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ARAŞTIRMA / RESEARCH

Cardiomyopathy in patients with type 1 tyrosinemia, and the effect of nitisinone treatment on cardiomyopathy

Tip 1 tirozinemi hastalarında kardiyomiyopati ve nitisinon tedavisinin kardiyomiyopatiye etkisi

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Abstract

Purpose: This study aimed to retrospectively evaluate the frequency of cardiomyopathy and its response to routinely used nitisinone treatment in patients with tyrosinemia type 1.

Materials and Methods: Participants of this descriptive cross-sectional study were Tyrosinemia Type 1 patients who were under the care of a single metabolic unit. The primary outcome of the study was "presence of abnormal echocardiographic findings" at diagnosis and the impact of nitisinone treatment on the detected findings.

Results: Of the 54 patients enrolled in the study, 21 (38.9%) were female and 33 (61.1%) were male. 41 patients were evaluated using echocardiography at the time of diagnosis. 9 (21.9%) of them had hypertrophic cardiomyopathic alterations varying in severity. In the follow-up period, second echocardiographic examinations revealed improvements in cardiac alterations while on nitisinone treatment. Thirteen patients dropped out of follow-up. Of the remaining 41 patients, 10 (24.4%) patients died in the follow-up period, whereas 31 (75.6%) remained alive. Plasma aspartate aminotransferase (AST), total bilirubin, and direct bilirubin concentrations were significantly higher in patients witj normal cardiac evaluation.

Conclusion: Echocardiographic examination should be done in all tyrosinemia type 1 patients including those with an absence of cardiac manifestations. The presence of cardiomyopathy may indicate a poor prognosis. Nitisinone is found to have a positive impact on cardiomyopathy in patients with type 1 tyrosinemia.

Keywords:. Tyrosinemia Type 1; cardiomyopathy; nitisinone; prognosis

Öz

Amaç: Bu çalışma, tip 1 tirozinemi hastalarında kardiyomiyopati sıklığını ve rutin olarak kullanılan nitisinon tedavisine yanıtını retrospektif olarak değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel olan bu çalışmadaki olgular, tek bir metabolizma ünitesinin takibinde olan Tirozinemi Tip 1 hastalarıdır. Çalışmanın önceliği tanı anında "anormal ekokardiyografik bulguların varlığını" ve nitisinon tedavisinin bu bulgulara etkisini değerlendirmektir.

Bulgular: Çalışmaya alınan 54 hastanın 21'i (%38,9) kız, 33'ü (%61,1) erkekti. 41 hasta tanı anında ekokardiyografi ile değerlendirildi. Dokuzunda (%21,9) farklı şiddette hipertrofik kardiyomiyopatik değişiklikler mevcuttu. Takip döneminde yapılan ikincil ekokardiyografik incelemeler, nitisinon tedavisinin kardiyak durumda iyileşmeye sebep olduğunu ortaya koydu. On üç hasta takipleri bıraktı. Geriye kalan 41 hastanın 10'u (%24,4) kaybedildi, 31 (%75,6) hasta ise hayatta kaldı. Ekokardiyografik değişiklikleri olan hastalar, ekokardiyografik anormalliği olmayan hastalarla karşılaştırıldığında, plazma aspartat aminotransferaz (AST), total bilirubin ve direkt bilirubin konsantrasyonları açısından istatistiksel olarak anlamlı farklılıklar bulundu

Sonuç: Kardiyak bulgusu olmayanlar da dahil olmak üzere tüm tirozinemi tip 1 hastalarında ekokardiyografik inceleme yapılmalıdır. Kardiyomiyopatinin varlığı kötü bir prognoza işaret edebilir. Nitisinonun tip 1 tirozinemili hastalarda kardiyomiyopati üzerinde olumlu bir etkisinin olduğu bulunmuştur.

