Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Causes of hereditary metabolic diseases in patients presenting with developmental delay

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ARTICLE INFO

Keywords:
Developmental delay
Intellectual retardation
Inherited metabolic disease

Received: Dec 05, 2022
Accepted: Feb 28, 2023
Available Online: 24.03.2023

DOI:
10.5455/annalsmedres.2022.12.353

Abstract

Aim: Developmental delay has many causes such as intrauterine infections, brain malformations, chromosomal anomalies, metabolic diseases. Between 0.8% and 15% of developmental delays are due to inherited metabolic diseases. Early diagnosis of these patients is very important in terms of the fact that some of them can be treated and also genetic counseling can be given to the family. In this study, it is aimed to emphasize the importance of reporting the clinical, biochemical and imaging characteristics, follow-up and treatment processes of the patients diagnosed with hereditary metabolic disease in patients with unexplained developmental delay/intellectual retardation, followed by the Metabolism 4 outpatient clinic of Başakşehir Çam and Sakura City Hospital.

Materials and Methods: This retrospective study was conducted on the data obtained from the medical files of 192 patients aged 0-18 years, who were followed up with developmental delay/intellectual retardation between May 2021 and May 2022 in the metabolism 4 outpatient clinic of our tertiary care center.

Results: The female/male ratio of the patients was 13/36, and the age range was between 3 months and 17 years. 34 patients were diagnosed with a hereditary metabolic disease and 15 patients with a non-metabolic genetic disease. There was consanguineous marriage in 23/32 of the patients with hereditary metabolic disease and 6/15 of the other patients. The most common Inherited metabolic disease groups are mitochondrial diseases, and lysosomal storage diseases.

Conclusion: Patients can present at any age, and hereditary metabolic disease group has an important place in the etiology and has a great importance in terms of including many treatable diseases. For this reason, referral of patients who apply to outpatient clinics with developmental delay/intellectual retardation to metabolism outpatient clinics is of vital importance in terms of diagnosis, treatment, family screening and genetic counseling.

Introduction

Development is a process of maturation that begins with fertilization and ends with maturity. Child development is considered as the maturation of brain function that differs from growth. The order of developmental stages is similar in every child, however the rate of development varies in children, depends on the presence of chronic medical disorders, genetic and environmental factors. Development can be divided into subgroups, including language, motor, psychosocial and cognitive development [1]. Delay is considered when a child does not gain a developmental milestone at the expected age [2]. Although there are no definitive records, it is believed that 5-10% of outpatients presenting in various medical centers are comprised of patients presenting with developmental delay [3].

Developmental retardation may become discernable in infancy or early childhood, however milder delays become recognizable over time and are more commonly diagnosed during the early school years movement [4]. Early determination of developmental issues is crucial as it provides early investigation for definitive diagnosis and management whenever feasible. Developmental delay does not correspond with a diagnosis, nevertheless it is used as a term in distinct clinical manifestations and prognosis including a wide variety of etiologies covering metabolic, genetic, malformation syndromes, endocrine, vascular, infectious, traumatic, toxic and environmental causes [5].

In the literature there are many reports of metabolic disease patients with developmental delay, however the data on the incidence of metabolic diseases in patients with un-

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explained developmental delay are scarce. The aim of this study is presenting the clinical, biochemical and imaging characteristics, follow-up and treatment processes of patients presenting with unexplained developmental delay/intellectual retardation (DD/IR) followed by Başakşehir Çam and Sakura City Hospital Metabolism 4 outpatient clinic and diagnosed with hereditary metabolic disease (HMD) and to emphasize the importance of referral to metabolism clinics.

