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Retrospective assessment of hepatic involvement in patients with inherited metabolic disorders: nine-year single-center experience

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Abstract

Objectives: This study aimed to identify clinical, laboratory, and radiological features that could serve as red flags for diagnosing inherited metabolic disorders (IMDs) with hepatic involvement in childhood.
Methods: We retrospectively reviewed the medical records of 1,237 children from a pediatric metabolism department, with suspected or diagnosed IMDs. Patients with hepatic involvement were divided into two groups: Group 1 (diagnosed with IMDs) and Group 2 (undiagnosed). Demographic, clinical, laboratory, and radiological data were compared between the groups.
Results: Hepatic involvement was observed in 415 patients (33.5 %), with 206 (49.2 %) diagnosed with IMDs. Group 1 had higher rates of consanguineous marriage and affected siblings. Complex molecule disorders (20.4 %), mitochondrial (16.0 %), and lipid metabolism disorders (16.0 %) were the most common IMDs. Dysmorphic findings were more frequent in Group 1 (28.2 vs. 16.3 %, p=0.004), while diarrhea was less common (4.4 vs. 12.0 %, p=0.005). Ammonia and lactate levels were higher in Group 1 (p<0.001 and p=0.032, respectively). Hepatomegaly was more frequent in Group 1 (53.3 vs. 22.6 %, p<0.001). Pathological abdominal ultrasonography was the only significant multivariate predictor (OR: 89.377, p=0.026). Overall survival was 87.7 %, with no difference between groups.
Conclusions: Consanguineous marriage, affected siblings, dysmorphic findings, absence of diarrhea, and pathological abdominal USG are key predictors of IMDs in hepatic involvement cases.

Keywords: inherited metabolic disorders; hepatomegaly; cirrhosis; acute hepatic insufficiency

Introduction

Inherited metabolic diseases (IMDs) are single gene disorders caused by enzymatic defects in metabolic pathways in which cumulative incidence is estimated as high as 1/800 [1]. IMDs include a heterogeneous group of conditions that can affect multiple organs, including the liver. Metabolic liver diseases have been categorized the signs and symptoms as hepatomegaly; hepatocellular disease with either elevation of transaminases or frank acute liver failure; cholestasis; steatosis; fibrosis or cirrhosis; and liver tumors. Previous studies have found that among the approximately 1,000 IMD documented to date are more than 140 distinct types (such as lysosomal storage disorders, glycogen storage disorders, and mitochondrial storage disorders) that can potentially affect the liver [2]. Approximately one-third of cases presenting with hepatomegaly, acute hepatic insufficiency, cirrhosis, or cholestasis during childhood can be attributed to IMDs [3]. Studies have reported that IMDs are accountable for two-thirds of cases involving acute hepatic insufficiency in children below the age of two and around 10–15 % of cases in children below the age of 18. The mortality rate in these cases has been reported in the range of 22–65 % [2]. Another report suggests IMDs contribute to approximately 8–13 % of all liver transplant cases in childhood [2, 4].

Considering the high birth rate (1,079,842 in 2021) and the frequency of consanguineous marriages (23.4 %) in Turkey, we speculated that the prevalence of inherited metabolic disorders in patients presenting with liver involvement would be higher than in other countries [5].

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In this study, we aimed to identify some clinical, laboratory, and radiological features that could serve as red flags for diagnosing IMDs in cases with hepatic involvement in childhood.

Main points

- Hepatic involvement was present in 33.5 % of patients with suspected or diagnosed inherited metabolic disorders (IMDs).
- Consanguineous marriage and a family history of IMDs were significant predictors of IMD diagnosis.
- Dysmorphic features, elevated ammonia and lactate levels, and hepatomegaly were more frequent in patients with IMDs.
- Pathological findings on abdominal ultrasonography were the strongest predictor of an IMD diagnosis.
- There was no difference in overall survival between patients with and without a confirmed IMD diagnosis.

Materials and methods

Patient cohort and data extraction

The present study involved a retrospective review of the demographic, clinical, laboratory and radiological data of a total of 1,237 cases who were followed up due to a confirmed diagnosis or suspicion of IMD in the Pediatric Metabolism Department at Ankara University Faculty of Medicine between 2012 and 2021. Four hundred 15 patients with hepatic involvement were divided into two groups – Group 1, those diagnosed with IMDs, – and Group 2, those diagnosed with IMDs excluded. Group 1 was further divided into carbohydrate metabolism disorder, organic acidemia, fatty acid oxidation disorder, mitochondrial disorder, lipid metabolism disorder, inherited metabolic disorders of complex molecules, urea cycle disorder and aminoacidopathies subgroups. The demographic, clinical, laboratory and radiological findings of the subgroups were compared.

Diagnostic criteria for liver involvement and standardization of imaging and laboratory assessments

Liver involvement was defined using a combination of biochemical, imaging, and histopathological criteria to ensure a standardized diagnostic approach. These criteria were applied as follows:

- Biochemical markers

Liver function tests were analyzed to identify hepatocellular injury and cholestatic patterns. The thresholds used were:

- ALT and AST: Elevated levels≥1.5 times the upper limit of normal.
- Bilirubin: Total bilirubin>1.2 mg/dL or direct bilirubin>0.3 mg/dL.
- Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT): Levels≥2 times the upper limit of normal, indicating cholestasis.
- Synthetic function markers: Serum albumin<3.5 g/dL and/or international normalized ratio (INR) >1.2 were considered indicative of compromised liver function.
- Imaging findings.

Examinations were conducted by two radiologists specialized in hepatic involvement. Imaging modalities were performed to detect structural and morphological changes in the liver.

