

Inherited metabolic disorders among Turkish children with intellectual disability: A single-center experience

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Abstract

Aim: We aimed to determine the frequency of inherited metabolic disorders (IMD) among Turkish children with intellectual disability using laboratory tests for IMD.

Materials and Methods: Children older than 5 years of age with intellectual disability admitted to the Pediatric Neurology Outpatient Clinic for any neurological symptom between July 1, 2018, and December 31, 2018 were analyzed. Children with intellectual disability of unknown etiology at admission were included in the study. Complete blood count, serum biochemical analysis, thyroid function tests, serum ammonia, lactate, homocysteine, biotinidase activity, serum amino acids, acylcarnitine profile, and urine organic acid analysis results were evaluated.

Results: A total of 163 patients (108 boys) were included in the study. The female to male ratio was 1: 2. The ages of the patients were between 5 and 17 years and the mean age was 9.4 ± 3.6 years. Four patients were diagnosed with IMD. Two of them had mitochondrial disease, 1 of them had isovaleric acidemia, and 1 of them had 3-Methylcrotonyl-CoA carboxylase deficiency. The accompanying symptoms of intellectual disability were psychiatric symptoms, dysarthria, ataxia, tremor and seizure in children diagnosed with IMD. We found that the percentage of IMD was 2.5% among Turkish children with intellectual disability.

Conclusion: In our study, all IMDs identified in children with intellectual disability were treatable. That result emphasizes the significance of evaluating children for inherited metabolic disorders among children with intellectual disability.

Keywords: Brain disease; child; metabolic

INTRODUCTION

Intellectual disability (formerly mental retardation) is one of the most common neurological problems in childhood (1). It affects approximately 2-3% of the population (2). Determining the etiology of intellectual disability is a major challenge due to the several possible etiologies, and the extensive and costly examinations. The basic diagnostic approach includes clinical history, family history, evaluation of developmental milestones, dysmorphology assessment, neurological examination and utilizing appropriate laboratory and neuroimaging tests (1).

Overall, 10% to 81% of patients with intellectual disability had an identified underlying etiology (3-6). It has been suggested that the possibility of identifying an inherited metabolic disorder (IMD) is relatively low among patients with intellectual disability (6,7). However, the proper evaluation of patients in terms of underlying etiology is crucial, because early recognition of IMD may improve symptoms of intellectual disability by specific treatment of the disease (8).

In our study, we aimed to determine the frequency of IMD among Turkish children with intellectual disability of unknown etiology.

MATERIALS and METHODS

This was a single-center retrospective study, including children admitted to the Pediatric Neurology Outpatient Clinic between January 1, 2018, and December 31, 2018. The study protocol was approved by the Ethics Committee at the Bakirkoy Dr. Sadi Konuk Research and Training Hospital. All patients agreed to participate in the study and written informed consents were obtained from the legal guardian of each participant.

Participants

Children older than 5 years of age with an intellectual disability admitted to the Pediatric Neurology Outpatient Clinic for any neurological symptom were analyzed. Children with intellectual disability of unknown etiology at admission were included in the study. Intellectual disability was defined according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (9). Children with insufficient data were excluded from the study.

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Clinical and laboratory data

Demographic characteristics, neurological examination findings, whether the presence of epilepsy, laboratory, and brain magnetic resonance imaging findings were abstracted from medical records. All patients' complete blood count, serum biochemical analysis (liver enzymes, renal function tests, uric acid, creatinine kinase, total cholesterol, triglyceride), thyroid function tests, serum ammonia, lactate, homocysteine, biotinidase activity, serum amino acids, acylcarnitine profile, and urine organic acid analysis results were evaluated. All of the laboratory tests were performed within the first month after their admission to the Pediatric Neurology Outpatient Clinic. Brain magnetic resonance imaging (MRI) findings were recorded. The parents' written informed consent was obtained then genomic DNA from peripheral blood was extracted using standard techniques in children with IMD.

Children with laboratory evidence of IMD were assessed, and a final diagnosis was made by a physician specialized in pediatric metabolic diseases (M.E.). All children with a diagnosis of IMD undergone a genetic study.

RESULTS

A total of 163 patients (108 boys) were included in the study. The female to male ratio was 1:2. The ages of the patients were between 5 and 17 years, and the mean age was 9.4 ± 3.6 years. The rate of consanguinity between the parents was 28%. Sixty-three patients (39%) had a diagnosis of epilepsy.