Materials and Methods

This retrospective study was conducted on the data obtained from the medical files of 192 patients aged 0-18 years, who were followed up with DD/IR between May 2021 and May 2022 in the metabolism 4 outpatient clinic of our tertiary care center. Demographic, clinical, laboratory findings were investigated. Complete blood count, biochemistry, blood gas, lactate, homocysteine, plasma amino acids, acylcarnitine analysis, urine organic acid, urine amino acid, ammonia, very long chain fatty acids analyzes were performed from all patients as first-line examinations. Isoelectric focusing and/or lysosomal enzyme analyzes were performed as a second step in patients without specific findings in first-line examinations. 49 patients diagnosed with IMD or other genetic diseases with biochemical and/or genetic analysis were included in the study. Patients who did not have any features in their metabolic tests and/or could not be diagnosed with genetic analysis were not included in the study. Ethical approval was obtained from the Ethics Committee of Başakşehir Çam ve Sakura City Hospital (No. 2022. 04. 127; decided 27/04/2022).

Results

The files of 192 patients who presented with DD/IR were reviewed retrospectively. Forty-nine patients from 47 families diagnosed with genetic and/or biochemical diagnostic methods were included in the study. Initial diagnosis were established due to the clinical, biochemical and imaging findings then confirmed with molecular genetic testing. Whole exam sequencing was performed in patients with normal biochemical results however supporting a metabolic or genetic disease with clinical, family history and/or brain imaging findings. Demographic, clinical, laboratory findings and diagnoses of the patients are shown in Table 1. The female/male ratio of the patients was 13/36, and the age range was between 3 months and 17 years. IMD was diagnosed in 34 patients, and a non-metabolic genetic disease was diagnosed in 15 patients. There was consanguineous marriage in 23/32 of the patients with IMD and 6/15 of the other patients. The most common finding accompanying developmental delay was epilepsy (7/49). The most common IMD groups are mitochondrial disease (Leigh, Leigh-like syndrome, MELAS, Oxidative Phosphorylation Disorder 35, Complex 1 deficiency, fumaric aciduria, riboflavin transport disorder, mitochondrial myopathy), (9/34 patients) and lysosomal storage disease (GM1 gangliosidosis, Krabbe disease, Niemann pick type A/B, MLD, fucosidosis), (11/34). Congenital glycosylation defect (CDG) type 1 in three patients, urea cycle defect (citrullinemia) in one patient, organic acidemia in three patients (malonic acidemia and methylcrotonylglycinuria), cerebral creatinine deficiency in one patient, GLUT1 deficiency, homocystinuria, nonketotic hyperglycinemia, Lesch Nyhan's disease, Zellweger's disease, and cerebral iron storage disease, were diagnosed. All patients diagnosed with a congenital metabolic disease with biochemical, clinical and imaging findings diagnosed with a metabolic apart from patient 7,10, 13, 14 diagnosis were confirmed by molecular genetic analysis. Patient 7, 10, 13, 14 did not accept to perform genetic analysis or did not come for follow up. The results of the biochemical analysis are shown in Table 2. Abnormal findings were present in 26 of 35 patients who had brain magnetic resonance imaging (MRI) (Figure 1). Corpus callosum anomaly in 3 patients, periventricular leukomalacia in 7 patients, subcortical involvement in 5 patients, cerebral atrophy in 1 patient, cerebellar anomaly in 5 patients, basal ganglia, thalamus and brainstem involvement in 3 patients, ventricular dilatation in 5 patients, gyral thickening in 1 patient and infarct like involvement in one patient were detected (Table 3). Mitochondrial cocktail therapy (carnitine, coenzyme Q10, biotin, thiamine, riboflavin) was applied to the patients who were followed up with the diagnosis of mitochondrial disease, and allogeneic hematopoietic stem cell transplantation was planned to the patient who was followed up with the diagnosis of MLD that is one of the lysosomal diseases. Other patients were given only supportive treatment. Natural protein restricted diet in the patient with citrullinemia, oral creatinine supplementation in the cerebral creatine deficiency, ketogenic diet in the patient with GLUT1 deficiency, be-

