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Original Article

The prevalence, results, and treatments of the patients followed up with a diagnosis of metabolic disease in the pediatric intensive care unit: A single-center experience

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ABSTRACT

Objective: Inborn errors of metabolism (IEM) are a rare, inherited, heterogeneous group of diseases that are mostly symptomatic in the pediatric age group. Late diagnosis and delays in intervention can result in acute metabolic decompensation, progressive neurological damage, or death. IEM patients are responsible for significantly increased morbidity and mortality in intensive care units. Rapid, aggressive, and supportive treatment in pediatric intensive care units can reduce morbidity and mortality in IEM patients.

Method: Patients diagnosed with IEM and/or diagnosed during hospitalization in the tertiary Pediatric Intensive Care Unit (PICU) between February 2021 and November 2022 were retrospectively analyzed. During this period, 962 hospitalized patients were screened and patients with a diagnosis of IEM were included in the study. Demographic data, laboratory analysis, treatment characteristics, PICU, and length of hospital stay were recorded retrospectively.

Results: Twenty-three patients diagnosed with IEM were included in the study. The mean age of the patients was 48 months, and the majority of participants were female. 5/23 patients were followed up with the diagnosis of intoxication type, 10/23 patients with energy metabolism disorder type, and 8/23 patients with complex molecule disorder type. The median lactate level was (6.7 mmol/L, range: 0.8-32) higher in patients (7/23) who died in the PICU than in those who survived (p=0.016). Continuous renal replacement therapy was used in 6/23 (26%) patients, and invasive mechanical ventilation was applied to 3/23 (56.5%) patients.

Conclusion: IEM patients are challenging for pediatric intensive care professionals at the diagnostic and therapeutic levels. Undiagnosed patients at the time of admission to the PICU require a high degree of suspicion for prompt diagnosis and treatment. It is thought that the newborn screening program should be expanded. Aggressive and supportive treatment and specific metabolic disease treatment can be lifesaving, but these patients still have a high mortality rate.

Keywords: Inborn errors of metabolism, pediatric intensive care unit, continuous venovenous hemodiafiltration, invasive mechanical ventilation

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INTRODUCTION

Inborn errors of metabolism (IEM) are a rare, inherited, heterogeneous group of diseases that are mostly symptomatic in the pediatric age group. Although they are seen as rare as 1:100.000 births one by one, their incidence is 1:800-1:2500 births when considered as a group.[1] IEMs result from a deficiency or abnormality of an enzyme or cofactor, or a transport defect. In general, it leads to an accumulation or deficiency of metabolite.

IEM can be classified into three subgroups according to their physiological characteristics: 1- Intoxication type (urea cycle disorders, amino acidopathies, organic acidurias), which occurs with metabolic crises due to the damage in the metabolic pathway causing the accumulation of toxic metabolites; 2- Energy metabolism disorders (mitochondrial disorders, glycogen metabolism disorders, fatty acid oxidation defects), which result from insufficient energy production, involving organs with higher energy needs such as muscles and the brain; and 3- Complex molecule type (lysosomal and peroxisomal storage diseases) with an accumulation of complex molecules in solid organs due to enzyme deficiency.[2] In IEM patients, especially those with intoxication type and energy metabolism disorders, the acute metabolic crisis is observed when energy insufficiency occurs. Late diagnosis and delayed intervention can result in acute metabolic decompensation, progressive neurological damage, or death. IEM patients are responsible for significantly increased morbidity and mortality in intensive care units. Generally, IEM patients with complex molecule type also need intensive care for organ failures, such as congestive heart failure, respiratory failure due to organ system involvement, or severe infections. The most common causes of hospitalization in IEM patients are metabolic decompensations, septicemia, and respiratory problems. Rapid, aggressive, and supportive treatment in pediatric intensive care units can reduce morbidity and mortality in IEM patients.

In our study, we aimed to describe the demographic, clinical, and laboratory characteristics, causes of hospitalization, and mortality rate of patients with a diagnosis of IEM in the tertiary pediatric intensive care unit.

