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Hepatosplenomegaly in children: A gateway to inherited metabolic disorders

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ABSTRACT

Objective: Hepatomegaly and/or splenomegaly (HSM) are common clinical findings with a broad differential diagnosis, including infectious, hematologic, malignant, and inherited metabolic diseases. Although inborn errors of metabolism (IEM) are rare, they constitute critical and often treatable causes of HSM. This study aimed to evaluate pediatric patients presenting with hepatomegaly and/or splenomegaly for underlying metabolic disorders and to identify diagnostic indicators that may facilitate early recognition and appropriate management of IEM.

Materials and Methods: This retrospective study evaluated 223 children presenting with hepatomegaly, splenomegaly, or hepatosplenomegaly between June 2023 and October 2025 at a pediatric metabolic clinic. Only those with genetically confirmed diagnoses of IEM were included in the final cohort. Clinical features and laboratory findings were evaluated.

Results: Twenty-seven patients (15.4%) received a confirmed IEM diagnosis. The most frequent disorders were glycogen storage diseases (n=13, 7.4%), followed by Gaucher disease (n=6, 3.4%), acid sphingomyelinase deficiency (n=3, 1.7%), and single cases of Niemann-Pick type C, Mucopolysaccharidosis type II, GM1 gangliosidosis, hereditary fructose intolerance, and galactosemia. Consanguinity was present in 84.6%, and characteristic systemic findings such as hypoglycemia, hyperlipidemia, cytopenias, cholestasis, neurological involvement, or coarse facies served as critical diagnostic clues.

Conclusion: Inborn errors of metabolism should be considered in children presenting with hepatomegaly and/or splenomegaly, particularly in the presence of accompanying systemic findings, especially in regions with high consanguinity rates. Recognition of diagnostic clues may facilitate earlier referral, reduce diagnostic delays, and enable timely initiation of disease specific treatments, including enzyme replacement therapy or dietary modification.

Keywords: Hepatomegaly, inborn errors of metabolism, splenomegaly

Introduction

Hepatosplenomegaly (HSM), defined as enlargement of the liver and spleen, is a clinical finding frequently encountered in both hospitalized patients and outpatient clinics. Clinically, hepatomegaly is detected by palpation and percussion of the liver edge below the right costal margin, while splenomegaly is identified by palpation of the spleen below the left costal margin. Physical examination findings may vary according to the patient's age, body habitus, and examiner experience. Therefore, ultrasonography is considered the preferred imaging modality for confirming organ enlargement, as it provides objective measurements and allows comparison with age- and height-adjusted normative reference values.

Hepatomegaly and splenomegaly may result from a wide range of etiologies, including infectious, neoplastic, toxic, and inflammatory conditions (1). Hepatosplenomegaly may be a presenting feature of several inborn errors of metabolism (IEM), despite their rarity. These disorders often affect various organ systems and can present across all ages, from the neonatal period to adulthood. The most commonly reported inborn errors of metabolism associated with hepatomegaly and/or splenomegaly include lysosomal storage disorders (such as Gaucher disease, acid sphingomyelinase deficiency (ASMD), Niemann Pick type C (NPC) mucopolysaccharidoses and cholesteryl ester storage disease) and disorders of carbohydrate metabolism, particularly glycogen storage diseases (1). Due to

the varied clinical presentation of these disorders, a thorough clinical evaluation supported by specific laboratory and genetic testing is crucial for an accurate diagnosis.

This study aimed to identify underlying IEM in children with hepatomegaly and/or splenomegaly referred to a tertiary pediatric metabolism clinic. Additionally, the study sought to determine the clinical and laboratory clues that should prompt clinicians to consider metabolic diseases when diagnosing hepatosplenomegaly. By characterising these diagnostic indicators, we hope to facilitate the earlier recognition of IEM and reduce diagnostic delays.

Materials and Methods

This retrospective study initially evaluated children with hepatomegaly, splenomegaly, or hepatosplenomegaly between June 2023 and October 2025. A total of 223 patients referred to the Pediatric Metabolism Clinic at Adana City Training and Research Hospital were initially included. After excluding 48 patients who were lost to follow-up, 175 were included in the final analysis. No predefined age restriction was applied; the age of the included patients ranged from 1 to 15 years. Organomegaly was confirmed by clinical examination and ultrasonography. Liver and spleen size were evaluated interpreted according to published age-and height-adjusted normative reference values for Turkish children (2,3). Among these, only patients who subsequently received a confirmed diagnosis of IEM were included in the final analysis, while those with acute infectious diseases, hematologic malignancies, autoimmune or rheumatologic disorders, or incomplete clinical data were excluded. Detailed clinical history, including additional symptoms, family history, and parental consanguinity, was systematically obtained. All patients underwent standardized laboratory testing, including complete blood count, liver function tests, coagulation profile, lipid panel, and metabolic screening tests (plasma amino acids, acylcarnitine profile, and urine organic acids), performed in accordance with institutional protocols. Targeted tests, including lysosomal enzyme assays, urine carbohydrate chromatography, and other diagnosis-specific metabolic studies, were added when clinically indicated.