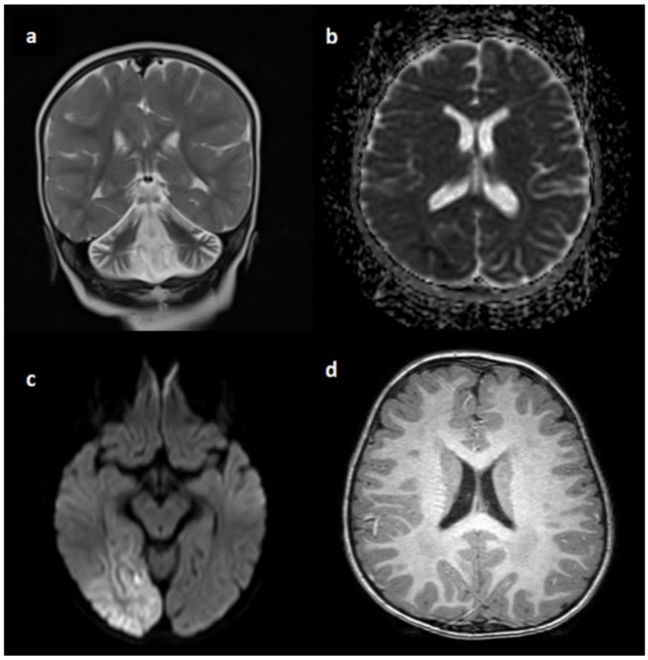

Figure 1. MRI images of patients. a) Cereballar hypoplasia in the patient with pontocereballar hypoplasia type 0, b and c) Difussion restriction in the right occipital region of the patient with MELAS on ADC sequence and diffusion MRI respectively, d) Leukodystrophy in the patient with MLD.

Table 1. Demographic, clinical and laboratory features of patients.