Anahtar kelimeler: Tirozinemi Tip 1; kardiyomiyopati; nitisinon; prognoz

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INTRODUCTION

Tyrosinemia Type 1 is an autosomal recessively inherited metabolic disease caused by the deficiency of the fumarylacetoacetate hydrolase (FAH), an enzyme catalyzing the final step in tyrosine catabolic pathway. FAH catalyzes the hydrolysis of fumarylacetoacetate to fumarate and acetoacetate. The deficiency of FAH leads to an increase in plasma tyrosine and succinylacetone concentrations. Accumulated succinylacetone is known to be a toxic substance that can damage the liver, kidney and peripheral nerves in tyrosinemia type 1 patients[1,2].

Tyrosinemia type 1 patients can be categorized into three groups according to the age of onset, namely, 'acute' form if symptoms started within the first six months after birth, 'subacute' form if symptoms occurred within six months to one year, and 'chronic' form if the patient's symptoms appear after one year of age[3]. The prognosis is worse in cases with early-onset group[4].

If untreated, tyrosinemia type 1 may lead to severe liver damage progressing into hepatocellular carcinoma, renal tubular dysfunction associated with growth retardation and rickets, porphyria-like neurological crisis, respiratory failure, coagulopathy, hypertrophic cardiomyopathy, electrolyte imbalances and metabolic acidosis[5-9].

The underlying mechanism of cardiomyopathy in tyrosinemia type 1 patients is yet unclear. It has been hypothesized to be due to the toxicity of accumulated fumarylacetoacetate, a tyrosine metabolite. The healing of cardiomyopathy following nitisinone therapy or liver transplantation supports this hypothesized mechanism[10]. Nitisinone given at a dose of 1-2 mg/kg/day prevents the formation of toxic metabolites like fumarylacetoacetate, maleylacetoacetate, succinylacetoacetate and succinylacetone. The Nitisinone blocks the activity of p-OH-phenylpyruvate dioxygenase that catalyzes the conversion of 4-hydroxyphenylpyruvate to homogentisate in the second step of the tyrosine degradation pathway[6,9]. Untreated children usually die before the age of 10 due to liver failure, neurological crisis or hepatocellular carcinoma[11]. Nitisinone and a low-tyrosine diet, both, improves liver functions and secondary rickets findings, prevents cirrhosis and renal tubular acidosis, promotes normal growth, and provides >90% survival rate[11].

The main objectives of the present study were: to determine the frequency of cardiomyopathy among tyrosinemia type 1 patients; to investigate the relationship between some demographic, clinical and laboratory parameters with the development of cardiomyopathy; and evaluate the impact of nitisinone on detected cardiac alterations.

MATERIALS AND METHODS

Ethical approval for this descriptive cross-sectional type study was obtained from Hacettepe University Faculty of Medicine, Clinical Research Ethics Committee (GO:18/886-40). The patients' data were retrieved from the hospital's electronic patient registry (Nucleus Automation System) and patient files. The study was conducted at Hacettepe University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Metabolism, which is one of the largest reference centers for metabolic diseases in Turkey.

Study group consisted of patients who were followed up with the diagnosis of tyrosinemia type 1 (54 cases) at the department of pediatric metabolism between 1990-2019 years.

Procedure

The primary variable of the study was the "presence of alterations compatible with cardiomyopathy on echocardiography" at diagnosis. Independent variables were: age, sex, age at diagnosis, age of onset of symptoms, parental consanguinity, presence of hepatomegaly, liver failure, rickets, growth retardation, cirrhosis, liver nodules, bleeding tendency, hepatocellular carcinoma, history of liver transplantation, nitisinone treatment and succinylacetone concentrations in urine samples. The age at initiation of nitisinone treatment, detection of cardiac murmur on auscultation, plasma alanine aminotransferase (ALT) (U/L), aspartate aminotransferase (AST) (U/L), total bilirubin (mg/dl), direct bilirubin (mg/dl), tyrosine levels (μmol/L); international normalized ratio (INR) and alterations in echocardiographic findings after the initiation of nitisinone treatment data were also recorded from patient's files. Nitisinone is already routinely used in the treatment of these patients. Therefore, it was not given for this study. The effect of nitisinone treatment was recorded from the patient files retrospectively.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS for Windows, Version 25.0, Chicago, IC, USA) program was used for statistical analysis. The results were displayed as mean and standard deviation where the variables were numerical and frequency and percentage if categorical. The compliance of numerical variables to normal distribution was evaluated using the Shapiro-Wilk test. Mann-Whitney U test was used for continuous data in binary comparisons. Chi-square test was used to compare categorical data. The Fisher's exact test was preferred in cases where the Chi-square test assumptions were not fulfilled. Additionally, the Kruskal-Wallis test was used for multiple-group comparisons.