Genetic analyses were conducted for all patients with suspected inborn errors of metabolism. Depending on clinical suspicion, next-generation sequencing–based targeted gene panels or whole-exome sequencing were performed, followed by Sanger confirmation when appropriate. Clinical diagnoses were established through integration of clinical, laboratory, radiological, and genetic findings. Missing or incomplete data were excluded from the final analysis.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics (version 23.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean and standard deviation or median, whereas categorical variables were reported as counts and percentages.

Results

A total of 223 patients who were referred to the Pediatric Metabolism Clinic with hepatomegaly, splenomegaly, or hepatosplenomegaly were included in the study After excluding 48 patients lost to follow-up, 175 patients were included in the final analysis. Of these, 27 (15.4%) were diagnosed with an IEM. The most frequent diagnoses were GSD (13 patients, 7.4%; Type I = 4, Type III = 2, Type IXA = 2, Type IXB = 2, Type VI = 3), Gaucher disease (6 patients, 3.4%), ASMD deficiency (3 patients, 1.7%), Niemann-Pick type C disease (1 patient, 0.57%), MPS II (1 patient, 0.57%), GM1 gangliosidosis (1 patient, 0.57%), hereditary fructose intolerance (1 patients, 0.57%), and galactosemia (1 patient, 0.57%).

Among patients with a confirmed IEM, 84.6% had consanguineous parents. Five patients (18.5%) had a positive family history of IEM. All patients displayed additional clinical features relevant to their underlying conditions. In patients with GSD, hepatomegaly was consistently present in patients with GSD. Elevated liver enzyme levels were evident, with mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels of 70.2 ± 26.7 U/L and 79.3±30.1 U/L, respectively. Hypertriglyceridemia was also observed, with mean triglyceride levels of 248.8 ± 155.0 mg/dL. Additionally, hypoglycemia was observed in six patients, all of whom had a diagnosis of GSD type I or III (mean blood glucose: 44.2±4.8 mg/dL) while elevated creatine kinase levels were detected in two patients (1422 and 2300 U/L) diagnosed with GSD type III (Table I). Short stature and growth retardation were also observed in three patients. Of the six patients diagnosed with Gaucher disease, four presented with hepatosplenomegaly, and two with isolated splenomegaly. All patients exhibited thrombocytopenia (mean platelet count: 83.167±32.514/μL) and anemia (mean hemoglobin: 8.2±1.2 g/dL) while serum alanine aminotransferase (16.0±5.5 U/L) and aspartate aminotransferase (55.7±17.9 U/L) levels were within normal limits. Patients diagnosed with ASMD deficiency presented with hepatosplenomegaly accompanied by thrombocytopenia and anemia (The mean platelet count was 136.±19.80/μL, and the mean hemoglobin level was 9.6±0.5 g/dL). Mean ALT and AST levels were 129.3±26.7 U/L and 222.3±46.4 U/L, respectively. All patients diagnosed with ASMD had decreased high-density lipoprotein (26.3±2.3 mg/dL) cholesterol levels. Elevated triglyceride levels were detected in two patients (437 and 396 mg/dL). NPC was identified in one patient and, in addition to hepatosplenomegaly, displayed neurological involvement, including hypotonia, seizures and supranuclear gaze limitation. In patients with GM1 gangliosidosis, coarse facial features, mental retardation, and a cherry-red spot on fundoscopic examination were observed. In those with MPS II (neuropathic phenotype), coarse facial features, developmental delay, dysostosis multiplex on radiologic imaging, and increased urinary glycosaminoglycans (20.3 mg/mmol creatinine) were noted. Another patient, diagnosed with hereditary fructose intolerance, showed isolated hepatomegaly together with hypoglycemia, metabolic acidosis, elevated lactate levels (4 mmol/L), and dietary fructose avoidance was observed. The patient with galactosemia exhibited hepatomegaly, cholestasis, elevated liver enzymes (ALT: 103 U/L; AST: 77 U/L), feeding difficulties and cataract. The accompanying clinical and laboratory features of these metabolic disorders are summarized in Table I.

