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Maternal Inborn Errors of Metabolism Detected in Expanded Newborn Metabolic Screening

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What is already known on this topic?

- *Newborn screening (NBS) is a population-based screening method with a pivotal role in detecting diseases before the development of preventable complications .*
- *In Turkey, there is no national expanded NBS program for inborn errors of metabolism (IEM).*
- *Pathologic results in expanded NBS may be due to medications, inappropriate sampling methods, or maternal originated IEM.*

What this study adds on this topic?

- *This is the first study addressing the importance of metabolic screening via tandem mass spectrometry for early diagnosis of IEM in adulthood in Turkey.*

ABSTRACT

Objective: Pathologic results in expanded metabolic screening tests may be due to the medications, inappropriate sampling methods, or the maternal originated inborn errors of metabolism. The aim of this study is to identify mothers with inborn errors of metabolism through the pathologic expanded metabolic screening results of their babies.

Materials and Methods: Babies who were under 1 year of age and had a pathologic result of an expanded newborn screening for inborn errors of metabolism and their mothers were included in this retrospective single-centered study. Data of expanded metabolic screening results of both babies and their mothers were recorded. Clinical and laboratory findings relevant to suspected inborn errors of metabolism due to the pathologic screening results analysis were also noted for the mothers.

Results: Seventeen babies and their mothers were enrolled. Expanded metabolic screening results were found compatible with inborn errors of metabolism in 4 (23.5%) of 17 mothers. Two of these mothers were diagnosed with 3-methylcrotonyl-CoA carboxylase deficiency and 2 mothers were diagnosed with glutaric aciduria type 1.

Conclusion: Inborn errors of metabolism can present in any period of life, and this is the first study to address the importance of metabolic screening via tandem mass spectrometry in terms of early diagnosis of inborn errors of metabolism not only in pediatric aged patients but also in adulthood in Turkey. The performance of expanded metabolic screening tests may be an important step in terms of detecting maternal inborn errors of metabolism that are not diagnosed until adulthood.

Keywords: Inborn errors of metabolism, adulthood, newborn screening, maternal metabolic disorders, expanded metabolic screening

INTRODUCTION

Newborn screening (NBS) is a population-based screening method that aims to detect a disease before clinical signs and preventable complications develop. The principles of development and methodology of a screening test were mainly described by the World Health Organization according to Wilson and Jungner guidelines and The American College of Medical Genetics and Genomics.[1,2] To date, different screening methods have been developed regarding the early diagnosis of inborn errors of metabolism (IEM). Newborn screening for IEM was first started in 1960 by introducing the Guthrie test for screening of phenylketonuria (PKU).[3] Another major advance in NBS of IEM was the development of tandem mass spectrometry (MS/MS) which played a pivotal role in identifying multiple IEMs in a single test.[4] In recent years, next-generation deoxyribonucleic acid sequencing has been assessed

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as a second-tier NBS testing to identify the pathological genetic variants responsible for IEMs.[5,6]

The disease coverage of expanded NBS in terms of IEMs widely varies from the global perspective and is largely influenced by public health policies. Expanded NBS testing for amino acid metabolism disorders, organic acidemias, fatty acid oxidation disorders, and galactosemia has been widely applied in European countries.[7,8] In recent years, some of the complex molecule disorders including especially lysosomal storage disorders and X-linked adrenoleukodystrophy in which enzyme replacement therapy and/or bone marrow transplantation can be curative if initiated in early stages have also started to be included in the scope of screening in Europe and the USA.[7,9-11]

In Turkey, the national NBS program was first started with PKU screening in dried blood spot samples in 1987 and was extended to the whole country in 1993. Today, PKU, congenital hypothyroidism, biotinidase deficiency, congenital adrenal hyperplasia, cystic fibrosis, and spinal muscular atrophy are within the scope of national NBS.[12,13] Unfortunately, the lack of a national expanded NBS program in Turkey leads to diagnosis only after complications and clinical findings related to IEMs have developed.

