CASE REPORT / OLGU SUNUMU

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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

A Case of Late-Presenting Methylmalonic Acidemia from a Country Without Extended Newborn Screening

Genişletilmiş Yenidoğan Programı Olmayan Bir Ülkede Geç Başlangıçlı Metilmalonik Asidemi Olgusu

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Abstract

Methylmalonic acidemia (MMA) is an autosomal recessive disorder that may be caused by a complete (mut^0) or partial (mut^-) deficiency of the methylmalonyl-CoA mutase, by defects in the synthesis or transport of the co-factor, or by a deficiency in methylmalonyl-CoA epimerase. Most patients with MMA present with such signs and symptoms as lethargy, feeding problems, tachypnea and hypotonia after breastfeeding within the first few days or weeks of life. In untreated cases, life-threatening acidosis, hyperammonemic encephalopathy, coma and death can occur. In the present study we emphasize the importance of the early suspicion of inherited metabolic disorders in the differential diagnosis and treatment of an MMA case who applied to the emergency department with atypical clinical findings after the age of 1, and who rapidly developed coma findings. Although MMA frequently presents itself during the first days of life, it should be kept in mind in the differential diagnosis of metabolic acidosis, especially in older patients with a high risk of inherited metabolic disorders and with atypical clinical and laboratory findings.

Key Words: Metyhlmalonic Acidemia, Organic Acidemia, Ketoacidosis

Öz

Metilmalonik asidemi (MMA), metilmalonil-CoA mutazının tam (mut^0) veya kısmi (mut^-) eksikliğinden, kofaktörün sentezindeki veya taşınmasındaki kusurlardan veya metilmalonil-CoA epimeraz eksikliği nedeniyle ortaya çıkan otozomal resesif geçişli metabolik bir hastalıktır. MMA'lı hastaların çoğu, yaşamın ilk birkaç günü veya haftasında emzirmeden sonra uyuşukluk, beslenme sorunları, taşipne ve hipotoni gibi belirti ve semptomlar gösterir. Tedavi edilmeyen olgularda hayatı tehdit eden asidoz, hiperamonyemik ensefalopati, koma ve ölüm görülebilir. Bu çalışmada acil servise 1 yaşından sonra atipik klinik bulgularla başvuran ve hızla koma bulguları gelişen bir MMA olgusunun ayırıcı tanı ve tedavisinde kalıtsal metabolik hastalıklardan erken şüphelenilmesinin önemi vurgulanmıştır. Metilmalonik asidemi sıklıkla yaşamın ilk günlerinde ortaya çıksa da, özellikle kalıtsal metabolik bozukluk riski yüksek, atipik klinik ve laboratuvar bulguları olan yaşı daha büyük hastalarda metabolik asidoz ayırıcı tanısında akılda tutulmalıdır.

Anahtar Kelimeler: Metilmalonik Asidemi, Organik Asidemi, Ketoasidoz

Introduction

Isolated methylmalonic acidemia (MMA) is an autosomal recessive disorder that can be caused by a complete (mut^0) or partial (mut^-) deficiency of the methylmalonyl-CoA mutase, by defects in the synthesis or transport of the co-factor, or by a deficiency in methylmalonyl-CoA epimerase (1). Genetically, methylmalonyl-CoA mutase is encoded by *MUT*; cobalamin A, B or D deficiency as caused by a disorder associated with 5-deoxyadenosylcobalamin is encoded by *MMAA*, *MMAB*, and

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MMADHC; and the deficiency of methylmalonyl-CoA epimerase is encoded by *MCEE* (2). The rate of isolated MMA is nearly <1 per 100,000 newborns (3). Most patients with MMA present such signs and symptoms as lethargy, feeding problems, tachypnea and hypotonia after breastfeeding within the first few days or weeks of life. The main treatments are a lifelong low-protein diet and medication. In untreated cases, life-threatening acidosis, hyperammonemic encephalopathy, coma and death can occur (4). Intracellular cobalamin metabolism and associated defects are shown in Figure 1.