Table I: Clinical findings accompanying hepatomegaly and/or splenomegaly in patients diagnosed with metabolic disorders, and the percentage distribution of diagnoses among all metabolic disorders

Disease	Frequency*	Hepatomegaly	Splenomegaly	Other Findings
Glycogen storage disease (I, III, IXA, IXB, VI)	13 (48.1)	+	-	Hypoglycemia (6), elevated liver enzyme, hypertriglyceridemia, elevated CK (2),
Gaucher disease	6 (22.2)	-	+	Thrombocytopenia, anemia
ASMD	3 (11.1)	+	+	Thrombocytopenia, anemia, mild elevated liver enzyme,
NPC	1 (3.7)	+	+	Seizures,developmental delay, supranuclear gaze limitation
MPS II	1 (3.7)	+	-	Coarse facial features, developmental delay, dysostosis multiplex and increased urinary glycosaminoglycans
GM1 Gangliosidosis	1 (3.7)	+	-	Coarse facial features, cherry red spot , developmental delay
Hereditary fructose intolerance	1 (3.7)	+	-	Hypoglycemia, metabolic acidosis elevated lactate levels
Galactosemia	1 (3.7)	+	-	Hypoglycemia, cholestasis, cataract

***:** *n(%),* ***ASMD:** *Acid Sphingomyelinase Deficiency,* ***CK:** *Creatine Kinase;* ***GSD:** *Glycogen Storage Disease;* ***HSM:** *Hepatosplenomegaly;* ***IEM:** *Inborn Errors of Metabolism;* ***MPS:** *Mucopolysaccharidosis;* ***NPC:** *Niemann–Pick Disease Type C. The symbol "+" indicates presence and "–" indicates absence of the respective clinical finding.*

Discussion

Hepatosplenomegaly in the pediatric population can result from both inherited and acquired causes. Common etiologies include infections, hematologic and oncologic disorders, liver and biliary diseases, as well as metabolic disorders (4,5). In children presenting with this condition, IEM represents rare but clinically critical diagnoses that must be considered. IEM can involve multiple organ systems and may present at various ages; therefore, early recognition and appropriate referral are essential not only for optimizing patient prognosis and providing accurate genetic counseling to families, but also for initiating timely treatment that can substantially reduce morbidity. These considerations highlight the importance of routinely including IEM in the differential diagnosis of HSM and adopting a multisystemic, metabolically oriented diagnostic approach.

Despite these considerations, the proportion of patients ultimately diagnosed with an IEM varies substantially between cohorts. Previous studies have reported that a significant proportion of patients assessed for potential metabolic disorders were ultimately diagnosed with an IEM. In Bulut et al.'s (6) study, 55.9% of patients received an IEM diagnosis. In contrast, this proportion was markedly lower in our cohort (15.4%). There may be several possible explanations for this situation. Firstly, in previous years, physicians may have referred patients to pediatric metabolic specialists after preliminary etiological investigations, and only those in whom a diagnosis could not be established may have been referred. In recent years, however, many patients with hepatomegaly or splenomegaly have been referred to pediatric metabolic units even in the absence of typical metabolic features. While this has increased the number of patients undergoing metabolic evaluation, it has naturally resulted in a lower proportion of confirmed metabolic diagnoses.

In our cohort, a high proportion of patients' parents were consanguineous. Additionally, all patients presented with accompanying clinical and laboratory findings, including growth retardation, coarse facial features, hypoglycemia, hyperlipidemia, thrombocytopenia, anemia, metabolic acidosis, and cholestasis depending on the specific underlying disorder. These factors collectively represent important diagnostic clues for identifying IEM. The most frequently diagnosed disorder in our study was GSD. In hepatic forms of GSDs, hypoglycemia and hepatomegaly constitute the predominant clinical manifestations, whereas types with primary muscle involvement are characterized by exertional muscle weakness and progressive myopathy (7-9). Moreover, in GSD IIIa both liver and muscle (skeletal and cardiac) involvement may occur while early hepatomegaly, fasting hypoglycemia, hyperlipidemia, and elevated liver enzymes dominate the picture in childhood, progressive myopathy, elevated CK, exercise intolerance, and eventual cardiomyopathy may develop over time (10). Laboratory assessments in both groups commonly reveal elevated liver transaminases, along with metabolic acidosis, hypertriglyceridemia, and hypercholesterolemia. In our cohort, affected patients exhibited hypoglycemia and hyperlipidemia, underscoring the diagnostic value of these findings for early recognition and timely referral. The individual with GSD type III additionally showed elevated CPK levels, consistent with the muscle involvement characteristic of this subtype.