Pathologic results in expanded NBS tests may be due to the medications used by the baby and/or mother, sampling methods or the maternal originated IEMs. In neonates, metabolites of maternal originated IEM may be transferred to the baby by placental route or breastfeeding, leading to expanded NBS results with abnormal metabolic profile.[14-16]

Data regarding the prevalence of IEMs diagnosed with expanded NBS in children and the frequency of maternal IEM diagnosed with the positive NBS result in their children have been limited to case reports since expanded NBS is not a part of the national NBS program in Turkey. Here, we aimed to identify the mothers in whom the pathologic expanded NBS results of their babies revealed a diagnosis of an IEM. The main objective of this study is to address the importance of metabolic screening in terms of early diagnosis of IEM not only in pediatric aged patients but also in adulthood in Turkey.

MATERIALS AND METHODS

Study Design and Participants

This retrospective study was conducted between January 2019 and March 2021 with babies who were admitted to the outpatients' clinic of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Pediatric Nutrition and Metabolism Department. As expanded NBS is not a part of national screening in Turkey, neonates who were born in university and public hospitals could not be enrolled into the study. However, expanded NBS is routinely performed for the majority of neonates who were born in private hospitals. Cerrahpaşa Faculty of Medicine is a reference center for pediatric metabolic disorders, and our study group consisted of babies who were born in private hospitals, had an abnormal expanded NBS result, and were finally referred to pediatric nutrition and metabolism department of Cerrahpaşa Faculty of Medicine.

In our outpatients' clinic, a maternal originated IEM is evaluated to identify any metabolites that may pass to the infant via the placenta or through breastfeeding in case of an abnormal metabolic profile in the neonate. In this study, babies who were under 1 year of age at admission and had a pathologic result of an expanded NBS for IEM performed by MS/MS and their mothers were included if:

- babies were under regular follow-up
- an expanded screening for IEM was performed for the mothers of the babies to investigate the existence of any IEMs.

Babies who were admitted because of a pathologic result of national NBS test apart from expanded NBS for IEM, in whom screening tests were performed after the first year of life and with missing data were excluded from the study. Mothers who did not give consent for their own metabolic sampling despite the pathological screening results of their babies because of family issues were also excluded.

Data Collection

In this study, clinical and biochemical data of the babies and their mothers were collected retrospectively. Data regarding age, sex, timing, and results of the expanded NBS for IEM were recorded for the babies. Clinical and laboratory findings including plasma acylcarnitine profile, urinary organic acid analysis, plasma amino acid analysis, blood gases analysis, plasma ammonia and lactate levels, and vitamin B12 levels which were performed according to the suspected IEM due to results of the NBS analysis were also noted in detail. Results of the expanded screening for IEMs belonging to the mothers of the babies included in the study were recorded. Clinical and laboratory findings relevant to suspected IEM due to the pathologic screening results analysis similar to the neonates were also noted for the mothers.

Ethical Considerations

All procedures followed were in accordance with the ethical standards of the local Ethical Committee of Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine and with the Helsinki Declaration of 1975, as revised in 2013 (E83045809-604.01.02-32719). All mothers included in the study gave informed consent for themselves and their babies.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 21.0 (IBM corp., Armonk, NY, USA). Descriptive statistics was used to describe data. Continuous variables were displayed as median (25th; 75th percentiles) while categorical data were expressed in frequency (percentages).

RESULTS

Demographic Features

During the study period, 23 babies with pathological result of expanded NBS were referred to our outpatients' clinic for IEM examination. Six of the 23 mothers refused the performance of their own metabolic sampling, 17 babies and their mothers were enrolled into the study. Nine babies (52.9 %) were female and 8 (47.1 %) were male. The median age at the time of metabolic screening was 30.6 days ranging between 13 and 116 days.

Assessment of Inborn Errors of Metabolism in the Babies

None of the babies was symptomatic and they were referred for investigation of an underlying IEM because of pathologic expanded NBS results. According to the abnormality of metabolic screening analysis, 4 (23.5%) had elevated propionylcarnitine (C3), 4 (23.5%) had elevated 3-hydroxyisovalerylcarnitine (C5OH), 4 (23.5%) had decreased free carnitine (C0), 2 (11.7%) had elevated tyrosine, 1 (5.8%) had elevated hexanoylcarnitine (C6), 1 (5.8%) had elevated tetradecenoilcarnitine (C14:1), and 1 (5.8%) had elevated isovalerylcarnitine (C5) concentration according to reference ranges.

