Kearns-Sayre syndrome presenting as somatomedin C deficiency and complete heart block

Somatomedin C eksikliği ve tam kalp bloku ile kendini gösteren Kearns-Sayre sendromu

Yakup Ergül, M.D., Kemal Nişli, M.D., Arda Saygılı, M.D.,[#] Aygün Dindar, M.D.

Department of Pediatric Cardiology, İstanbul Faculty of Medicine, İstanbul University; [#]Acıbadem Hospital, both in İstanbul

Kearns-Sayre syndrome (KSS) is a rare mitochondrial disease in which neuromuscular structures, endocrine glands, and cardiac conduction systems are most commonly involved. An 11-year-old boy was admitted with blurred consciousness, respiratory instability, and bradycardia of two-hour onset. He was immediately intubated. His medical history included growth retardation and myopic refractive defect for six years, therapy for somatomedin C deficiency for 15 months, and bilateral ptosis for three months. On physical examination, he was unconscious, had a peak heart rate of 40/min, blood pressure of 60/20 mmHg, and a weak pulse. Laboratory findings showed elevated blood lactate and blood pyruvate levels and an increased lactate/pyruvate ratio. The electrocardiogram showed complete atrioventricular block and echocardiography showed mitral valve prolapse. Following implantation of a temporary transvenous cardiac pacemaker, his heart rate and clinical condition improved. Further analysis with cranial magnetic resonance (MR) imaging demonstrated hyperintense signal changes in the subcortical white matter of the two cerebral hemispheres, bilateral thalamus, putamen, cerebral peduncles, dorsal medulla, and midbrain. The typical clinical and MR findings confirmed the initial diagnosis of KSS. A permanent cardiac pacemaker was implanted into the right ventricle.

Key words: Heart block/etiology; child; Kearns-Sayre syndrome/complications; mitochondrial diseases; pacemaker, artificial.

Kearns-Sayre sendromu (KSS) en sık nöromusküler doku, endokrin bezleri ve kardiyak ileti sisteminin tutulduğu nadir bir mitokondri hastalığıdır. On bir yaşında erkek çocuk, son iki saat içinde gelişen bilinç bulanıklığı, solunum düzensizliği ve bradikardi nedeniyle yatırıldı. Hastaya hemen entübasyon yapıldı. Tıbbi öyküsünde hastada altı yıldır büyüme geriliği ve uzağa refraksiyon defekti olduğu, somatomedin C eksikligi nedeniyle 15 aydır tedavi gördüğü ve üç aydır iki taraflı pitozis olduğu öğrenildi. Fizik muayenede bilinci kapalı olan hastanın zirve kalp hızı 40/dk, kan basıncı 60/20 mmHg ve nabzı zayıf idi. Laboratuvar incelemesinde kan laktat ve piruvat düzeyleri yüksek, laktat/piruvat oranı artmış bulundu. Elektrokardiyografide tam atriyoventriküler blok, ekokardiyografide mitral kapakta sarkma saptandı. Hastaya acilen geçici transvenöz kalp pili takılması sonrasında kalp hızı ve klinik durumunda düzelme görüldü. Daha ileri inceleme için yapılan kraniyal manyetik rezonans görüntülemede, her iki beyin yarıküresinde subkortikal beyaz cevherde, ikitaraflı talamus, putamen, beyinsapı, dorsal medulla ve ortabeyinde hiperintens sinyal değişiklikleri izlendi. Tipik klinik ve manyetik rezonans bulguları KSS öntanısını kesinleştirdi. Hastanın sağ ventrikülüne kalıcı kap pili takıldı.

Anahtar sözcükler: Kalp bloku/etyoloji; çocuk; Kearns-Sayre sendromu/komplikasyon; mitokondri hastalığı; kalp pili.

Kearns-Sayre syndrome (KSS) is a multisystemic mitochondrial disease characterized by an onset before 20 years of age and presence of progressive external ophthalmoplegia and retinitis pigmentosa along with one of the following three symptoms which are called as a triad: complete heart block, ataxia, or protein increase in the cerebrospinal fluid.[1-3] Many neurological or endocrine disorders may accompany the disease.[4,5] We report on a patient who was transferred to the intensive care unit due to blurred consciousness, respiratory instability, and complete atrioventricular (AV) block and eventually diagnosed as having KSS. The cardiovascular complications and diagnostic importance of neuroradiological findings of this syndrome are discussed.