Patient no:	Age	Sex	Consanguinity	Symptom and finding	Laboratory	Brain MRI	Diagnosis
1	6 mo	M	-	Axial hypotonia, no head control	Blood lactate and plasma alanine increase, dicarboxylic aciduria	Basal ganglion and brainstem involvement	Leigh syndrome (MT-TW homoplasmic mutation)
2	10 mo	M	+	Axial hypotonia, no head control, seizures	Blood lactate and plasma alanine increase, glutaric aciduria	Bilateral frontal, parietal, temporal subcortical white matter involvement	Leigh like syndrome
3	7 y	F	+	Congenital bilateral cataract, mild motor and intellectual retardation	Normal	Normal	Myopathy, mitochondrial progressive, with congenital cataract and developmental delay (GFER homozygous mutation)
4	3,5 y	M	-	Neonatal metabolic acidosis, motor, and speech retardation	Lactic acidosis, plasma alanin increase, lactic aciduria, pyruvic aciduria, 3 -OH butyric aciduria, glutaric aciduria, fumaric aciduria	Dysgenetic corpus callosum, frontotemporal subcortical white matter involvement	Leigh like syndrome (MT-ND5 heteroplasmic mutation)
5	1 y	M	+	Dysmorphism, hypotonia, no head control, no gaze following	Fumaric aciduria	Non communicating hydrocephaly, gyral fading, cerebellar atrophy	Fumaric aciduria (FH homozygous mutation)
6	8 y	M	-	Seizure, headache, vision loss, weakness	Blood lactate increase	Imaging consistent with right occipital infarction, lactate peak in MRS	MELAS (MT-TL 1 homoplasmic mutation))
7	20 mo	F	+	Motor retardation	Recurrent malonic aciduria	Periventricular and subcortical white matter involvement	Malonic acidemia
8	2,5 y	M	-	Motor retardation, frequent falling,	Increased creatine kinase, transaminases, low residual alglucosidase alfa	N/A	Glycogen storage disease type 2 (Pompe disease) (GAA compound heterozygous mutation)
9	6 y	M	+	Dysarthria, frequent fall down, intellectual disability	CSF/Blood glycine increased	Normal	GLUT1 deficiency (SLC2A1 heterozygous mutation)
10	10 y	M	-	Speech retardation, intellectual disability	Low blood creatinine and guanidinoacetate	Normal MRI, low creatine peak in MRS	Cerebral createine deficiency (arjinin: glisin amidinotransferase deficiency)
11	9 mo	F	+	Motor retardation, axial hypotonia, coarse face, dysostosis multiplex, hepatosplenomegaly	Increased plasma lysosomal enzyme levels	N/A	Mucolipidosis type II (GNPTAB homozygous mutation)
12	2,5 y	M	+	Abnormal gait, mild course face, genu valgum deformity, widening of metaphysis, pectus carinatum, gibbus, hepatomegaly, shortening of extremities and upper body	Decreased leukocyte N-acetyl galactosamine 6 sulfatase level	N/A	Mucopolysaccharidosis type IVA
13	6 mo	M	+	Regression of social smiling and eye contact	Decreased level of galactosylceramidase	Periventricular leukodystophy	Krabbe disease
14	3 mo	F	+	Axial hypotonia, motor retardation, limited eye contact and gaze following, hepatosplenomegaly	Increased transaminases, decreased level of leukocyte sphingomyelinase	N/A	Niemann Pick type A/B
15	3 y	M	-	Abnormal gait, ataxia	Low level of leukocyte arylsulfatase	Periventricular leukodystrophy, increased signal in corpus callosum	Metachromatic leukodystrophy (ARSA homozygous mutation)
16	9 mo	M	+	Coarse face, motor and cognitive retardation, hydrocephaly, hepatomegaly, dysostosis multiplex	Low level of leukocyte beta galactosidase	N/A	GM1 gangliosidosis (GLB1 homozygous mutation)
17	4 mo	M	+	Coarse face, axial mild hypotonia, hepatosplenomegaly	Low level of leukocyte beta galactosidase	N/A	GM1 gangliosidosis (GLB1 homozygous mutation)
18	3,5 y	M	+	Frequent fall, mild ataxia	Low level of leukocyte beta galactosidase	Normal	GM1 gangliosidosis (GLB1 homozygous mutation)
19 (18 sibling of no 18)	13 y	M	+	Frequent fall down, mild ataxia, loss of ability to go up/down stairs, hepatomegaly	Low level of leukocyte beta galactosidase	N/A	GM1 gangliosidosis (GLB1 homozygous mutation)
20	7 mo	F	+	Motor retardation, microcephaly	Normal	Pachygyria of posterior horns of lateral ventricles, generalized calcification of white matter	Methylchrotonylglycinuria (+ pseudotorch syndrome) (MCCC2 homozygous mutation and OCLN homozygous mutation)
21	19 mo	F	+	Speech retardation, delayed walking milestones	Increased blood C5OH acylcarnitine, 3OH isovaleric aciduria and 3-methylchrotonylglycinuria	Normal	Methylchrotonylglycinuria (MCCC2 homozygous mutation)
22	8 mo	M	+	Axial hypotonia, motor retardation and microcephaly	Mild dicarboxylic aciduria	Corpus Callosum hypogenesis	Combined Oxidative phosphorylation disorder 35 (TRIT1 homozygous mutation)