In the present study we emphasize the importance of the early suspicion of inherited metabolic disorders in the differential diagnosis and treatment process of an MMA case who presented to the emergency department with atypical clinical findings after the age of 1 and who rapidly developed coma findings.

A 13-month-old male patient was admitted to the pediatric emergency with fever and tachypnea after several vomiting episodes.

The patient was born at full term, weighing 3800 grams after an uneventful pregnancy within a non-consanguineous marriage. He was hospitalized with early neonatal sepsis. His vaccines were administered on time, and no complications developed. The patient's neurodevelopmental milestone history was normal.

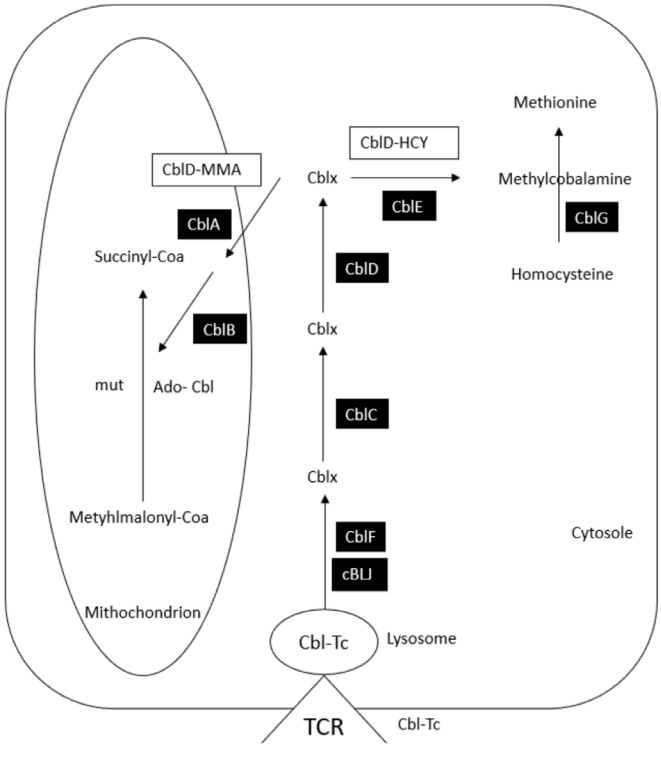

Figure 1: Intracellular cobalamin metabolism and associated defects

At the time of admission, his Glasgow coma scale (GCS) was 15, body temperature was 38.8 °C, pulse rate was 170/minute, respiratory rate was 60/minute, oxygen saturation was 96% and blood pressure was 110/60 mmHg. Peripheral pulse values were normal and the capillary filling time was shorter than 2 seconds. The liver was 2 cm palpable below the ribs, and other system examinations were unremarkable.

Laboratory test results revealed metabolic acidosis (pH: 7.03, PCO_2: 11.6 mmHg HCO_3: 2.9 mmol/L, lactate: 2.0 mmol/L, anion gap: -21). Blood biochemistry was normal: C-reactive protein: 14.6 mg/L, procalcitonin: 0.15 ng/mL, erythrocyte sedimentation rate: 5 mm/h; hemogram hemoglobin: 11.6 gr/dL platelet count: 394,000/mm^3, WBC: 15,000/mm^3 and absolute neutrophil count: 10,000/mm^3. Ammonium levels could not be measured at the hospital to which the patient was first admitted due to the lack of the necessary technical facilities. Ketones were +++ detected in urinalysis. As the patient had metabolic acidosis with increased anion gap and ketonemia, inherited metabolic disorders such as organic acidemias and ketolysis defects were first considered.

As the patient had dehydration, 20 cc/kg saline was twice loaded on the patient at admission. Ceftriaxone was started empirically as sepsis could not be excluded. The glucose infusion rate was 6 mg/kg/min with sodium 3 mEq/kg and sodium bicarbonate 2 mEq/kg administered as a fluid mixture. Despite administering repetitive doses of bicarbonate infusions, the acidosis persisted in the blood gases (pH: 7.15 pCO_2: 26 mmHg HCO_3: 8.7 mmol/L) The patient was intubated and followed up on mechanical ventilator in the intensive care unit due to regression in GCS. As the central nervous system pathologies associated with infections could not be excluded in the patient, vancomycin and acyclovir were added to the treatment regimen, and bicarbonate treatment was continued. The patient was in need of pediatric intensive care and department of pediatric metabolism support, leading to a referral to a tertiary-level healthcare institution on the second day of admission.

