Olgu Sunumu

BARTH SYNDROME: A rare infantile cardiomyopathy

Nurdan EROL[1], Derya BÜYÜKKAYHAN[2]

ABSTRACT

Barth Syndrome, a rarely encountered recessive X-linked disease, mutates the Taffazzin gene located at Xq28 locus. Clinical findings of the syndrome include cardiomyopathy, proximal muscle myopathy, feeding difficulties, growth retardation, cyclic neutropenia, and suseptibility to infection. A case, diagnosed as Barth Syndrome, was presented in the study. The patient, a male, suffered from vomiting and feeding problems on the third day of life and succumbed to severe infection and neutropenia in the newborn period. He was diagnosed with cardiomyopathy including dilatation, hypertrophy, and non-compaction of the left ventricle characterized by a decreased systolic function.

In the sixth month of life, he was admitted to the hospital with feeding problems, failure to thrive, septisemia, congestive heart failure, and a large thrombotic lesion on the right buttock. He died after a short time. The diagnosis of Barth Syndrome was made according to his clinical history and clinical echocardiographic findings. İn order to improve prognosis for these patients, a timely diagnosis is essential along with the immediate implementation of treatment for cardiomyopathy and infection.

KEY WORDS: Barth syndrome, cardiomyopathy, metabolic cardiac disease, Tafazzin gene

BARTH SYNDROME: NADİR BİR İNFANTİL KARDİYOMİYOPATİ

ÖZET

Barth sendromu; Xq28 bölgesinde yer alan Taffazzin genindeki mutasyona bağlı olarak gelişen X bağlı resesif geçiş gösteren nadir sendromdur. Sendromun klinik bulguları; kardiyomiyopati, proksimal kas miyopatisi, beslenme bozuklukları, gelişme geriliği,siklik nötropeni ve enfeksiyonlara eğilimdir.

Bu çalışmada; Barth Sendromu tanısı alan bir olgu sunulmaktadır. Yaşamının üçüncü gününde başlayan kusma, beslenme bozukluğu ile başvuran erkek olgu, yenidoğan döneminde ciddi enfeksiyonlar ve nötropeni tedavisi gördü.Bu evrede sol ventrikülde dilatasyon,hipertrofi ve nonkompakşın ve sistolik fonksiyonda azalma ile kardiyomiyopati tanısı aldı. Yaşamının altıncı ayında tekrar beslenme bozukluğu,gelişme geriliği,-sağ kalça üzerinde geniş trombotik lezyon, septisemi ve konjestif kalp yetmezliği ile başvurdu ve kısa sürede hasta kaybedildi. Olguya Barth Sendromu tanısı hastanın klinik ve ekokardiyografi bulgularına, hikayesine ve hastane kayıtlarına göre konuldu.Bu sendro-

1Istanbul Medeniyet University Goztepe Education and Research Hospital, Pediatric Clinics, Istanbul, Turkey.
2Istanbul Medeniyet University Goztepe Education and Research Hospital, Neonatology Clinic, Istanbul, Turkey.

Yayın Gönderim ve Kabul Tarihi: 30.03.2015 - 04.05.2015

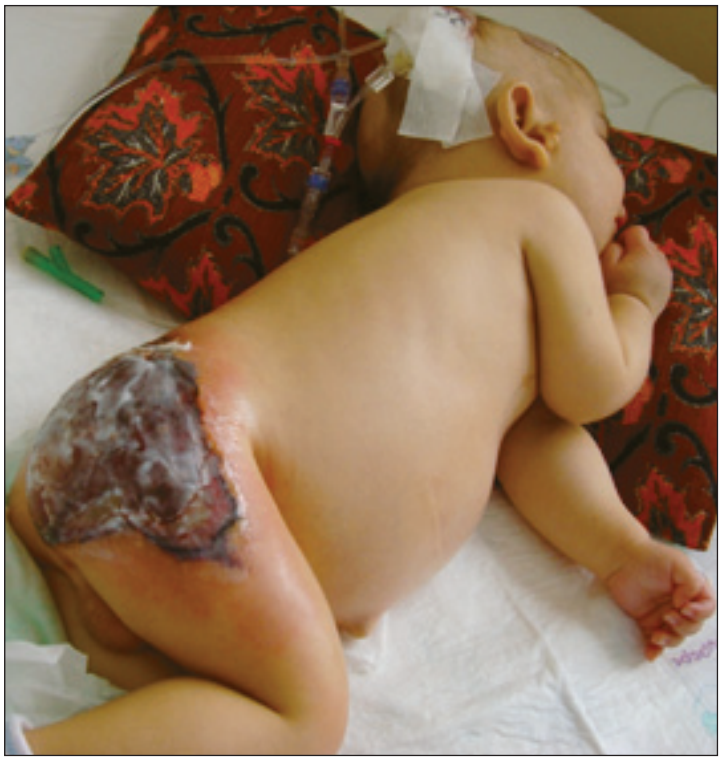

Figure 1: Large thrombotic lesions on the right buttock during the last infection period.

ma sahip olgularda prognozun iyileştirilmesi zamanında teşhis edilmesi, kardiyomiyopati ve enfeksiyonların etkin ve hemen tedavisi esasdır.