23	3 y	M	+	Motor retardation and neurodegeneration	Mild dicarboxylic aciduria	Diffuse symmetric abnormal signal changes in cerebral peripheral (including U fibers)- deep white matter, cerebellar white matter, internal-external capsules, brain stem, globus pallidus-thalamus, corpus callosum	Complex I deficiency (NDUFS8 homozygous mutation)
24	8 y	M	+	Motor retardation, weakness	Ethylmalonic aciduria, axonal polyneuropathy in sensory fibers in electromyography	Normal	Riboflavin transport disorder (SLC52A2 homozygous mutation)
25	3,5 y	M	-	Hypotonia, motor and mild cognitive retardation, neurodegeneration	Increased levels of very long chain fatty acids	Ventricular dilatation	Zellweger syndrome (PEX1 homozygous mutation)
26	2 y	M	+	Motor and cognitive retardation, generalized dystonia, epilepsy	Elevated levels of blood uric acid	Nonspecific findings	Lesch Nyhan Syndrome (HPRT1 homozygous mutation)
27	5 y	F	+	Cognitive and speech retardation, epilepsy	Increased homocysteine and methionine levels	Posterior periventricular leukomalacia	Homocystinuria (CBS homozygous mutation)
28	2 y	F	+	Generalized developmental delay, ataxia	Normal	Cerebellar atrophy	Cerebral iron storage disorder (PLA2G6 homozygous mutation)
29	1,5 y	M	+	Generalized developmental delay, dystonia, epilepsy	Increased CSF/blood gycine	Corpus callosum agenesis, dilatation of lateral ventricles	Non ketotic hyperglycinemia (GLDC homozygous mutation)
30	1,5 y	M	+	Generalized developmental delay, hypotonia, epilepsy	Type I pattern in transferrin isoelectric focusing	Dilatation of lateral ventricles	Congenital glycosylation defect type I (ALG1 homozygous mutation)
31 (sibling of no 30)	3 y	F	+	Motor and cognitive retardation, hypotonia, epilepsy	Type I pattern in transferrin isoelectric focusing	N/A	Congenital glycosylation defect type I (ALG1 homozygous mutation)
32	2 y	M	-	Speech and motor retardation, mild intellectual disability	Type I pattern in transferrin isoelectric focusing	Normal	Congenital glycosylation defect type I (ALG1 homozygous mutation)
33	7 mo	M	+	History of birth with meconium, no gaining of motor function	Moderate plasma citrulline increasing	Generalized cystic encephalomalacia	Citrullinemia type I (ASS1 homozygous mutation)
34	2, 5 y	M	+	Motor retardation, epilepsy	Normal	Cerebellar hypoplasia	Pontocerebellar hypoplasia type 0 (CLP1 homozygous mutation)
35	2,5 y	M	-	Facial dysmorphism, delayed motor milestones, fine motor retardation	Normal	N/A	Mowat Wilson Syndrome (ZEB2 heterozygous mutation)
36	1,5 y	M	-	Prematurity, facial dysmorphism, no speech, motor retardation	Normal	Billateral frontal atrophy	Pitt Hopkins syndrome (TCF4 heterzygous mutation)
37	9,5 mo	M	+	Axial hypotonia, motor retardation	Nonspesific	Bilateral frontal atrophy	KBG syndrome (ANKRD11 heterozygous mutation)
38	8 mo	M	-	Motor retardation, facial dysmorphism	Normal	N/A	Kabuki make up syndrome (KMT2D heterozygous mutation)
39	6 mo	M	-	Hypotonia, no head control, motor retardation	Normal	N/A	Prader willi syndrome
40	6,5 y	M	-	Long face, large ears, intellectual disability, speech retardation	Nonspecific	N/A	Fragile X syndrome
41	6 y	M	-	Atypical autism, cognitive retardation, no speech, hyperventilation	Normal	N/A	DIGFAN syndrome (MORC2 heterozygous mutation)
42	4 y	M	+	Gait abnormality, weakness, speech retardation, intellectual disability	Normal	Normal	**IDDECA** (INTELLECTUAL DEVELOPMENTAL DISORDER WITH OR WITHOUT EPILEPSY OR CEREBELLAR ATAXIA) (RORA heterozygous mutation)
43	13.5 y	F	-	Motor and intellectual retardation, facial dysmorphism	Nonspesific	Bilateral periventricular cystic area	Coffin Siris syndrome (ARID1B heterozygous mutation)
44	4 y	M	+	Motor and cognitive retardation, facial dysmorphism	Nonspecific	Left lateral ventricular dilatation	Dyke-davidoff-masson syndrome
45	2,5 y	F	+	No gaining motor function, axial hypotonia, hypertonia of extremities	Nonspecific	Normal	Spastic paraplegia 52 (AP4S1 homozygous mutation)
46	17 y	F	-	Motor retardation, bilateral glaucoma	Nonspecific	N/A	Coffin siris syndrome (ARID1B heterozygous mutation
47	1 y)	F	+	Motor retardation	Nonspecific	Prominence of cerebellar folia	Pontocerebellar hypoplasia type 1d (EXOSC9 homozygous mutation)
48	2 y	M	-	Motor retardation, epilepsy	Nonspecific	Normal	Episodic kinesigenic dyskinesia 1 (PRRT2 heterozygous mutation)
49	10 mo	M	+	Delayed motor milestones, axial hypotonia	Low level of leukocyte alpha fucosidase	Nonspecific	Fucosidosis (FUCA1 homozygous mutation)

