

## Treatment Approach of a Patient Affected by Both Argininosuccinic Aciduria and Methylmalonic Aciduria

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### Abstract

Most of the inborn errors of metabolism (IEM) are autosomal recessively inherited and they are more frequent in the countries where consanguineous marriages are commonly practiced. Rarely, more than one IEM are seen in the siblings of one family or in the same sibling. Here we report a patient with both argininosuccinic aciduria (ASA) and methylmalonic acidemia (MMA) and our therapeutic approach. First sibling of the family died with MMA, second sibling was diagnosed with ASA, and third sibling was diagnosed with both ASA and MMA. Here we report therapeutic approach of this patient. Dietary regimen of the patient was planned with MMA being the basis. When a patient was admitted with a history of sibling with an IEM, possibility of another disorder should always be kept in mind particularly in the countries that consanguineous marriages are commonly practiced.

**Keywords:** Argininosuccinic aciduria; Methylmalonic acidemia; Inborn errors of metabolism

### Introduction

Most of the inborn errors of metabolism (IEM) are autosomal recessively inherited and they are more frequent in the countries where consanguineous marriages are commonly practiced. Rarely, more than one IEM are seen in the siblings of one family or in the same sibling. Here we report a patient with both argininosuccinic aciduria (ASA) and methylmalonic acidemia (MMA) and our therapeutic approach.

Argininosuccinic aciduria results from deficiency of enzyme argininosuccinate lyase (ASL), the fourth step of the urea cycle, in which argininosuccinic acid is cleaved to produce arginine and fumarate. Elevated plasma ammonia concentration, elevated plasma citrulline concentration, and elevated argininosuccinic acid in the plasma or urine establish the diagnosis of ASL deficiency. Molecular genetic testing of *ASL* gene, and assay of ASL enzyme activity confirms the diagnosis [1].

Isolated methylmalonic acidemia/aciduria is caused by complete or partial deficiency of the enzyme methylmalonyl-CoA mutase (*mut0* enzymatic subtype or *mut-* enzymatic subtype, respectively), a defect in the transport or synthesis of its cofactor, adenosyl-cobalamin (*cblA*, *cblB*, or *cblD* variant 2 type), or deficiency of the enzyme methylmalonyl-CoA epimerase. Definitive diagnosis of isolated methylmalonic acidemia relies on analysis of organic acids in plasma and/or urine by gas-liquid chromatography and mass spectrometry. Establishing the specific enzymatic subtype of methylmalonic acidemia requires studies on vitamin B<sub>12</sub> responsiveness, <sup>14</sup>C propionate incorporation assays, complementation analysis, and cobalamin distribution assays [2].

Although chronic management of both diseases consist of a low-protein diet, the treatment of more than one disorders affecting aminoacid metabolism was challenging.

### Case Report

A 2 -day- old male patient was admitted to neonatal intensive care unit in our hospital since a previous sibling had been diagnosed with ASA. Parents were distant relatives. The first child of the family had died due to methylmalonic acidemia (MMA) in the neonatal period in another center. Second sibling had been referred to our clinic with encephalopathy and suspected MMA in the neonatal period, but surprisingly she had been diagnosed with ASA based on laboratory findings and then confirmed by molecular genetic analysis. She had been treated and followed up in our clinic, but the family refused prenatal diagnosis in this third pregnancy.

The patient was a term baby and birth history was uneventful. Physical examination was normal at admission. Laboratory investigations revealed elevated C3 propionyl carnitine levels (8.31 μmol/L N: 0.28-2.90), elevated citrullin (59.16 μmol/L N: 3.0-46.7) and argininosuccinic acid (0.58 μmol/L N: 0.0-0.10) on serum tandem MS, 26 folds elevated methylmalonic acid on urinary organic acid analysis. Serum ammonia level was high (355 μg/dl N: 20-120). Urine tandem MS analysis revealed increased argininosuccinic acid levels (49.30 μmol/L). Both ASA and MMA were diagnosed.

In the patient, dietary treatment was very challenging. Because MMA could be more risky in terms of metabolic crisis and life-threatening, the dietary regimen of the patient was planned with MMA being the basis, and planned as 1 g/kg/day aminoacid mixture free of valine, isoleucine, methionine and threonine with 0.5 g/kg/day natural protein. All the replacement therapies were commenced. Sodium benzoate 250 mg/kg/day and arginine 250 mg/kg/day started for ASA, and carnitine 100 mg/kg/day, cyanocobalamine 1000 μg/day were given both for MMA. Cultured fibroblast analysis revealed *CblA/B* defect.

In the follow-up period he tolerated natural protein up to 1,25 g/kg/day, and until 2.5 years old, he didn't have a severe hyperammonemia or metabolic acidosis attack. At 2 years old his weight was 7,2 kg (<3 percentile), height was 76 cm (<3 percentile), head circumference was

46 cm (10-25 percentile). He had mild-moderate global developmental delay. And, unfortunately he died at another center when he was 2.5 years old.

## Discussion

MMA and ASA are IEMs that affect protein catabolism. MMA is an autosomal recessively inherited disorder caused by mutations in the *MUT* locus encoding the methylmalonyl CoA mutase or *MMAA* or *MMAB* genes for cobalamin A/B complementation groups [3]. Patients with defects in the synthesis of adenosylcobalamin (AdoCbl) including cbl A and B which is caused by mutation in the *MMAB* gene on 12q24 are usually responsive to vitamin B<sub>12</sub> therapy. Incidence of MMA is reported as 1/50.000-1/100.000. ASA is also an autosomal recessive disorder of the urea cycle caused by the mutations in the Argininosuccinate Lyase (*ASL*) gene located on 7cen-q11.2 and occurs in approximately 1 in 70,000 live births. Here, the clinical and laboratory findings and our therapeutic approach were presented for this extremely rare case, the dietary regimen of the patient was planned with MMA being the basis, because risk of severe metabolic crisis and death was much more higher for MMA than ASA in the neonatal period. In the condition of more than one disorder that affect the protein metabolism, to treat the patient being the basis of the disorder that has more life-threatening risk might be rational.

Consanguineous marriages increase the rate of autosomal recessive disorders and consanguineous parents may be carrier for more than one same recessive disease. Particularly in the countries that consanguineous marriages are commonly practiced, more than one

IEM in the siblings of one family or in the same sibling is possible. Presence of other genetic diseases including cystic fibrosis, hereditary fructose intolerance, Goldenhar's syndrome, Duchenne muscular dystrophy, together with phenylketonuria in the same patient were reported [4-7]. Phenylketonuria and glycogen storage disease type III in sibs of one family was also reported [8]. When a patient was admitted with a history of sibling with an IEM, possibility of another disorder should always be kept in mind.

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