Among all patients, 4 children were diagnosed with IMD. Two of them had mitochondrial disease, 1 of them had isovaleric acidemia, and 1 of them had 3-Methylcrotonyl-CoA carboxylase (3MCC) deficiency (Table 1). All patients diagnosed with IMD had consanguineous parents and a positive family history for intellectual disability of unknown etiology. Psychiatric symptoms, dysarthria, ataxia, tremor, and seizure were the accompanying symptoms besides intellectual disability. None of the patients had isolated mental disability. In our study, we found that the percentages of IMD was 2.5% in children aged 5-17 years with intellectual disability.

Case 1

An 11-year-old male patient had a moderate intellectual disability, attention deficit hyperactivity disorder, and

Table 1. Demographic and clinical features of children with inherited metabolic disorders

Case	Age	Sex	Consanguineous marriage	Family history of patient with intellectual disability	Clinical findings	Brain magnetic resonance imaging	Final diagnosis
1	11	Male	+	+	Attention deficit hyperactivity disorder, Seizure	Normal	Mitochondrial disease
2	10	Female	+	+	Peripheral facial paralysis	Periventricular hyperintensity	Isovaleric acidemia
3	15	Male	+	+	Dysarthria, Obsessive-compulsive disorder	Normal	3-Methylcrotonyl-CoA carboxylase deficiency
4	13	Female	+	+	Tremor, Strabismus, Epilepsy	Chronic infarct regions in cerebellum and frontal lobe	Mitochondrial disease

epilepsy. He admitted to the outpatient clinic for further evaluation after both of his 9-months-old brother and 8-months-old cousin diagnosed with West syndrome caused by mitochondrial disease concurrently. He was born as the second child of consanguineous parents. Neurological examination revealed mild ataxia and hyperlaxity. Visual examination was unremarkable. He was able to follow simple commands, and answer simple

questions. Complete blood count, serum biochemistry, and ammonia were normal. Serum lactate was 39 mg/dL (normal range: <19.4 mg/dL). Serum amino acid analysis revealed a significantly elevated level of alanine as 1238 $\mu\text{mol/L}$ (normal range: 208-588 $\mu\text{mol/L}$). Urine organic acid analysis was normal. Echocardiography was normal. Electroencephalography (EEG) showed epileptic activity in the left temporal region. Brain MRI was unremarkable.

DNA sequence analysis of mitochondrial genes revealed a heteroplasmic mutation in MT-ST1 gene (m.15326A> G; p.Ile164Val). Antioxidant cocktail (L-Carnitine, Coenzyme Q10, α -lipoic acid, vitamin B complex [cyanocobalamin, pyridoxine, riboflavin, and thiamin]) and dichloroacetate supplementation were started. Afterward, a decrease in serum lactate level up to 20 mg/dL, and partial improvement in intellectual functions (forming a 3-word sentence from a one-word speech) were observed.

Case 2

A 13-year-old girl with mild intellectual disability presented with tremor on her hands. Two years ago, she had a history of hospitalization for fever and seizure. Antenatal and postnatal history was unremarkable. She was the fourth child of consanguineous parents. She had relatives diagnosed with intellectual disability. Neurological examination revealed strabismus, intentional tremor, dysmetria, and ataxic gait. Ophthalmic examination revealed no optic atrophy. Complete blood count, serum biochemistry, and ammonia were normal. Serum lactate (25 mg/dL, normal range: <19.4 mg/dL) was elevated.

Urine organic acid analysis was normal. EEG was unremarkable. Brain MRI revealed hyperintensity within the middle right frontal lobe and left inferior cerebellar hemisphere on T2-weighted and FLAIR sequences. Brain magnetic resonance spectroscopy showed lactate peaks at the basal ganglia level (Figure 1). She diagnosed with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) based on the laboratory and brain MRI findings. There was no radiologic and clinical relapse during a 1-year follow-up under-treatment of antioxidant cocktail (L-Carnitine, Coenzyme Q10, α -lipoic acid, vitamin B complex [cyanocobalamin, pyridoxine, riboflavin, and thiamin]) and dichloroacetate supplementation. Brain MRI showed a chronic infarct area in the left frontal region at the last examination. DNA sequence analysis of mitochondrial genes detected a heteroplasmic mutation in MT-ND5 gene (m.12706T> C; p.Phe124Leu).