MATERIAL AND METHOD

In our study, patients diagnosed with IEM and/or diagnosed during hospitalization in the tertiary PICU of Manisa City Hospital between February 2021 and November 2022 were retrospectively analyzed.

The study protocol was approved by the local ethics committee of Bakırçay University. Children, aged between 1 month and 18 years, who presented to the PICU with a metabolic emergency and were diagnosed with IEM, were included in the study conducted between February 2021 and November 2022. We included children diagnosed with IEM for the first time on admission to the PICU and children diagnosed with metabolic disease in the neonatal period or on their previous admission. Children without a diagnosis of IEM, with missing data, and without a definitive diagnosis at discharge or death were excluded from the study.

Demographic data (age, gender, and cause of hospitalization), PRISM score, laboratory analysis (liver function tests, renal function tests, hemogram, infection parameters, blood gas parameters), culture results (urine, blood culture), treatment characteristics, PICU and length of stay (LOS) were retrospectively recorded. All patients were followed up until discharge or death.

The patients were divided into three groups: Intoxication types (amino acidopathies, organic acidurias, urea cycle defects, carbohydrate intolerances, metal disorders, and porphyrias), energy metabolism disorders (Glycolysis, glycogenosis, gluconeogenesis defects, creatine pathway, pentose phosphate pathway defects, mitochondrial disorders), and complex molecule type (lysosomal storage diseases, peroxisomal disorders, congenital disorders of glycosylation, and cholesterol synthesis defects).

All samples were analyzed by one laboratory with the same technique. Plasma amino acid levels were determined by the LC-MS/MS kit (Shimadzu LCMS-8040 Liquid Chromatography Mass Spectrometer, ImmuChrom GmbH kit). DBS were pre-processed following the instruction of NeoBaseTM non-derivatized MS/MS kit (PerkinElmer, MA, United States), using 1525u high-performance liquid chromatography (HPLC) (Waters Technologies, Milford, MA, United States) and ACQUITY TQD mass spectrometer (Waters, Milford, MA, USA) for quantitative analysis. The analytes included 11 amino acids and 31 acylcarnitine. Urinary organic acid analysis was performed by modifying the method described by Christou et al. Analysis was performed on GC-2010 Plus Gas Chromatography System, Shimadzu Manufacturing Co, Japan. Four-phenylbutyric acid was used as an internal standard, and ethyl acetate was used to extract the organic acids. The organic acids were derivatized using the N, O-Bis(trimethylsilyl) trifluoroacetamide, and trimethylsilyl chloride. Creatinine was measured according to the Jaffe method.[3]

Statistical analyses

Statistical analysis was performed using SPSS software version 22.0 (SPSS, Chicago, IL) for Windows. The distribution of data was evaluated using the Kolmogorov-Smirnov test. We used the one-way ANOVA test to compare more than two groups with normal distribution and homogenous variance and the Kruskal-Wallis test for non-normally distributed data. To compare categorical data, Fisher's exact test with Monte Carlo simulation was used. We presented the descriptive results with normal-distributed data as mean ± standard deviation and skewed data as median (interquartile range (IQR) 25/75). Categorical data were expressed as frequency (%), while numerical data were expressed as mean ± standard deviation. In all statistical tests, p-values<0.05 were considered significant.

RESULTS

Between February 2021 and November 2022, 962 pediatric patients were followed up in the pediatric intensive care unit. Of these, 23 (2.4%) were followed up with a diagnosis of IEM. Five (21.7%) patients were followed up with a diagnosis of intoxication type, 10 (43.5%) patients with an energy metabolism disorder type, and 8 (34.8%) patients with a complex molecule disorder type (Figure 1). Of these 23 patients, seven (30.4%) were diagnosed during hospitalization. The median age of IEM patients was 48 months (IQR, 9-86) and 52.2% were female, while the median age of non-IEM patients was 26 months (IQR, 12-124) and 51% were female. The etiology of PICU hospitalization of IEM patients was metabolic decompensation in 8 (34.8%), respiratory failure in 8 (34.8%), severe sepsis in 5 (21.7%), and cardiovascular failure in 2 (8.7%) patients. There was a history of consanguinity in 17 (73.91%) patients. Thirteen (56.5%) patients in the IEM group and 320 (34%) patients in the non-IEM group were followed up with invasive mechanical ventilation. Mortality was 7 (30.4%) in IEM patients and 62 (6.6%) in non-IEM patients. The median lactate level was (6.7 mmol/L, range: 0.8-32) higher in patients (7/23) who died in the PICU than the patients who survived (p=0.016). The demographic and clinical characteristics of the IEM and non-IEM patients were presented in Table 1.