Criteria included:

- Hepatomegaly: Defined as liver dimensions exceeding normal limits on ultrasound or cross-sectional imaging.
- Steatosis: Diagnosed using ultrasound or quantified by controlled attenuation parameter (CAP) on transient elastography, with a CAP score>250 dB/m indicating significant steatosis.
- Fibrosis: Measured by liver stiffness on transient elastography, with≥7 kPa suggesting significant fibrosis.
- Nodularity: Identified on contrast-enhanced CT or MRI as regenerative or dysplastic nodules.
- Histopathological evaluation.

If liver biopsy was performed on patients, the biopsy specimens were analyzed as follows:

- Hepatocellular injury: Presence of ballooning, necrosis, or inflammation.
- Steatosis: Graded as mild (5–33 %), moderate (34–66 %), or severe (>66 %).
- Fibrosis: Staged using the METAVIR scoring system (F0–F4).

Patient inclusion criteria

For patients referred to the pediatric metabolism department with suspected inherited metabolic disorders and followed up, including those diagnosed with inherited metabolic disorders (Group 1) or excluded (Group 2):

a) Patients with liver involvement at the time of referral.
b) Patients who developed liver involvement during follow-up, were included.

Exclusion criteria

In this study, all patients were assessed for liver involvement in relation to the following conditions, which were subsequently excluded from the study: viral hepatitis, autoimmune hepatitis, toxic hepatitis, obesity-related fatty liver disease, and Wilson's disease. In the neonatal period, the conditions excluded were biliary atresia, Alagille syndrome, choledochal cyst, total parenteral nutrition (TPN)-associated cholestasis, genetically progressive familial intrahepatic cholestasis, and TORCH group infections.

Approval for the study was granted by the Ankara University Faculty of Medicine Ethics Committee (Decision date: 17.09.2021, decision no: İ7-532-21).

Statistical analysis

The study data were analyzed using IBM SPSS Statistics (Version 26.0. Armonk, NY: IBM Corp.). Descriptive statistics included mean, standard deviation (SD) and median (minimum-maximum) values for continuous variables, and numbers (percentage) for categorical variables. A Shapiro–Wilk test was used to test for the normal distribution of continuous variables, an independent samples t-test was used to compare normally distributed variables between the two groups, a Mann-Whitney U test was used to compare variables without normal distribution, a one-way analysis of variance (ANOVA) was used to compare normally distributed numeric variables between three or more groups, and a Kruskal–Wallis test was used to compare variables without normal distribution. A Chi-square test or Fisher's exact test was used for the comparison of nominal variables (contingency tables). Any parameters that demonstrated a significant difference in these tests were subjected to further evaluation with a logistic regression analysis. The odds ratio (OR) was calculated within a 95 % confidence interval (CI) in a logistic regression analysis. The level of statistical significance was set at $p<0.05$.

Results

Sociodemographic findings

Of the 1,237 patients enrolled in the study, hepatic involvement was determined in 415 (33.5 %), of which 206 (49.2 %) were under follow-up with a diagnosis of IMD (Tables 1 and 2). 204 (49.2 %) patients were female and 211 (50.8 %) were male. There was no difference in sex distribution between Group 1 and Group 2 (Table 3). The mean age of all patients was 26.5 ± 37.7 months and there was no difference in age between groups. Two-hundred-thirty-four (56.4 %) patients had a history of consanguineous marriage. The consanguineous marriage rate of Group 1 was higher than Group 2. (66.5 % vs. 46.4 $p<0.001$). The rate of sibling history with IMD diagnosis in Group 1 was higher than in Group 2 (15.0 vs. 4.3 %, $p<0.001$). A history of a deceased sibling was also detected more in Group 1 than in Group 2 (27.2 %, 18.7 %, $p=0.039$) (Table 1) (Table 3). In multivariate regression analysis, the presence of consanguineous marriage in parents (OR: 2.117, 95 %CI: 1.399–3.203) and the presence of a sibling with a diagnosis of IMDs (OR: 3.200, 95 %CI: 1.428–7.172) stood out as the essential sociodemographic characteristics for Group 1 (Table 4).

Table 1: Demographic and clinical characteristics of the patients with hepatic involvement.

Parameters	Study group (n=415)
IMD diagnosis present/absent, n (%)	206 (49.6)/209 (50.4)
Gender F/M, n (%)	204 (49.2)/211 (50.8)
Age, months	
Mean ± SD (min-max)	26.5 ± 37.7 (0.0–179.0)
Median [25th-75th percentile]	9.0 [2.0–36.0]
Body weight SDS	
Mean ± SD (min-max)	−0.1 ± 1.82 (−8.0 – +4.6)
Median [25th-75th percentile]	0.3 [−1.28 ± 1.2]
Height SDS	
Mean ± SD (min-max)	0.15 ± 1.78 (−7.0 – +4.0)
Median [25th-75th percentile]	0.6 [-0.95 – +1.41]
Consanguineous marriage in parents, n (%)	234 (56.4)
Presence of a sibling with a diagnosis of IMD, n (%)	40 (9.6)
Deceased sibling, n (%)	95 (22.9)
Family history of a similar disorder, n (%)	113 (27.2)
Jaundice, n (%)	53 (12.8)
Vomiting, n (%)	90 (21.7)
Diarrhea, n (%)	34 (8.2)
Acholic feces, n (%)	4 (1.0)
Dysmorphic findings, n (%)	92 (22.2)
Hypotonicity, n (%)	100 (24.1)
Hepatomegaly on physical examination, n (%)	164 (39.5)
Splenomegaly on physical examination, n (%)	68 (16.4)
Icterus, n (%)	19 (4.6)
Hepatic insufficiency, n (%)	62 (14.9)
Abnormal neurological examination finding, n (%)	117 (28.2)
Neonatal cholestasis, n (%)	71 (17.1)
Liver biopsy, n (%)	37 (8.9)
Chronic liver disease, n (%)	59 (14.2)
Other system involvement, n (%)	267 (64.3)
Liver transplant, n (%)	8 (1.9)
Survival, n (%)	364 (87.7)

Table 2: Distribution of diagnoses of inherited metabolic disorders.