Received: September 12, 2009 *Accepted:* January 6, 2010

Correspondence: Dr. Aygün Dindar. İstanbul Üniversitesi İstanbul Tıp Fakültesi, Çocuk Kardiyolojisi Bilim Dalı, 34093 Çapa, İstanbul, Turkey. Tel: +90 212 - 414 20 00 e-mail: aygundindar@hotmail.com

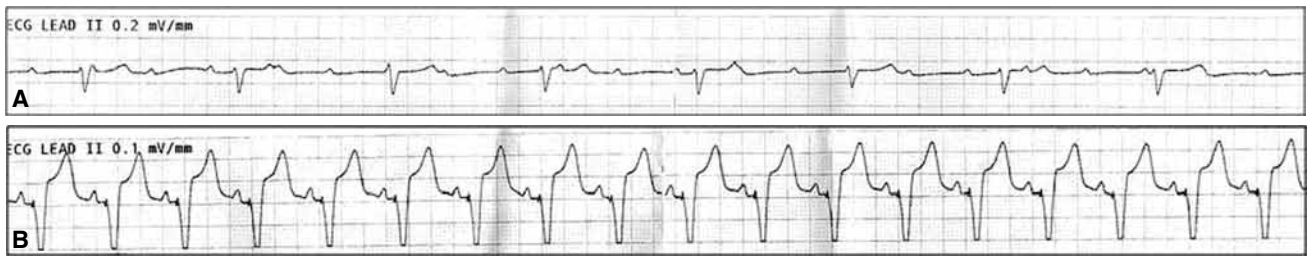

Figure 1. Electrocardiograms showing DII derivation **(A)** with complete atrioventricular block (heart rate 43/min) on admission and **(B)** following implantation of a transvenous permanent ventricular cardiac pacemaker (heart rate 93/min).

CASE REPORT

An 11-year-old boy was admitted with fatigue, behavior change, and amnesia of two-day history and blurred consciousness and respiratory instability that developed within the past two hours. He was immediately referred to our unit following intubation. Prenatal and birth history of the patient was normal. His medical history until presentation included the following: growth retardation and myopic refractive defect for six years, therapy for somatomedin C deficiency for 15 months, decline in school success for the past year, and bilateral ptosis for three months. No drug or trauma history was present. On physical examination, he was unconscious, with a body temperature of 36.8 °C, peak heart rate of 40/min, blood pressure of 60/20 mmHg, and a weak pulse. A comprehensive examination revealed height and weight below the third percentile, decreased bilateral proximal muscle strength, ptosis in bilateral eyelids, and total limitation in external eye movements. Both eyes demonstrated myopia and retinitis pigmentosa. The other physical examination findings were normal.

Laboratory findings were as follows: pH 7.25, base excess 18, blood sugar 380 mg/dl, simultaneous blood lactate 3.8 mmol/l (normal 0.5-2.2 mmol/l), blood pyruvate 0.14 mmol/l (normal 0.076±0.026 mmol/l), and lactate/pyruvate ratio 27.1 (high). Blood electrolytes and other biochemical parameters were normal. Regarding metabolic diseases, blood amino acid levels, urinary organic acid levels, and tandem mass spectrometry screening were normal. The chest roentgenogram showed a normal cardiothoracic ratio (48%) and pulmonary vascular appearance. The electrocardiogram showed complete heart block with AV dissociation (Fig. 1a). Echocardiography showed mitral valve prolapse (MVP) and no mitral insufficiency. Pericardial effusion and left ventricular dysfunction were not detected. The acidosis and hyperglycemia resolved during the follow-up, but complete AV block persisted; therefore, a temporary pacemaker

