CASES OF INBORN ERRORS OF METABOLISM DIAGNOSED IN CHILDREN WITH AUTISM

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Background and purpose – Autism spectrum disorder is a neurodevelopmental disorder with a heterogeneous presentation, the etiology of which is not clearly elucidated. In recent years, comorbidity has become more evident with the increase in the frequency of autism and diagnostic possibilities of inborn errors of metabolism.
Methods – One hundred and seventy-nine patients with diagnosis of autism spectrum disorder who presented to the Pediatric Metabolism outpatient clinic between 01/September/2018-29/February/2020 constituted the study population. The personal information, routine and specific metabolic tests of the patients were analyzed retrospectively.
Results – Out of the 3261 patients who presented to our outpatient clinic, 179 (5.48%) were diagnosed with autism spectrum disorder and were included in the study. As a result of specific metabolic examinations performed, 6 (3.3%) patients were diagnosed with inborn errors of metabolism. Two of our patients were diagnosed with classical phenylketonuria, two with classical homocystinuria, one with mucopolysaccharidosis type 3D (Sanfilippo syndrome) and one with 3-methylchrotonyl Co-A carboxylase deficiency.
Conclusion – Inborn errors of metabolism may rarely present with autism spectrum disorder symptoms. Careful evaluation of the history, physical examination and additional findings in patients diagnosed with autism spectrum disorder will guide the clinician in the decision-making process and chose the appropriate specific metabolic investigation. An underlying inborn errors of metabolism may be a treatable cause of autism.

Keywords: *inborn errors of metabolism, autism spectrum disorder, metabolism*

VELESZÜLETETT METABOLIKUS RENDELLENESSÉGGEL DIAGNOSZTIZÁLT AUTISTA GYERMEKEK
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Háttér és cél – Az autizmus spektrum zavar heterogén tünetekkel jelentkező idegrendszeri fejlődési zavar, aminek az etiológiája nem kellően tisztázott. A közelmúltban, az autizmus gyakoriságának növekedése és a veleszületett metabolikus rendellenességek diagnosztikai lehetőségeinek bővülése miatt egyre több komorbiditásra is fény derült.
Módszerek – A vizsgálatban olyan autizmus spektrum zavar diagnózissal rendelkező betegek vettek részt, akik 2018. szeptember 1. és 2020. február 29. között a Gyermekbetegek Metabolizmusambulanciáján részesültek ellátásban (n = 179 fő). A betegek személyes adatait, rutin és speciális metabolikus teszteredményeit retrospektív módon elemeztük.
Eredmények – Az ambulanciánkon ezen idő alatt megjelent 3261 beteg közül 179-en (5,48%) rendelkeztek autizmus spektrum zavar diagnózissal, ők képezik vizsgálatunk betegpopulációját. A speciális metabolikus kivizsgálás eredményeképpen 6 beteg (3,3%) esetében állítottunk fel veleszületett metabolikus rendellenesség diagnózist. Két betegünk klasszikus phenylketonuria, két betegünk klasszikus homocystinuria, egy betegünk 3D típusú mucopolysaccharidosis (Sanfilippo-szindróma) és egy 3-metil-krotonil-CoA-karboxiláz-hiány diagnózist kapott.
Következtetés – A veleszületett metabolikus rendellenesség ritkán autizmus spektrum zavarhoz társulhat. A kórtörténet pontos felvétele, az alapos fizikális vizsgálat és a tünetek gondos mérlegelése az autizmus spektrum zavarban szenvedő betegek esetében segítheti a klinikust a döntéshozatali folyamatban, és elvezethet a megfelelő metabolikus kivizsgáláshoz. Ha az autizmus hátterében veleszületett metabolikus rendellenességet találunk, az hatékony kezelést eredményezhet.

Kulcsszavak: *veleszületett metabolikus rendellenesség, autizmus spektrum zavar, anyagcsere*

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication deficiencies, repetitive and unusual sensory-motor behaviors. This disease has a heterogeneous spectrum, its severity can vary from mild to severe[1]. The diagnosis is made on the basis of behavior. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria, published by the American Psychiatric Association in 2013, aimed to make the diagnosis of ASD more understandable[1, 2]. There is a significant increase in the number of childhood ASD cases worldwide, especially during the last twenty years. The increase in the number of cases brought many studies for the disease[1].

The prevalence of ASD is 1% and 4 times more in males. Today, it is estimated that 1 in 59 children in the USA have autism[3–5].

The etiology of ASD remains uncertain; genetic, epigenetic and environmental factors play a role in the development of the disease. Genetic disorders (such as Fragile X, Prader-Willi, Angelman syndromes) are reported to be responsible for 10-20% of the cases[4].