Among 17 babies, one (Baby 4) was diagnosed as IEM regarding the laboratory findings relevant to abnormalities in expanded NBS. She had elevated C5OH concentrations at the time of admission and a diagnosis of 3-methylcrotonyl-CoA carboxylase (MCC) deficiency was made due to an abnormal urinary organic acid profile. Data concerning the data demographic and laboratory findings of the babies with abnormal expanded NBS tests are given in Table 1.

Assessment of Inborn Errors of Metabolism in the Mothers

Expanded metabolic screening results were found compatible with an IEM in 4 (23.5%) of 17 mothers. Two of these mothers were diagnosed with 3-MCC deficiency (Mother 2, Mother 15) and 2 mothers were diagnosed with glutaric aciduria type 1 (GA-1) (Mother 16, Mother 17). In these 4 patients, detailed data on clinical history and laboratory findings of maternal metabolic disorders are given in Table 2.

Mother 2

She was a case of a 28-year-old asymptomatic woman, and she was first investigated for an IEM after her 18-day-old healthy baby was referred to our outpatients' clinic with suspicion of an organic acidemia due to elevated C5OH level in expanded newborn metabolic screening. She had no intellectual disability and her medical history was uneventful in terms of acute metabolic decompensation. She complained of myalgia triggered by prolonged exercise, chronic fatigue, and headache. In MS/MS, C0 level was low and C5OH level was elevated according to reference ranges. In her organic acid analysis, excretion of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine was elevated which was compatible with 3-MCC deficiency. Molecular analysis of *MCC1* was performed and exon 18 could not be amplified by polymerase chain reaction, suggesting a homozygous deletion of the region; however, multiple ligation-dependent probe amplification could not be performed. Oral carnitine supplementation (1 g/day) and biotin treatment (5 mg/day) were initiated following the diagnosis.

Mother 15

She was a case of a 34-year-old woman. She had been following up with a diagnosis of systemic lupus erythematosus (SLE) and she had chronic complaints relevant to SLE. She had no intellectual disability and did not describe any metabolic decompensation attack. As her 58-day-old healthy baby was referred to our outpatients' clinic with an elevated C5OH level in expanded NBS, she started to be investigated in terms of a maternal originated metabolic disorder. In MS/MS, C0 was low and C5OH level was elevated according to reference ranges. In her organic acid analysis, the excretion of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine was elevated. Diagnosis of 3-MCC deficiency was molecularly confirmed by showing a homozygous variant (c.803G>C, p.Arg268Thr) in *MCC2*. Oral carnitine supplementation (1 g/day) and biotin treatment (5 mg/day) were initiated following the diagnosis.

Mother 16

She was a case of a 33-year-old woman with complaints of chronic fatigue and vertigo. She had macrocephaly which was

Table 1. Data Concerning the Demographic and Laboratory Findings of the Babies with Abnormal Expanded Newborn Screening

	Sex	Age at Admission	Expanded Metabolic NBS Result Abnormality	Pathological Second Tier Tests Results	Remarks
B1	Female	116 days	C3:7.12 (N: <6.8 µmol/L)		
B2	Male	18 days	C5-OH:7.23(N: <0.80 µmol/L)		
B3	Female	30 days	C6:0.28 (N: <0.12 µmol/L)		
B4	Female	48 days	C0:3.87 (N: 8.60-90 µmol/L) C5-OH:21.27 (N: <0.80 µmol/L)	Elevated excretion of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine	*MCC1* gene: homozygote c.543T>G (p.Tyr181Ter) mutation
B5	Male	16 days	Tyr:387 (N: 26.9-275 µmol/L)		
B6	Female	36 days	C5-OH: 0.98 (N: <0.80 µmol/L)		
B7	Female	18 days	Tyr:300.8 (N: 26.9-275 µmol/L)		
B8	Male	22 days	C14:1:0.09 (N: <0.03 µmol/L)		
B9	Male	13 days	C3:7.06 (N: <6.8 µmol/L)		
B10	Male	15 days	C3:9.6 (N: <6.8 µmol/L)		
B11	Male	20 days	C0:7.5 (N: 8.60-90 µmol/L)		
B12	Male	24 days	C0:7.42(N: 8.60-90 µmol/L)		
B13	Female	19 days	C3:7.53 (N: <6.8 µmol/L)		
B14	Female	18 days	C5:3.68 (N: <0.6 µmol/L)		
B15	Female	58 days	C5-OH:3.74 (N: <0.80 µmol/L)		
B16	Male	36 days	C0:3.87 (N: 8.60-90 µmol/L)		
B17	Female	15 days	C0:6.5 (N: 8.60-90 µmol/L)		

B, baby; N, normal; NBS, newborn screening.

