. We should start NTBC administration initially while considering the indication of liver transplantation(Lindstedt et al. 1992; Kelsey et al. 1993; Grompe et al. 1995). However, development of liver cancer cannot be prevented in some cases even after NTBC administration (Michell et al. 2001), and performing liver transplantation is necessary in severe cases without improvement after NTBC administration. Development of liver cancer is not found in the cases in Japan, but performing liver transplantation without delay is necessary when liver cancer is found (Nakamura et al. 2015).

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