RESULTS

Of the study group, 21 patients (38.9%) were female whereas 33 patients (61.1%) were male. The median age at diagnosis was 147 days (4 days-5.17 years), age at the onset of complaints was 90 days (4 days-1.47 years) and the age of commencing nitisinone therapy was 180 days (4 days-13.7 years). The median time interval between the beginning of symptoms and establishment of correct diagnosis was 57 days (0 days-4.19 years). 41 patients had been evaluated by echocardiography during their follow-up. Of these, 9 (21.9%) patients had cardiac abnormalities with varying degrees of hypertrophic cardiomyopathic alterations (Figure 1). 3 patients with cardiomyopathy did not show up for their follow-up visits. 2 patients were reported to have died from non-cardiac causes. In all patients' cardiac alterations had improved while on nitisinone treatment during follow-up period.None of the patients with normal baseline echocardiographic findings developed signs and symptoms of cardiomyopathy in the course of follow-up. Therefore, second echocardiography was not deemed necessary for them.

46 children (85.2%) were diagnosed with Tyrosinemia Type 1 on the basis of suggestive signs and symptoms, 2 patients (3.7%) had been detected on national phenylketonuria screening and 6 cases (11.1%) had been diagnosed because of the presence of an affected sibling in the family. Thirteen patients dropped out of follow-up. Our search found that 10 (24.4%) of 41 remaining patients had died at an average age of 6.53 years, 31 (75.6%) patients were alive and clinically doing well.

The most common finding at the time of presentation was hepatomegaly (87%, n= 47), while growth retardation was found in half of the patients (n=27), and a heart murmur was detected in 25.9% (n=14) (Table 1).

Table 1. Clinical findings of patients at the time of diagnosis

	Absent	**Present**
	n / %	n / %
Consanguinity between spouses	13 / 24.1	41 / 75.9
Liver failure	28 / 51.9	26 / 48.1
Rickets	33 / 61.1	21 / 38.9
Hepatomegaly	7 / 13	47 / 87
Growth retardation	27 / 50	27 / 50
Cirrhosis	43 / 79.6	11 / 20.4
Nodule in the liver	35 / 64.8	19 / 35.2
Coagulopathy	37 / 68.5	17 / 31.5
Hepatocellular carcinoma	49 / 90.7	3 / 5.6
Succinylacetone in urine	9 / 16.7	45 / 83.3
Liver transplant	42 / 77.8	4 / 7.4
Cardiac murmur	40 / 74.1	14 / 25.9
Nitisinone treatment	7 / 13	47 / 87

Table 2. Comparison of the various clinical characteristics of the study groups according to the presence or absence of cardiomyopathy

