MEANDROS MEDICAL AND DENTAL JOURNAL
March 2025 (1):33-41

Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj.1614784

Research Article

CLINICAL FEATURES, GENETIC SPECTRUM, AND OUTCOMES OF HEREDITARY TYROSINEMIA TYPE 1: A MULTICENTER STUDY FROM SOUTHEASTERN TÜRKIYE

Emine GÖKSOY [1]*, Ayşe ERGÜL BOZACI [2], Berrak BİLGİNER GÜRBÜZ [3]

[1] Pediatric Metabolism Department, Faculty of Medicine, Adnan Menderes University, Aydın, Türkiye
[2] Pediatric Metabolism Department, Faculty of Medicine, Akdeniz University, Antalya, Türkiye
[3] Pediatric Metabolism Department, Ankara Bilkent City Hospital, Ankara, Türkiye
*Correspondence: emine.goksoy@adu.edu.tr

Received: *07 January 2025*
Revised: *17 February 2025*
Accepted: *17 February 2025*
Published: *20 March 2025*

ABSTRACT

Objective: Hereditary Tyrosinemia Type 1 (HT1) is a metabolic disorder due to fumarylacetoacetate hydrolase deficiency, which can lead to liver and kidney damage. This study aims to expand our knowledge of the clinical presentation, diagnosis, and outcomes of HT1 patients from southeastern Türkiye, a region with high consanguinity rates.

Materials and Methods: This retrospective multicenter study included 20 HT1 patients from three metabolic centers in southeastern Türkiye between January 2018 and March 2021. Demographic, clinical, laboratory, and genetic data were retrieved. Patients were divided into acute, subacute, and chronic forms according to the beginning of their symptoms. The statistical analyses consisted of descriptive and inferential methods.

Results: The parents of all 20 cases (9F/11M) were consanguineous. The mean diagnostic age was 10.53±12.54 months, with an average diagnostic delay of 2.96±4.42 months. The most common form was acute HT1 (55%), followed by chronic (25%) and subacute (20%) forms. Common finding was hepatomegaly (40%). Tubulopathy was frequent in chronic HT1 (80%). Increased α-fetoprotein levels were found in 60% of the cases at the diagnosis. Hepatocellular carcinoma developed in three patients. Two died of the disease. Genetic studies showed that the most common mutation was c.554-1G>T (27%).

Conclusion: The study highlights the clinical burden and the challenge in managing HT1 in Türkiye, attributed to late diagnosis resulting from absence of the newborn screening (NBS). Although studies have demonstrated that early nitisinone treatment improves outcomes, long-term follow-up for complications like hepatocellular carcinoma is imperative. NBS needs to be extended to reduce morbidity and mortality associated with HT1.

Keywords: Hereditary tyrosinemia type 1, hepatocellular carcinoma, nitisinone.

MEANDROS MEDICAL AND DENTAL JOURNAL
March 2025 (1):33-41

Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj.1614784

INTRODUCTION

Herediter Tyrosinemia type 1 (HT-1, OMIM 276700) is an autosomal recessive hereditary metabolic disorder that is caused by a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH), which is responsible for the final step of the tyrosine (Tyr) catabolic pathway, leading to liver and kidney damage with the accumulation of toxic metabolites, especially succinylacetone (SUAC). It has acute, subacute, and chronic forms (1,2). The estimated prevalence of HT-1 is 1 in 100,000 to 120,000 live births worldwide (2). However, due to the founder effect in some regions, such as the province of Quebec in Canada, there is a higher incidence of 1 in 16,000 live births (1). Specific epidemiological data on HT-1 are limited, and the incidence of HT1 in Türkiye is currently unknown.