Diagnosis of IMD, n (%)	Study group (n=206)
Inherited metabolic disorders of complex molecules	**42 (20.4)**
Niemann-pick type A/B	11 (26.2)
Mucopolysaccharidosis	9 (21.4)
Gaucher's disease	7 (16.6)
Niemann-pick type C	6 (14.3)
GM1 gangliosidosis	4 (9.5)
Zellweger syndrome	3 (7.1)
Congenital disorder of glycosylation type1a (PMM2-CDG)	1 (2.3)
Congenital disorder of glycosylation type1b (MPI-CDG)	1 (2.3)
Mitochondrial disorders	**33 (16.0)**
Mitochondrial DNA depletion syndrome	8 (24.3)
Deoxyguanosine kinase deficiency	6 (18.12)
Coenzyme Q10 deficiency	5 (15.15)
Leigh syndrome	5 (15.15)
Combined oxidative phosphorylation deficiency	3 (9.0)
Respiratory chain complex I deficiency	2 (6.0)
Mitochondrial complex 3 deficiency	1 (3.0)
Coenzyme Q6 gene defect	1 (3.0)
Coenzyme Q2 gene defect	1 (3.0)
Lipid metabolism disorders	**33 (16.0)**
Familial hypercholesterolemia	24 (72.7)
Hypertriglyceridemia	5 (15.15)
Hypolipoproteinemia	4 (12.12)
Organic acidemias	**31 (15.0)**
Maple syrup urine disease	12 (38.7)
Methylmalonic acidemia	10 (30.3)
Propionic acidemia	3 (9.0)
Isovaleric acidemia	2 (6.0)
Cobalamin synthase defect	4 (12.0)
Carbohydrate metabolism disorders	**23 (11.2)**
Galactosemia	9 (39.0)
Glycogen storage disease type 1	8 (34.8)
Fructose intolerance	2 (8.7)
Fructose-1,6-bisphosphatase deficiency	1 (4.3)
Glycogen storage disease type 3	1 (4.3)
Glycogen storage disease type 0	1 (4.3)
Glycogen storage disease type 4	1 (4.3)
Urea cycle defect	**20 (9.7)**
Citrullinemia type 1	11 (55.0)
OTC deficiency	3 (15.0)
Carbamoyl phosphate synthetase 1 deficiency	3 (15.0)
NAGS deficiency/CPS deficiency	2 (10.0)
Argininosuccinic aciduria	1 (5.0)
Aminoacidopathies	**16 (7.8)**
Tyrosinemia type 1	13 (81.2)
Transient tyrosinemia of the newborn	2 (12.5)
Tyrosinemia type 3	1 (6.2)
Fatty acid oxidation disorders	**8 (3,9)**
Fatty acid oxidation disorder	4 (50)
Primary carnitine deficiency	2 (25)
Very long chain fatty acid oxidation disorder	1 (12.5)
Medium-chain acyl-CoA dehydrogenase deficiency	1 (12.5)

CPS, carbamoyl phosphate synthetase; NAGS, N-acetylglutamate synthase; OTC, ornithine transcarbamylase.

Diagnoses in IMDs

When we divided Group 1 according to main titles of disorders, it was seen that the most common group was inherited metabolic disorders of complex molecules (20.4 %). Mitochondrial disorders (16.0 %) and lipid metabolism disorders (16.0 %) were in second place. These diagnoses were followed by organic acidemias (15.0 %), carbohydrate metabolism disorders (11.2 %), urea cycle defect (9.7 %), aminoacidopathies (7.8 %), and fatty acid oxidation disorders (3.9 %) (Table 2).

Clinical findings

When the clinical findings were examined, no difference was detected between Group 1 and Group 2 in terms of jaundice, vomiting, acholic feces, hypotonicity, hepatosplenomegaly, icterus, acute hepatic insufficiency, and abnormal neurological examination findings. However, dysmorphic findings were detected more in Group 1 than in Group 2 (28.2 vs. 16.3 %, p=0.004). Diarrhea was occured less in Group 1 than in Group 2 (4.4 vs. 12.0 %, p=0.005) (Table 3). Multivariate regression analysis showed that the presence of dysmorphic findings (OR: 1.885 95 % CI: 1.146–3.103) and the absence of diarrhea (OR: 0.298 95 % CI: 0.130–0.680) were more likely to indicate Group 1.

Laboratory tests

When laboratory tests were examined, it occurred that there was no significant difference between Group 1 and Group 2 in terms of blood glucose, creatinine, BUN, albumin, bilirubin, transaminases, coagulation parameters, creatine kinase, lipid parameters, blood gas parameters, alpha-fetoprotein, and ferritin levels (Table 5). However, ammonia level and serum lactate level were higher in Group 1 than in Group 2 (240 ± 422 vs. 51.2 ± 39, $p<0.001$ and 34 ± 76 vs. 17.3 ± 10.8, $p=0.032$, respectively). In multivariate analysis, no significant results were obtained regarding hyperammonemia and high serum lactate (Table 6). In addition, the rate of pathological findings in blood carnitine/acylcarnitine analysis and pathological findings in urinary organic acid analysis was higher in Group 1 than in Group 2 (79.4 vs. 60.7 %, $p<0.001$ and 42.5 vs. 5.4 % $p<0.001$, respectively) (Table 5). (Urinary reducing substances positivity rate was higher in Group 1 than in Group 2 (66.7 vs. 41.0 % $p=0.017$).

