Hereditary Tyrosinemia Type 1 in Turkey

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Abstract

Hereditary tyrosinemia type 1 (HT1, OMIM 276700) is a rare autosomal recessively inherited inborn error of metabolism in the tyrosine catabolic pathway due to deficiency of the enzyme fumarylacetoacetate hydrolase. The clinical features of HT1 are widely heterogenous even within the same family members. Clinical features includes acute or chronic liver disease with increased risk of hepatocellular carcinoma, hypophosphatemic rickets due to renal tubular dysfunction, glomerulosclerosis, failure to thrive, neurological porphyria-like crisis, hypertrophic cardiomyopathy and hypoglycemia due to hyperinsulinism. Currently, the treatment in HT1 consists of two principles: inhibition of the formation of toxic metabolites by nitisinone [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione; NTBC] and reduction of tyrosine levels by dietary treatment. In this chapter besides presenting the data for 42 patients that had been followed up by Pediatric Metabolic Diseases and Nutrition Unit, Cerrahpasa Medical Faculty, Istanbul University, we also evaluated the data abstracted from the previously published case studies in order to better understand the disease course and gain further insight in the current diagnosis and treatment for HT1 in Turkey.

Keywords

Tyrosinemia type 1 • Nitisinone • Turkey

Abbreviations

ALAD	δ-aminolevulinic acid dehydratase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
d-ALA	δ-aminolevulinic acid
FAA	Fumaryl acetoacetate
FAH	Fumarylacetoacetate hydrolase
HCC	Hepatocellular carcinoma
HT1	Hereditary tyrosinemia
HTIV	Hereditary tyrosinemia type 1

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LDLT	Living donor liver transplantation
MAA	Maleyl acetoacetate
MRI	Magnetic resonance imaging
NBS	Newborn screening
OLT	Orthotopic liver transplantation
PBGS	Porphobilinogen synthase
SA	Succinyacetone
SAA	Succinylacetate
TAT	Tyrosine aminotransferase
WISC-R	Wechsler Intelligence Scale for Children-Revised

15.1 Introduction

Hereditary tyrosinemia type 1 (HT1, OMIM 276700) is a rare autosomal recessively inherited inborn error of metabolism in the tyrosine catabolic pathway due to deficiency of the enzyme fumarylacetoacetate hydrolase (FAH) (Chakrapani et al. 2012). FAH catalyzes the final step in the tyrosine degradation and blockage leads to accumulation of the upstream toxic metabolites and their derivatives fumarylacetoacetate (FAA), maleylacetoacetate (MAA), succinylacetoacetate (SAA) and succinylacetone (SA) that are responsible for the tissue damage with progressive hepatic, renal and neurological findings (McKiernan et al. 2015; Jorquera and Tanguay 2001; Tanguay et al. 1990; Sassa and Kappas 1983). The human *fah* gene is mapped to chromosome 15q. Overall 95 mutations have been reported within the *fah* gene (Angileri et al. 2015) (and see Morrow et al., Chap. 3).

The clinical features of HT1 are widely heterogenous even within the same family members. Three main clinical forms have been described based on the age at symptom onset: the *acute* form, which presents in the first 6 months of life; the *subacute* form, presenting within 6 months and 1 year of age; the *chronic* form, which appears after the first year of age (van Spronsen et al. 1994; Chakrapani et al. 2012). Clinical features includes acute or chronic liver disease with increased risk of hepatocellular carcinoma, hypophosphatemic rickets due to renal tubular dysfunction, glomerulosclerosis, failure to thrive, neurological porphyria-like crisis, hypertrophic cardiomyopathy and hypoglycemia due to hyperinsulinism (Chakrapani et al. 2012; Mitchell et al. 1990; Mohamed et al. 2013; Arora et al. 2006; Baumann et al. 2005). Patients who survive beyond infancy can develop chronic renal failure (Kvittingen et al. 1991).

Currently, the treatment in HT1 consists of two principles: inhibition of the formation of toxic metabolites by nitisinone [2-(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione; NTBC] and reduction of tyrosine levels by dietary treatment (Holme and Lindstedt 1992).

Before the introduction of nitisinone, the natural history of the disease usually resulted in death. The treatment consisted of symptomatic treatment with tyrosine restricted diet until liver transplantation. Low tyrosine (tyr) and phenylalanine (phe) diet was not effective in the acute form and had limited success in the chronic form, neither did it prevent hepatocellular carcinoma (HCC) (van Spronsen et al. 1994). The 1 year survival rate was 38% when the smptoms started <2 months of age, 74% between 2 and 6 months of age and 96% >6 months of age. The main causes of death were liver failure, HCC and porphyria-like neurological crises (van Spronsen et al. 1994).

Nitisinone is a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase (Lindstedt et al. 1992) leading to the suppression of MAA, FAA and SA accumulation and the accumulation of tyrosine (Mckiernan 2006). Nitisinone had significantly improved survival in HT1, with a clinical response of 90% and a decrease in the risk of early development of HCC in those who began treatment at an early age. The maximal benefit of the drug is achieved when the treatment is started in the early stages of life (Holme and Lindstedt 1998; Lock et al. 1998; Santra and Baumann 2008; Larochelle et al. 2012; Nakamura et al. 2015; Couce et al. 2011; El-Karaksy et al. 2011; McKiernan et al. 2015). Universal newborn screening (NBS) with SA extracted from newborn dried blood spots, as a biochemical marker, is feasible and has been established in some countries. Early detection with NBS can allow the treatment to be started

before the development of clinical symptoms (Larochelle et al. 2012; McKiernan et al. 2015).

In Turkey, where nationwide NBS for HT1 is not mandatory, diagnosis still depends on clinical suspicion and laboratory investigations. Pediatric Metabolic Diseases and Nutrition Unit, Cerrahpasa Medical Faculty, Istanbul University is one of the first Metabolic Diseases Center in Turkey initiating nitisinone therapy in HT1 patients, since 1993.