Toxic metabolites accumulated in HT-1, especially SUAC, cause oxidative damage, mitochondrial dysfunction, and apoptosis in hepatocytes and renal tubular cells (3). HT-1 typically presents as liver disease, including jaundice, hepatomegaly, and failure to thrive in infants (4). Clinical manifestations vary depending on the age of onset of symptoms. Renal involvement can cause Fanconi syndrome with aminoaciduria, glycosuria, and hypophosphatemia with rickets. On examination, hepatomegaly, and a characteristic "cabbage-like" odor can be detected (4,5). The accumulation of SUAC inhibits delta-aminolevulinic acid dehydratase (ALA-D) enzyme, disrupting porphyrin synthesis. This condition may lead to severe pain and tingling due to peripheral nerve involvement, and paralysis due to motor neuron impairment (4). Additionally, nitisinone (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, NTBC) therapy increases plasma tyrosine levels by blocking the metabolic pathway further upstream to prevent the formation of SUAC. This leads photophobia caused by corneal deposits, palmoplantar keratoderma, and cognitive impairment due to disrupted neurotransmitter synthesis may occur (3,4,6). Laboratory tests may show mildly elevated liver enzymes, SUAC (in urine or blood), and cardiomyopathy (1,7). Even with therapy, there is a substantial risk of cirrhosis, and the development of hepatocellular carcinoma (3). HT-1 diagnosis is based on clinical findings, as well as elevated levels of tyrosine and methionine in blood, and detection of SUAC in the urine or blood, which is a specific metabolite for HT-1 (1). The diagnosis should be confirmed by detecting a mutation in the FAH gene (NM_000137.3) for a definitive diagnosis (1). Early diagnosis through NBS is crucial for effective management and improved outcomes (1,2).
The use of NTBC, a powerful inhibitor of the 4-hydroxyphenylpyruvate dioxygenase enzyme that prevents the formation of SUAC, which is held responsible for the main damage, has revolutionized the management of HT-1 and significantly reduced the risk of liver failure and HCC when started early. According to studies, renal involvement and neurological crises could be prevented by early initiation of NTBC (3,5,6). However, due to NTBC treatment, elevated plasma tyrosine levels result in ophthalmological and skin disorders that require lifetime dietary restrictions on tyrosine and phenylalanine (6). Liver transplantation may be considered for patients if they develop liver cancer or do not respond to medical treatment (8).

Our study aims to expand our knowledge of clinical outcomes to improve our comprehension of the disease course and to contribute to the literature on current clinical practices for HT1 in Türkiye.

MATERIALS AND METHODS

This study provides a comprehensive overview of the clinical approach and patient data collection related to HT1 at the three important metabolic centers in the Southeastern part of Türkiye. Medical records from HT1 patients followed at the Pediatric Metabolic Diseases Unit of Gaziantep Children's Hospital, Diyarbakır Children's Hospital, and Adana City Hospital between January 2018 and March 2021 (26/11/21-933).

Patients were identified based on high SUAC levels in their urine or blood, as well as FAH gene analysis (excluding P19). Three main clinical forms were categorized based on the age at symptom onset: the acute form (onset of symptoms at <6 months of age), the subacute form (onset of symptoms at 6-12 months of age), and the chronic form (onset of symptoms at >12 months of age) according to van Spronsen classification (9). Diagnostic delay was defined as the time interval (in months) between the onset of symptoms and the final diagnosis of HT1.

Demographic information (gender, consanguinity, family history, age of onset symptoms, current age), clinical information (symptoms such as irritability, jaundice, pallor, abdominal distension, tendency to bruise, fever, abdominal pain, abnormal urine odor; physical examination findings such as hepatomegaly, splenomegaly, anthropometric measurements, eye and neurological findings), laboratory findings (Serum alanine amino transferase-ALT, aspartate transaminase-AST, alpha-fetoprotein-AFP, total bilirubin, direct bilirubin, serum tyrosine, phenylalanine, methionine, urea, creatinine levels, urinary tubular functions, blood

MEANDROS MEDICAL AND DENTAL JOURNAL
March 2025 (1):33-41

Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj.1614784

Table 1. Main symptoms, clinical and laboratory findings at diagnosis by presentation type of patients with HT1.