Table 3: Demographic and clinical characteristics of patients in groups 1 and 2.

Parameters	Group 1 (n=206)	Group 2 (n=209)	p-Value
Sex F/M, n (%)	106 (51.5)/100 (48.5)	98 (46.9)/111 (53.1)	0.352
Age, months			
Mean ± SD (min-max)	27.4 ± 39.1 (0–179)	25.9 ± 36.4 (1–172)	0.856
Median [25th-75th percentile]	9.5 [1.75–35.2]	9 [2–37]	
Body weight SDS,			
Mean ± SD (min-max)	1.70 ± 1.70 (−8.0 – 1.0)	1.94 ± 1.94 (-8–4.6)	0.902
Median [25th-75th percentile]	0.30 [-1 – 1]	0.30 [-1.5–1.25]	
Height SDS			
Mean ± SD (min-max)	1.63 ± 1.63 (-7–3.20)	0.05 ± 1.91 (-6–4)	0.712
Median [25th-75th percentile]	0.60 [-0.6–1.4]	0.70 [-1.13–1.4]	
Consanguineous marriage in parents, n (%)	137 (66.5)	97 (46.4)	<0.001
Sibling with a diagnosis of IMD, n (%)	31 (15.0)	9 (4.3)	<0.001
Deceased sibling, n (%)	56 (27.2)	39 (18.7)	0.039
Family history of a similar disorder, n (%)	72 (35.0)	41 (19.6)	<0.001
Jaundice, n (%)	21 (10.2)	32 (15.3)	0.118
Vomiting, n (%)	49 (23.8)	41 (19.6)	0.303
Diarrhea, n (%)	9 (4.4)	25 (12.0)	0.005
Acholic feces, n (%)	1 (5.0)	3 (1.4)	0.623[a]
Dysmorphic findings, n (%)	58 (28.2)	34 (16.3)	0.004
Hypotonicity, n (%)	49 (23.8)	51 (24.4)	0.883
Hepatomegaly on physical examination, n (%)	88 (42.7)	76 (36.4)	0.186
Splenomegaly on physical examination, n (%)	39 (18.9)	29 (13.9)	0.164
Icterus, n (%)	8 (3.9)	11 (5.3)	0.501
Acute hepatic insufficiency, n (%)	30 (14.6)	32 (15.3)	0.831
Abnormal neurological examination finding, n (%)	53 (25.7)	64 (30.6)	0.268
Neonatal cholestasis, n (%)	33 (16.0)	38 (18.2)	0.559
Liver biopsy, n (%)	17 (8.3)	20 (9.6)	0.638
Chronic liver disease, n (%)	30 (14.6)	29 (13.9)	0.841
Other system involvement[b], n (%)	125 (60.7)	142 (67.9)	0.122
Liver transplant, n (%)	6 (2.9)	2 (1.0)	0.147
Survival, n (%)	176 (85.4)	188 (90)	0.161

IMD, inherited metabolic disorder; M, male; F, female; max, maximum; min, minimum; SD, standard deviation; SDS, standard deviation score,[a] Fisher's exact test. [b]Other system involvement (endocrinopathies, cardiopulmonary system involvement, eye involvement, hearing, presence of extrahepatic gastrointestinal tract involvement, etc.).

Radiological tests

In ultrasonography evaluation, no difference was found between Group 1 and Group 2 regarding splenomegaly, hepatosteatosis, hepatic nodule, and cirrhosis. Hepatomegaly was detected more frequently in Group 1 than in Group 2 (53.3 vs. 22.6 % p<0.001). The presence of at least one pathological finding (hepatomegaly, hepatic nodules, hepatosteatosis, cirrhosis, and splenomegaly) on abdominal ultrasonography was also higher in Group 1 than in Group 2 (62.5 vs. 25.6 %, p<0.001). At least one pathological finding on abdominal USG was the only significant laboratory parameter in multivariate analysis (OR: 89.377, 95 %CI:1.722–4,639.048, p=0.026) (Table 6).

Among the patients in Group 1, hepatomegaly was most commonly observed in those with carbohydrate metabolism disorders (82.5 %) and aminoacidopathy (68.8 %), and splenomegaly was also more common among those with carbohydrate metabolism disorders (30.4 %) and disorders of complex molecules (47.6 %). Patients diagnosed with inherited metabolic disorders of complex molecules (86.1 %) and aminoacidopathy (78.6 %) exhibited a greater prevalence of pathological findings on ultrasound, including hepatomegaly, splenomegaly, hepatic nodules, hepatosteatosis and cirrhosis than the other diagnostic groups in the study. Hepatic nodules were most commonly observed (42.9 %) in patients with aminoacidopathies.

Prediction of IMDs and survial

In multivariate regression model, one pathological finding on abdominal ultrasonography (OR: 89.377, 95 %CI:1.722–4,639.048, p=0.026) were found to be the most significant

Table 4: Logistic regression analysis of demographic and clinical characteristics in predicting inherited metabolic disorders.