Variable		Absent		Present		
		n	%	n	%	p
Sex	Female	12	37.5	4	44.4	0.49
	Male	20	62.5	5	55.6	
Parental consanguinity	Absent	7	21.9	3	33.3	0.38
	Present	25	78.1	6	66.7	
Hepatomegaly	Absent	4	12.5	0	0.0	0.35
	Present	28	87.5	9	100	
Liver failure	Absent	19	59.4	2	22.2	**0.04**
	Present	13	40.6	7	77.8	
Rickets	Absent	21	65.6	6	66.7	0.64
	Present	11	34.4	3	33.3	
Growth retardation	Absent	20	62.5	3	33.3	0.12
	Present	12	37.5	6	66.7	
Cirrhosis	Absent	25	78.1	9	100	0.15
	Present	7	21.9	0	0.0	
Liver nodule	Absent	19	59.4	8	65.9	0.10
	Present	13	40.6	1	34.1	
Coagulopathy	Absent	25	78.1	3	33.3	**0.01**
	Present	7	21.9	6	66.7	
Succinylacetone in urine	Absent	7	21.9	1	11.1	0.42
	Present	25	78.1	8	88.9	
Cardiac murmur	Absent	23	71.9	3	33.3	**0.04**
	Present	9	28.1	6	66.7	
Death	Dead	4	15.4	2	33.3	0.31
	Stable	22	84.6	4	66.7	
Nitisinone	Absent	4	12.5	3	33.3	0.16
	Present	28	87.5	6	66.7	

Table 3. Comparison of numerical values according to echocardiography results

	CMP	n	Median	Min	Max	p
Age at diagnosis (days)	Absent	32	118	4	1890	0.42
	Present	9	180	30	659	
Age of onset of complaints (days)	Absent	27	90	4	540	0.49
	Present	9	57	4	328	
Age of starting (days) Nitisinone	Absent	28	180	4	2160	0.70
	Present	6	158	18	568	
ALT (U/L)	Absent	32	30	8	312	0.359
	Present	9	31	23	129	
AST (U/L)	Absent	32	52	21	245	**0.024**
	Present	9	89	56	196	
Total bilirubin (mg/dl)	Absent	32	1.7	0.5	20.1	**0.035**
	Present	9	5.4	0.6	9.2	
Direct bilirubin (mg/dl)	Absent	32	0.57	0	5.6	**0.001**
	Present	9	2.41	0.2	6.2	
INR	Absent	32	1.70	1.02	5.69	0.312
	Present	9	1.75	1.20	5.66	
Tyrosine (µmol/L)	Absent	32	7.7	2.1	17.7	0.206
	Present	9	14.5	2.7	19	

CMP: Cardiomyopathy.

Comparison of categorical findings according to presence of cardiomyopathy were summarized in Table 2. There were no statistically significant differences between the groups in terms of gender distribution, parental consanguinity, frequency of rickets, growth retardation and cirrhosis. However, liver failure and coagulopathy were significantly more frequent in the cardiomyopathy group (p=0.04 and 0.01). The mortality rate was higher in patients with cardiomyopathy but this difference as compared to the non-cardiomyopathy group was not statistically significant (p=0.31).

Based on the echocardiography results, no statistically significant difference was found when the age of diagnosis and the age of onset of complaints were compared. However, there was a significant difference between the echocardiography groups concerning AST, total bilirubin, and direct bilirubin levels (p=0.02, p= 0.03, and p=0.001, respectively) (Table 3).

DISCUSSION

In the evaluation of the echocardiographic findings, 21.9% (n= 9) of the patients were found to have alterations compatible with cardiomyopathy. All the patients with cardiomyopathy had hypertrophic alterations of various degrees. All these patients showed improvement with the addition of nitisinone to their treatment.

Although the incidence of tyrosinemia type 1 is estimated at 1:100,000 worldwide, its exact frequency in Turkey is not known[12]. On the other hand, it has been stated that there would be higher rates of hereditary metabolic diseases with autosomal recessive inheritance due to the relatively high rate of consanguineous marriages[13]. In a study conducted in Turkey, the rate of consanguineous marriages was reported as 59.5% in patients with tyrosinemia type 1[9]. However, in other studies investigating rare genetic diseases, the kinship marriage rate was around 80%[14,15]. Consanguineous marriages rate in this study was found closer to those reported in rare diseases.

This study revealed that the median age at diagnosis was about six months, and there were cases of delayed diagnosis up to the age of five. Delay in the treatment of tyrosinemia type 1 leads to permanent liver damage resulting in hepatocellular carcinoma. This makes early diagnosis of tyrosinemia of utmost importance in Turkey where the incidence of this particular disease is relatively high. For the early diagnosis of tyrosinemia type 1, it is necessary to include it in the national newborn screening program[9,12,16].