	Acute (n:11)	Subacute (n:4)	Chronic (n:5)	Total (n:20)
Main symptoms				
Irritability	8 (72%)	1 (25%)	0	9 (45%)
Jaundice	7 (63%)	1 (25%)	0	8 (40%)
Growth retardation	1 (9%)	2 (50%)	4 (80%)	7 (35%)
Pallor	4 (45%)	3 (75%)	0	7 (35%)
Abdominal distention	2 (18%)	1 (25%)	3 (60%)	6 (30%)
Tendency to bruise	0	2 (50%)	4 (80%)	6 (30%)
Fever	5 (45%)	0	0	5 (25%)
Abdominal pain	0	0	3 (60%)	3 (15%)
Abnormal urine odor	1 (9%)	1 (25%)	0	2 (10%)
Clinical and laboratory findings				
Hepatomegaly/splenomegaly	4 (45%)	1 (25%)	3 (60%)	8 (40%)
Coagulopathy	6 (54%)	1 (25%)	2 (40%)	9 (45%)
Chronic liver disease	2 (18%)	1 (25%)	4 (80%)	7 (35%)
Jaundice	6 (54%)	0	1 (20%)	7 (35%)
Tubulopathy	1 (9%)	1 (25%)	4 (80%)	6 (30%)
Hypotonia	3 (27%)	2 (50%)	0	5 (25%)
Intellectuel disability	0	0	3 (60%)	3 (15%)

SUAC/urine SUAC levels), radiological findings (abdominal ultrasonography, MRI) of patients diagnosed with HT-1 from three centers were collected using case report forms. Laboratory findings were evaluated based on the time of diagnosis. Furthermore, they were monitored throughout follow-up to assess the response to treatment. Parameters that normalized after treatment but increased during follow-up were documented. Histopathological findings from liver biopsies, if available, were also documented.

Serum AFP results were analysed according to age-specific normal values. Since AFP reference values in the neonatal period are much higher than the other periods, AFP values were evaluated as high or normal (10).

The neurodevelopmental status of patients was evaluated by using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), Denver II test, and Wechsler Scale IQ test (WISC-R; Wechsler Intelligence Scale for Children for age 7–17 years), with the total score considered for assessment.

All patients were treated with a tyrosine and phenylalanine-restricted diet. Plasma tyrosine levels were targeted at < 400µmol/l. Nitisinone treatment was initiated immediately with a dose of 1–2 mg/kg/day.

Statistical analysis

Statistical analyses were performed using the SPSS software package (ver.18.0; SPSS Inc., Chicago, IL, USA). Numerical variables were expressed as mean ± standard deviation (SD) for normally distributed data and median (range) for non-normally distributed data. Descriptive statistics, categorical variables were presented as numbers and percentages. The normality of data distribution was assessed using the Shapiro-Wilk test.

RESULTS

The study included 20 patients (9F/11M) with HT1 from 18 families. All the parents of patients had consanguinity. The mean age at the onset of symptoms was 7.57± 8.33 months (min: 3 days, max: 30 months). The mean age of the patients at diagnosis was 10.53± 12.54 months (min: 6 days, max: 48 months). The mean diagnostic delay time was 2.96±4.42 months (min: 3 days, max: 18 months.). 11 patients (55%) had acute form, 4 patients (20%) had subacute form, and 5 patients (25%) had chronic form of disease. Very early-onset symptoms (<2 months of age) were seen in 5 patients (25%). The main symptoms are listed in Table 1. All our patients, although 2 of our patients had a sibling history, were diagnosed after the onset of symptoms.

MEANDROS MEDICAL AND DENTAL JOURNAL
March 2025 (1):33-41
Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj.1614784

Table 2. Main laboratory findings at diagnosis.

Patient	AST (IU/L)	ALT (IU/L)	INR	AFP (ng/ml)	AFP results	Tubulopathy	Serum tyrosine level (µmol/L)
P1	106	88	1.5	98	high	absent	493
P2	380	250	1.6	75000	high	absent	479
P3	50	45	0.9	5	normal	absent	352
P4	38	40	1	12	normal	absent	402
P5	65	88	1.4	200	high	absent	261
P6	79	69	0.9	75	high	absent	185
P7	77	83	1	234	high	absent	164
P8	186	103	1.7	83500	high	absent	286
P9	75	66	1	153	high	exist	289
P10	34	28	0.8	2	normal	exist	664
P11	46	43	1.2	5	normal	absent	89
P12	145	108	1.6	196000	high	absent	439
P13	77	65	1.2	2500	normal	absent	429
P14	39	34	0.9	4	normal	absent	723
P15	38	25	0.9	10	normal	absent	463
P16	65	55	3	789	high	exist	905
P17	68	55	2	425	high	exist	881
P18	38	22	0.9	4	normal	exist	458
P19	85	66	6.1	685000	high	absent	670
P20	95	78	1.9	135	high	exist	557.44