CSF: Cerebrospinal fluid, MRI: Magnetic resonance imaging.

Table 2. Biochemical findings

Biochemical analysis	Patient number	Diagnosis
Biochemistry (blood)		
Uric acidemia	1	Lesch Nyhan syndrome
Low creatinine	1	Cerebral creatine deficiency
High lactate	4	Leigh- Leigh like syndrome, MELAS
High homocysteine	1	Homocystinuria
Plasma aminoacids		
High citrulline	1	Citrullinemia
High alanine	3	Leigh- Leigh like syndrome
High glycine	1	Nonketotic hyperglycinemia
Methionine	1	Homocystinuria
Organic acids (urine)		
Fumaric acid	2	Fumaric acidria, Leigh syndrome
Lactic acid	1	Leigh syndrome
Pyruvic acid	1	Leigh syndrome
Glutaric acid	1	Leigh syndrome
Dicarboxylic acids	3	Complex I deficiency, Leigh syndrome
Malonic acid	1	Malonic acidemia
Ethylmalonic acid	1	Riboflavin transport disorder
3-OH isovaleric acid	2	Leigh like syndrome, Methylcrotonylglycinuria
3- Methylcrotonylglycine	1	Methylcrotonylglycinuria
3- OH butyric acid	1	Leigh syndrome
Acylcarnitine analysis (dried blood spot)		
C5OH	1	Methylcrotonylglycinuria
Transferrin isoelectric focusing		
Type I pattern	3	CDG type I
Very long chain fatty acids		
High C22-24	1	Zellweger syndrome
Lysosomal enzymes (leukocyte)		
Beta galactosidase deficiency	4	GM1 gangliosidosis
Sfingomyelinase	1	Niemann Pick type A/B
Alfa glucosidase deficiency	1	Pompe disease
N-Acetylgalactose amine 6 sulfatase deficiency	1	Mucopolysaccharidosis 4A
Arylsulfatase deficiency	1	Metachromatic leukodystrophy
Galactosylceramidase deficiency	1	Krabbe disease
Fucosidase deficieny	2	Fucosidosis
Increased plasma lysosomal enzyme	1	Mucolipidosis II

taine, folic acid, vitamin B12 and pyridoxine treatment in the patient with homocystinuria, allopurinol in the patient with Lesch Nyhan were started. In the follow-ups, patients except with lysosomal storage diseases responded partially to the treatment. Since the patient with MLD is a candidate for stem cell transplantation, his response to treatment will be evaluated with follow-ups.

Discussion

The aim of this study was to share the experience of the evaluation and diagnostic research of children with developmental delay in our tertiary care center. Our retrospective series had a relatively large sample size; however, the applicability of our results to the general population warrants further prospective, multicenter studies in children with developmental delay. In this study it was shown that global developmental delay is not a rare cause of metabolic diseases and early diagnosis and treatment can be lifesaving in this population.

