

OLGU SUNUMU

RESPIRATORY FAILURE IN LEIGH SYNDROME

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SUMMARY

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Leigh syndrome, resulting from a disorder in the respiratory chain production of adenosine triphosphate within the mitochondria of affected cells, is characterized by various nonspecific clinical presentations including psychomotor regression, hypotonia, ataxia, bulbar and respiratory dysfunction. Acute respiratory failure is a frequent symptom and a common cause of death. Supportive therapies are especially essential in these periods. Medical treatment has been focused on maximizing the oxidative or bioenergetic ability of the patient's mitochondria. In this case report, therapeutic success with carnitine, ketogenic diet and non invasive mechanical ventilation support in 22 years old Leigh syndrome patient with respiratory failure was presented.

KEYWORDS: Leigh Syndrome; Respiratory Failure; Carnitine.

ÖZET

LEIGH SENDROMUNDA SOLUNUM YETMEZLİĞİ

Leigh sendromu, etkilenen hücrenin mitokondrisinde, solunum zincirinin adenozin trifosfat üretiminde bozukluk sonucu ortaya çıkan, psikomotor regresyon, hipotoni, ataksi, bulber ve solunumsal disfonksiyonları da içeren pek çok nonspesifik klinik bulgu ile karakterize bir sendromdur. Akut solunum yetmezliği sık görülen semptomlardandır ve ölümün de yaygın nedenlerindendir. Bu dönemlerde destek tedavisi özellikle gereklidir. Medikal tedaviler hastanın mitokondrisinde oksidatif ya da biyoenerjetik kabiliyeti artırmaya yöneliktir. Bu olgu sunumunda solunum yetmezliği olan 22 yaşında Leigh sendromlu hastada, karnitin, ketojenik diyet ve noninvazif mekanik ventilasyon desteği ile gözlenen terapötik başarı sunuldu.

ANAHTAR KELİMELELER: Leigh Sendromu; Solunum Yetmezliği; Karnitin.

INTRODUCTION

Leigh syndrome (subacute necrotizing encephalomyelopathy), first described in 1951, is a heterogeneous neurological disease that results from a disorder in the respiratory chain production of adenosine triphosphate within the mitochondria of affected cells (1). It affects primarily infants and young children and characterized by various nonspecific clinical presentations, including psychomotor regression, hypotonia, ataxia, bulbar and respiratory dysfunction (2). The pathologic findings include symmetric necrotic lesions with demyelination, vascular proliferation, and gliosis in the basal ganglia, diencephalon, and brainstem (3). We present the intensive care unit management of Leigh syndrome with respiratory failure.

CASE

Twenty-two year-old male patient with Leigh syndrome applied to our hospital for respiratory distress. In his medical history, he began to demonstrate developmental regression at 8 years of age. T2 weighted magnetic resonance imaging (MRI) revealed symmetric high signal areas in the basal ganglia, substantia nigra, and inferior colliculus bilaterally and diagnosed as Leigh syndrome at age of nine. Two years younger sister was also diagnosed as Leigh syndrome at the age of 1 and died in 3 years of age. Spasticity and hyperreflexia were observed in all four limbs with legs more than arms at the age of 13. Over the course of the next 3 years, he developed increased weakness and spasticity in his lower limbs. Coordination of the lower limbs appeared to dec-

line. He had difficulty in swallowing both liquid and solid foods at the age of 20.

In his last arrival to our hospital, he had fever, cough and dyspnea. Physical examination revealed bilaterally decreased breath sounds and crackles with auscultation of the lung. Laboratory results were in normal range except elevated white blood cells (WBC) ($17.2 \times 10^9 \text{ L}^{-1}$). He had diagnosed as pneumonia and antimicrobial therapy with cephtriaxon 2x1 gr intravenous (i.v) and metranidasol 3x500 mg IV was started. Cranial MRI of his last arrival to our hospital was shown in Figure 1. According to his arterial blood gas (ABG) results; (pH: 7.23, PCO_2 : 69 mmHg, PO_2 : 46 mmHg) and respiratory rate (>30) mechanic ventilation (MV) with synchronized intermittent mandatory ventilation (SIMV) mode was started. Mechanical ventilation mode was changed to spontaneous mode in 7th day. On 8th day ABG results were as follows: pH: 7.41, PCO_2 : 32 mmHg, PO_2 : 78 mmHg. His WBC count decreased to $8.2 \times 10^9 \text{ L}^{-1}$. He was extubated at the 8th day according to blood gas results and clinical findings. His 12th day ABG results were as follows: pH: 7.25, PCO_2 : 61 mmHg, PO_2 : 72 mmHg. He was reintubated and MV with SIMV mode was started. Pneumonia was thought to be the main result of respiratory failure in hospital admission. Despite good clinical and laboratory results we couldn't achieve desired therapeutic result. So we decided to add supplemental agents. Carnitine therapy was introduced with a dose of $50 \text{ mg kg}^{-1} \times 1$ peroral (PO) and ketogenic diet was started. An impressive clinical response was observed. He was extubated in 14th day his arterial

blood gas results were as follows: pH: 7.42, PCO_2 : 38 mmHg, PO_2 : 86 mmHg and in order to prevent CO_2 retention with spontaneous breathing non invasive mechanical ventilation was started with a home type mechanic ventilator. No CO_2 retention was observed during the two weeks following period and his appetite developed, he gained weight and he was discharged with his home type ventilator.