Abreviations: AST: Aspartate transaminase; ALT: Serum alanine amino transferase; INR: International Normalized Ratio; AFP: Serum a-fetoprotein
Normal values of liver transaminase: ALT (6–50 IU/L for 0–5days, 35–140 for 1–19 years), AST: (5-45 IU/ml for 0–5days, 15–55 IU/ml for 1–19 years)

The primary clinical findings included hepatomegaly and/or splenomegaly in 8 patients (40%). Hypotonia was detected in 5 patients (25%), and intellectual disability (ID) in 3 patients (15%), based on total scores from standardized developmental tests (Table 1). Coagulopathy and jaundice were seen in 6/11 (36.3%) patients as the most common findings in the acute form. In the subacute form, there was no jaundice. In chronic type 4/5 patients had (80%) tubulopathy (Table 1).

One patient (P19) presented with hyperinsulinemic hypoglycemia at the time of diagnosis requiring continuous diazoxide treatment until death. Additionally, hepatocellular carcinoma (HCC) developed in three patients (P9, P16, and P17). Patient 17 died while waiting for transplantation after HCC, and the other one (P19) died due to acute liver failure in the newborn period. NTBC started immediately after the elevated SUAC results. It was used at a dose of 2 mg/kg/d for 4 (20%) patients and 1mg/kg/d for 16 (80%) patients.

Twelve patients (60%) (Table 2) had high AFP levels at the time of diagnosis. All patients had elevated serum tyrosine levels and increased urinary excretion of SUAC by gas chromatography-mass spectrometry (qualitative). Patient 9 was prescribed NTBC treatment at a dose of 1g/kg/day after being diagnosed at 4 months of age. Although AFP levels normalized within six months, a subsequent increase was observed during follow-up. ALT, AST, and serum Tyr levels were documented in Table 2. None of the patients underwent liver transplantation.

The most common mutation in our study was c.554-1G>T (27%), followed by c.315-3C>G (22%) and c.1062+5G>A (16%), respectively. Other detected mutations were c.441_448del, c.554-1G>A, c.709C>T, c.698A>T, and c.520C>T (Table 3). All mutations were detected as homozygous.

DISCUSSION

This study is the first multicenter study in our country showing the course and outcomes of HT1 and reflects the results of the southeastern region of Türkiye, which has a very high rate of consanguineous marriage(11). The present study describes the relation between phenotype

MEANDROS MEDICAL AND DENTAL JOURNAL
March 2025 (1):33-41
Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj.1614784

Table 3. Clinical type, clinical findings, and mutations of the patients

Patient	Current age (month)	Age at diagnosis (month)	Type	Clinical Findings				Mutation*		
				HM/SM	Renal involvement	Neurologic involvement	Others	Exon	Nucleotid	Protein
1	36	6	Acute					9	c.709C>T	R237X
2	19	6 days	Acute					8	c.698A>T	D233V
3	51	12	Subacute					5	c.441_448del	
4	168	6	Acute					5	c.441_448del	
5	10	3	Acute						NA	
6	37	6	Acute	+				3	c.315-3C>G	
7	40	3	Acute					12	c.1062+5G>A	
8	84	6 days	Acute			ID		3	*c.315-3C>G*	
9	17	4	Acute	+		Hypotonia		6	*c.554-1G>T*	
10	204	18	Chronic		+	ID+epilepsy		6	c.520C>T	R174X
11	21	8	Subacute	+		Hypotonia		6	c.554-1G>T	
12	132	10 days	Acute	+				6	c.554-1G>T	
13	9	1	Acute	+		Hypotonia		6	c.554-1G>T	
14	72	18	Chronic					3	c.315-3C>G	
15	10	8	Subacute			Hypotonia		3	c.315-3C>G	
16	36	20	Chronic	+	+	ID		12	c.1062+5G>A	
17	60	48	Chronic	+	+	ID		12	c.1062+5G>A	
18	84	12	Subacute		+			6	*c.554-1G>T*	
19	1.5	1	Acute		+		Hyperinsulinemic Hypoglycemia		NA	
20	84	36	Chronic	+	+			6	c.554-1G>A	

NA: Not available. * All patients with available genetic data have homozygous mutations. ** Patients P9, P16, and P17 were diagnosed with HCC. *** Patients P17 and P19 died due to disease-related complications.

and genotype as well as the long-term outcome of HT1 in Türkiye. Although the exact incidence of HT1 in Türkiye remain unclear, it is expected to be high due to given the high prevalence of inborn errors of metabolism (5,12). All our patients were born from consanguineous marriages.