Table 2. Data Concerning the Clinical and Laboratory Findings of Maternal Originated Inborn Errors of Metabolism

Family	Age at Admission	Expanded Metabolic NBS Result Abnormality	Urinary Organic Acid Analysis	Molecular Analysis	Remarks
F2-B	18 days	C0:6.48 (N: 8.60-90 µmol/L) C5OH:7.23 (N: <0.80 µmol/L)	Normal	NP	Asymptomatic
F2-M	28 years	C0:7.45 (N: 8.60-90 µmol/L) C5OH:20.8 (N: <0.80 µmol/L)	Elevated excretion of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine	*MCC1* gene: homozygote deletion of exon 18	Myalgia triggered by prolonged exercise, chronic fatigue, and headache
F15-B	58 days	C5OH:3.74 (N: <0.80 µmol/L)	Normal	NP	Asymptomatic
F15-M	34 years	C0:6.40 (N: 8.60-90 µmol/L) C5OH:32.47 (N: <0.80 µmol/L)	Elevated excretion of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine	*MCC2* gene: homozygote c.803G>C(p.Arg268Thr) mutation	Diagnosis of systemic lupus erythematosus
F16-B	36 days	C0:5.96 (N: 8.60-90 µmol/L)	Normal	NP	Asymptomatic
F16-M	33 years	C0:3.40 (N: 8.60-90 µmol/L) C5DC:3.52 (N:<0.21 µmol/L)	Elevated excretion of glutaric and 3-hydroxyglutaric acid	*GCDH* gene: homozygote R88H(c.263G>A) mutation	Chronic fatigue and vertigo, abnormal MRI findings
F17-B	15 days	C0:2.27 (N: 8.60-90 µmol/L)	Normal	NP	Asymptomatic
F17-B	28 years	C0:3.20 (N: 8.60-90 µmol/L) C5DC:0.43 (N: <0.21 µmol/L)	Elevated excretion of glutaric and 3-hydroxyglutaric acid	*GCDH* gene:c.641C>T(p .T214M)/c.1204C>T(p. R402W) mutation	Intermittent headaches, dizziness, and forgetfulness, abnormal MRI findings

B, baby; C0, free carnitine; C5DC, glutarylcarnitine; C5OH, 3-hydroxyisovalerylcarnitine; F, family; M, mother; N, normal; NBS, newborn screening; NP, not performed.

first noticed in the first decade of her life and it was thought to be a benign familial macrocephaly. Her neurological examination was normal. Her 36-day-old healthy baby was referred to our outpatients' clinic with a low C0 level in expanded newborn metabolic screening. In terms of a possible maternally originated low plasma carnitine level, MS/MS was performed, and her metabolic screening revealed low C0 and elevated glutarylcarnitine (C5DC) levels according to reference ranges. In her organic acid analysis, excretion of glutaric and 3-hydroxyglutaric acid was elevated which was compatible with GA-1. Diagnosis of GA-1 was molecularly confirmed by showing a homozygous variant (R88H, c.263G>A) in *GCDH*. Her brain magnetic resonance imaging (MRI) which was performed following the diagnosis revealed subcortical enlargement in the frontal part of both cerebral hemispheres and symmetrical hyperintensities in the subcortical area, periventricular region, and corpus callosum (Figure 1A). After the diagnosis of GA-1, oral carnitine supplementation (1 g/day) was initiated. Kidney functions were re-evaluated in terms of the decrease in glomerular filtration rate, which was defined as a comorbidity of the disease, and it was found to be normal.