Anahtar kelimeler: Barth Sendromu, kardiyomiyopati, metabolik kardiyak hastalık, Taffazzin geni

INTRODUCTION

The incidence of infantile cardiomyopathy ranges between 0-28-1.24/100.000 in different countries.1 Most of them consist of dilated cardiomyopathies (DCM). Among DCM's, Barth syndrome is a rarely seen disease[1].

Barth syndrome, (BTHS; OMIM#302060) was firstly defined by Barth in the year 1983.2,3,4 Barth syndrome is a rarely encountered X-linked, and recessively transmitted disease that causes cardiolipin deficiency in the mitochondrial membrane associated with mutations in the tafazzin gene located at the Xq28 locus[2].

Clinical manifestations of the Barth syndrome include ventricular hypertrophy, and noncompaction, endocardial fibroelastosis associated with dilated cardiomyopathy, proximal skeletal muscle myopathy, feeding diffuculties, growth retardation, cyclic neutropenia, and predisposition to infections[2,5]. In this study, a case diagnosed with Barth syndrome is presented based on clinical, laboratory, and echocardiographic findings.

CASE

The male infant patient was the third child in the family born at 36 weeks by spontaneous vaginal delivery. His weight at birth was 2500 gr, his height, 46 cm and his head circumferance was 34 cm in diameter. The parents are not consangious and their other two children are female and in good health.

The patient suffered from vomiting and feeding difficulties as early as the third day of life. He was accepted into the pediatric surgery clinic and was operated for duedonal stenosis on the tenth day of life. His condition did not improve, so consequently, he was taken to the Neonatal Intensive Care Unit.

Upon pediatric cardiologic consultation, he was diagnosed with cardiomyopathy including dilatation, hypertrophy and noncom-

paction of the left ventricle characterized by decreased sistolic function as evidenced in the echocardiogram (Fig 2,3). Anticongestive therapy was initiated and the case was followed by the pediatric cardiology unit as well. The metabolic tests resulted as negative.

During the follow up, sistolic disfunction and cardiomyopathic findings persisted. At sixth months, the child was admitted to the pediatric clinic with feeding problems, failure to thrive, septisemia, large thrombotic lesions on the right buttock (Fig 1) and congestive heart failure. Inotropic therapy and a broad-spectrum antibiotic combinations were administered. Pseudomonas were evidenced in wound cultures. After three days, the child's condition deteriorated and he was admitted into the Intensive Care Unit. The same day, he died.

At this last admission to the hospital, We were inclined to believe that he had clinical Barth syndrome, but genetic tests could not performed in time. Our conclusions were based on an investigation into hospital records throughout his extensive stay in the Neonatal Intensive Care Unit where he experienced feeding problems and failure thrive. Records show that initial therapy was administered for severe candida septisemia and persisting neutropenia. After that, the child was admitted several times due to severe infection.

Upon further discussion with the child's other physicians and further analyzation of echocardiograms, my suspicions of the diagnosis of Barth Syndrome were confirmed. The diagnosis is supported by the child's male gender, his feeding problems, his failure to thrive, his frequent and severe infections and neutropenia and cardiomyopathia.

DISCUSSION

According to the Barth Syndrome Foundation, the prevalence of the disease is estimated to range between 1/300000 and 1/400000.2 In this disease group, limited case series have been cited in literature, and accordingly inadequate information about the natural course of the disease is available[6,7].