In this chapter, besides presenting the data for 42 patients that had been followed up by Pediatric Metabolic Diseases and Nutrition Unit, Cerrahpasa Medical Faculty, Istanbul University we also evaluated the data abstracted from the previously published case studies in order to better understand the disease course and gain further insight in the current diagnosis and treatment for HT1 in Turkey.

15.2 Methods

Information from the medical records of HT1 patients diagnosed at the Pediatric Metabolic Diseases Unit of Cerrahpasa Medical Faculty, Istanbul University between December 1993 and May 2016 was collected and included detailed history, family history including consanguinity and siblings with HT1 or with suggestive symptoms, demographic information, gender, age at first clinical symptom, age at diagnosis, clinical-biochemical and radiological data. HT1 diagnosis based on either by presence of elevated SA in urine/blood samples or mutation analysis. None of the patients were screened at birth for HT1. All patients were treated with a tyrosine and phenylalanine restricted diet under the supervision of a clinical dietician to maintain a plasma level below 400 μmol/L as recommended. Forty patients were treated with nitisinone according to a standard protocol starting nitisinone at 1–2 mg/kg/day, q.d. or b.i.d. at diagnosis. The nitisinone dose was adjusted afterwards according to blood nitisinone levels determined either by plasma or dried blood samples. Plasma levels were considered adequate between 30 and 60 μmol/L. Two patients were only treated with diet due to unavailability of nitisinone.

For these 42 patients, clinical and biochemical data at diagnosis and follow-up including liver and renal functions, blood alpha-fetoprotein (AFP), urine or blood SA, urine delta-aminoalevulinic acid (δ-ALA) (when available), plasma Tyr levels, liver and renal imaging (by ultrasound, CT or MRI) findings, growth parameters, compliance with the treatment, and adverse effects were evaluated. If available, the histopathological findings from the liver biopsies were recorded.

15.2.1 Published Cases

The following terms were used to search for HT1 cases the PubMed database from 1966 to May 2016: Tyrosinemia type 1 or hereditary tyrosinemia type 1 or fumarylacetoacetate hydrolase deficiency or hepatorenal tyrosinemia and Turkish or Turkey with filters for case reports, clinical trials, and review articles. The search yielded 22 publications.

15.2.2 Statistical Analysis

Data are displayed as mean and standard deviation and/or median and range for continuous variables and as frequency and percentage for categorical variables. Non-parametric Mann–Whitney U-test was used for abnormally distributed data. P-values <0.05 were considered statistically significant.

15.2.3 Description of Clinical Characteristics of Turkish Patients with HT1

Information was collected on 112 patients with HT1. Of these, 42 cases were followed by Pediatric Metabolic Diseases Unit of Cerrahpasa Medical Faculty, while information on 69 cases was extracted from the literature.

Forty-two HT1 patients diagnosed at Pediatric Metabolic Diseases Unit of Cerrahpasa Medical Faculty, aged between 15 days and 100 months at the time of diagnosis. Twenty-six were male and 16 were female. None of the patients was detected by expanded newborn screening for HT1 but two patients were diagnosed by selective screening in the newborn period due to an affected sibling history. All patients were symptomatic at the age of diagnosis, even diagnosed with selective screening. Mean age at onset of clinical symptoms was 8.8 months (range 0–54 months) and the mean age at diagnosis was 18.1 months (range 0.43–100 months). Fifteen of the 42 cases presented as acute HT1, 13 with subacute HT1 and 14 with chronic HT1. Very early onset of symptoms (<2 months of age) was detected in five patients. The majority of the cases were male (62%). Clinical diagnosis was based on presense of SA in urine/blood samples for all cases. All but one patient excreted SA in their urine at the time of diagnosis. One patient did not excrete SA in his urine despite a mild increase in plasma SA level and the diagnosis was made via mutation analysis (c.1A > G/c. (1096–1098) del TCG, compound heterozygous mutation). No enzymatic studies were performed.

On family history, consanguinity was noted in 25 patients (59.5%). Prematurity was noted in six patients without any other risk factor for premature labor. Three patients were noted to be large for gestational age due to gestational diabetes and one to be small for gestational age.

Table 15.1 Chief clinical symptoms at diagnosis

Complaints	n (%)
Pallor	32 (76.2)
Anorexia	31 (73.8)
Abdominal distention	31 (73.8)
Irritability/abdominal pain	27 (64.3)
Abnormal urine odor	22 (52.4)
Growth retardation	17 (40.7)
Fever	13 (31)
Jaundice	11 (26.2)
Nasal bleeding	11 (26.2)
Hematemesis/melena	9 (21.4)
Vomiting	7 (16.7)
Diarrhea	4 (9.5)

Table 15.2 Main clinical manifestations at diagnosis

Clinical manifestations	n (%)
Hepatomegaly	41 (97.6)
Splenomegaly	36 (87.5)
Abdominal distention	31 (73.8)
Anemia	32 (76.2)
Rickets	27 (64.3)
Ascites	17 (40.5)
Growth retardation	14 (33.3)
Jaundice	11 (26.2)
Epistaxis	11 (26.2)
Gastrointestinal bleeding	9 (21.4)
Petechia/ecchymosis	5 (12)
Lethargy	3 (7.1)

The onset of clinical symptoms was at 2. ± 1.2, 4.2 ± 2.7 and 20.4 ± 16.2 months in acute, subacute and chronic HT1 patients, respectively. The median interval between the first complaints and diagnosis was 1.3 months (range, 0–3.1) in acute, 5.3 months (range 0.5–11) in subacute and 21.5 months (range, 1–67) in chronic HT1. The main clinical manifestations at diagnosis were hepatomegaly (97.6%), splenomegaly (87.5%), hepatic dysfunction (82%) and renal tubular dysfunction (59.5%) (Tables 15.1 and 15.2). On initial anthropometric evaluation six patients were found to be ≤2 SD for weight and five were ≤2 SD for length. Biochemical parameters at diagnosis revealed a marked increase in alpha-fetoprotein (AFP) level for all ages, with a high variability (between 35 and 624,000 ng/ml). AFP level of chronic HT1 patients was significantly lower than the acute and subacute HT1 patients ($P < 0.0001$ and $P < 0.0001$, respectively). Plasma tyrosine, phenylalanine and methionine levels were all increased (Table 15.3), while erythrocyte porphobilinogen synthase (ePBGS) was markedly decreased. Altered coagulation parameters due to hepatic dysfunction were observed all but four patients of 42 patients (90%).

