Patient report

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An asymptomatic mother diagnosed with 3-methylcrotonyl-CoA carboxylase deficiency after newborn screening

Abstract

Background: 3-Methylcrotonyl-CoA carboxylase (3-MCC) deficiency is an autosomal recessively inherited disease of leucine catabolism. It is the most commonly observed organic acidemia where tandem mass spectrometry can be performed in newborn screening. The clinical phenotypes may differ from neurological involvement in newborns to asymptomatic adults. Diagnosis is made by increased 3-hydroxyisovaleric acid in blood and 3-methylcrotonylglycine in urine.

Case report: We would like to present an interesting case of a 32-year-old asymptomatic mother, who was investigated metabolically and diagnosed with 3-MCC deficiency, after a 7-day-old healthy baby referred to our unit with the preliminary diagnosis of organic academia during her extended newborn screening.

Results: All of the metabolic findings of the baby were normal except for very low carnitine levels. Her mother's total and free carnitine levels were also extremely low. Urine organic acid analysis revealed excessively increased 3-methylcrotonylglycine and 3-hydroxyisovaleric acid. Acylcarnitine profile showed markedly elevated C5 hydroxy 3 hydroxyisovalerylcarnitine and decreased C2 acetylcarnitine. In order to confirm the diagnosis of 3-methylcrotonylglycinuria, molecular analysis was done, and IVS3-1G>C/p.T556I compound heterozygote mutation was detected. p.T556I is a novel mutation.

Conclusion: We would like to emphasize performing extended metabolic investigations in case of suspicion of metabolic disease in order to diagnose metabolic diseases both in babies and in asymptomatic mothers.

Keywords: carnitine; leucine; neonatal screening; 3-methylcrotonyl-CoA carboxylase deficiency.

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Introduction

3-Methylcrotonyl-CoA carboxylase (3-MCC) is a biotin-dependent mitochondrial carboxylase enzyme. It catalyzes the conversion of 3-methylglutaconyl-CoA to 3-methylcrotonyl-CoA at the fourth step of leucine catabolism. Adenosine triphosphate and bicarbonate are used in this reversible reaction. Isolated biotin-resistant 3-MCC deficiency (MIM#s: *MCCA*-210200 and *MCCB*-210210) is an autosomal recessively inherited disease of leucine catabolism, known as 3-methylcrotonylglycinuria (1). Although 3-MCC deficiency is considered to be a rare disorder, it is reported as the most commonly encountered organic acidemia in North America, Europe, and Australia, where newborn screenings are performed by using tandem mass spectrometry (2). The incidence is approximately 1/36,000 (3). Clinical phenotypes of patients diagnosed with 3-MCC deficiency differ from asymptomatic adults to fatal newborn cases with serious neurological involvement (4). On the other hand, it was also reported that the majority of children diagnosed during the newborn screening programs may also be asymptomatic all through their lives (2, 5, 6). In 3-MCC deficiency, 3 hydroxyisovalerylcarnitine (3-HIVA-C), 3-methylcrotonyl-CoA, and 3-methylcrotonic acid are increased, and serious secondary carnitine deficiency is detected. Accumulated acyl-CoAs are conjugated by glycine and are converted to 3-methylcrotonylglycine (MCG). Characteristically, 3-hydroxyisovaleric acid (3-HIVA) and 3-MCG

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are observed to be increased excessively in the patient's urine. Biotin intake at pharmacological doses does not change this picture. Mild protein restriction in the diet may cause general recovery and decreased number of attacks during treatment of symptomatic babies. Glycine and carnitine replacements are recommended because they increase the excretion rate of toxic substances (4).

Considering the present case as interesting, we reported here a 32-year-old asymptomatic mother of a newborn referred to our unit with suspicion of an organic acidemia as a result of extended newborn screening program investigations. We determined increased 3-HIVA and decreased carnitine in the mother's blood and further diagnosed her with 3-MCC deficiency.