Upon admission to the tertiary level healthcare center, the plasma ammonia level was 175 (umol/L) and blood ketones: 0.9 mmol/L. Intravenous carnitine 100 mg/kg/day, oral biotin supplementation 2x5 mg and intramuscular hydroxocobalamin 1000 mcg were administrated with high glucose fluid infusion. In tandem MS, upon observing C3 propionyl carnitine elevation with 5.14 (umol/L) (RR: 0.28-2.9) and excretions of methylmalonic acid in urine organic acids (methylmalonic acid 16.7 times higher than the internal standard), MMA was considered as a differential diagnosis. Cranial imaging with CT and MRI revealed findings in correlation with MMA and with bilateral globus pallidus involvement. A genetic test was then ordered due to a pre-diagnosis of cobalamin A/B defect. After obtaining a detailed family history, we learned that the patient's

cousin (the child of his mother's sister) was being followed up with a diagnosis of MMA. A *MUT* gene analysis of the patient's cousin revealed a homozygous p.L674F (c.2020C>T) mutation, and the same homozygous p.L674F (c.2020C>T) mutation was identified in our patient in a molecular genetic analysis.

Afterwards, the patient could tolerate oral food, and oral intake was increased incrementally with a content of 1.5 gr/kg/g protein (75% natural foods + 25% medical formula). The treatment continued with hydroxocobalamin (1000 mcg/dose; oral 2 days a week, intramuscularly 1 day a week), and carnitine treatment was given as 100 mg/kg/day orally on an outpatient basis.

The patient was discharged to be followed-up by the pediatric metabolic diseases outpatient clinic. Upon re-evaluation 6 months after discharge, there had been no metabolic decompensation and neurodevelopmental findings were normal.

We present this case of methylmalonic acidemia diagnosed after 1 year of age. Although the disease usually presents in the neonatal period, in some cases it may present late. It is difficult to diagnose before the emergence of symptoms, especially in countries where newborn screening is unavailable. In the present study we wanted to emphasize the importance of awareness of organic acidemia in cases presenting with atypical findings, especially in regions where no newborn screening is performed.

Methylmalonic acidemia typically presents during the first week or first month of life as an organic acidemia resulting from a defect in the branched chain amino acid metabolism (1). The disease manifests with infections, recurrent vomiting triggered by excessive protein intake and other stress factors, poor feeding, respiratory distress, hypotonia, encephalopathy and neurologic deficits that can progress into a coma. Less frequently, hematologic abnormalities and renal findings may be identified (5). In our case, after the patient experienced vomiting and respiratory problems, there was a rapid evolution into encephalopathy and coma, but no accompanying hematological abnormalities or renal damage. These findings are non-specific in pediatric patients, and diagnosis may be difficult if the clinician does not consider inborn metabolism errors in the differential diagnosis.

In a metanalysis by Almási et al. (1) in 2019, the incidence of MMA was below 2:100 000; however, in regions where consanguineous marriages are common, the incidence was found to be higher. As consanguineous marriages are common in our country, metabolic diseases can be seen more frequently. According to the data of the Turkish Statistical Institute, the rate of consanguineous marriages among registered marriages in our country is around 21-24% (6), and so the possibility of inherited metabolic disorders should be kept in mind in cases with clinical and laboratory correlations. Our patient had no history of consanguineous marriage, although a family member had previously been diagnosed with MMA, although this information was lacking at the time of the initial application. Since family history is a factor that increases the inherited metabolic disorders suspicion index, if the family could have presented us with this information at the time of the first application, a positive outcome could have been achieved in the diagnosis-treatment process (7).