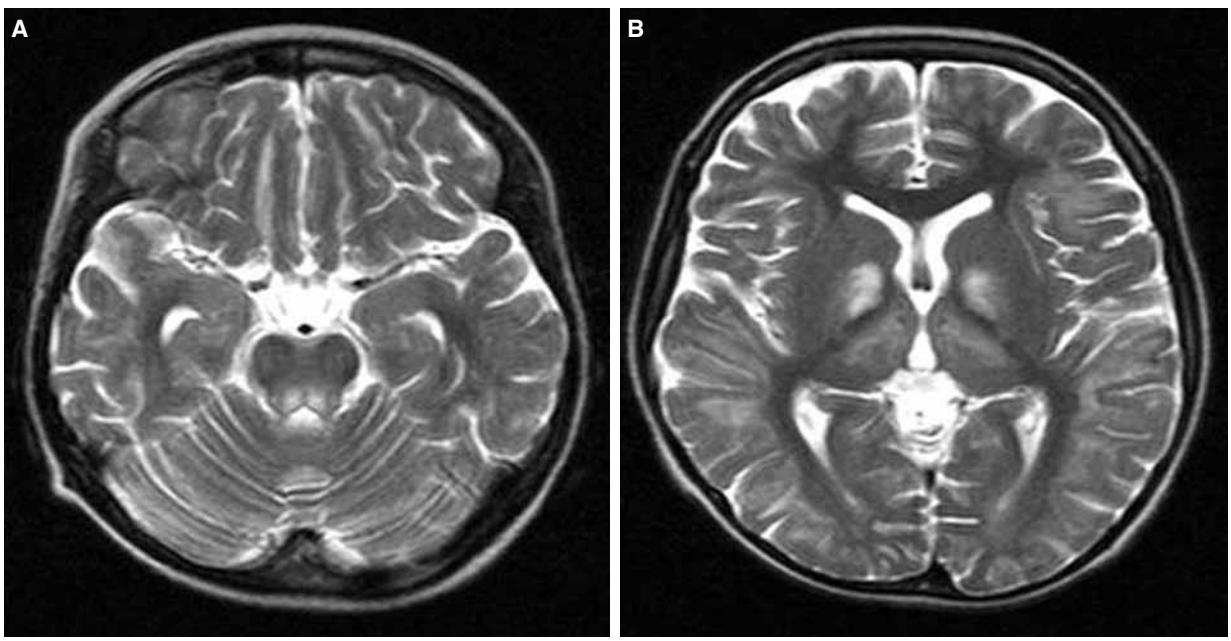

Figure 2. (A, B) Cranial T2-weighted MRI sections showing bilateral lesions with hyperintense signals in the subcortical cerebral white matter, midbrain, thalamus, and putamen.

of 80/min ventricle rate was implanted into the right ventricle through the jugular vein. Upon elevation of the heart rate, the patient exhibited a normal clinical profile and the initial diagnosis was made as KSS considering complete AV block, retinitis pigmentosa, external ophthalmoplegia, and growth retardation. After the removal of the temporary pacemaker, further analyses were initiated. Electroencephalography showed disorganization. T2-weighted cranial magnetic resonance imaging (MRI) demonstrated hyperintense signal changes in the subcortical white matter of the two cerebral hemispheres, bilateral thalamus, putamen, cerebral peduncles, dorsal medulla, and midbrain (Fig. 2). A muscle biopsy of the patient showed no sign of ragged red fibers. Endocrinological laboratory analysis showed normal levels of blood sugars, insulin, hemoglobin A1c, cortisol, free T4, thyroid stimulating hormone, prolactin, calcium, phosphorus, and alkaline phosphatase. The typical clinical and MRI findings confirmed the diagnosis of KSS. A permanent transvenous single-chamber ventricular pacemaker was implanted into the right ventricle (Medtronic, USA) (Fig. 1b).

DISCUSSION

Kearns-Sayre syndrome is a disease of mitochondrial encephalomyopathy that occurs secondary to mitochondrial DNA abnormality.[2] It can be diagnosed by determination of its characteristic features including onset before 20 years of age, progressive external ophthalmoplegia, and retinitis pigmentosa, along with the presence of at least one of the signs of the triad: complete heart block, ataxia, or protein increase in the cerebrospinal fluid.[1,2] It is particularly associated with various endocrine and metabolic disorders such as short height, gonadal deficiency, diabetes mellitus, thyroid diseases, hypoaldosteronism, and hypoparathyroidism.[4-6] Moreover, growth hormone (GH) deficiency may also be seen, which is generally not responsive to GH replacement.[7] In our case, somatomedin deficiency was determined, but recombinant somatomedin C treatment was discontinued due to failure to obtain a significant response. In some cases, more symptoms may occur, such as nystagmus, myopia, vestibular disorders, proximal muscle weakness, encephalopathy attacks, and diverse myopathies.[5,6] Cranial T2-weighted MR images of pediatric patients with neurological involvement show subcortical white matter involvement as well as involvement of one or more of the following strong characteristics of KSS: brain stem, globus pallidus, and thalamus.[8] In our case, besides diffuse subcortical involvement, the thalamus, brain stem, and putamen were found to be affected, as well.