It has been reported that patients with tyrosinemia type 1 most frequently present with hepatomegaly, coagulopathy and growth retardation[17]. In this study, hepatomegaly was the most common finding at the time of diagnosis. Also, failure to thrive was detected in half of the patients. In light of these findings, it can be said that tyrosinemia type 1 should be considered in the list of the differentials when hepatomegaly along with growth retardation is detected in early months of life.

Cardiomyopathy is a very rare finding in children. In the United States, its incidence has been reported as 1.13 cases per 100,000 children[18]. However, it may be a dominant finding in metabolic diseases such as mitochondrial disorders, glycogen storage disease, lysosomal storage diseases, and fatty acid oxidation disorders[18].

Cardiomyopathy is frequently reported in tyrosinemia type 1 patients. In a study investigating the prevalence of cardiomyopathy in tyrosinemia type 1, 30% of the patients were reported to have cardiomyopathy at the time of diagnosis; mostly in the form of interventricular septal hypertrophy.[10] The frequency of cardiomyopathy in our study was 21%.

Arora et al.[10] reported that tyrosinemia type 1 patients may not exhibit signs and symptoms related to the cardiovascular system despite the presence of cardiomyopathy. Moreover, in this study it has been stated that even cardiac murmur may be absent in some patients with cardiac alterations. Hence, it can be concluded that cardiac evaluation should be done in tyrosinemia type 1 patients even in the absence of suggestive clinical signs and symptoms of cardiac involvement.

It has been previously claimed that the presence of cardiomyopathy may be related to the severity of the disease in patients with tyrosinemia type 1[19]. Lindblad et al.[19], from autopsy findings and the presence of higher α-fetoprotein levels in patients with cardiomyopathy, thought that cardiomyopathy might be related to the severity of FAH deficiency.

Nitisinone therapy was first used in the treatment of tyrosinemia type 1 in the late 1990s and it was approved by the Food and Drug Administration (FDA) in 2002[20]. Cardiomyopathy has been reported to be significantly less common in those treated with

nitisinone at the onset of the disease[10]. Additionally, it has also been stated that cardiomyopathies seen in tyrosinemia type 1 can be controlled with nitisinone treatment or liver transplantation[17,21]. In line with previous publications, we found that the rate of cardiac pathology was significantly lower in those receiving nitisinone therapy. Cardiac pathologies improved in almost all patients who received nitisinone treatment. In addition, no pathologic cardiac symptom was found in the subsequent follow-ups of the patients who received nitisinone treatment and those whose initial echocardiographic findings were normal.

Since this study was retrospective in nature and the data collection was based on the hospital records, it might have some limitations. Echocardiographic data of 13 patients could not be accessed due to discontinued follow-up. Other limitations of this study included: the lack of long-term follow-up results and previous findings plus some of the laboratory parameters as well.

In conclusion, it would be beneficial to include tyrosinemia type 1 disease in the national screening program to detect and initiate treatment as early as possible. Echocardiography should be performed in tyrosinemia type 1 patients regardless of whether they have signs and symptoms suggesting cardiac involvement. The presence of cardiac pathology may indicate a poor prognosis. Nitisinone therapy might have a positive impact on the cardiac alterations in tyrosinemia type 1.

Yazar Katkıları: Çalışma konsepti/Tasarımı: BBG, TC, HSS; Veri toplama: BBG, HHA, AD; Veri analizi ve yorumlama: BBG, HHA, AT; Yazı taslağı: BBG, TC, TK; İçeriğin eleştirel incelenmesi: TC, HSS, AD, AT, BBG; Son onay ve sorumluluk: BBG, HHA, KÇ, TK, HSS, AD, AT, TC; Teknik ve malzeme desteği: -; Süpervizyon: BBG, HHA, TC, TK; Fon sağlama (mevcut ise): yok.
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