Inborn errors of metabolism (IEM) occur in one of 800 live births, and may be responsible for ASD in recent years[3]. Comorbidities have become more evident with the increase in the frequency of autism and diagnostic possibilities of congenital metabolic diseases (IEMs). Although the percentage of ASD is not known in patients diagnosed with IEM in the literature, IEMs accompany approximately in 2% of patients with ASD[3, 6]. In countries with a high rate of consanguineous marriages, this figure is said to be probably close to 5%[3].

Our country has a high rate of consanguineous marriage, and there are not many studies evaluating the co-occurrence of ASD and IEMs. With this study, we aimed to determine the rate of IEMs with ASD comorbidity in our country and also to reveal the types of IEMs accompanying the ASD cases.

Methods

Patients who were diagnosed with ASD according to DMS-V criteria by the Child and Adolescent Psychiatry specialist and referred to the Pediatric Metabolism outpatient clinic between the 1st of September 2018 and the 29th of February 2020 constituted the study population. The demographic characteristics and laboratory findings of the patients were analyzed retrospectively from the hospital database.

During this period, 6824 patients were enrolled in the Pediatric Metabolism outpatient clinic. There were 3261 patient records when the repeated visits were removed. In the database scan, 239 of these patients had the diagnosis of ASD. Cases with other underlying genetic / neurological diseases were excluded from the study. When repeated visits of these patients were removed, 179 patients were recruited.

Birth history, consanguineous marriage of parents, the presence of neurometabolic disease in the family, neuromotor development stages were recorded from the personal records of the patients. Complete blood counts, electrolytes, glucose levels, liver transaminases, urea, creatinine, uric acid, creatine phosphokinase (CPK), total cholesterol, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, arterial blood gas, serum ammonia and lactate levels were recorded from patients' records. Vitamin B12, folate, homocysteine, carnitine-acylcarnitine profile, plasma aminoacid analysis and urine organic acid analysis were the specific metabolic tests and were recorded from patients' records.

The written informed consents were taken from the legal guardian of the patients. The study was performed with adherence to the Helsinki Protocol and approved by the local Ethics Committee (Approval number 48670771-514.10).

Results

One hundred and seventy-nine (5.48%) of 3261 patients who applied to the Pediatric Metabolism outpatient clinic between the 1st of September 2018 and the 29th of February 2020 had the diagnosis of ASD. As a result of laboratory and metabolic examinations, 6 (3.3%) of 179 ASD patients were diagnosed with IEMs (**Table 1** is a summary of this ASD+IEM patients' data).

The first case was a 17-year-old male patient with hyperactivity, stereotypical movements, mental retardation, impaired reciprocal communication complaints. The patient was diagnosed as ASD 13 years ago. His phenylalanine level was 1470 µmol / L (23-120 µmol / L), the tyrosine level was 45 µmol / L (27-275 µmol / L) in the plasma aminoacid profile. The patient did not have a response to the BH4 loading test and was not examined under the screening program in the neonatal period. According to these results, the patient was diagnosed as classical phenylketonuria (PKU) and special nutritional therapy was started. The patient could not adapt to nutritional therapy due to late diagnosis and other treatments (large neutral aminoacids) were begun.

Table 1. *Summary of the six ASD+IEM patients' data*

Case	Gender	Current age (year)	Autism diagnosis age (year)	Consanguinity	Physical examination	Epilepsy	Diagnosis
1	M	17	4	-	hyperactivity, stereotypical movements, mental retardation, impaired reciprocal communication	-	PKU
2	M	15	3	+	hyperactivity, mental retardation, seizures, difficulty in reciprocal communication	+	PKU
3	M	6	3	+	without eye contact, with hyperactivity, speech retardation	-	HCU
4	M	15	10	+	without eye contact, hyperactivity, mental retardation, difficulty with socialization	-	HCU
5	F	7	3.5	+	learning disability, hyperactivity, coarse face appearance	-	MPS type III (Sanfilippo syndrome)
6	M	5.5	2.5	-	hyperactivity, speech retardation	-	3-MCC deficiency

M: male, F: female, PKU: phenylketonuria, HCU: homocystinuria, 3-MCC: 3-methylcrotonyl-CoA carboxylase, MPS: mucopolysaccharidosis

The second case, very similar to the first one, was a 15-year-old male patient with parental consanguinity, had complaints of hyperactivity, mental retardation, seizures, difficulty in reciprocal communication and has been followed with the diagnosis of autism since he was 3 years old. The patient's phenylalanine level was 1320 µmol / L (23-120 µmol / L) and the tyrosine level was 51 µmol / L (27-275 µmol / L) in the plasma aminoacid profile. Also, a mutation was detected in a homozygous state in the *PAH* gene (IVS10-11 G>A). Special nutrition treatment was initiated for the patient with a diagnosis of classical PKU who did not respond to the BH4 loading test. The patient's compliance with nutritional therapy was good, his hyperactivity and seizure frequency decreased after the treatment.