Tubulopathy was detected 36/42 (85%) of patients with one or more components such as generalized aminoaciduria, metabolic acidosis, proteinuria, glucosuria and hypophosphatemic rickets of varying severity. Urinary phospahte results were available for 13 patients and 12 had

Table 15.3 Biochemical parameters at diagnosis

Parameter	Normal	n	Mean	Range	SD
Plasma					
AFP (ng/ml)	<13	42	99,222	35–624,000	137,647
ALT (IU/L)	0–40	41	34.2	11–102	21.2
AST (IU/L)	0–40	41	70.7	25–186	31.7
GGT(IU/L)	3–25	40	119.8	19–341	80.6
Total bilirubin (mg/dl)		36	1.97	0.41–6.10	1.27
Direct bilirubin (mg/dl)		36	0.99	0.06–3.3	0.8
Ca (mg/dl)	8.4–10.8	40	9.08	7.51–11.1	0.87
P (mg/dl)	2.7–5.5	40	2.99	1.2–6.1	1.29
ALP (IU/L)	60–525	41	1407	170–4430	1062.9
Total protein (g/dL)	5.6–8	39	5.64	3.4–8.3	1.17
Albumin (g/dL)	3.2–5.4	39	3.31	1.9–4.7	0.76
Hemoglobin (g/dL)		40	9.75	6.4–19	2.27
Thrombocyte (/mm^3)	150,000–400,000	40	129,025	33,000–577,000	82349
Coagulation					
PT (s)	10.4–14	40	31.2	13.3–70	15.5
PT activity (%)	70–130	40	36.2	11.34–90	21.4
INR	0.85–1.15	40	2.74	1.05–6.15	1.38
aPTT (s)	26–40.8	40	66.88	29.9–144	28.8
Plasma					
Tyr (μmol/L)	50–130	40	410.7	23–1095	286.1
Phe (μmol/L)	40–120	40	133.2	15–415	99.9
Met (μmol/L)	20–50	40	368.9	13.3–1590	381.9
ePBGS (nkat/g Hb)	0.58–1.25	17	0.071	0.00–0.32	0.10
SAp	<0.1	20	35.5	0.73–136	33.23
Urine					
SA (mmol/mol creatinin)	<1	19	503.3	1.40–1800	560.3
DALA (mmol/mol creatinin)	0–3	16	123.6	11–350	11.7
SA (qualitative)	Undetectable	42	Increased		

AFP α-fetoprotein, *ALP* alkaline phosphatase, *ALT* alanine transaminase, *aPTT* activated partial thromboplastin time, *AST* Aspartate transaminase, *Ca* calcium, *DALA* δ-aminolevulinic acid, *ePBGS* erythrocyte porphobilinogen synthase, *GGT* γ-glutamine transaminase, *INR* international normalized ratio, *Met* methionine, *P* phosphorus, *Phe* phenylalanine, *PT* prothrombin time, *SA* succinylacetone, *SAp* plasma succinylacetone, *Tyr* tyrosine

abnormal tubulary phosphate excretion. Clinical, radiological and biochemical rickets was detected in 27 patients (64.3%). Hypoglycemia was detected in 11 patients, two were hyperinsulinemic and required temporary slow rate i.v. dextrose infusion. Hepatic ultrasonography showed hepatomegaly in 40 children and liver nodules in 28 (66.7%). Multiple hypoechoic nodules were detected in 20 and hyperechoic nodules were detected in 21 patients. Five patients had macronodular appearance detected either on ultrasonography or MRI. Increase in renal echogenity was detected on renal ultrasonography in 24 children and nephrocalcinosis was detected in five children on presentation. Liver biopsy was performed in 13 children and all had active cirrhosis and one also had hepatic macrovesicular steatosis. None of the 15 patients with initial echocardiography, had restrictive cardiomyopathy. One had mild interventricular septal hypertrophy and

mild mitral insufficiency, one had small ventricular defect, one had secundum atrial septal defect and one had patent foramen ovale and mild pulmonary stenosis.

Information on 69 cases extracted from the literature regarding the age of diagnosis (43/69) yielded a mean age at the diagnosis of 15.3 months (range 0,06–108 months (Dursun et al. 2011; Coskun et al. 1991; Bay et al. 2012; Yagci et al. 2015; Onenli Mungan et al. 2016). Diagnosis was based on the presence of SA in urine. Five patients had additional confirmatory enzyme analysis in fibroblasts and 44 had mutation analysis. One patient did not excrete SA in his urine and the diagnosis was made via mutation analysis (Dursun et al. 2011). Two cases were detected by selective newborn screening and five cases were detected by selective screening, because of an affected sibling. The average age at diagnosis was 10.5 months (range 1–45 months) in those diagnosed via selective screening (Dursun et al. 2011; Onenli Mungan et al. 2016; Rootwelt et al. 1994).