In 63% of these established cases, a familial trait has been determined.6 Although the clinical picture becomes manifest with symptoms of cardiomyopathy, skeletal muscle myopathy, cyclic neutropenia, and growth retardation, these characteristic features can demonstrate variations from case to case with ensuing underdiagnosis of the disease[2,5]. Genetic factors may possibly effect phenotypic characteristics, and severity of cardiomyopathy. In Barth syndrome, ge-

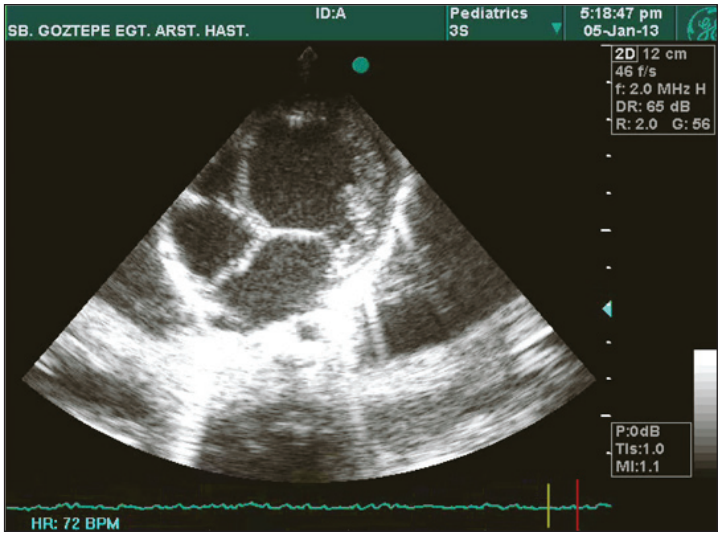

Figure 2: The 2D Echocardiogram show cardiomyopathy with left ventricular dilatation, hypertrophy and noncompaction during the last infection period.

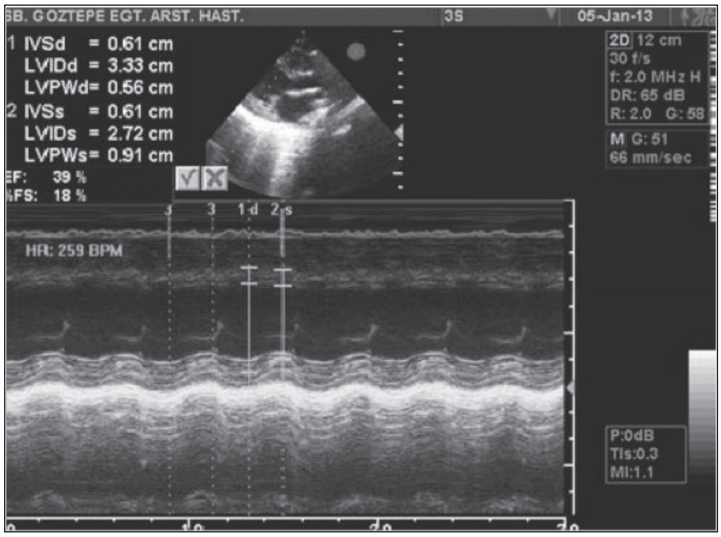

Figure 3: The M Mod Echocardiogram show systolic disfunction during the last infection period.

neral diagnosis of cardiomyopathy, and genetic identification are evidenced at average of 5 and a half months in the case of cardiomyopathy and at 6 years genetically after onset of the disease[6].

Clinical manifestations can onset during prenatal period. This condition leads to stillbirth, miscarriages, and cardiomyopathy.6 In cases with clinical symptoms starting to emerge during the neonatal period, the disease demonstrates an aggressive progression[2,6,7]. Initial clinical symptoms of our case during the neonatal period were predominantly vomiting, malnutrition, infection, and neutropenia. These initial symptoms suggested the presence of a metabolic disease that was not confirmed by the results of relevant medical investigations. Baseline mild lower carnitine level were detected in metabolic screening tests, however further laboratory test results revealed the presence of normal carnitine values. Cardiomyopathy was also detected during this disease stage.

Cardiomyopathy manifests itself in many forms[7]. Our case had also progressively displayed dilated, hypertrophic, and non-compaction cardiomyopathy with decreased systolic functions as is the case with the classical type of cardiomyopathy peculiar to Barth syndrome. Medical anticongestive therapy induces occasional remission in cardiomyopathy, however systolic functions decrease after cessation of therapy or during periods of infection.

İnspite of, our case demonstrating remissions with medical therapy, in accordance with literature findings, the patient's systolic dysfunction never improved. At his last referral to our clinic, minimal improvement were detected in patient's systolic function.

Although its etiopathogenesis is not fully elucidated, neutropenia progressing with myelocyte arrest in bone marrow is one of the important clinical features of Barth syndrome. Occasionally, neutropenia is the first characteristic of this syndrome and it may preceed other symptoms. Neutropenia generally demonstrates a cyclic course, however it is sometimes persistant[5].

Granulocyte colony stimulating factor (G-CSF) mandatory for the treatment of neutropenia in developing cases of Barth syndrome, was used in our patient particular during serious neonatal infection that progression with neutropenia, In this syndrome, serious infection is one the determinating factors of prognosis[2]. Our patient was severe neonatal candida septicemia ,after the neonatal period severe bacterial infections occured. At the end-stage of the disease he died beca-

use of an extensive thrombotic skin lesion and pseudomonas septisemia with a resulting cardiac, and metabolic decompensation. During our literature review, we failed to encounter a case report with an infectious complication similar to ours.