Our third patient was a 6-year-old male patient without eye contact, with hyperactivity and speech retardation. The patient had parental consanguinity and was diagnosed with autism 3 years ago. In his plasma aminoacid analysis methionine was 686 µmol / L (7-47 µmol / L), homocystine was 20 µmol / L (0-1 µmol / L) and blood homocysteine was 265 µmol / L (3.3-8.3 µmol / L). The patient's urine organic acid analysis was normal and the patient was diagnosed as classic homocystinuria (HCU) due to cystathionine-beta-synthase (CBS) deficiency. A homozygous (c.1058 C> T) mutation was also detected in the patient's *CBS* gene. The patient started cofactor therapy (pyridoxal phosphate, folic acid) and special nutritional therapy restricted from methionine. After treatment his hyperactivity and speech became better.

The fourth case was a 15-year-old male patient with parental consanguinity, no eye contact, hyperactivity, mental retardation and difficulty with socialization. In his plasma aminoacid analysis, methionine was 549 µmol / L (7-47 µmol / L), homocystine was 17 µmol / L (0-1 µmol / L), blood homocysteine was 229 µmol / L (3.3-8.3 µmol / L). The patient, whose urine organic acid analysis was normal, was diagnosed as classic homocystinuria (HCU) due to cystathionine-beta-synthase (CBS) deficiency. Cofactor treatment and special nutritional therapy were planned for the patient, but his parents did not accept treatment.

Our fifth case was a 7-year-old girl with learning disabilities, hyperactivity, and coarse face appearance. She had parental consanguinity and additional examinations were made because of the coarse face appearance. Her echocardiography and eye examination was normal, but dysostosis multiplex findings were detected in the skeletal radiographs, and enzyme analysis was asked for the differential diagnosis of mucopolysaccharidosis. The patient's N-acetylglucosamine-6-sulfatase enzyme level was found to be 0.6 nmol / mg / 24hr (> 1.2 nmol / mg / 24hr) and she was diagnosed as MPS type 3D (Sanfilippo syndrome). Since there is no enzyme replacement therapy treatment in Sanfilippo syndrome, she was followed up with symptomatic treatments.

Our sixth case was a 5.5-year-old male patient who was diagnosed with autism at the age of 2.5 years, his parents complained of hyperactivity and speech retardation. In his carnitine-acylcarnitine profile C0 (free) carnitine was 2.48 µmol / L (8.6-90.0 µmol / L), 3-OH isovaleryl (C5-OH) carnitine was 18.5 µmol / L (0-0.8 µmol / L). In his urine organic acid analysis 3-hydroxyisovaleric acid 1136 mmol/mol creatinine (6.9-25 mmol/mol creatinine)

and 3-methylcrotonoylglycine 4942 mmol/mol creatinine (0 mmol/mol creatinine) were found. The patient was diagnosed with 3-methylchrotonyl Co-A carboxylase (3-MCC) deficiency, and carnitine, cofactor (biotin) treatment and special nutritional therapy were started. After carnitine treatment, C0 (free) carnitine was 35 µmol / L (8.6-90.0 µmol / L), 3-OH isovaleryl (C5-OH) carnitine was 44.5 µmol / L (0-0.8 µmol / L) in the carnitine-acylcarnitine profile. Although it was a short time after the treatment, the patient's hyperactivity decreased, and his speech improved.

In addition, family screening of all patients diagnosed with metabolic disease was made to their parents and siblings. One of the siblings who was 19 months old, diagnosed with HCU had a mild neuromotor developmental delay. The homocysteine level was found to be very high in this case, the same mutation was detected in the *CBS* gene, and he was diagnosed as classic HCU. After treatment his neuromotor delay regressed and he began to walk. The father of a patient diagnosed with 3-MCC had forgetfulness complaint. His 3-OH isovaleryl (C5-OH) carnitine level was high in carnitine-acylcarnitine profile, and there were breakthroughs in urine organic acid analysis, supporting the 3-MCC disease diagnosis. With family screening, two relatives were diagnosed with IEMs.

Discussion

Inborn errors of metabolisms may present with autistic symptoms with a higher percentage than in the general population[7]. Especially in recent years, the causal role of IEMs presenting with autism has been emphasized and some IEMs are thought as preventable causes of autism. The importance of performing metabolic tests for the diagnosis of these patients with accompanying symptoms apart from ASD is indicated[8]. In our study, we determined the prevalence of IEMs as 3.3% in ASD cases, compatible with other studies[3, 6, 9].