Data was available for 48 patients regarding the distribution of HT1 subtype; 24 of the cases were acute HT1 (34.8%), 8 were subacute (11.6%) and 14 (20.3%) were chronic. Very early onset of symptoms (<2 months) was noted in two cases. Information regarding the sex of the patients was available in 29/69 cases and most majority was female (17/29; 58%) (Coskun et al. 1991; Sener 2005a, b; Yagci et al. 2015; Onenli Mungan et al. 2016).

Abdominal distention (30/44), hepatomegaly (30/44), splenomegaly (13/44), failure to thrive (15/43), rachitis (15/43), irritability (5/34), abdominal distention (30/44), diarrhea (9/44), polyuria-polydipsia (6/44), vomitting (4/44), melena (5/44), ascites (9/43), intermittent hypertension (3/44), and jaundice (2/44) were the most common symptoms and disease manifestations described in Turkish HT1 patients in the literature (Coskun et al. 1991; Dursun et al. 2011; Bay et al. 2012; Onenli Mungan et al. 2016).

In the group of patients (35/69) with plasma tyrosine level reported, the level ranged between 143 and 1385 μmol/L. Data was available for 26 patients regarding AFP level at diagnosis that revealed a marked increase with a wide variability (37–855,000 ng/ml), for 42 patients regarding ALT and AST (10–144 and 13–312 IU/L, respectively). Altered coagulation parameters due to hepatic dysfunction were observed all but four patients of 31 patients reported (87%) (Coskun et al. 1991; Dursun et al. 2011; Bay et al. 2012).

In the group of patients with mutational analysis (40/69), we found 12 different mutations. In accordance with the literature the most common mutation was IVS6-1G>T (26%) followed up by D233V (22%), and IVS3-3C>G (10%) mutations. Eight patients were homozygous for IVS6-1G>T mutation. IVS12+5G>A (three patients), V166G (two patients), R237X (two patients), IVS9+2T>C (two patients) c.191delA (one patient), c.(440–441) del8nt (one patient), R174X (one patient), N232K(one patient), N334Tfsx (one patient), V259D (one patient), A134D (one patient) mutations were also described in Turkish patients (Rootwelt et al. 1994, 1996; Dursun et al. 2011; Onenli Mungan et al. 2016).

15.2.3.1 Adherence to Therapy

Among 42 patients followed in our clinic only two patients were treated only with low tyrosine and phenylalanine diet. Although the dietary compliance was good, patients died due to severe hepatic dysfunction and massive gastrointestinal bleeding. The average time for the rest of the 40 patients in treatment was 70.4 months (range, 2–255 months) with a median of 128 months. During this period, dietary compliance was good in 13 patients (Tyr <400 μmol/L), moderate in 13 patients (Tyr 400–600 μmol/L) and poor in 16 patients (Tyr >400 μmol/L). No information about the dietary compliance was available in the published cases, except one with corneal pseudodendritic lesions with a plasma Tyr level of 840 μmol/L (Gulmez Sevim et al. 2015).

15.2.3.2 Response to Nitisinone Treatment

In our patient's group, nitisinone treatment was started at <6 months of age in 16 patients (38.1%), 7–12 months in nine patients (21.4%), 13–24 months in four patients (9.5%) and after 24 months in 11 patients (26.2%). The mean

interval between diagnosis and nitisinone treatment was 18 days (range, 0–120 days). Long-term follow up of the patients was carried out for a mean period of 70.5 months (range 2–255 months).

The mean dose of nitisinone was 1.2 mg/kg/day (range 0.6–2 mg/kg/day) with an average plasma level of 41 μmol/L. The dose was adjusted according to the plasma nitisinone level that was considered to be adequate, between 30 and 60 μmol/L. No urinary SA excretion was detected under nitisinone treatment, but interruption of the treatment led to re-excretion.

Adherence to nitisinone therapy was very good in all 42 patients except two chronic HT1 patients. Good metabolic control was achieved in 35/40 patients with normalization of the hypoprothrombinemia and decrease in AFP. Despite good adherence to therapy, four patients did not respond to nitisinone treatment; one subacute HT1 patient died due to severe hepatic dysfunction (patient S1, Table 15.4), one chronic HT1 patient died due to hepatic dysfunction and variceal bleeding as a result of portal hypertension (patient C5), and one subacute patient had a succesfull liver transplant at 16 months of age (patient S7). One chronic HT1 patient was under evaluation for LT due to partial response and HCC suspicion at the time of writing.

Among 36 patients who had been followed for >48 months, AFP normalized (<13 μg/L) in 7/24 (29.1%) within the first year of therapy, in 11/24 (45.9%) at 12–24 months, and in 6/24 (25%) at 25–48 months of therapy.

Table 15.4 Cause of death in hereditary tyrosimenia type 1 patients

Patient no	HT1 subtype	Treatment	Length of follow-up (months)	Cause of death
A1	Acute	Nitisinone+low tyr+Phe diet	5.65	Septic shock
A2	Acute	Nitisinone+low tyr+Phe diet	10	Aspiration pneumonia
S1	Subacute	Nitisinone+low tyr+Phe diet	2.7	Non-responder; hepatic insufficiency with increasing jaundice and intractable coagulopathy despite 5 months of therapy
S2	Subacute	Nitisinone+low tyr+Phe diet	12	Hepatocellular carcinoma
S3	Subacute	Low tyr+Phe diet	2	Massive bleeding due to hepatic insufficiency
S4	Subacute	Nitisinone+low tyr+Phe diet	12	Porphyria like attack during interruption of treatment
S5	Subacute	Nitisinone+low tyr+Phe diet	46	Acute liver rejection after LDLT due to hepatocellular carcinoma
C1	Chronic	Low tyr+Phe diet	2	Hepatic insufficiency and massive esophageal variceal bleeding
C2	Chronic	Nitisinone+low tyr+Phe diet	12	Hepatic insufficiency and massive esophageal variceal bleeding after permanent cessation of NTBC treatment (parents' decision)
C4	Chronic	Nitisinone+low tyr+Phe diet	55	Hepatocellular carcinoma after permanent cessation of NTBC treatment (parents' decision)
C5	Chronic	Nitisinone+low tyr+Phe diet	2.2	Hepatic insufficiency and massive esophageal variceal bleeding (partial responder)
C6	Chronic	Nitisinone+low tyr+Phe diet	4	Metastatic hepatocellular carcinoma