DD/IR is an entity that affects 150 million children globally and its incidence varies between 1% and 3% [6,7]. Since multiple genetic and peripheral factors play a role in the development of the disease, the definitive etiologic identification of IR/GDD while still in its early stages of emergence may improve the effectiveness of therapy and quality of life [8-10]. While severely affected children can be recognized before the age of 2 years, some mildly affected children may be diagnosed only after they reach school age because of less obvious symptoms such as poor growth and gross motor skills [11,12].

Etiological causes of DD/IR include perinatal complications, cerebral dysgenesis, chromosomal abnormalities, genetic/dysmorphic syndromes, metabolic disorders, hypothyroidism, neurocutaneous syndromes, and intrauterine infection. In the study conducted by Özmen et al. on the etiology of children with global DD, IMD was diagnosed in 4% of the patients [13]. In the study conducted by Altitimi et al. 20 (17%) patients were diagnosed with IMD by Tandem Mass spectrometry (MS/MS) analysis of 112 infants with DD in a region that newborn screening for IMD was not performed [14]. Another reason for this high rate was the high rate of consanguineous marriage. The rate of consanguineous marriage in the study was 17/20. They most frequently diagnosed phenylketonuria and maple syrup urine disease (MSUD). The reason why these diseases were not seen in this study was that phenylketonuria disease was included in the newborn screening program in our country and MSUD patients were mostly admitted to emergency outpatient clinics with acute encephalopathy attack in the neonatal period. In the study conducted by Liao et al., 8 patients (0.8%) were diagnosed with IMD as a result of genetic examinations for the etiology of 1051 patients with intellectual and/or global DD aged between 6 months and 18 years (2 glutaric aciduria type 1, 2 glutaric aciduria type 2, one ornithine aminotransferase, pyruvate carboxylase, very long chain fatty acid oxidation defect, and malonic acidemia) [15].

In our country, phenylketonuria and biotinidase deficiency are involved in the newborn screening program. In this way, complications can be prevented with treatment started before clinical findings develop in these patients.

Table 3. Imaging findings.

Patient no	Diagnosis	Corpus Callosum anomaly	Periventricular leukomalasia	Subcortical involevement	Cerebral atrophy	Cerebellar anomaly	Basal ganglion involvement	Brainstem involvement	Thalamic involvement	Ventricular dilatation	Gyral anomaly	Infarct like involvement	Other
1	Leigh syndrome		+				+	+	+				
2	Leigh like syndrome			+									
3	Leigh like syndrome	+		+									
4	Fumaric aciduria					+				+	+		
5	MELAS											+	
6	Malonic acidemia		+	+									
7	Krabbe		+										
8	MLD		+										
9	GM1												
10	Fucosidosis		+	+									
11	CDG type 1									+			
12	Zellweger syndrome									+			
13	Homocystinuria		+										
14	Cerebral iron storage disease					+							
15	Non ketotic hyperglycinemia	+								+			
16	Complex 1 deficiency		+	+		+	+	+	+				
17	Oxidative phosphorylation disorder	+											
18	Pontocerebellar hypoplasia type 0					+							
19	Pitt Hopkins syndrome				+								
20	Pontocerebellar hypoplasia type 1d					+							
21	Dyke-davidoff-masson syndrome									+			
22	KGB syndrome				+								
23	Methylcrotonylglycinuria (+ pseudotorch syndrome)										+ (Calcification of white matter)		
24	Lesch Nyhan syndrome												+
25	Citrullinemia												Generalized cystic encephalomalacia

In this study, clinical, laboratory and brain MRI findings of 49 patients diagnosed with DD were examined. Inherited metabolic disorders are considered a crucial cause of morbidity and mortality in pediatric population. Delayed diagnosis and failure to treat of these metabolic disorders in a timely manner lead to more harmful effects such as intellectual disability, neuropsychological abnormalities, poor prognosis, and increased risk of mortality [16]. In this study, a high rate of IMD was found in pediatric population presenting with unexplained developmental delay. A consanguineous marriage cause a higher incidence of autosomal recessive disorders and increases the prevalence of IMD [17]. In this study, most of the IMD cases had a history of positive consanguinity (61%).