Patients with Barth syndrome generally die during their infancy. Heart failure secondary to cardiomyopathy, respiratory distress during periods of infection, decrease in oxygen saturation, and metabolic decompensation are responsible for death during this period[2].

The origin of metabolic decompensation has been associated with lactic acidosis secondary to 3-methylglutaconic aciduria[9,10]. As a Result , close monitorization in cases of Barth syndrome is necessary indispensable. After infancy, mortality rates drop , In the literature, a scarce number of adult cases with this syndrome have been cited[11]. Based on the echocardiographic findings obtained at the patient's last referral to our clinic, we entertained the possibility of the presence of Barth syndrome.However we were unable to evaluate his case until re-examined his hospital records retrospectively.

The male gender of our patient, the clinical course of the disease, the frequently recurring serious infections, the findings of neutropenia, the specific cardiomyopathy, and the echocardiographic data clinically established the diagnosis of Barth syndrome. Because of rapid deterioration in his clinical status, and subsequent his death during short short, genetic diagnosis could not be occured.

In order improve prognosis in these patients,Barth Syndrome can not overlooked.Better recognation of its sign and symptoms, a timely diagnosis,the maintance of high level of suspicion, the iniation of treatment for cardiomyopathy and infection as quickly as possible,and due importance given to metabolic decompansation are critical.İn the long run strong relationships and the sharing of information and knowledge between clinics and their is very important so as to yield favoruable and promising outcomes in these cases.

REFERENCES

1. Hong YM. Cardiomyopathies in children. Korean J Pediatr. 2013;56(2):52-59
2. JefferiesJ L. Barth Syndrome. American Journal of Medical Genetics Part C (Seminars in Medical Genetics). 2012;163C:198–205
3. Barth PG, Scholte HR, Berden JA, Van der Klei Van Moorsel JM, Luyt Houwen IE, Van'tVeer Korthof ET, Van der Harten JJ, Sobotka Plojhar MA. An X linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leucocytes. J Neurol Sci. 1983;62:327–355
4. Barth PG, Valianpour F, Bowen VM, Lam J, Duran M, Vaz FM, Wanders RJ. X-linked cardioskeletal myopathy and neutropenia (Barth syndrome): an update. Am J Med Genet A. 2004;126:349–354
5. Clarke SLN, Bowron A, Gonzale IL, Groves SJ, Newbury-Echob R, Clayton N, Martin RP, Tsai-Goodman B, Garratt V, Ashworth M, Bowen VM, McCurdy KR, Damin MK, Spencer CT, Toth MJ, Kelley RI, Steward CG. Barth Syndrome. Orphanet Journal of Rare Diseases. 2013;8:23
6. Spencer CT, Bryant R M, Day J, Gonzales IL, Colan S , Thompson WR, Berthy J, Redfarn SP, Byrne BJ. Cardiac and Clinical Phenotype in Barth Syndrome. Pediatrics. 2006;118:e337
7. Rigaud C, Lebre AS, Touraine R, Beaupain B, Ottoleighi C, Chabli A, Ansquer H, Ozsahin H, Flippo S, Lonlay P, Borm B, Rivier F, Vaillant MC, Dramard MM, Goldenberg A, Viot G, Charron V, Rio M, Bonnet D, Donadieu J. Natural history of Barth syndrome: a national cohort study of 22 patients. Orphanet Journal of Rare Diseases. 2013;8:70
8. Schlbame M, Ren M. Barth Syndrome, a human disorder of cardiolipin metabolism. FEBS Letters. 2006;580:5450–5455
9. Yen TY, Hwu WL, Chien YH, Wu MH, Lin MT, Tsao LY, Hsieh WS, Lee NC. Acute metabolic decompensation and sudden death in Barth syndrome: report of a family and a literature rewiew. Eur J Pediatr. 2008;167:941–944
10. Ferri L, Donati MA, Funghini S, Malvagia S, Catarzi S, Lugli L, Ragni L, Bertini E, Vaz F M, Cooper DN, Guerrini R, Morrone A. New clinical and molecular insight on Barth Syndrome. Orphanet Journal of Rare Diseases. 2013;8:27
11. Molina MS, Navarro GN, Molina FE, Martinez MJB, Escudero F, Espejo FR. Barth syndrome in adulthood: a clinical case scientic letters. Rev Esp Cardiol. 2013;66(1)64-73