In tests performed for MMA, metabolic acidosis, ketonemia, hyperammonemia and cytopenia have been identified (8). MMA diagnosed patients have low levels of free carnitine in their blood and high levels of methylmalonyl carnitine esters. In a urine analysis, methylmalonic acid excretion is shown to have increased. While a diffuse cerebral edema is detected in the hyperammonemic acute process, at follow-up, signal intensity abnormality (predominantly diffuse T2-hyperintensity) and diffusion restriction in cerebral white matter, volume loss in the cortex, delay in myelin maturation, focal necrosis of the basal ganglia, especially in globi pallid, and basal ganglia calcification in old age are detected (9). In the case presented here, ketoacidosis, high levels of urinary excretion for methylmalonic acid among urine organic acids and elevated C3 level in Tandem MS analysis were detected. Moreover, cranial imaging findings supported MMA with bilateral globus pallidus involvement.

MMA frequently appears as an early onset condition, while the late onset form is less common and frequently has a milder clinical course (10). In a study by Şeker Yılmaz et al. (11) of 37 patients with MMA, 51% of the sample were diagnosed during the first month of life and 16% (6 patients) after 12 months. The latest diagnosis was in a male aged 29 months who was identified to have a mutation of the *MUT* gene. In a study by Heringer et al. (12) that analysed the data sets of 567 organic aciduria diagnosed patients from the European registry and network for intoxication type metabolic diseases registry, the age of diagnosis was 6-8 days for early onset MMA and 210-348 days for late onset MMA. In a study by Saini et al. (13) presenting two cases, the MMA patients were asymptomatic at birth, but presented with septic shock and a diabetic ketoacidosis-like picture at 8 and 12 months. Our patient was diagnosed at 13 months, and was admitted with vomiting, coma and metabolic acidosis with anion gap. The reason for the late diagnosis of these patients in literature may be due to the fact that methylmalonic acidemia is not included in newborn screening programs, as in our country. All of these case presentations suggest that mild forms of MMA can be symptomatic in the older age group. *MUT*-type MMA patients were found to have more widespread metabolic crises than patients with other isolated MMA types (cblA and cblB defects) (5). Furthermore, different mutations of the *MUT* gene have been shown to be associated with the efficacy of vitamin B12 treatment, as stated in other studies (14,15). In our patient, the analysis of the *MUT*

gene revealed homozygous p.L674F (c.2020C>T). According to the American College of Medical Genetics criteria, this variant (chr6-49403273G>A, c.2020C>T, p.Leu674Phe, rs1164271240) is classified as "pathogenic" for MMA. The frequency of this variant is reported as a "very rare variant" (0.0004%) according to gnomAD data (16). This variant was previously described homozygously in a 1.5-month-old female Turkish MMA patient. The authors shared that the patient is 4.5 years old, still alive, and under follow-up (17). The patient responded to a low protein diet, hydroxocobalamin and carnitine replacement (18-20).

Patients can develop such complications as developmental delay, hypotonia, epilepsy, psychological behavioral abnormalities, anemia, kidney function abnormalities and pulmonary hypertension in the long term (8), and so the early recognition of acute episodes and appropriate treatment are thought to prevent long term sequelae. Our patient, like other late-onset MMA cases, had a mild clinical course, as was expected (10). When the patient was re-evaluated 6 months after discharge, his neurodevelopmental findings were normal and there were no complications in other systems.

Although methylmalonic acidemia frequently presents during the first days of life, it should be kept in mind in the differential diagnosis of metabolic acidosis in older age patients. It is important to raise awareness of congenital metabolic diseases among clinicians, especially in regions such as our country where consanguineous marriages are common and there is no newborn screening program.

Ethics

Informed Consent: Written consent was obtained from the patient and family members for photos.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Ö., P.A., M.K.Y., E.K., T.K., F.T.E., Concept: G.Ö., P.A., M.K.Y., E.K., F.T.E., Design: G.Ö., P.A., M.K.Y., E.K., T.K., F.T.E., Data Collection and Processing: G.Ö., P.A., M.K.Y., F.T.E., Analysis or Interpretation: G.Ö., P.A., M.K.Y., E.K., Literature Search: G.Ö., P.A., M.K.Y., Writing: G.Ö., P.A., M.K.Y.

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