Mother 17

She was a case of a 28-year-old woman who was first investigated for an IEM after her 15 day-old healthy baby was referred to our outpatients' clinic with a decreased C0 level in expanded newborn metabolic screening. Her medical history was uneventful. She was complaining of intermittent headaches, dizziness, and forgetfulness. She had no macrocephaly and her neurological examination was entirely normal. Tandem mass spectrometry was performed, and her metabolic screening revealed low C0 and elevated C5DC levels according to reference ranges. In her organic acid analysis, excretion of glutaric and 3-hydroxyglutaric acid was elevated which was compatible with GA-1. Diagnosis of GA-1 was molecularly confirmed by showing a compound heterozygote variant (c.641C>T, p.T214M /c.1204C>T, p.R402W) in *GCDH*. Her brain MRI which was performed following the diagnosis revealed bilateral opercular atrophy, subcortical and periventricular white matter involvement, and symmetrical hyperintensities in the putamen (Figure 1B). After the diagnosis of GA-1, oral carnitine supplementation (1 g/day) was initiated. Due to the presence of clinical findings such as intermittent headache and dizziness and high plasma lysine (210 µmol/L) concentration in amino acid analysis, her daily protein intake was organized by avoiding lysine-rich natural protein food sources. Similar to Mother 16, renal function tests which were performed after the diagnosis of GA-1 revealed no abnormality.

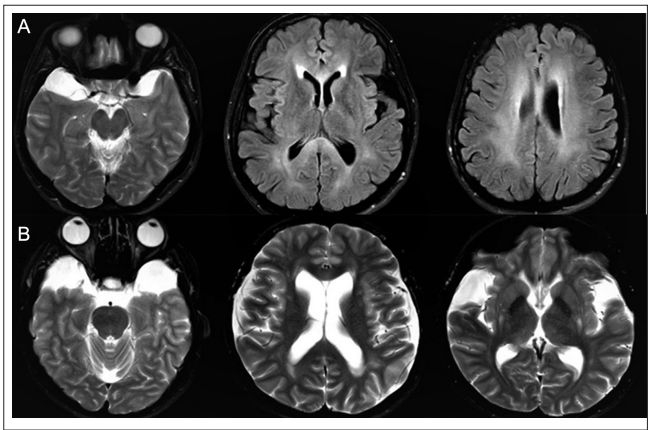

Figure 1. Brain MRI findings of Mother 16 and Mother 17. (A) Brain MRI of Mother 16 revealed subcortical enlargement in the frontal part of both cerebral hemispheres and symmetrical hyperintensities in the subcortical area, periventricular region, and corpus callosum. (B) Brain MRI of Mother 17 revealed bilateral opercular atrophy, subcortical and periventricular white matter involvement, and symmetrical hyperintensities in the putamen. MRI, magnetic resonance imaging.

DISCUSSION

To date, a large amount of data have been reported worldwide regarding the prevalence of IEMs diagnosed with expanded NBS in pediatric patients and the frequency of mothers diagnosed with IEM with positive NBS result in their children. However, data on these subjects are limited since expanded NBS is not a part of the national NBS program in our country. In this study, four mothers were diagnosed with IEM as a result of the evaluation of the pathological NBS results of 17 children. All 4 mothers had been complaining of nonspecific symptoms for a long time; however, they could only be diagnosed following the evaluation of pathological NBS results of their children. Considering these features, it is the first study to address the importance of metabolic screening via MS/MS in terms of early diagnosis of IEM not only in pediatric aged patients but also in adulthood in Turkey.