Parameters	Univariate regression model		Multivariate regression model	
	Or (95 % CI)	p-Value	Or (95 % CI)	p-Value
Sex	0.833 (0.567–1.224)	0.352		
Age, months	1.001 (0.996–1.006)	0.675		
Body weight SDS	1.037 (0.932–1.154)	0.504		
Height SDS	1.067 (0.954–1.193)	0.258		
Consanguineous marriage in parents	2.293 (1.541–3.410)	<0.001	2.117 (1.399–3.203)	<0.001
Presence of a sibling with a diagnosis of inherited metabolic disorder	3.937 (1.824–8.496)	<0.001	3.200 (1.428–7.172)	0.005
History of a deceased sibling	1.627 (1.023–2.588)	0.040		
Family history of a similar disorder	2.202 (1.410–3.438)	0.001		
Jaundice	0.628 (0.349–1.130)	0.121		
Vomiting	1.279 (0.801–2.043)	0.303		
Diarrhea	0.336 (0.153–0.739)	0.007	0.298 (0.130–0.680)	0.004
Acholic feces	0.335 (0.35–3.247)	0.345		
Dysmorphic findings	2.017 (1.252–3.249)	0.004	1.885 (1.146–3.103)	0.013
Hypotonicity	0.967 (0.617–1.516)	0.883		
Hepatomegaly on physical examination	1.305 (0.880–1.963)	0.186		
Splenomegaly on physical examination	1.450 (0.858–2.450)	0.166		
Icterus	0.727 (0.286–1.847)	0.503		
Hepatic insufficiency	0.943 (0.549–1.618)	0.831		
Abnormal neurological examination finding	0.785 (0.511–1.205)	0.268		
Neonatal cholestasis	0.858 (0.514–1.432)	0.559		
Liver biopsy	0.850 (0.432–1.673)	0.638		
Chronic liver disease	1.058 (0.610–1.836)	0.841		
Other system involvement[a]	0.728 (0.487–1.090)	0.123		
Liver transplant	3.105 (0.619–15.566)	0.168		
Survival	0.655 (0.362–1.187)	0.163		

CI, confidence interval; OR, odds ratio; SDS, standard deviation score. [a]Other system involvement (endocrinopathies, cardiopulmonary system involvement, eye involvement, hearing, presence of extrahepatic gastrointestinal tract involvement, etc.).

parameters to predict an IMD. The overall survival was 87.7 %, and there was no difference between Group 1 and Group 2 (85.4 vs. 90.0 % p=0.161). The survival was the shortest in the patients with mitochondrial disorders (14.2 %).

Discussion

A significant proportion of inherited metabolic disorders are accompanied by hepatic involvement. The findings of the present study emphasize the significance of a positive family history, physical examination findings, as well as radiological findings in predicting the diagnosis of IMDs. Although blood laboratory tests such as hyperammonemia and hyperlactatemia were detected more frequently in the IMDs group, laboratory parameters were insignificant in predicting IMDs.

Due to the autosomal recessive inheritance nature of IMDs, consanguineous marriage in parents and the presence of a sibling with a diagnosis of IMD increase the likelihood of a diagnosis of IMD [6, 7]. In a study examining patients with a diagnosis of IMD and hepatic involvement, 57.8 % were children of a consanguineous marriage, 24.5 % had a sibling diagnosed with IMD and 21 % had lost a sibling to the disease [8]. In another study involving patients who were initially followed up for hepatic insufficiency and later diagnosed with IMD, approximately 50 % had a positive family history of IMDs, and the study also reported a sensitivity of 75 % and a specificity of 66.7 % for a positive family history as a predictive factor for IMD [9]. The findings of the present study concur with existing literature, underscoring the significance of garnering a comprehensive family history, particularly in populations where consanguineous marriages are prevalent. In addition, in our study, the presence of a sibling diagnosed with IMD, and the history of the sibling's death were determined as essential parameters in the prediction of IMDs.

Inherited metabolic disorders can manifest with various clinical symptoms. Dysmorphism can also be detected in most IMDs. Although there are many inherited metabolic diseases in which dysmorphism and liver disease occur together, the main ones include peroxisomal diseases, lysosomal diseases,

Table 5: Comparison of laboratory parameters and the results of radiological imaging studies between groups.