Diagnosis

In our study, the mean age at diagnosis was 10.53 ± 12.54 months (range: 6 days to 48 months), with a mean diagnostic delay of 2.96 ± 4.42 months (range: 3 days to 18 months). Literature from Türkiye revealed a mean diagnostic age of 15.3 months (range: 0.06 to 108 months) in extracted 43/69 patients (5). In cases identified through selective screening (2 patients via NBS and five patients screened due to affected siblings), the mean age at diagnosis was 10.5 months (range: 1 to 45 months). In Palestine, the mean age at diagnosis was 8 months (13). Conversely, in Pakistan, there was a considerable delay, with the average age of symptom onset at 8 months and diagnosis at 34.7 months, resulting in an average delay of 26.8 months (14). In Spain, despite the lack of newborn screening (NBS), the mean age at diagnosis was 4.3 ± 3.6 months, reflecting prompt clinical recognition and early initiation of nitisinone treatment (15). With the screening of HT1 with the newborn screening program, early diagnosis and treatment have become possible, and the reduction of such serious deteriorations and mortality rates has been achieved. All our patients were diagnosed after the onset of symptoms. Therefore, in our country diagnosis depends on clinical suspicion and laboratory findings. In regions with organized newborn screening programs, the occurrence of NBS decreases the delay of diagnosis. Countries with well-organized health system, like Spain, have better opportunities for early diagnosis and treatment. However, regions like Pakistan which lacks good health facilities may experience diagnosis delays. Furthermore, high clinical suspicion and awareness of the health care provider's community is necessary for early diagnosis. Screened affected siblings of the patients as implemented in Türkiye may help to minimize the diagnostic delays for subsequent cases.

Clinical presentation with subtypes

Our study identified three main clinical forms of HT1 based on symptom onset: acute (55%), subacute (20%), and chronic (25%). This distribution contrasts with previous studies in Türkiye, where the acute form was reported in

35% (5) and 27% (16). A multicenter study in Spain reported a higher prevalence of acute form HT1, which is 67%. This may be due to the high percentage of acute liver failure in the acute form (15). Similarly, Dweikat et al. (13) reported nearly half of the cases as acute in Palestine, resembling our findings. Our study, conducted in the Southeastern Türkiye, found that this region has higher birth rates that may increase detection of the acute form, which typically presents early. The time of diagnosis may also be affected by difficulties in accessing health services. The higher prevalence of the acute form in our study may be due to differences in birth rates and demographics across the region, genetic factors, and access to health care, which are essential for understanding the population and developing appropriate screening and management systems.

In contrast to earlier research conducted in Türkiye, the primary symptoms in our study were jaundice and irritability. Many parents reported misdiagnosis with infantile colic due to irritability, and this may cause a delay in the exact diagnosis. Similarly, the largest cohort study in Türkiye, attention was drawn to patients diagnosed with infantile colic due to irritability (5). This finding emphasizes how crucial it is to include HT1 when making a differential diagnosis for children who exhibit persistent irritability, a common but generic symptom that is sometimes mistaken for benign illnesses like infantile colic.

Neurological and metabolic complications

In the present study, although hypotonia and intellectual disability (ID) were rare conditions, they were observed in 5 patients (20%) and in 3 patients (15%) at the time of diagnosis, respectively. Hypotonia has been reported in HT1 patients, particularly in severely affected infants or during porphyria-like crises, as also described in previous studies (4). Additionally, Hajji et al. reported isolated hypotonia in 2 out of 33 patients (17). Concerning intellectual disability, studies emphasized that high plasma tyrosine levels under NTBC treatment may be associated with neurocognitive impairment (6,18). Although the precise mechanism is still unknown, research using mouse models suggests that tyrosinemia, not NTBC treatment, is the cause of the cognitive deficits (19).

Neurologic crises presenting with porphyria-like symptoms and restrictive cardiomyopathy have been rarely documented; however, both conditions have shown responsiveness to nitisinone therapy (7,20,21). None of our patients exhibited neurologic crises or cardiomyopathy.