Glutaric aciduria type 1 is a cerebral organic acidemia caused by the defective enzyme activity of glutaryl-CoA dehydrogenase which catalyzes the dehydrogenation of glutaryl-CoA and decarboxylation of glutaconyl-CoA to crotonyl-CoA in lysine degradation pathway. Enzymatic deficiency results in the accumulation of potentially neurotoxic glutaric acid, 3-hydroxyglutaric acid and glutaryl-CoA in body fluids especially in cerebrospinal fluid. The most common phenotype of GA-1 is named as "classical GA-1" and characterized by progressive macrocephaly, dystonic movement disorder, and acute loss of acquired motor skills triggered by an infectious disease. However, a recently described phenotype of the disease "late onset GA-1" has entirely different clinical manifestations from the classical phenotype. Chronic headaches, epilepsy, tremor, and dementia can be listed as the frequent signs of late-onset GA-1.[17,18] Chronic kidney disease and peripheral neuropathy were also found to be relevant to late-onset form. In recent years, evidence regarding the oncogenic effect of glutaric acid and 3-hydroxyglutaric acid has been shown. In medical literature, different brain neoplasms in adult patients have been reported and the possibility of an increased susceptibility to brain neoplasms in late-onset GA-1 has been highlighted.[19-21] Apart from these complications of the disease, there is still conflict in the management of pregnancy in adult female GA-1 patients. An uneventful clinical course has been reported for mothers with GA-1 who received emergency treatment during the peripartum period.[22] However, there are also uncomplicated pregnancies for the women who did not receive any specific therapy.[23] As the pregnancy and peripartum period could be a catabolic state possibly triggering an acute metabolic decompensation, it is recommended to supervise the management by an interdisciplinary team.[18] Considering all these reasons, it is obvious that adult GA-1 patients should be diagnosed and followed up to prevent acute and chronic complications. There is extremely limited data regarding maternal GA-1 cases diagnosed via the pathologic NBS result of their newborns. Yahyaoui et al[24] reported a newborn who was admitted with a suspicion of carnitine transporter deficiency due to decreased C0 level in expanded NBS. The acylcarnitine profile of his mother revealed elevated C5DC, and in her urine organic acid analysis, there was a remarkable excretion of glutaric and 3-hydroxyglutaric acid. Maternal GA-1 diagnosis was made with the molecular analysis of *GCDH* gene. Carnitine supplementation was started despite she was totally asymptomatic. A brain MRI could not be performed. In our study, 2 of 18 mothers were diagnosed as maternal GA-1. Chronic fatigue and headaches, dizziness, and forgetfulness were the common symptoms of the mothers. Both mothers had abnormal MRI findings which also supported the diagnosis of GA-1.

The 3-MCC deficiency is an organic acidemia caused by the defective enzyme activity of 3-MCC which is responsible for the leucine degradation pathway. Enzymatic deficiency results in the accumulation of 3-hydroxyisovaleric acid and 3-methylcrotonyl glycine in body fluids. The clinical presentation of 3-MCC deficiency is reported to be highly variable from asymptomatic patients to a severe phenotype with neurological findings. Vomiting, muscle tone alterations, involuntary movements, neurodevelopmental delay, seizures, and altered level of consciousness can be listed through clinical findings of the disease in symptomatic patients.[25,26] There is a large amount of data about pathologic screening results pointing to 3-MCC deficiency in newborns; however, maternal 3-MCC deficiency was reported in a few studies and case reports. In a study conducted with 5 mothers diagnosed as 3-MCC deficiency via the pathologic NBS of their children, 2 mothers were symptomatic. One of these mothers complained of fatigue and weakness, especially during pregnancy and the other one had myopathy, weakness, increased liver enzymes, and hepatosteatosis.[27] The largest cohort of maternal 3-MCC deficiency consists of a study conducted with 20 mothers. One of these 20 mothers had complaints of muscle weakness during childhood and her complaints improved following the carnitine supplementation.[28] There is considerable conflict about whether 3-MCC deficiency should be included in screening programs. This conflict mainly depends on the fact that most children diagnosed with 3-MCC deficiency by NBS have been reported to have remained asymptomatic. The generally recommended approach is to manage an emergency protocol and prevent energy depletion during any catabolic state such as intercurrent illness, operations, and prolonged fasting. Since pregnancy is a condition that increases energy requirement, maternal 3-MCC deficiency patients should be promptly managed during pregnancy and postpartum period. Carnitine deficiency which could result in cardiomyopathy should be treated properly.[29] In our study, 2 mothers were diagnosed with 3-MCC deficiency. Both mothers had low C0 levels and chronic symptoms possibly due to energy depletion.

The small sample size was the first limitation of our study. The lack of a standard expanded NBS program as a part of a public health policy was the main reason for the small cohort in our study. The second major limitation of the study was that the enzymatic activity was not studied in mothers diagnosed with 3-MCC deficiency as there are many healthy individuals with 3-MCC deficiency in the community.

CONCLUSION

In conclusion, IEMs can present in any period of life. Differing from childhood, adult IEM patients can manifest nonspecific symptoms. In this context, the performance of expanded metabolic screening tests may be an important step in terms of detecting a maternal IEM that is not diagnosed until adulthood.

Ethics Committee Approval: This study was approved by Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (Approval No: E83045809-604.01.02-32719, Date: 17/02/2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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