Parameters	Group 1 (n=206)	Group 2 (n=209)	p-Value
Blood glucose, mg/dL			
Mean ± SD (min-max)	82 ± 22 (24–166)	89 ± 25 (47–196)	0.160
Median [25th–75th percentile]	83 [67–96]	86 [75–98]	
Creatinine, mg/dL			
Mean ± SD (min-max)	0.41 ± 0.40 (0.02–3.3)	0.42 ± 0.46 (0.04–3.77)	0.730
Median [25th–75th percentile]	0.3 [0.18–0.44]	0.27 [0.20–0.42]	
BUN, mg/dL			
Mean ± SD (min-max)	10.5 ± 8.7 (0.40–65)	11.47 ± 12 (1–109)	0.308
Median [25th–75th percentile]	9 [4.1–13]	9 [6–12.4]	
Albumin, g/L			
Mean ± SD (min-max)	3.7 ± 0.65 (2.1–5.2)	3.74 ± 0.7 (2.2–7.2)	0.772
Median [25th–75th percentile]	3.8 [3.2–4.2]	3.8 [3.3–4.2]	
Total protein, g/L			
Mean ± SD (min-max)	5.9 ± 1.1 (3.3–9.2)	5.9 ± 1.1 (3.3–9.1)	0.952
Median [25th–75th percentile]	6 [5.1–6.7]	5.8 [5.1–6.8]	
Total bilirubin, mg/dL			
Mean ± SD (min-max)	3.9 ± 6.1 (0.09–44)	4.9 ± 7.2 (0.09–42.7)	0.205
Median [25th–75th percentile]	0.9 [0.52–5.03]	1.2 [0.52–7.2]	
Direct bilirubin, mg/dL			
Mean ± SD (min-max)	1.3 ± 2.8 (0.02–18.24)	1.76 ± 4 (0.03–25)	0.472
Median [25th–75th percentile]	0.36 [0.16–0.81]	0.37 [0.18–1.05]	
Direct bilirubinemia, n (%)	152 (77.6)	142 (70.6)	0.117
AST, U/L			
Mean ± SD (min-max)	344 ± 855 (13–8,997)	432 ± 1,610 (3–21,410)	0.998
Median [25th–75th percentile]	113 [56.5–284.5]	110 [60–243]	
Elevated AST (>35 U/L), n (%)	189 (92.2)	200 (95.7)	0.135
ALT, U/L			
Mean ± SD (min-max)	322 ± 1,893 (5–26,780)	311 ± 887 (9–9,899)	0.363
Median [25th–75th percentile]	90 [43–202]	92 [40–249]	
Elevated ALT (>35 U/L), n (%)	162 (79)	165 (78.9)	0.985
ALP, U/L			
Mean ± SD (min-max)	421 ± 393 (30–3,629)	417 ± 440 (27–3,052)	0.332
Median [25th-75th percentile]	318 [224–472]	291 [213–425]	
GGT, U/L			
Mean ± SD (min-max)	170.8 ± 217 (5–1,635)	180 ± 376 (9–4,380)	0.574
Median [25th–75th percentile]	92 [23–234]	71 [27–190]	
Elevated GGT (>42 U/L), n (%)	141 (69.5)	139 (67.1)	0.616
INR			0.188
Mean ± SD (min-max)	1.69 ± 1.34 (0.83–10)	1.56 ± 1.02 (0.78–7.77)	
Median [25th–75th percentile]	1.18 [1.06–1.75]	1.17 [1–1.6]	
Elevated INR (>1.1), n (%)	107 (69.5)	100 (63.7)	0.280
CK, ng/mL			
Mean ± SD (min-max)	699.3 ± 3,284 (8.50–33,356)	575.52 ± 1,944 (8.39–19,925)	0.445
Median [25th–75th percentile]	136 [76–227]	130 [76.5–305]	
Ammonia, mmol/L			
Mean ± SD (min-max)	240 ± 422 (8–3,229)	51.2 ± 39 (11–439)	<0.001
Median [25th–75th percentile]	93 [51.75–245]	49 [36.7–61]	
Total cholesterol, mg/dL			
Mean ± SD (min-max)	188 ± 111 (40–1,079)	170 ± 84 (78–664)	0.213
Median [25th–75th percentile]	164 [124–227]	157 [128–198]	
Triglyceride, mg/dL			
Mean ± SD (min-max)	211 ± 797 (33–2,871)	306 ± 354 (14–8,554)	0.147
Median [25th–75th percentile]	150 [81–198]	132 [81–245]	
LDL, mg/dL			
Mean ± SD (min-max)	110 ± 74 (13–580)	98 (12–365) [71–118]	0.707
Median [25th–75th percentile]	88 [64–140]		

Table 5: (continued)

Parameters	Group 1 (n=206)	Group 2 (n=209)	p-Value
HDL, mg/dL			
Mean ± SD (min-max)	50.8 ± 30 (0.7–298)	98 ± 22 (3–142)	0.622
Median [25th–75th percentile]	48 [34–62]	45 [34–56]	
Serum lactate, mmol/L			
Mean ± SD (min-max)	34 ± 76 (0.8–609)	17.3 ± 10.8 (1.20–45)	0.032
Median [25th–75th percentile]	18 [11.9–35.2]	15 [10.3–23]	
pH			
Mean ± SD (min-max)	7.39 ± 0.11 (6.94–7.70)	7.37 ± 0.17 (6–7.62)	0.171
Median [25th–75th percentile]	7.41 [7.37–7.45]	7.40 [7.34–7.44]	
HCO_3, mmol/L			
Mean ± SD (min-max)	20.54 ± 5.4 (1.50–40)	20.75 ± 5.7 (6–37)	0.925
Median [25th–75th percentile]	21 [18–23]	20 [17.8–23.6]	
AFP, ng/mL			
Mean ± SD (min-max)	10,279 ± 23,104 (0.57–113,922)	8,516 ± 21,756 (0.77–98,291)	0.838
Median [25th–75th percentile]	9,0.38 [2.28–2,036]	16.5 [2.57–2,525]	
Methionine, mmol/L			
Mean ± SD (min-max)	24.35 ± 78 (5.37–168)	41 ± 21.9 (1.20–541)	0.302
Median [25th–75th percentile]	17 [14–26.6]	19 [10.9–27.5]	
Tyrosine, mmol/L			
Mean ± SD (min-max)	149 ± 262 (5–1,770)	94.2 ± 125 (21.801–98.291)	0.765
Median [25th–75th percentile]	59.5 [36–124]	60 [43–90.5]	
Phenylalanine, mmol/L			
Mean ± SD (min-max)	66.1 ± 107 (5.4–766)	58.54 ± 46 (24–400)	0.500
Median [25th–75th percentile]	42 [31.5–62]	48 [39–69]	
Alanine, mmol/L			
Mean ± SD (min-max)	354 ± 308 (0–1,337)	330.8 ± 174 (0–966)	0.597
Median [25th–75th percentile]	265 [124.8–505]	289 [213–447]	
A1AT, g/L			
Mean ± SD (min-max)	28.8 ± 140 (0.60–828)	1.54 ± 0.43 (0.79–3.81)	0.185
Median [25th–75th percentile]	1.33 [1.13–1.78]	1.42 [1.29–1.81]	
Ferritin, ng/mL			
Mean ± SD (min-max)	181.5 ± 487 (0.19–4,637)	333 ± 785 (4.50–5,385)	0.888
Median [25th–75th percentile]	36 [20–95.5]	37.5 [14–210]	
Urinary reducing substances positivity, n (%)	22 (66.7	25 (41.0)	0.017
Urinary ketone positivity (%)	27 (16.5)	25 (14.5)	0.609
Hypoglycemia, n (%)	17 (8.3)	11 (5.3)	0.230
Pathological finding in carnitine/acylcarnitine assessment, n (%)	166 (79.4)	125 (60.7)	<0.001
Pathological finding in urinary organic acid analysis, n (%)	54 (42.5)	9 (5.4)	<0.001
Pathological USG finding (HM, SM, hepatic nodule, hepatosteatosis, cirrhosis), n (%)	85 (62.5)	34 (25.6)	<0.001
Hepatomegaly on USG, n (%)	72 (53.3)	30 (22.6)	<0.001
Splenomegaly on USG, n (%)	42 (31.1)	28 (21.1)	0.061
Hepatosteatosis on USG, n (%)	27 (20.0)	16 (12.0)	0.075
Hepatic nodule on USG, n (%)	9 (6.7)	4 (3.0)	0.163
Cirrhosis on USG, n (%)	3 (2.2)	1 (0.8)	0.321