HT1 hereditary tyrosimenia type 1

Six patients (three subacute and three chronic HT1 patients) had persistent high AFP with normal liver function tests despite nitisinone treatment. All were diagnosed with hepatocellular carcinoma or hepatic adenoma. One subacute HT1 patient died during follow up (patient S2; Table 15.4), five had liver transplantation (patient S5, S7, C3, C7 and C10).

Secondary increase in AFP after normalisation was also detected in five patients (one acute, two subacute, two chronic). Two patients responded to increase of nitisinone dose (The acute and subacute HT1 patient) while two patients did not (patient S6 and C3, Table 15.5) and both were liver transplanted (both patients were proved to have HCC) After termination of nitisinone treatment patient C4 (Table 15.4) died due to hepatocellular carcinoma, despite normalization of AFP level while under nitisinone treatment. None of the patients with HCC had normal plasma AFP level.

Eight patients underwent liver transplantation, all living donor liver transplantations (LDLT) (Table 15.5). The median age at transplantation was 81.8 months (range, 16–172 months) and the median age of treatment at the time of transplantation was 52.1 months (range, 4–159 months). Suspected HCC with normal liver function tests was the reason for LDLT in two subacute (patients S6 and S5) and three chronic HT1 patients (patients C3, C7 and C10). Non-compliance with both nitisinone and dietary treatment along with HCC suspicion was the reason for LDLT in patient C3. He had neither maintained adequate nitisinone nor Tyr (4.7 μmol/L and 567 μmol/L, respectively). Serious difficulty in adherence to dietary treatment was the reason LDLT for two chronic HT1 patients (patient C8 and C9); both maintained adequate nitisinone level (54.7 and 79.1 μmol/L, respectively) but had high plasma Tyr concentration (430 and 693 μmol/L, respectively). Hepatocellular carcinoma was detected incidentally in one subacute HT1 patient who underwent liver transplantation due to partial respons to nitisinone therapy with high alpha fetoprotein level and slight increase in PT and aPTT time. All patients but one are alive after liver transplantation (Table 15.5).

Hepacellular carcinoma was reported in 7/32 of patients reported by Dursun et al. (2011). All of these patients were reported to be treated irregularly and inadequetely with nitisinone and there was no data available concerning nitisinone plasma levels or urinary SA excretion. Among these seven patients five who carried N232K, D233V, V259D and IVS3-3C>G mutations developed liver cancer between 10 and 12 years of age. On patient with IVS6-1G>T mutation had normal AFP level although histological test results of liver tissue was compatible with neoplasm.

None of the 36 patients in our cohort with tubulopathy had glomerular involvement, nor developed renal insufficiency. Two patients required temporary supplementation of bicarbonates. Rickets was cured in all 27 patients. No data was available about the renal tubular or glomerular functions in the other published Turkish cases treated with nitisinone.

No porphyria-like neurologic crisis was detected under regular nitisinone treatment in our patients' group. Dursun et al. also reported disappearance of neurologic crisis after nitisinone treatment (Dursun et al. 2011). But interrupted nitisinone treatment for approximately 8 months resulted in death due to severe polyneuropathy with phrenic paresis and respiratory insufficiency in one subacute HT1 patient (S4), and severe abdominal pain due to porphyria-like attack for 2 and 3 months of interruption, respectively, in two of our subacute HT1 patients. Onenli Mungan et al. also reported a 9 months old patient with HT1 detected by selective newborn screening represented with neurologic crisis after 1 month discontinuation of nitisinone (Onenli Mungan et al. 2016).

The only patient with left ventricular septal hypertrophy in our patients' group responded well to nitisinone therapy with disappearance of the hypertrophy. Cardiomyopathy was not reported during the treatment. Dursun et al. also reported reversal of restrictive cardiomyopathy under nitisinone therapy (Dursun et al. 2011).

Height and weight development normalized in all but two patients who remained at <2 SDS for

Table 15.5 Hepatic transplantation in hereditary tyrosimenia type 1 patients

Patient no	HT1 subtype	Age at diagnosis	Time between diagnosis and treatment (months)	Reason for LT	Age at LT (months)	Type of LT	Result
S5	Subacute	9	0	Suspicion of HCC	55	LDLT	Died (acute liver rejection) (HCC was detected at transplantation)
S6	Subacute	12	26	Suspicion of HCC	172	LDLT	Alive (HCC was detected at transplantation)
S7	Subacute	9	0	Partial responder	16	LDLT	Alive (HCC was detected at transplantation)
C3	Chronic	27	30	Non-compliance with the treatment and suspicion of HCC	90	LDLT	Alive (HCC was detected at transplantation)
C7	Chronic	50	57	Suspicion of HCC	132	LDLT	Alive (Hepatic dysplasia detected at transplantation)
C8	Chronic	30	15	Non-compliance with dietary treatment	52	LDLT	Alive
C9	Chronic	39	90	Non-compliance with the dietary treatment	91	LDLT	Alive
C10	Chronic	43	1	Suspicion of HCC	47	LDLT	Alive (HCC was detected at transplantation)

LT liver transplantation, *LDLT* living donor liver transplantation

height and five remained at <2 SDS for weight in our patients' group.