Case 3

A 10-year-old girl with a known mild mental disability has had weakness of the muscles on the right side of

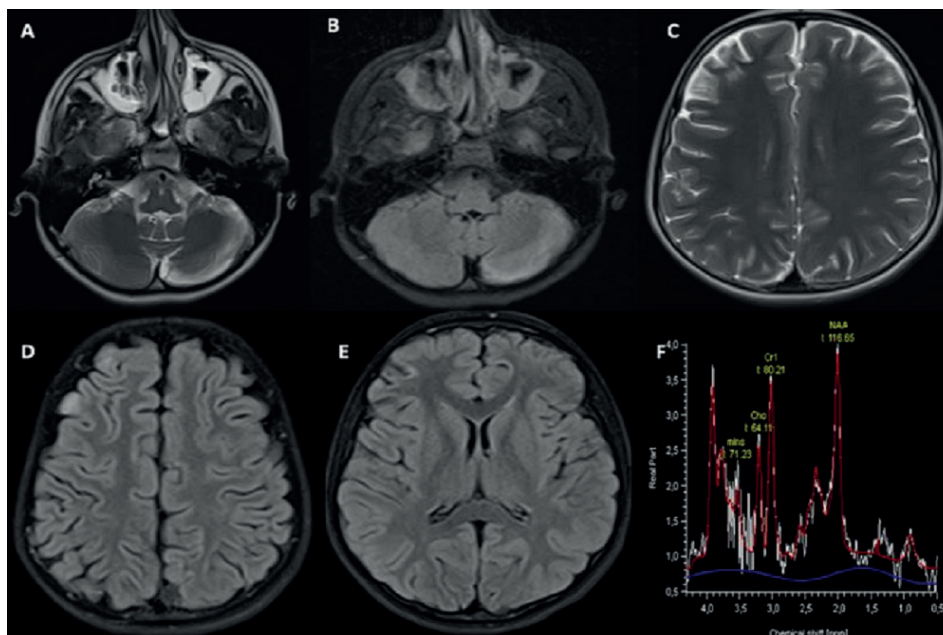


Figure 1. Brain magnetic resonance images of a 13-year-old girl with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). T2-weighted and FLAIR sequences (A, B) show hyperintensity within left inferior cerebellar hemisphere (C, D, E), and the middle right frontal lobe. (F) Brain magnetic resonance spectroscopy showed lactate peaks at the basal ganglia level

her face for a week. Antenatal and postnatal history was unremarkable. She was the only child of the consanguineous parents. Family history was positive for patients with intellectual disability in second-degree relatives. Neurological examination was unremarkable except for the right peripheral facial paralysis. Complete blood count, serum biochemistry, lactate, ammonia levels were normal. Serum amino acid analysis revealed an elevated arginine level (170 μ mol/L, normal range: 41-114 μ mol/L). Acylcarnitine profile showed normal free carnitine (35 μ mol/L, normal range: 29-61 μ mol/L) and an elevated isovalerylcarnitine (6.62 μ mol/L, normal range: 0.1-2.4

μ mol/L). Urinary isovalerylglycine excretion was 181 mmol/mol creatinine. Brain MRI revealed hyperintensity in periventricular deep white matter and thin corpus callosum on T2-weighted and FLAIR sequences (Figure 2). Low protein diet, L-Carnitine and glycine were started after the diagnosis of isovaleric acidemia. Peripheral facial paralysis, which resolved completely after 1 month, was thought to develop coincidentally to isovaleric acidemia.

Case 4

A 15-year-old male patient presented with speech disorder which was progressing for 2-years. Antenatal and postnatal history was unremarkable. He was

diagnosed with obsessive-compulsive disorder and mild intellectual disability 1 year ago. He was the first child of consanguineous parents, and his 12-year-old brother was healthy. He had relatives with intellectual disability and psychiatric disorders. Neurological examination showed dysarthria and deep tendon reflexes were increased. Complete blood count, serum biochemistry, lactate, ammonia, amino acid values were normal. Acylcarnitine profile showed low free carnitine (3.4 $\mu\text{mol/L}$, normal range: 29–61 $\mu\text{mol/L}$) and elevated 3-hydroxyisovaleric-carnitine (C5-OH) (18.7 $\mu\text{mol/L}$, normal range: 0.5-3.4).

There was urinary 3-methylcrotonyl glycine excretion (319 mmol/mol creatinine). Brain MRI was normal. Based on the clinical and laboratory data, he diagnosed with 3MCC deficiency. The MCCC1 gene sequence was normal, the MCCC2 gene sequence revealed c.295G> C p.(Glu9Gln) homozygous pathogenic variant. After the initiation of L-Carnitine supplementation and a leucine restricted diet, a significant improvement was observed in speech fluency and controlling psychiatric symptoms.