Patient 19 in our study presented with persistent hyperinsulinemic hypoglycemia requiring continuous diazoxide treatment until death, a condition infrequently reported in HT1. Baumann et al. (22) reported 3 HT-1 patients with hyperinsulinemic hypoglycemia. They stated that they controlled the condition with diazoxide and chlorothiazide and tapered it over months. Naser et al. (23) emphasized the need for higher-dose treatment in the case they presented. Sethuram et al. (24) reported that the same condition was observed in the HT-1 case along with the transient hypertyrosinemia case and attributed the hyperinsulinism to elevated insulinotropic amino acids. Our patient revealed persistent, resistant hypoglycemia, and high-dose diazoxide treatment was used. This shows that early recognition and management of hyperinsulinemic hypoglycemia in Tyrosinemia Type 1, especially in severe cases, requires personalized treatment strategies.

Laboratory findings

In our study, consistent with previous studies, the most frequent laboratory findings included impaired liver function, elevated AFP levels, and increased plasma tyrosine levels, often accompanied by abnormal liver functions (5,13,15,16,21). In patients with the acute form of HT1, laboratory results aligned with findings reported in the literature. Interestingly, however, all patients diagnosed with the subacute form exhibited normal liver enzyme levels, preserved liver synthetic function, and normal AFP values at the time of diagnosis. This situation may be due to the small number of patients, and it also suggests that liver involvement may be obscured due to the less severe subacute form. Since all these patients had high plasma tyrosine levels, it has become important to measure plasma amino acids, especially in patients with nonspecific symptoms such as growth retardation, loss of appetite, and irritability.

In our study, elevated AFP levels were observed in 81.8% of patients with the acute form of HT1, and 60% of those with the chronic form, whereas none of the patients with the subacute form exhibited elevated AFP levels. Among acute cases with normal AFP levels, the ages at diagnosis were notably early at 1 and 6 months. Similarly, Rokaite et al. (25) stated that AFP concentrations are often high in the acute form, and may be normal in the chronic form. Furthermore, a study conducted by Aktuglu-Zeybek et al. (5) in our country revealed that AFP elevations were statistically significantly higher in the acute form. Despite these arguments, the difference in AFP levels between clinical forms has limited efficacy as a definitive diagnostic marker for differentiation. However, high AFP levels are

still supportive and still an important indicator of response to treatment, especially in acute forms(4–6).

Genetic variability

A review of the literature reveals that the most common mutation identified in Turkish patients and in the Mediterranean region, consistent with our findings, is c.554-1G>T, detected in five patients (25%) in our cohort. In the analyses conducted by Dursun et al. (21), c.315-3C>G, one of the three most frequent mutations in the Turkish population, was identified as the second most common mutation in our study. Furthermore, c.1062+5G>A, a mutation reported as rare globally in the literature review by Aktuğlu-Zeybek et al. (5), was found to be the third most frequent mutation in our cohort. Similar to other studies, no genotype-phenotype correlation was identified for the frequently observed mutations in our study.

Long-term outcomes

Tubulopathy was identified in 30% of the patients, with a prevalence of 80% (4/5) in those with the chronic form, 25% (1/4) in the subacute form, and 9% (1/11) in the acute form. As all patients were initiated on NTBC therapy immediately after diagnosis, it can be hypothesized that earlier initiation of NTBC treatment may effectively prevent the development of tubulopathy (1,3,6). Aktuğlu-Zeybek et al. (5) reported tubulopathy in 85% of HT-1 patients, while Yazıcı et al. (16) reported 66%. However, the lower acute case rates in these studies (35%, and 27%, respectively) may have contributed to the higher prevalence of tubulopathy. Similarly, Gokay et al. (26) also detected tubulopathy in 71% of patients, and the rate of acute forms in their study was 42%. However, the small sample size in this study significantly limits its generalizability. Dweikat et al. (13) detected tubulopathy half of the cases in acute form.

HCC developed in patient 9, who experienced a re-elevation of AFP levels despite treatment during follow-up. It is generally accepted that secondary AFP elevation is a risk factor for the development of HCC and that patients who start treatment before the age of one have a lower risk of HCC. In our case, although treatment was started in the fourth month and AFP levels returned to normal, the development of HCC may have been due to the patient receiving a dose of 1 g/kg/day of NTBC. The inability to measure NTBC levels represents a limitation of our study.