Overall, the primary causes of death in patients with HT1 patients under nitisinone therapy are hepatocellular carcinoma (three patients; patient S2, C4 and C6), hepatic insufficiency (patient S1, patient C1), cirrhosis and variceal bleeding (patient C5), porphyria like attack (patient S4), acute rejection after liver transplantation (patient S5), sepsis (patient A1), aspiration pneumonia (patient A2) (Table 15.4). Both patients who were only treated with low tyrosine and phenylalanine diet, died due to hepatic insufficiency.

Among 34 Turkish patients under treatment with nitisinone therapy, one died after liver transplantation, one due to hepatocellular carcinoma, one due to porphyria like neurologic crisis due to discontinuation of therapy (Dursun et al. 2011; Onenli Mungan et al. 2016). No etiology was reported in five patients that died on the follow-up (Dursun et al. 2011).

15.2.3.3 Adverse Effects of Nitisinone

No adverse effect required interruption of nitisinone treatment. Two patients in our patients' group complained of foreign body sensation in

the eyes at plasma tyrosine concentration 865 and 1290 μmol/L with subepithelial corneal opacities. Eye symptoms resolved with strict adherence to diet and decrease of plasma tyrosine <400 μmol/L. No cutaneous lesions were detected. Two patients had transient leukopenia and two had transient thrombopenia without clinical consequences.

No adverse effect of nitisinone was reported on 69 cases extracted from the literature except one patient who presented with corneal pseudodentritic lesions due to increase in plasma tyrosine level and responded to strict compliance to the dietary treatment at a 4 week follow-up (Gulmez Sevim et al. 2015).

Eleven patients in our patients' group had cognitive evaluation: two undertook the age-appropriate Wechsler Scale IQ test (WISC-R; Wechsler Intelligence Scale for Children for age 7–17 years), eight were assessed with the Stanford-Binet Intelligence Scale, and one was assessed with the Cattell Culture Fair Intelligence Test. The mean total IQ was 85 (range 50–115). Low IQ score was associated with special education attendance. WISC-R was repeated at a 1 year and 7 months interval in one patient and Stanford-Binet IQ test was repeated at a 3 year interval in one patient. Both revealed a decline from 74 to 73 and 91 to 88, respectively. Two patients were assessed with both Stanford-Binet Intelligence Scale and WISC-R at a 3 year interval, which revelead a decline from 95 to 84 and 104 to 100, respectively. Eleven patients were evaluated with the Denver II test. The mean total score was 92 (range, 70–100).

15.3 Discussion

This case series represents the largest analysis of data and longterm outcome of HT1 patients in Turkey. Turkey, with a high rate of consanguineous marriages, has a high estimated prevelence of inborn errors of metabolism (Ozalp et al. 1990; Tuncbilek and Ozguc 2007). HT1 has a birth incidence of approximately 1 in 100,000 in most countries but the exact incidence of HT1 in Turkey is still unknown. Consanguinity was noted in 25/42 of our patients (59.5%).

Diagnosis still depends on the clinical suspicion and laboratory investigations as HT1 is not a part of the nationwide screening program, in Turkey. None of the patients was detected by expanded newborn screening for HT1 but two patients were diagnosed by selective newborn screening in the first week of life, due to an affected sibling history (Aktuglu Zeybek et al. 2015; Dursun et al. 2011; Onenli Mungan et al. 2016). Anorexia, pallor, abdominal distension, irritability with abdominal pain were the most common complaints detected in our patients' group. Interestingly babies were most commonly diagnosed with infantile colic at the onset of symptoms. Due to severity of the disease the interval between the onset of clinical symptoms is shortest in acute HT1 patients an longest in the chronic HT1 patients. In all patients reported the initial clinical manifestations ranged from asymptomatic hepatomegaly to severe hepatic insufficiency. Rickets, splenomegaly, diarrhea and anemia were the other most common clinical findings. Neurologic crisis with porphyria like symptoms and restrictive cardiomyopathy was rarely reported but both responded to nitisinone therapy (Coskun et al. 1991; Dursun et al. 2011; Onenli Mungan et al. 2016).

Laboratory diagnosis of HT1 depends on urinary excretion of SA and mutation analysis. As plasma tyrosine that may not always be elevated is not recommended for diagnosis and newborn screening (Dhillon et al. 2011; Morrissey et al. 2011; Zytkovicz et al. 2013). Mild increase in ALT, AST and ALP with hepatic synthesis dysfunctions and elevated AFP are usually the most common laboratory findings in Turkish HT1 patients as reported in the literature (Coskun et al. 1991; Dursun et al. 2011; Bay et al. 2012). The laboratory findings were most striking in acute and subacute HT1 patients.

All Turkish patients reported, excreted SA in their urine except one in our group and one that was reported by Dursun et al. (2011). Detection of increased plasma SA and mutation analysis confirmed the diagnosis in these patients. This finding has previously reported in the literature

(Haagen and Duran 1987; Rinaldo et al. 2006; Cassiman et al. 2009; Blackburn et al. 2016). Haagen and Duran (1987) proved that this finding was due to the low sensitivity of the test method used, but Cassiman et al. (2009) considered that this finding might be due to the residual activity of the FAH enzyme and Blackburn et al. (2016) hypothesized that the p.R142G variant can bind and catabolize SAA efficiently, resulting in undetectable levels of SA. Collecting a 24 h urine sample (all urine portions freezed at −20 °C, separetely) might also increase the chance for SA detection in urine samples where plasma SA and mutation analysis is not available (Aktuglu Zeybek et al. 2015). No significant difference in urinary SA excretion was noted between acute, subacute and chronic HT1 patients.