Case report

A 7-day-old female newborn who was referred to our unit as having low free carnitine level was selected for the extended newborn screening program. In the patient's history, the baby was born after 38 weeks of gestation weighing 4200 g through cesarean section after a normal pregnancy period. There was no problem during and after the delivery, baby had her first vaccination at the hospital, and the mother was breast-feeding the baby. In the family history, the father was 47 years old and had three healthy children from his first marriage. The mother was 32 years old, and the newborn was her first baby. There was neither consanguinity between the parents nor any known metabolic diseases or fetal deaths of unknown etiology in the family. The physical examination findings at visit showed weight at 4220 g (75–90 percentile (p)), length at 49 cm (10–25 p), head circumference of 37 cm (50 p), and anterior fontanelle of 2×2 cm, open and with normal bulging. There was no dysmorphic characteristic and no pathological finding other than mild icterus in the physical examination. The newborn did not have a different odor. Newborn reflexes were normal. During basal laboratory investigations, metabolic acidosis, hypoglycemia, hyperammonemia, and ketosis were not detected in the patient. In tandem mass spectrometry, 3-HIVA-C was high, and serum carnitine level was detected as 6 μmol/L (n=12–46); the urine organic acid analysis was normal. The patient was followed up for carnitine replacement at 50 mg/kg/day dose. Concomitantly, it was considered that existent laboratory results might have originated from the mother, and her metabolic investigations were performed. Results from the mother were total carnitine of 3.8 μmol/L (n=34–78) and free carnitine of 0.6 μmol/L (n=25–54). In the tandem mass spectrometry, it was observed that the 3-HIVA-C was very high, and urine organic acid analysis revealed excessively increased 3-MCG and 3-HIVA excretions. Therefore, the 32-year-old mother was diagnosed with 3-MCC deficiency. In the genetic analysis, combined heterozygote mutations of IVS3-1G>C(c.282-1G>C) and p.T556I(c.1667C>T) were determined in the MCCB gene. A mildly restricted protein diet (1.5 g/kg), carnitine at 100 mg/kg/day, and glycine at 175 mg/kg/day were recommended to the mother, and she was enrolled in the follow-up program. In the third month of carnitine replacement treatment, carnitine values of the mother were low, while carnitine levels of the baby were normal. In the follow-up visits, physical growth and mental-motor development of the baby were consistent with the age. The mother, who had no neurological problem or metabolic decompensation attack, refused to accept her illness.

Discussion

In countries with extended newborn screening programs, 3-MCC deficiency has become the most common congenital metabolic disease, and asymptomatic and previously undiagnosed individuals are now being diagnosed with a careful approach (7). Biochemical phenotype is not helpful in estimating clinical phenotype in this metabolic disease, because signs are variable due to high incidence and low clinical penetration. As many patients can be asymptomatic, there is not a complete consensus for the treatment of those individuals (2). It was reported that metabolites, which were detected in the newborn screening programs and which raised the suspicion of an inherited metabolic disease, might have originated from undiagnosed asymptomatic mothers with 3-MCC deficiency through the placenta (7, 8). Moreover, it was also shown in some studies that abnormal metabolites and low carnitine levels in babies might also be related to breast milk (9). Therefore, metabolic investigations should also be performed in the mother in the case of a suspicion. The present case was a randomly selected baby for the newborn screening program, extended by tandem mass spectrometry, who was referred to our clinic after detection of low free carnitine level by this analysis. Carnitine treatment was initiated in the patient without any decompensating metabolic signs and with normal organic acid results, and was then followed up. In the meantime, it was decided that carnitine deficiency might have originated from the mother, so metabolic and genetic investigations were requested. From the results of the investigations, the mother was diagnosed with 3-MCC deficiency. The mother refused to accept the

diagnosis, but as we showed details of the deficiency she accepted to take treatment. After a 1-year follow-up, no problem was observed in either the mother or the baby. After 3 months of treatment, the drug was discontinued, because carnitine level was measured to be normal in the baby. While there are efforts to extend the newborn screening program in our country, we are routinely performing quantitative amino acid analysis in all patients referred to our unit with the preliminary diagnosis of phenylketonuria and organic acid analysis in patients who are referred with the preliminary diagnosis of biotinidase deficiency. We have diagnosed eight more patients with other metabolic diseases apart from the presented case through this approach. The present case was an interesting one, because the 32-year-old female patient was asymptomatic, and she had no problem during catabolic states, such as pregnancy and cesarean section. The mother attended our clinic to have her newborn tested for inheritable metabolic diseases because newborn screening procedures indicated a suspicion. However, ultimately, the mother was diagnosed with 3-MCC deficiency. Similar to our case, in 1998 Gibson et al. diagnosed 3-MCC deficiency in four mothers who were investigated for abnormal newborn screening results in their healthy children in the Amish/Mennonite population (8). Frazier et al. reported in their retrospective multi-center study between years 1997 and 2005 that 3-HIVA-C levels were very high in 14 healthy babies of eight asymptomatic mothers (3). In 2010, Eichhorst investigated a baby with abnormal newborn screening results and diagnosed the asymptomatic mother with 3-MCC deficiency. During a 4-month follow up, he reported that blood 3-HIVA-C levels were parallel with levels in breast milk, and although those values in the baby decreased over time, they increased again because the mother's 3-HIVA-C levels increased, and its metabolites were passed to the infant via breast milk, which caused abnormal screening values in the baby (9). Grünert et al. evaluated 88 cases with 3-MCC deficiency diagnosis in their 2012 year paper by clinical and biochemical signs and enzymatic and molecular analyses. They reported that nine of these cases were diagnosed after their babies were diagnosed following newborn screening procedures. They also reported that the age range of nine mothers with 3-MCC deficiency was between 24 and 38 years; six of them were asymptomatic, while one of them had a few hypoglycemic metabolic attacks during febrile diseases, and she developed cardiomyopathy and paresthesia signs; another one of the cases had complaints of chronic fatigue (2).

In conclusion, the present case is reported to emphasize that metabolic investigations should be performed in all babies determined with high 3-HIVA-C during the screening programs; and if especially urine organic acid analyses are within normal limits, passage through placenta and/or breast milk should be considered, and the mothers of those newborns should also be investigated for 3-MCC deficiency.

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