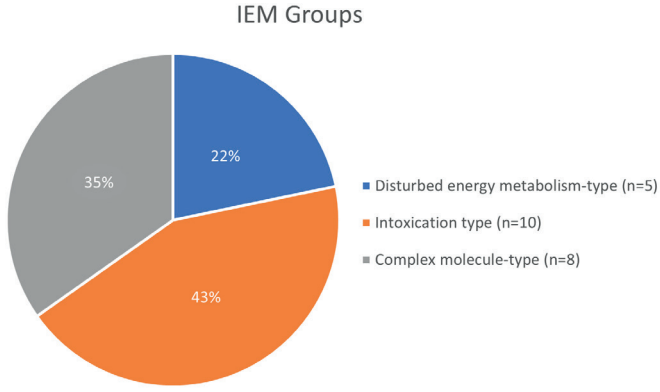

Figure 1. Inborn errors of metabolism Etiology

There was no significant difference in the mean ages between disease groups. Respiratory supportive treatments, such as invasive mechanical ventilation, were most commonly required in patients with complex molecule disorder type (p=0.022).

Table 1. Demographic and clinical characteristics of the IEM and non-IEM patients

Parameters	IEM patients (n=23) n, %	Non-IEM patients (n=939) n, %
Gender M/F	11/12 (47.8/52.2)	453/480 (48/51)
Age (month)*	48 (9-86)	26 (12-124)
Consanguinity rate	17 (73.91)	80 (8.51)
Death sibling history	4 (17.39)	17 (1.81)
PRISM III score*	6 (2-12)	5.6 (1-23.2)
Respiratory Support	13 (56.5)	320 (34)
Duration of mechanical ventilation*	3 (0-8)	9 (3-21)
Lactat level mmol/L*	6.7 (0.8-32)	2.0 (1.3-3.1)
Length of PICU stay (days)*	7 (5-22)	15 (3-101)
Length of hospital stay (days)*	11 (8-22)	22 (4-166)
Mortality in PICU	7 (30.4)	62 (6.6)

PICU: Pediatric Intensive Care Unit, IEM: Inborn Errors of Metabolism, PRISM III score: Pediatric Risk of Mortality III score.
* Median, IQR (Interquartile range)

Table 2. Demographic and clinical characteristics of patients according to disease groups

Parameters	Intoxication-type n=5	Disorders of disturbed energy metabolism-type n=10	Complex molecule-type n=8	p
Age (month) median, (IQR)	47 (14.5-58.5)	42.5 (6.5-97)	63.5 (23.2-150)	0.487
Gender M/F n	2/3	4/6	5/3	0.624
PRISM III score median, (IQR)	2 (2-12)	7 (2-12)	7 (2.25-10)	0.739
Treatment n (%)				
Metabolic Arrangements	1 (20)	4 (40)	5 (62.5)	0.341
RBC Transfusion	2 (40)	5 (50)	2 (25)	0.594
FFP	0	3 (30)	1 (12.5)	0.350
Platelet Transfusion	1 (20)	4 (40)	1 (12.5)	0.429
CRRT n (%)	1 (20)	3 (30)	2 (25)	0.924
Diagnosed in PICU n (%)	1 (14.3)	5 (71.4)	1 (14.3)	0.518
Respiratory Support n (%)	1 (20)	5 (50)	7 (87.5)	0.022
Duration of mechanical ventilation, median (IQR)	0 (0-1.5)	3 (0-8)	9 (2.5-22.5)	0.392
Length of PICU stay (days), median (IQR)	6 (3-14)	9 (5.7-16.7)	15 (5.2-33)	0.359
Length of hospital stay (days), median (IQR)	12 (5.5-16.5)	10.5 (7.7-19)	17 (8.5-33)	0.487
Mortality n (%)	1 (20)	4 (40)	2 (25)	0.702

M: Male, F: Female, RBC: Red blood cell, FFP: Fresh Frozen Plasma, PRISM III score: Pediatric Risk of Mortality III score.