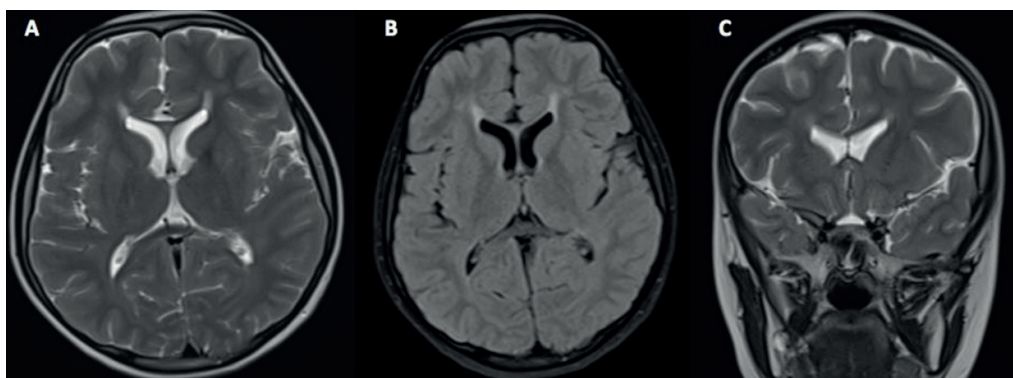


Figure 2. Magnetic resonance images of a 10-year-old child with isovaleric acidemia. (A) Axial T2-weighted, (B) axial FLAIR and (C) coronal T2-weighted sequences reveal hyperintensity in periventricular deep white matter and thin corpus callosum

DISCUSSION

In this study, the frequency of IMD among Turkish children with intellectual disability was evaluated. We found that the percentage of IMD was 2.5% in children aged 5-17 years with intellectual disability. In previous studies, the frequency of IMD varied from 0.2% to 8.4% in children with intellectual disability (5). That frequency was found to be high in studies where specific IMDs and consanguineous marriages were common, and low in regions where extended neonatal screening programs were applied (5,10,11). The newborn screening program of Turkey consists of phenylketonuria, hypothyroidism, biotinidase deficiency started in 1994, 2006, and 2008, respectively. It was also pointed out that the already used methods for screening phenylketonuria and biotinidase deficiency could lead to undiagnosed cases due to relatively low sensitivity of the method (12,13). The lack of expanded neonatal screening programs and higher frequency of consanguineous marriages are possible risk factors for the likelihood of IMD in Turkey. In our study, the overall frequency of consanguineous marriages was approximately 1:3, and all patients diagnosed with IMD had a history of consanguineous marriage. However, it should keep in mind that the mode of inheritance is maternal in some of the mitochondrial disorders.

There is no consensus on the recommended laboratory tests for IMD in children with intellectual disabilities (1). In a study in which a two-step approach for IMD diagnosis was evaluated in patients with intellectual disability caused by IMD, the rate of diagnosis by the first-line tests was found to be 64%, similar to previous

studies (8,14,15). In that study, serum ammonia, lactate, amino acids, homocysteine, acylcarnitine profile, copper and ceruloplasmin, and urinary organic acids, purine, pyrimidines, creatinine metabolites, oligosaccharides, and glycosaminoglycans were defined as first-step tests. The diagnostic tests in our study included most of the tests recommended as the first-line.

It was emphasized that a stepwise diagnostic approach for diagnosis of IMD may promote early diagnosis and reduce unnecessary costs in children with intellectual disability. Also, it has been reported that the first-step tests may diagnose %60 of treatable IMDs (8). In our study, IMDs lead to intellectual disability was mitochondrial diseases, isovaleric acidemia, and 3-MCC deficiency. These three diseases were defined in the group of treatable IMDs (14).

It was stated that 22 of 81 treatable IMDs could be diagnosed by urine organic acid analysis. Therefore, urine organic acid analysis was defined as the most favorable test among the first-line tests (14). In our study, urine organic acid analysis was diagnostic in 2 out of 4 patients diagnosed with IMD.

IMD rarely has been associated with isolated intellectual disability. It has been reported that the likelihood of IMD as the underlying cause increases in the presence of psychiatric symptoms, cerebellar findings, epilepsy and autistic findings accompanying intellectual disability (1). In our study, psychiatric symptoms, dysarthria, ataxia, tremor, and epilepsy were present in children with intellectual disability who were diagnosed with IMD. However, it was emphasized that the presence of

an isolated or progressive intellectual disability cannot exclude the diagnosis of IMD (14). As in our cases presented with any neurological symptom who has already known an intellectual disability, the proper evaluation of patient besides the referral symptom could clarify the underlying etiology of intellectual disability.

Our study had some limitations. The retrospective design of the study and the relatively small sample size were certain limitations. Also, the exclusion of children under 5 years old may cause to overlook some IMD that start at an early age and cause intellectual disability.

CONCLUSION

In our study, all IMDs identified in children with intellectual disability, which were mitochondrial diseases, isovaleric acidemia, and 3-MCC deficiency, was in the treatable group of IMD. This study emphasizes the significance of diagnostic tests for IMD and proper evaluation of children with intellectual disability.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: The study protocol was approved by the Ethics Committee at the Bakirkoy Dr. Sadi Konuk Research and Training Hospital.

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