AFP, alpha-fetoprotein; A1AT, alpha 1 anti-antitrypsin; HM, hepatomegaly; LDH, lactate dehydrogenase; SM, splenomegaly; USG, ultrasonography.

mitochondrial diseases, and congenital glycosylation defects [10]. In our study, dysmorphism was more common in the IMDs group and was the most important physical examination finding in the prediction of IMDs. This parameter is so significant because the most common diagnoses in our research population are inherited metabolic disorders of complex molecules and mitochondrial disorders. Diagnoses such as mucopolysaccharidosis, GM1 gangliosidosis, and Zellweger syndrome, which are under the leading diagnostic group of inherited metabolic disorders of complex molecules, have been reported with well-defined dysmorphism in the literature [11, 12].

Gastrointestinal problems are common in IMDs. Loss of appetite and vomiting are widespread in attacks of organic acidemia and urea cycle disorders, which are acute intoxication-type hereditary metabolic diseases. Swallowing difficulties are common in lysosomal diseases and mitochondrial diseases. Gastroesophageal reflux and constipation are severe problems in IMDs accompanied by hypotonicity. However, diarrhea is less common in IMDs than other GI problems [11, 12]. In our study, diarrhea was detected more frequently in the group without a diagnosis of IMDs. In multivariate analysis, the absence of diarrhea was a strong enough result to predict IMDs.

Table 6: Logistic regression analysis of laboratory parameters and the results of radiological imaging studies in predicting inherited metabolic disorders.

Parameters	Univariate regression model		Multivariate regression model	
	Or (95 % CI)	p-Value	Or (95 % CI)	p-Value
Elevated creatinine	0.980 (0.635–1.513)	0.928		
Elevated BUN	0.991 (0.973–1.010)	0.368		
Elevated albumin	0.936 (0.707–1.238)	0.641		
Elevated total protein	0.998 (0.838–1.188)	0.981		
Elevated total bilirubin	0.978 (0.949–1.008)	0.149		
Elevated direct bilirubin	1.435 (0.913–2.257)	0.117		
Elevated AST	0.532 (0.229–1,232)	0.141		
Elevated ALT	1.005 (0.626–1.612)	0.985		
Elevated ALP	1.000 (1.000–1.000)	0.909		
Elevated GGT	1.113 (0.734–1.687)	0.616		
Elevated INR	1.298 (0.809–2.082)	0.280		
Elevated CK	0.873 (0.545–1.398)	0.571		
Elevated ammonia	1.022 (1.013–1.030)	<0.001		
Elevated total cholesterol	1.002 (0.999–1.005)	0.139		
Elevated triglycerides	1.000 (1.000–1.001)	0.263		
Elevated LDL	1.003 (0.999–1.007)	0.127		
Elevated HDL	1.004 (0.995–1.013)	0.396		
Elevated serum lactate	1.030 (1.005–1.056)	0.018		
Elevated pH	3.542 (0.508–24.704)	0.202		
Elevated HCO_3	0.993 (0.949–1.040)	0.770		
Elevated AFP	1.000 (1.000–1.000)	0.655		
Elevated A1AT	1.128 (0.827–1.539)	0.446		
Elevated ferritin	1.000 (0.999–1.000)	0.071		
Pathological USG findings (HM, SM, hepatic nodule, hepatosteatosis, cirrhosis)	4.853 (2.880–8.178)	<0.001	89,377 (1,722–4639,048)	0.026
Hepatomegaly on USG	3.924 (2.312–6.659)	<0.001		
Splenomegaly on USG	1.694 (0.974–2.946)	0.062		
Hepatosteatosis on USG	1.828 (0.934–3.578)	0.078		
Hepatic nodule on USG	2.304 (0.692–7.672)	0.174		
Cirrhosis on USG	3.000 (0.308–29.213)	0.344		
Urinary reducing substances	1.347 (1.143–1.842)	0.019		
Urinary ketone	0.857 (0.474–1.549)	0.609		
Hypoglycemia	1.611 (0.735–3.529)	0.233		
Pathological finding in carnitine/acylcarnitine profile	1.400 (1.258–1.619)	<0.001		
Pathological finding in urinary organic acid analysis	12.904 (6.045–27.546)	<0.001		

AFP, alfa fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase A1AT, alpha 1 antitrypsin; CK, creatine kinase; GGT, gamma glutamyl transferase; HM, hepatomegaly; LDH, lactate dehydrogenase; SM, splenomegaly; USG, ultrasonography.