Although the length of stay in the PICU was longer in the complex molecule disorder type, this was not statistically significant. Mortality rates were higher in the energy metabolism disorder type, however, it did not differ significantly between disease groups. CRRT was performed in 6 (26.1%) patients. Although mortality was higher in patients who underwent invasive mechanical ventilation (p=0.022), there was no statistically significant relationship with the duration of mechanical ventilation (p=0.392). The median length of stay in the PICU was longer in patients who died, but this was not statistically significant. The clinic, laboratory, and treatment characteristics by disease groups are presented in Table 2. IEM patients followed in the PICU are shown in Table 3.

DISCUSSION

Five million people in Türkiye and 350 million people in the world have a rare disease.[4] Approximately 50% of the patients are children. 30% of children with rare diseases do not reach the age of 5 years. Inborn errors of metabolism are rare diseases; however, as a group, they are relatively more common. Their incidence in the community varies depending on the consanguineous marriage rates, newborn screening programs, developing technology, ethnicity, and level of awareness. It is estimated that the incidence of IEM is higher in countries where consanguineous marriages are more common, such as Türkiye.[5] IEM can present at any stage of life. Neonatal screening programs and their scope differ by country. In Türkiye, screening for phenylketonuria and congenital hypothyroidism was started in 2006, screening for biotinidase deficiency in 2008, screening for cystic fibrosis in 2015, and screening for congenital adrenal hyperplasia in 2022. Since extended newborn screening is not performed in our country, patients whose clinical findings start after the neonatal period need PICU care. In addition, the need for intensive care is more frequent in IEM patients due to metabolic decompensation episodes, multisystem involvement, secondary immunodeficiency, and progressive course.

In the literature, the frequency of IEM in the PICU was reported as 2.6% by Kamate et al.[6], 2% by Lipari et al.[7], and <1% by Ruttiman et al.[8] In our study, 962 patients were followed in the PICU between February 2021 and November 2022, 939 patients with non-IEM and 23 patients with IEM, aged 0-18 years. We focused on those with a confirmed diagnosis of IEM. The incidence of metabolic disease was 2.39%, which is consistent with the literature. This frequency is similar to the malignancy (3.3%) and septic shock (2.4%) incidences in the PICU reported in other studies.[9] The consanguinity rate was 8.51% in non-IEM

Table 3. Patients' diagnosis and demographic characteristics (n=23)

	Patient	Gender	Age at admission (month)	Consang. (Yes/No)	Diagnosis	Intervention	Outcome
Intoxication type (n=5)	P1	M	9	Yes	MSUD	Metabolic decompensation, CVVHDF	Alive
	P2	F	69	Yes	GA-1	Acute encephalopathyc crisis	Alive
	P3	F	20	Yes	Hereditary Fructose Intolerance	Metabolic acidosis	Alive
	P4	M	48	No	NAGS	Metabolic decompensation	Alive
	P5	F	47	Yes	MMA	Metabolic decompensation, IMV	Decesead
Disturbed energy metabolism-type (n=10)	P6	F	33	Yes	Dopamine transporter deficiency	IMV	Alive
	P7	F	7	Yes	Mitochondrial DNA depletion syndrome	Severe lactic acidosis, IMV	Decesead
	P8	M	203	Yes	MNGIE	Sepsis, CVVHDF, IMV	Decesead
	P9	M	2	Yes	MCAD	Metabolic decompensation, CVVHDF, IMV	Decesead
	P10	F	8	No	Mitochondrial DNA depletion syndrome	Severe lactic acidodis	Alive
	P11	F	5	Yes	Congenital lactic acidosis	Severe lactic acidodis, CVVHDF, IMV	Decesead
	P12	F	86	Yes	Pyruvate carboxylase deficiency	Metabolic decompensation	Alive
	P13	M	52	Yes	GSD III	Acute liver failure	Alive
	P14	F	84	Yes	Ketolysis defect	Metabolic decompensation	Alive
	P15	M	130	Yes	GSD IX	Rhabdomyolisis	Alive
Complex molecule-type (n=8)	P23	F	156	No	MPS type I	IMV	Alive
	P16	M	19	No	MPS type II	IMV	Alive
	P22	F	36	Yes	MPS type III	IMV	Alive
	P17	M	175	Yes	MPS type IV	IMV	Alive
	P18	M	9	Yes	Mucolipidosis (I-cell)	CVVHDF, IMV	Decesead
	P21	M	67	No	Gaucher's disease I	IMV	Alive
	P19	F	60	No	Tay-Sachs Disease	IMV	Alive
	P20	M	132	Yes	CDG	Sepsis, CVVHDF, IMV	Decesead