The pathogenesis of IMDs that cause DD/IR is not fully known. However, disorders affecting the structure and functions of the brain, energy metabolism, energy substrate disorders, neurotransmitter abnormalities, and disorders affecting the use of metabolites that affect the normal formation of myelin are known pathologies [18,19]. Hoytema van Konijnenburg et al. defined 116 (139 genes) treatable causes of intellectual disability in their review [20]. This number is quite high and it is a result that emphasizes the importance of early diagnosis of patients once again.

The typical metabolic study (chromatography of lactate, ammonia, plasma amino acids and urinary organic acids) has a diagnostic profit of less than 1% to 5% [21], so it only supports testing with the presence of clinical red flags. However, previous studies were designed to determine an etiological cause and ignored the therapeutic approach. Series with a longer metabolic study identified a diagnostic profit of more than 5% [22]. The rate of patients diagnosed with the results of routine metabolic investigations of DD/IR patients ranged from 0.8% to 2.5% in various studies [23,24], however it was reported that up to 14% of the patients could be diagnosed with IMD by detailed metabolic reassessment [25,26]. In this study, 35/192 (17,7 %) of patients were diagnosed with metabolic diseases with performing biochemical detailed tests and

molecular genetic analysis. Laboratory findings of 18 patients in this study were unremarkable. Among them, those with metabolic diseases were only cerebral iron storage disease, methylcrotonylglycinuria (+pseudotorch syndrome) and mitochondrial myopathy. Other patients had other genetic diseases. Metabolic examinations of 31 of 34 patients diagnosed with metabolic disease and had pathological findings related to the disease. This manifestation once again supports the effectiveness of metabolic tests in diagnosing.

MRI is the first imaging choice in the assessment of neurometabolic disorders. Most such disorders show specific MRI abnormalities, despite some images may have identical appearances and often alter with stage of presentation and age [27,28]. In a study by Ali Al Orf et al., based on imaging criteria, they showed that MRI has a high negative predictive value (76%) and sensitivity (around 80%) in estimating inherited neurometabolic disorders. With selected imaging criteria, they were able to suggest metabolic diseases such as certian aminoacidopathies, lysosomal storage diseases, and urea cycle disorders [29]. However, periventricular leukoencephalopathy, inflammatory or infectious diseases, metabolic disorders acquired with nutritional deficiencies may also present with similar findings [30]. Metabolic diseases such as MSUD, Krabbe and non-ketotic hyperglycinemia may cause MRI findings that mimic hypoxic ischemic encephalopathy [30,31]. For this reason, false positive or negative diagnoses will be prevented by evaluating the history, physical examination, clinical findings, laboratory, and imaging findings of the patients together. Remarkably patients diagnosed with IMD had pathological brain MRI findings that were mostly specific.

However, it should be underlined that the presence of nonspecific or normal MRI findings does not exclude the presence of metabolic diseases. It should be kept in mind that MRI findings may be normal, especially in cerebral creatinine deficiency, GLUT1 deficiency and other neurotransmitter deficiencies.

Conclusion

Consequently patients with DD/IR may present at any age and HMD has an importance in their etiology, which is of great importance in terms of including many treatable diseases. Widespread application of next-generation genomic and metabolomic testing and imaging methods in daily clinical practice has accelerated diagnosis and initiation of appropriate medical and/or dietary therapy for many patients. Therefore, referral of patients who apply to outpatient clinics with DD/IR to metabolism outpatient clinics is of vital importance in terms of diagnosis, treatment, family screening and genetic counseling.

Ethical approval

Ethical approval was obtained from the Ethics Committee of Başakşehir Çam ve Sakura City Hospital (No 2022. 04. 127; decided 27/04/2022).

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