Future perspectives

Over the years, there have been developments in treatment management, but there are still challenges in the long-term management of HT1. Monitoring for hepatocellular carcinoma is crucial, as the risk remains even during NTBC treatment. Gene therapy research can bring a potential curative approach, as it aims to address the underlying cause of the disease (27).Newer medications and improved biodistribution are also being developed to enhance NTBC adherence and treatment outcomes.

CONCLUSION

This study has some limitations. We were not able to measure nitisinone levels, which could provide important information on treatment efficacy and management. The retrospective nature of the study did not allow us to control for suspicious values. The fact that the examinations were performed in different centers may have caused variability in test results due to differences in methodologies and reference intervals. The follow-up period was relatively short, which limited our ability to evaluate long-term outcomes and disease progression.

Tyrosinemia Type 1 is a complex metabolic condition that, if left untreated, can have serious morbidity and mortality consequences. The disease severity in HT1 changed dramatically with the emergence of NTBC, changing the picture of disease management from a lethal one to a chronic one. Further studies and effective integrative approaches are alike needed to solve the remaining issues and enhance the welfare of HT1 patients. It is crucial for the management of the condition that it is diagnosed as early as possible, that treatment is instituted without delay, and that the patient is monitored regularly.

Acknowledgments

We sincerely thank our patients' family for their cooperation and willingness to participate in this study. We also extend our gratitude to our metabolic dietitians for their valuable support in dietary adjustments. Additionally, we acknowledge the hospital administration for their help in data collection.

Authorship contributions

Contributed to conception and design EG, Surgical and Medical Practices EG, AEB, BBG, collecting data EG, AEB, BBG, analysis EG, AEB, BBG, literatüre search EG, AEB, writing and editing EG.

Data availibity statement

The data that support the findings of this study are available upon reasonable request from the corresponding author.

Declaration of competing interest

Authors declared no conflict of interest.

Ethics

Ethical approval was obtained from Health Sciences University Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee by decision no: 933, dated 26/11/2021.

Funding

Authors declared no financial support.

REFERENCES

1. Chinsky JM, Singh R, Ficicioglu C, van Karnebeek CDM, Grompe M, Mitchell G, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. Genet Med. 2017;19(12):1380–95.

2. Stinton C, Geppert J, Freeman K, Clarke A, Johnson S, Fraser H, et al. Newborn screening for Tyrosinemia type 1 using succinylacetone – a systematic review of test accuracy. Orphanet J Rare Dis. 2017;12(1):48.

3. Holme E, Lindstedt S. Tyrosinaemia type I and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione). J Inherit Metab Dis. 1998;21(5):507–17.

4. Morrow G, Tanguay RM. Biochemical and clinical aspects of hereditary tyrosinemia type 1. Adv Exp Med Biol. 2017;959:9–21.

5. Aktuglu-Zeybek AC, Kiykim E, Cansever MS. Hereditary tyrosinemia type 1 in Turkey. Adv Exp Med Biol. 2017;959:157–72.

6. van Ginkel WG, Rodenburg IL, Harding CO, Hollak CEM, Heiner-Fokkema MR, van Spronsen FJ. Long-Term Outcomes and Practical Considerations in the Pharmacological Management of Tyrosinemia Type 1. Pediatric Drugs. 2019;21(6):413–26.

7. Bilginer Gürbüz B, Aykan H, Çiki K, Karagöz T, Sivri S, Dursun A, et al. Cardiomyopathy in patients with type 1 tyrosinemia, and the effect of nitisinone treatment on cardiomyopathy. Cukurova Med J. 2021 Dec 30;46(4):1419–25.

8. van Ginkel WG, Pennings JP, van Spronsen FJ. Liver cancer in tyrosinemia type 1. Adv Exp Med Biol. 2017;959:101–9.

9. van Spronsen FJ, Thomasse Y, Smit GP, Leonard J V, Clayton PT, Fidler V, et al. Hereditary tyrosinemia type I: a new clinical classification with difference in prognosis on dietary treatment. Hepatology. 1994;20(5):1187–91.