M: Male, F: Female, Consang.: Consanguinity, MSUD: Maple Syrup Urine Disease, GA-1: Glutaric aciduria type 1, NAGS: N-Asetil glutamate Sentetase Deficiency, MMA: Methyl malonic acidemia, MNGIE: Mitochondrial Neruogastrointestinal encephalomyopathy, MCAD: Middle chain Acetil CoA Dehydrogenase deficiency, GSD: Glycogene Storage disease, MPS: Mucopolisacaridosis, CVVHDF: Continuous Venovenous Hemodiafiltration, IMV: Invasive mechanical ventilation.

patients and 73.91% in IEM patients hospitalized in the PICU. There was a history of sibling death in %1.81 of non-IEM patients and 17.39% of IEM patients. Therefore, clinicians should be careful about IEM if patients have a history of consanguineous marriage or sibling death. IEM patients are mostly diagnosed before 1 year of age, except for those with lysosomal storage disease. Dionisi-Vici et al. reported in a large-scale study that 59% of IEM patients were diagnosed before the age of three years.[10] Considering all patient populations admitted to the PICU, Edae et al. reported a mean age of 48.13 ± 53.65 months.[11]

Lipari et al. reported that the median age at admission to PICU for IEM patients was 36 months.[7] In our study group, the median and mean age of the IEM patients at first admission to the PICU was 48 months and 63.35 months, respectively. The median and mean age of the non-IEM patients was 26 months and 22.3±64.1 months (min:1-max:204), respectively. The lack of standardization between studies, the differences in the number of patients, the types of IEM, and the differences in the socio-economic levels of the countries may cause variations.

In a study conducted in a tertiary PICU in Portugal, intoxication-type metabolic diseases were the most common IEM.[7] The metabolic disease type most frequently observed in the NICUs is usually the intoxication type IEM. Amino acidopathies and organic acidurias were the most frequently diagnosed IEM in the population on PICU admission[12], however, energy metabolism disorders were observed more frequently in our study. Intoxication type and disturbances in energy metabolism disorders were diagnosed earlier than the other types of IEM.[10] These differences between studies may be because our study was conducted in a single center within a limited time frame, and/or the lack of newborn screening in Türkiye.

Most IEM patients admit to the PICU with metabolic acidosis, encephalopathy with or without seizures, hepatic presentation, and cardiac presentation.[13] The studies reported that the most common admission etiology of IEM was metabolic decompensation due to infections in 70.4% and elective procedure in 29.5%. The most common clinical presentation was respiratory failure in 34.1%.[6,14] Consistent with the literature, the most common clinical presentation was metabolic decompensation and respiratory failure. These were followed by infections and congestive heart failure. In our study group, 30% of the patients were not diagnosed with IEM prior to admission to our PICU. In these clinical conditions, such as metabolic acidosis, respiratory failure, multisystem involvement, and encephalopathy, simple laboratory tests (ammonia, lactate), neuroimaging and first-line metabolic workup (Tandem MS/MS, urine organic acid analyses) tests should be studied in PICU patients. Patients diagnosed in the PICU highlight the lack of awareness among pediatricians and the non-specific presentation of IEM.