The most associated IEMs with ASD are phenylketonuria, creatine deficiency syndrome, adenylsuccinate lyase deficiency and purine-pyrimidine disorders[10]. Mitochondrial disorders, classical HCU, Sanfilippo syndrome, biotinidase deficiency can also present with features of autism[7–9, 11]. In this study, we diagnosed two PKU cases, two HCU cases, one Sanfilippo syndrome, and one case of 3-methylcrotonyl Co-A carboxylase (3-MCC) deficiency accompanying ASD.

Phenylketonuria (PKU) is an autosomal recessive disorder caused by the deficiency of phenylalanine hydroxylase enzyme that provides the conversion of phenylalanine to tyrosine. Untreated patients have hair and skin hypopigmentation, epilepsy, intellectual disability and behavior problems. These damages can be prevented with early diagnosis and special nutritional therapy[12]. Neonatal screening for PKU started in 2006 in Turkey. Two of our patients who were diagnosed as PKU were born before 2006 and were not screened for PKU. It is known that untreated PKU may present with ASD[3, 7], and if they were screened and diagnosed, they would have been treated.

Classical homocystinuria is a metabolic disease that develops due to cystathionine beta synthase deficiency in the catabolic pathway of methionine. Multiple system involvement is accompanied by patients. Developmental delay, intellectual disability can be seen in addition to the findings of skeletal system (excessive height, long limbs, scoliosis, and pectus excavatum), vascular system (thromboembolism) and eye (ectopia lentis and / or severe myopia)[13]. Two of our patients were diagnosed as HCU and had hyperactivity, speech retardation, and no eye contact. An improvement of one patient who adapted to the treatment was observed in the clinic.

Sanfilippo syndrome (MPS type 3) is a multisystem lysosomal storage disease characterized by progressive central nervous system degeneration, intellectual disability, developmental regression, behavioral problems and ASD[7, 14]. One of our patients had this diagnosis whose cardiac and eye findings were normal, but had pathological skeletal findings. And after the diagnosis the progression of the disease continued since there is no treatment available.

One of the rarely presented IEMs with ASD in the literature is 3-MCC deficiency. Arnold et al. retrospectively examined 35 cases with the diagnosis of 3-MCC deficiency, and found two cases with ASD[15]. The clinical findings of 3-methylcrotonyl Co-A carboxylase deficiency cases may differ. Lately diagnosed patients may present with severe clinical findings such as developmental delay, psychomotor retardation, mental retardation and seizures[16]. Our patient was diagnosed with ASD and also had hyperactivity and speech retardation. After treatment, the behavioral problems of the patient eased, and his father was also diagnosed with 3-MCC deficiency.

Another important comorbidity associated with ASD is epilepsy. The prevalence of epilepsy varies between 5% and 38% of ASD cases, and treatment-resistant epilepsy is common[17]. Epilepsy is clinically accompanied in most metabolic diseases with ASD. In cases with ASD and IEMs association, the

frequency and / or severity of seizures may decrease with the identification and treatment of metabolic disorder[17]. In our study, epilepsy was accompanied by one of the six ASD cases (16.6%) with IEM. This case was diagnosed with PKU and after beginning to nutritional therapy seizure frequency of this patient decreased.

In a retrospective study conducted by *Asato* et al. in 274 nonsyndromic ASD patients, it was shown that the diagnostic yield of routine metabolic disease screening for these rare IEMs, where autism is a symptom, is very low[8]. The recommended clinical practice is not routinely screening IEMs in nonsyndromic ASD patients[18].

It is very important to look for specific findings regarding detailed personal history, family history, and to do careful physical examination in patients with ASD. These findings may guide the clinician in the decision to conduct a metabolic study. In the presence of additional findings (epilepsy, mental retardation, psychiatric disorder, dysmorphic features, skeletal system findings, eye findings) accompanying ASD, it is very important to perform metabolic screening in these patients in order not to miss IEMs diseases.

There are limitations of our study. One is that we evaluated the patients with clinical, routine laboratory tests and metabolic tests. Some metabolic diseases (purine and pyrimidine disorders, disorders of vitamins and cofactors, creatine metabolism disorders) may not be diagnosed with these tests. We may have missed these diagnoses that require further investigations and imaging methods. In addition, we could not perform genetic analysis in all of our cases diagnosed with IEMs.

Conclusion

IEMs may rarely present with ASD symptoms. Careful evaluation of the history, physical examination and recording the additional findings in patients diagnosed with ASD will guide the clinician in the decision-making process of metabolic tests. An underlying IEM can be a treatable cause of autism.

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CONFLICT OF INTEREST
All authors declare that they have no conflict of interest.

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