DISCUSSION

Since Leigh's initial case report in 1951, Leigh syndrome remains an uncommon disorder. Clinical manifestations can be highly variable, making diagnosis of the disorder difficult. Diagnosis is usually confirmed by radiological or pathologic evidence of symmetric lesions affecting the basal ganglia, brainstem, and subthalamic nuclei (4). Leigh syndrome can be divided into both infantile and juvenile form. The infantile form typically has its onset in the first 2 years of life with the infant often having a history of developmental delay, hypotonia, and feeding difficulties. Juvenile forms occurring in later childhood to adolescence occur much less commonly. Typically these patients present with predominant extrapyramidal features such as dystonia and rigidity that slowly progress. Occasionally neurologic features remain unchanged for years until acute deterioration occurs, usually after decompensation with illness (5).

The pathogenesis of Leigh's syndrome has been elucidated and at present it appears to represent the neuropathologic end point of disordered cerebral mitochondrial energy production. The major biochemical defects that have been linked to its pathogenesis are: defects in mitochondrial respiratory chain enzymes, specially cytochrome oxidase (COX) complex I/II deficiency and deficiency of pyruvate dehydrogenase (PDH) complex. It is possible to detect these abnormalities by histochemical studies of fresh muscle tissue or cultured fibroblasts. Genetic abnormalities leading to these biochemical defects are heterogeneous and may be Mendelian, maternal (mitochondrial DNA mutation), X-linked (some enzymes of the PDH enzyme complex) or sporadic (6).

Radiological features are usually characteristic. Computerized Tomography (CT) scan typically shows low attenuation areas in basal ganglia (particularly putamen). Magnetic Resonance Imaging (MRI) shows symmetrical hypointense lesion on T1 weighted image becoming hyperintense on T2, involving basal ganglia and brainstem with sparing of the mamillary body which is highly specific of Leigh's syndrome (7,8).

The Leigh pattern of pathology is characterized by morphologic abnormalities distributed in distinct anatomo-

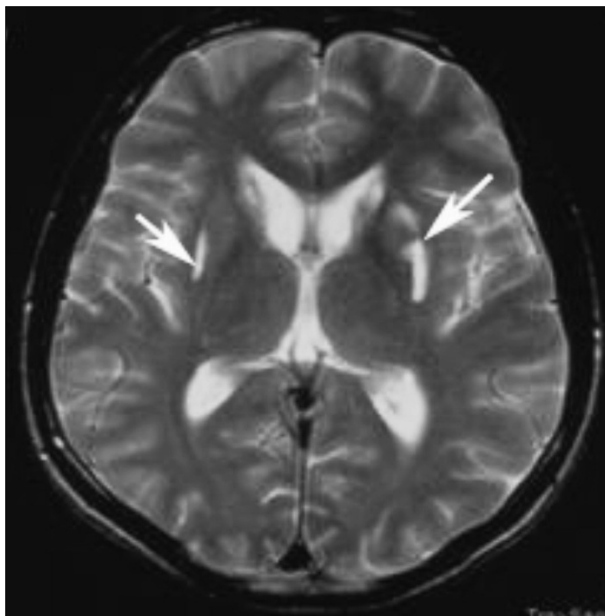


Figure 1. T2-weighted axial magnetic resonance imaging shows bilateral hyperintense lesions in the putamen (white arrows).

mic regions. The earliest change is spongiosis followed by capillary proliferation, astrogliosis and the appearance of histiocytes. The individual lesion involves both gray and white matter and tends to be patchy but is usually symmetrical in distribution (6).

Acute respiratory failure is a frequent symptom of Leigh's syndrome, found in to 64-72% of patients, and is a common cause of death (1,9). In this case non invasive mechanical ventilation support with home type mechanical ventilation was found to be very effective to prevent CO₂ retention due to his extrapulmonary respiratory failure. Medical treatment has been focused on maximizing the oxidative or bioenergetic ability of the patient's mitochondria. Coenzyme Q, which is involved in the respiratory chain distal to complex II has shown some benefit in a few series of patients with mitochondrial disease (10). Thiamine, an integral cofactor of the E1-E3 components of the pyruvate dehydrogenase (PDH) complex has been found to be effective in some cases (10). Ketogenic diet has also been found helpful in PDH deficiency which induces hepatic ketone body formation that the brain mitochondria can utilize as an alternative energy source instead of pyruvate (11). Carnitine which is involved in the transport of fatty acids across the inner mitochondrial membrane where the fatty acids will be metabolized for energy could be a supplemental therapy in these patients. In this case we use ketogenic diet and carnitine therapy together and an imperative clinical improvement was observed.

In conclusion from observed therapeutic success in this case, carnitine therapy and ketogenic diet to improve oxidative capacity and non invasive mechanical ventilation support could be an valuable alternative supportive therapy in Leigh syndrome patient with respiratory failure.

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