The most important factor in determining the prognosis of KSS is cardiac signs. Kearns-Sayre syndrome typically affects the heart, causing cardiac conduction defects and progressing to complete heart block manifesting as congestive heart failure, syncope, or sudden death in up to 57% of the patients.[6,9] Abnormalities in the cardiac conduction system may begin with left fascicular block with or without right bundle branch block. Patients with KSS may have an unpredictable progression to complete heart block with an associated mortality of 20%. Other abnormalities include prolongation of the PR interval, sinus dysrhythmia, and QT prolongation.[9] Albeit considerably rare, in some cases, MVP may be seen which may be accompanied by His-Purkinje block.[10] Guidelines of the ACC/AHA published in 2002 recommend implantation of a permanent pacemaker (even in asymptomatic cases) in neuromuscular diseases such as KSS due to possible unpredictable progression in any of the AV blocks.[11] In our patient, MVP was present and permanent pacemaker was eventually implanted for complete AV block.

Patients generally exhibit elevated levels of blood lactate, pyruvate, and an increased lactate/pyruvate ratio. Since KSS is a mitochondrial disease, mitochondrial respiratory chain defects in skeletal muscles may be seen in KSS, along with the presence of ragged red fibers at histological level; however, the absence of these two findings does not eliminate KSS in the diagnosis.[5,9] In such cases, neuroradiological findings or detection of mitochondrial DNA deletion may help the diagnostic process. In our case, no ragged red fibers were seen in muscle biopsy specimens and, owing to lack of technical support, we could not perform DNA polymerase chain reaction or Southern Blot test. However, typical clinical signs and characteristic neuroradiological findings required for KSS diagnosis were present.

In the presence of growth retardation, shortness of height unresponsive to somatomedin C therapy, and neurological symptoms such as ocular signs and proximal muscle weakness, KSS should be considered. Even in the presence of a normal muscle biopsy result, demonstration of typical clinical symptoms, neuroradiological signs, and particularly mitochondrial DNA deletion is of utmost importance. In these patients, early diagnosis of cardiac symptoms is very important because sudden and fatal complete heart blocks can

develop. If there is an AV conduction defect, especially accompanied by MVP, implantation of a permanent pacemaker should be considered.

REFERENCES

1. Ashizawa T, Subramony SH. What is Kearns-Sayre syndrome after all? Arch Neurol 2001;58:1053-4.
2. Welzing L, von Kleist-Retzow JC, Kribs A, Eifinger F, Huenseler C, Sreeram N. Rapid development of life-threatening complete atrioventricular block in Kearns-Sayre syndrome. Eur J Pediatr 2009;168:757-9.
3. Kenny D, Wetherbee J. Kearns-Sayre syndrome in the elderly: mitochondrial myopathy with advanced heart block. Am Heart J 1990;120:440-3.
4. Harvey JN, Barnett D. Endocrine dysfunction in Kearns-Sayre syndrome. Clin Endocrinol 1992;37:97-103.
5. Schmiedel J, Jackson S, Schäfer J, Reichmann H. Mitochondrial cytopathies. J Neurol 2003;250:267-77.
6. Altunbaşak S, Bingöl G, Özbarlas N, Akçören Z, Hergüner O. Kearns-Sayre syndrome. A case report. Turk J Pediatr 1998;40:255-9.
7. Berio A, Piazzi A. Kearns-Sayre syndrome with GH deficiency. Pediatr Med Chir 2000;22:43-6. [Abstract]
8. Chu BC, Terae S, Takahashi C, Kikuchi Y, Miyasaka K, Abe S, et al. MRI of the brain in the Kearns-Sayre syndrome: report of four cases and a review. Neuroradiology 1999;41:759-64.
9. Chawla S, Coku J, Forbes T, Kannan S. Kearns-Sayre syndrome presenting as complete heart block. Pediatr Cardiol 2008;29:659-62.
10. Katsanos KH, Pappas CJ, Patsouras D, Michalis LK, Kitsios G, Elisaf M, et al. Alarming atrioventricular block and mitral valve prolapse in the Kearns-Sayre syndrome. Int J Cardiol 2002;83:179-81.
11. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). Circulation 2002;106:2145-61.