The tyrosine and phenylalanine restricted diet alone was not effective in HT1 treatment (Coskun et al. 1991). Most common complications in untreated patients are hepatic failure, cirrhosis and hepatocellular carcinoma (Coskun et al. 1991; van Spronsen et al. 1994). Nitisinone has significantly improved survival and quality of life of Turkish HT1 patients, as reported in the literature (Lindstedt et al. 1992; Dursun et al. 2011; Masurel-Paulet et al. 2008; Aktuglu Zeybek et al. 2015; Simoncelli et al. 2015; McKiernan 2006, McKiernan et al. 2015). The recommended initial nitisinone dose ranges from 1 to 2 mg/kg/day, in one or two doses (Jenkins 2002; Roth 2007). Afterwards, the dose must be adjusted according to the plasma nitisinone level that is estimated to be sufficient to eleminate SA excretion (Counce 2011; El-Karaksy et al. 2010; Masurel-Paulet et al. 2008). Initial nitisinone dose ranged from 0.6 to 2 mg/kg/day given in two divided doses in our patients group. On the follow up, the mean nitisinone dose was 1.2 mg/kg/day, which was slightly higher than the recommended dose, 1 mg/kg/day (El-Karaksy 2011; Couce 2011). The mean nitisinone blood level on the follow-up was 39 μmol/L and was sufficient to eliminate SA excretion (Masurel-Paulet et al. 2008; El-Karaksy et al. 2011; Couce 2011).

Despite its effectiveness, still some patients do not (nonresponder) or partially respond to treatment (partial responder). No predictive factors have been identified for this lack of response (van Spronsen et al. 1994). Holme and Lindstedt (2000) described improvement in liver functions in 90% of cases treated with nitisinone before 6 months of age, but eight patients did not respond to treatment. One subacute HT1 patient in our group was found to be nonresponder to nitisinone treatment. The subacute HT1 patient (patient S1) was diagnosed at 8 months of age: although he was treated with nitisinone (2 mg/kg/day), he died due to progressive hepatic insufficiency in the second month of treatment (Table 15.4). Two patients (one subacute and one chronic HT1 patient) had partial response to nitisinone treatment with partial recovery in the coagulation profile, and were under evaluation for LT. The chronic HT1 patient (Patient C5) was diagnosed at 29 months of age and despite nitisinone treatment, the patient died at 10 months of treatment due to progressive cirrhosis and massive esophageal variceal bleeding. The subacute HT1 patient underwent succefull living donor liver transplantation (Table 15.5, patient S7). Unresponsiveness to nitisinone has already been reported but still the reasons for lack of response have not been clearly identified (van Spronsen et al. 1994) Methionine level can be an indicator for non/partial response. There was no significant difference in plasma methionine level between responders (mean, 356.3 μmol/L; range, 13.3–1590 μmol/L) and non/partial-responders in our patients group at presentation (mean, 465 μmol/L; range, 70–820 μmol/L) but the increased methionine did not decrease to normal (20–50 μmol/L) despite maintenance of adequate nitisinone and tyrosine. There was a significant difference between both groups during follow up: mean plasma methionine was 15.9 μmol/L (range, 12–39 μmol/L) in responders, while it was 265 μmol/L (range, 79–470 μmol/L) in non/partial-responders ($P < 0.001$). No further data was available regarding responsiveness and non/partial responsiveness in Turkish HT1 patients.

Although nitisinone had significantly improved survival in both our cohort and in Turkish patients described in the literature, the overall survival rate of the 40 patients treated with nitisinone was 75% (30/40) and 88% (22/24), respectively. This rate is

higher than in pre-nitisinone reports (van Spronsen et al. 1994). Still, the survival rate in the present cohort was lower than in the French, Spanish and Quebec series, with rates of 97.8%, 100%, 96%, respectively (Masurel-Paulet et al. 2008; Couce et al. 2011; Larochelle et al. 2012). The most striking difference between the present study and these studies was that nitisinone treatment was initiated after 6 months of age in 69% of the present patients and 60.6% of Turkish patients described (Dursun et al. 2011; Bay et al. 2012; Onenli Mungan et al. 2016). Temporary interruption of the treatment due to various reasons (e.g. health insurance problems) was common, leading to irregular and inadequate treatment with nitisinone. Permanent interruption of nitisinone treatment resulted in death in four patients. One patient died due to HCC, one patient due to hepatic insufficiency and two due to porphyria-like neurologic crisis. Although latest data suggest that early nitisinone treatment is the key factor in the good outcome of the neonatally treated patients, and that a combination of neonatal screening and early nitisinone treatment is recommended, even in early diagnosis patients, drug interruption can lead to increased mortality rate, especially due to HCC (Larochelle et al. 2012; Morrissey et al. 2011; Zytkovicz et al. 2013).

Liver cancer has been reported as an important risk for patients with HT1 treated with nitisinone (Holme and Lindstedt 1998; Seda Neto et al. 2014; Bahador et al. 2015). Development of HCC is the main risk for patients with the chronic form or who have been treated with nitisinone after 2 years of age (Holme and Lindstedt 2000; van Spronsen et al. 2005). The patients with persistent high AFP and/or has a slow AFP decline without reaching to normal are under particular risk (Koelink et al. 2006; Larochelle et al. 2012; Mayorandan et al. 2014). All six patients in our study group with persistent high AFP along with normal liver function tests are proved to have hepatocellular carcinoma. Secondary AFP increase was detected in four patients: two responded to dose increase while two patients did not and HCC was detected at liver transplantation. The present data support the findings of previous reports (Koelink et al. 2006; Larochelle et al. 2012). Close follow up of serum AFP, even of minor changes, is important for early detection of HCC and hepatocellular dysplasia especially in late-diagnosed patients. Also, disruption of the hepatic architecture was a common finding along with nodularity even at the time of presentation, especially in late diagnosed patients. Nitisinone treatment was not effective in complete reversion of the hepatic lesions and normalization of the architecture, except in two patients. De novo hyperechoic and hypoechoic nodule formation were also detected despite nitisinone treatment without increase in AFP. As all of our patients with HCC had hypoechoic nodules detected on ultrasound, although malign transformation was not definitely proven on abdominal MRI hypoechoic de novo nodule formation should always be an alert for HCC as HCC has been reported in HT1 patients without clear increase of AFP (van Ginkel et al. 2015).