10. Wu JT, Book L, Sudar K. Serum Alpha Fetoprotein (AFP) Levels in Normal Infants. Pediatr Res. 1981;15(1):50–2.

11. Hacettepe Universitesi Nufus Etutleri Enstitusu. Türkiye Nufus ve Saglık Arastirmasi. Hacettepe Universitesi Nufus Etutleri Enstitusu, T.C. Cumhurbaskanligi ve TUBITAK. Turkiye: Ankara; 2018: 47-48.

12. Ozalp I, Coskun T, Tokol S, Demircin G, Monch E. Inherited Metabolic Disorders in Turkey. J. Inher. Metab. Dis. 1990;13

13. Dweikat I, Qawasmi N, Najeeb A, Radwan M. Phenotype, genotype, and outcome of 25 Palestinian patients with hereditary tyrosinemia type 1. Metabol Open. 2021;9:100-83.

14. Khan SA, Fakih M, Taufiq N, Ahmerin A, Bangash A, Iqbal Malik M. Clinical Spectrum of Hereditary Tyrosinemia Type 1 in a Cohort of Pakistani Children. Clin Med Insights Pediatr. 2024;18.

15. Couce ML, Dalmau J, Del Toro M, Pintos-Morell G, Aldámiz-Echevarría L. Tyrosinemia type 1 in Spain: Mutational analysis, treatment and long-term outcome. Pediatr Int. 2011;53(6):985–9.

16. Yazıcı H, Er E, Canda E, Habif S, Kalkan Uçar S, Çoker M. Clinical Features of 29 Patients with Hereditary Tyrosinemia I in Western Turkey. J Pediatr Res. 2018;21:1–6.

17. Hajji H, Imbard A, Spraul A, Taibi L, Barbier V, Habes D, et al. Initial presentation, management and follow-up data of 33 treated patients with hereditary tyrosinemia type 1 in the absence of newborn screening. Mol Genet Metab Rep. 2022;8;33:100933

18. Bendadi F, De Koning TJ, Visser G, Prinsen HCMT, De Sain MGM, Verhoeven-Duif N, et al. Impaired cognitive functioning in patients with tyrosinemia type 1 receiving nitisinone. J of Pediatr. 2014;164(2):398–401.

19. Hillgartner MA, Coker SB, Koenig AE, Moore ME, Barnby E, MacGregor GG. Tyrosinemia type I and not treatment with NTBC causes slower learning and altered behavior in mice. J Inherit Metab Dis. 2016;6;39(5):673–82.

20. Önenli Mungan N, Yıldızdaş D, Kör D, Horoz ÖÖ, İncecik F, Öktem M, et al. Tyrosinemia type 1 and irreversible neurologic

crisis after one month discontinuation of nitisone. Metab Brain Dis. 2016;31(5):1181–3.

21. Dursun A, Özgül RK, Sivri S, Tokatlı A, Güzel A, Mesci L, et al. Mutation spectrum of fumarylacetoacetase gene and clinical aspects of tyrosinemia type I disease. J Inherit Metab Dis. 2011;1:17–21.

22. Baumann U, Preece MA, Green A, Kelly DA, Mckiernan PJ. Hyperinsulinism in tyrosinaemia type I. J Inherit Metab Dis. 2005;28:131-135.

23. Nasir S, Raza M, Siddiqui SI, Saleem A, Abbas A. Hereditary Tyrosinemia Compounded With Hyperinsulinemic Hypoglycemia: Challenging Diagnosis of a Rare Case. Cureus. 2020;12:e11541.

24. Sethuram S, Sperling MA, Gujral J, Romero CJ. Neonatal hyperinsulinism in transient and classical forms of tyrosinemia. Orphanet J Rare Dis. 2021;1:16(1).

25. Rokaitė R, Čibirkaitė A, Zeleckytė V, Lazdinytė G, Dženkaitis M. A Lithuanian Case of Tyrosinemia Type 1 with a Literature Review: A Rare Cause of Acute Liver Failure in Childhood. Medicina (Lithuania). 2024;60(1):1–9.

26. Gokay S, Ustkoyuncu PS, Kardas F, Kendirci M. The outcome of seven patients with hereditary tyrosinemia type 1. J Pediatr Endocrinol Metab. 2016;29(10):1151–7.

27. Ates I, Stuart C, Rathbone T, Barzi M, He G, Major AM, et al. Ex vivo gene editing and cell therapy for hereditary tyrosinemia type 1. Hepatol Commun. 2024;8(5):e0424