Treatment of IEM generally includes the removal of toxic metabolites, elimination of energy deficit, specific nutrition management, and supportive treatment in the intensive care unit. In a multicenter study, the need for mechanical ventilation in patients admitted to the PICU was 35%.[15] In our study group, the need for mechanical ventilation in all patients was 14.35% and 56.52% in IEM patients. The need for mechanical ventilation was significantly higher in IEM patients. We thought this was due to multisystem involvement and poor condition. Sivaraman et al. reported the mortality rate as 83.3% in patients who needed mechanical ventilation. Accordingly, mechanical ventilation treatment was found to be associated with mortality.[16] In our study group, the mortality rate was 53.86% in patients who needed invasive mechanical ventilation and 83.33% in those who needed invasive mechanical ventilation (p=0.007). The need for extracorporeal therapy need was 26.08%. The mortality rate was %83.33 in patients who needed extracorporeal therapy in our study group. Mortality rates due to metabolic disease in the PICU vary. In developed countries, the IEM-related mortality rate in the PICU was reported as 36% by Kamate et al.[6] and 28.6% by Jouvet et al.[17] In our study, the mortality rate was 30.4% in IEM patients and 6.6 % in non-IEM patients. A retrospective study in Italy reported an IEM-related mortality rate of 25.2%, with specific mortality rates up to 48.7% for primary lactic academia.[10] Consistent with the literature, when we compared disease groups in our study, the highest mortality was found for the energy metabolism disorder at 40%. Kamate et al. attributed the high mortality to less use of extracorporeal therapy, but the use of extracorporeal therapy was higher in our study group compared to other studies.[6] Despite this, our mortality rate was high. The reason for the increased use of extracorporeal therapy may be due to the presence of intoxication type and energy metabolism disorder (going with severe lactic acidosis) in a significant proportion of these patients. Lipari et al. reported that the median LOS in PICU was 1-2 days among metabolic disease groups, whereas complex molecule type had the longest LOS with 35 days.[7] In our study, the longest LOS was seen in the complex molecule type and the median LOS in the PICU was 15 days, and it was not statistically significant according to groups. The median LOS in the PICU was longer for patients who died, but this was not statistically significant.

Optimal outcomes in IEM depend on early recognition of symptoms and signs, rapid evaluation, and aggressive treatment. Variabilities can be moderated by early diagnosis and treatment via newborn screening in the country. Inadequacy of newborn screening tests, acute metabolic decompensation due to diagnostic delay, progressive course, delayed diagnosis, and delayed treatment have an impact on the high mortality. When the mean lactate levels of non-IEM-related deceased patients were compared with the IEM-related deceased patients, the median lactate was significantly higher in the IEM group. It may be due to the fact that it constitutes the majority of patients with

energy metabolism disorder including congenital lactic acidosis and intoxication type IEM. We thought that the reason might be due to the poor prognosis of IEM type (energy metabolism disorders) and late diagnosis (due to lack of newborn screening). Rapid and aggressive PICU management, including mechanical ventilation and extracorporeal therapy, is effective in reducing mortality.

This study has some limitations. This study was retrospective, conducted in a single center with small sample size and difficulties in accessing some laboratory tests.

CONCLUSION

These patients are challenging for pediatric intensive care professionals at the diagnostic and therapeutic levels. Undiagnosed patients at the time of admission to the PICU require a high degree of suspicion for prompt diagnosis and treatment. Metabolic decompensation and deterioration due to organ dysfunction are more common in children with a pre-existing IEM. A multicenter approach will be necessary to obtain comprehensive information It is thought that neonatal screening programmes should be expanded, particularly for intoxication-type IEM, considering the timing of symptom onset and presentation. Aggressive and supportive treatment and specific metabolic disease treatment can be lifesaving, but these patients still have a high mortality rate.

Ethical approval

This study has been approved by the İzmir Bakırçay University Non-invasive Clinical Research Ethics Committee (approval date 30/11/2022, number 792). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: GE; Concept: GE, AEB; Design: GE, AEB; Data Collection or Processing: GE, AEB; Analysis or Interpretation: GE; Literature Search: GE, AEB; Writing: GE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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