Renal tubular dysfunction with increased echogenicity was common in the present patients, as previously described (Couce et al. 2011; Mayorandan et al. 2014).

The findings resolved with nitisinone treatment although asymptomatic nephrocalcinosis persisted in 5/5 patients. None of the patients developed renal insufficiency during nitisinone treatment.

Episodes of acute neuropathy that clinically resemble porphyric crises occur in up to 50% of untreated children (Mitchell et al. 1990; van Spronsen et al. 1994). Succinylacetone acts as a competitive inhibitor of the enzyme delta aminolevulinic acid dehydratase in the haem biosynthetic pathway. This enzymatic block leads to increase in delta aminolevulinic acid and PBG. Neurological crises in HT1 are identical to those occurring in porphyria and lead poisoning, in which delta aminolevulinic acid is also increased (Russo et al. 2001). The mortality is up to 65% if left untreated (Chakrapani et al. 2012). Normalization of SA in blood, correction of the complete inhibition of PBGS in erythrocytes during nitisinone treatment protects against porphyric crisis (Lindstedt et al. 1992). Schlump et al. reported that interruption of nitisinone treatment can cause severe neurological crisis in patients with HT1 (Schlump et al. 2008). In the

present cohort, interrupted nitisinone treatment resulted in porphyria-like attacks in three patients, and death in one patient due to respiratory insufficiency. Kalkanoglu and Ucar reported two Turkish HT1 cases of acute pancreatitis mimicking neurologic crisis due to discontinuation of nitisinone treatment (Kalkanoglu and Coskun 1999; Ucar et al. 2016), resolved after continuation of nitisinone. Onenli Mungan also reported a case with severe neurologic crisis after discontinuation of nitisinone only for a month (Onenli Mungan et al. 2016).

Cardiomyopathy has been reported as a frequent finding in HT1 (André et al. 2005; Arora et al. 2006; Mohamed et al. 2013; Seda Neto et al. 2014). Neither the mechanism nor the natural history of this complication is understood. It is suggested that the cardiomyopathy may be due to direct cardiotoxicity of circulating Tyr metabolites during a critical period of vulnerability, and nitisinone reduces the level of these metabolites (Arora et al. 2006). We had only one patient with septal hypertrophy and Dursun reported one patient, both responded to nitisinone therapy.

Compliance with low Tyr low Phe diet is challenging in the follow-up of patients with HT1. The recommended level of Tyr, 200–400 μmol/L, is difficult to achieve. Noncompliance increases as the child grew older. Even patients with good and moderate compliance had periods of bad control. The serious dietary non-compliance problems led two patients to prefer LDLT in our group.

Variation of plasma tyrosine seems to be an important pathogenic factor in abnormal intellectual development and attention disorder in HT1 patients under long-term treatment with nitisinone (De Laet et al. 2011; Bendadi et al. 2014; Pohorecka et al. 2012; van Ginkel et al. 2015). Mouse model studies revealed that lower learning and cognitive differences caused by tyrosinemia type 1 and not by the treatment with NTBC (Hillgartner et al. 2016).

Eleven patients had cognitive evaluation and the mean total IQ was 85 (range, 50–115). Low IQ score was associated with special education. Repeated IQ evaluation revealed a decline in average IQ score in all four patients. These findings were consistent with recent studies (De Laet et al. 2011; Bendadi et al. 2014; Pohorecka et al. 2012; van Ginkel et al. 2015). Attention deficit and learning difficulties were also common, but behavior was not evaluated in the present cohort. Although exact mechanism for intellectual impairment still remains unknown it is hypothesized that elevated plasma tyrosine concentrations under NTBC treatment may be associated with neurocognitive functioning (van Ginkel et al. 2015). Mouse models revealed that tyrosinemia type I and Not treatment with NTBC causes slower learning and altered behaviour in mice (Hillgartner et al. 2016).

Genetic data documents obtained from the literature revealed the most prevelant mutation in Turkish patients were homozygosity for IVS6-1G>T (26%) followed up by D233V (22%). IVS6-1G>T has previously been reported as the most common mutation in Mediterranean populations (Bergman et al. 1998; Couce et al. 2011; Dursun et al. 2011; Mayorandan et al. 2014; Angileri et al. 2015). D233V which was the second most common seen mutation is specific to Turkish population (Dursun et al. 2011; Rootwelt et al. 1994, 1996). IVS12+5G>A was detected in three patients (Rootwelt et al. 1994; Dursun et al. 2011). V166G and V259D mutations, probably causing dysfunction via misfolding, was reported in three Turkish patients (Dursun et al. 2011). No clear genotype/phenotype correlation was found for the most common mutations (IVS6-1G>T, D233V, IVS3-3C>G) (Bergman et al. 1998; Dursun et al. 2011), although Counce reported that hepatic presentation was more common and the renal involvement less frequent in HT1 patients carrying IVS6-1G>T mutation than in patients with other mutations (Counce et al. 2011).

15.4 Conclusion

Nitisinone treatment is effective and improves both the short-term and the long-term prognosis of HT1. Still, early diagnosis on newborn screening is needed because late diagnosis along with delay in treatment carries the risk of persistence of hepatic disease and HCC. In countries where

HT1 is not part of newborn screening, it is important to be able to recognize the clinical and laboratory findings in order to prevent delay in diagnosis. More importantly, adding HT1 screening to the nationwide screening program in Turkey is necessary for early diagnosis and facilitation of early treatment, to decrease the mortality and morbidity of the disease.

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