Laboratory findings can guide clinicians in diagnosing IMDs [5]. Elevated total and conjugated bilirubin levels are common in patients with galactosemia, hereditary fructose intolerance and mitochondrial disorders [5, 12]. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were found to be higher than 100 IU/L in 41 % of patients with urea cycle disorders (14), and there have been previous studies reporting elevated ALT, bilirubin, INR and ammonia levels to be commonly observed in IMDs that result in acute hepatic insufficiency [13, 14]. In the present study, acute hepatic insufficiency was identified in 14.6 % of the patients. No significant difference was observed between Group 1 and Group 2 in terms of hepatic insufficiency. Therefore, the two groups had no significant difference in related blood parameters. Elevated serum lactate can be detected in mitochondrial diseases, glycogen storage diseases, and gluconeogenesis defects [15]. In our study, lactate was found to be higher in Group 1 than in Group 2. This is because mitochondrial diseases are the second largest group in our patient population. Hyperammonemia can be seen in any case of primary liver failure. However, hyperammonemia may be an important finding in IMDs, including urea cycle disorders, organic acidemias, fatty acid oxidation defects, and some mitochondrial diseases [16]. Although hyperammonemia was found to be higher in the group diagnosed with IMDs in our study, no significant results were obtained in the prediction of IMDs. Hyperammonemia can be observed in many other conditions, such as infection affecting the liver, anatomical problems, primary diseases of the liver, and toxicity, and that it is nonspecific. It is unsurprising that the group with more frequent abnormalities in urine reducing substance, carnitine/acylcarnitine profile, and urine organic acids, which are the first tests to indicate IMDs in the presence of pathological results, is Group 1.

Abdominal imaging findings of IMDs are valuable in specificating and suspecting diagnoses. An assessment of the echogenicity of the liver can also guide the diagnostic process. In patients with galactosemia, no increase in liver echogenicity is typically observed, while increased hepatic echogenicity has been reported in patients with glycogen storage disorders and hereditary fructose intolerance [17, 18]. An earlier study reported a change in parenchymal echogenicity in 41 % of the patients followed up for glycogen storage disorder type 1, 25 % of patients with glycogen storage disorder type 3, and 11 % of patients with glycogen storage disorder types 6 and 9 [19]. Hepatomegaly also can be seen in lysosomal diseases, glycogen storage diseases, gluconeogenesis defects, mitochondrial diseases, and congenital glycosylation defects [6, 20]. In our study, the most significant finding on abdominal ultrasonography was hepatomegaly. The fact that the most common diagnosis is inherited metabolic disorders of complex molecules may explain this situation. However, it is surprising that the splenomegaly finding expected in lysosomal storage diseases shows no difference between the two groups. The presence of hepatic nodules and cirrhosis are other findings that can be useful in a differential diagnosis. A study involving 38 patients diagnosed with tyrosinemia type 1 reported that 87 % of the sample were identified with a granular appearance in the liver, half of the patients had multiple hypoechoic nodules, 53 % of patients had hyperechoic nodules and cirrhosis was detected in 34 % of the cases [21]. A review of literature revealed cirrhosis to be the most frequently observed condition in conjunction with aminoacidopathies and carbohydrate metabolism disorders, alongside other IMDs [22]. When all the parameters, which were not significant when looked at individually, were gathered under one roof, the presence of any pathological finding on abdominal ultrasonography was seen more frequently in Group 1 than in Group 2, and this parameter appeared to be the only significant radiological parameter in the prediction of IMDs. Another issue that should be emphasized is that while hepatomegaly is detected in 42.7 % of patients on physical examination, this rate is 53.3 % on ultrasound. In other words, evaluating the organomegaly of a patient being examined for IMDs only through physical examination may cause the finding to be missed in some patients. For this reason, it is essential to perform radiological imaging and interpret it together with other clinical findings.

We present here a comprehensive analysis of the 9-year experience of our tertiary healthcare facility, which is dedicated to the diagnosis, treatment and follow-up of patients with IMDs. The present study revealed significant hepatic involvement in 33 % of the pediatric patients monitored in the Department of Pediatric Metabolism. The present study assessed physical examination findings, laboratory test results, and radiological imaging studies to evaluate hepatic involvement in different subgroups of patients with IMDs, and these comprehensive evaluations presented valuable diagnostic data for the distinction of various diagnostic subgroups. One significant limitation of the this study is related to the inaccessibility of various laboratory parameters due to missing data in the records and the retrospective nature of the study.

The assessment of patients presenting with a suspected IMD for hepatic involvement at the time of the initial presentation and during follow-up can play a crucial role in guiding the diagnostic process. The accurate diagnosis and the subsequent prompt initiation of treatment are vital for the reduction of morbidity and mortality, especially in patients with treatable IMDs who present with acute hepatic insufficiency. In young children presenting with prominent

hepatic involvement, it is important to consider the possibility of a yet-to-be-diagnosed IMD. The present study clarifies the need for further multicenter, prospective and long-term studies.

Research ethics: This study was approved by the Ankara University Faculty of Medicine Ethics Committee (Decision date: 17.09.2021, decision no: İ7-532-21).
Informed consent: Consent form was not obtained because this study was a retrospective study.
Author contributions: Fatma Tuba Eminoglu, Engin Kose, Merve Koc Yekeduz, Samira Bayramova designed the study, collected the data, interpreted results, and wrote the manuscript. Fatma Tuba Eminoglu, Engin Kose, Merve Koc Yekeduz, Samira Bayramova provided statistical analysis and aided in study design. Fatma Tuba Eminoglu, Engin Kose, Merve Koc Yekeduz, Samira Bayramova conceptualized the study, contributed to study design and data interpretation, supervised conduction of the study, and revised the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
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