Lysosomal storage disorders (LSDs) are IEM that are individually uncommon; however, as a group, they are relatively frequent, with an estimated overall incidence of approximately 1 in 5.000 live births (11). Hepatosplenomegaly (HSM) is a common feature observed across several LSDs, including Gaucher disease, ASMD, NPC, mucopolysaccharidoses (MPS I–VII), lysosomal acid lipase deficiency, GM1 gangliosidosis type I, galactosialidosis, and saposin C deficiency (1). In our study, patients presenting with HSM were diagnosed with Gaucher, ASMD, NPC disease, MPS II, and GM1 gangliosidosis. Many LSDs associated with organomegaly may show liver function tests within normal limits, and therefore normal biochemical results do not exclude these disorders (12). In our study, ALT and AST levels were normal in patients diagnosed with Gaucher disease, GM1 gangliosidosis, and MPS, and mild elevations were also noted in those with ASMD and NPC. In both Gaucher disease and ASMD, splenomegaly is frequently

accompanied by thrombocytopenia and other cytopenias. In our cohort, all six patients who presented with HSM and were diagnosed with Gaucher disease had thrombocytopenia and anemia. Similarly, both patients diagnosed with ASMD exhibited thrombocytopenia and anemia. Therefore, in these two disease groups, the presence of cytopenia alongside visceromegaly should be considered an important diagnostic clue (13). In addition, dyslipidemia, including decreased HDL cholesterol levels and hypertriglyceridemia, is reported in patients with ASMD (14). In our patients, low HDL cholesterol levels were detected in all cases, and elevated triglyceride levels were present in two. Enzyme replacement therapy (ERT) is currently used for the treatment of both Gaucher disease and ASMD. In Gaucher disease, ERT has been available for many years and provides highly favorable clinical outcomes. In contrast, prior to 2022, treatment for ASMD was limited to supportive care; currently, ERT demonstrates promising results, which is supported by numerous recent studies (15-19). Therefore, early recognition and diagnosis are critically important for patients with both Gaucher disease and ASMD. NPC is another lysosomal storage disorder that may present with hepatomegaly and is characterized by developmental delay, supranuclear gaze palsy, seizures and in later stages, psychosis, and cognitive decline (20,21). In our cohort, the patient diagnosed with NPC demonstrated supranuclear gaze limitation, developmental delay, and seizures. Thus, awareness that hepatomegaly in NPC is often accompanied by neurological manifestations is essential for timely recognition and accurate diagnosis. The other two lysosomal storage disorders associated with neurological findings in our cohort were GM1 gangliosidosis and MPS II with a neuropathic phenotype. GM1 gangliosidosis is characterized by psychomotor regression, hepatosplenomegaly, extensive Mongolian spots, coarse facial features, retinal cherry-red spot, and skeletal abnormalities (22). In the presented GM1 gangliosidosis case, coarse facial features, intellectual disability, and the presence of a cherry-red spot on fundoscopic examination were key findings that supported the differential diagnosis. Although isolated AST elevation has been reported in some neurodegenerative and lysosomal storage disorders, liver transaminase levels were within normal limits in our patient with GM1 gangliosidosis (23,24). In the MPS II case, coarse facial features, developmental delay, dysostosis multiplex evident on radiologic imaging, and increased urinary glycosaminoglycans were important for establishing the diagnosis.

Hereditary fructose intolerance (HFI) is another IEM that can lead to hepatomegaly. Clinical manifestations of HFI typically include hepatic dysfunction, hypoglycemia, lactic acidosis, proximal renal tubulopathy, hypophosphatemia, and growth delay (25). Symptoms occur after dietary exposure to fructose, and aversion to sugar-containing foods is frequently reported in affected patients (26). Symptoms occur after dietary exposure to fructose. In our patient, referral was prompted by hepatomegaly and elevated liver function tests. The presence of hypoglycemia, metabolic acidosis, elevated lactate levels, and avoidance of fructose-containing foods supported the diagnosis. Another patient in our cohort who presented with hepatomegaly was diagnosed with galactosemia. Clinical features often include cholestatic jaundice, hepatomegaly, vomiting, feeding intolerance, hypoglycemia, and, if untreated, progression to hepatic failure (27). Direct (conjugated) hyperbilirubinemia is an important clinical clue in many inherited metabolic disorders, including galactosemia. In our patient, the presence of hepatomegaly together with elevated liver enzymes, direct hyperbilirubinemia, and cataract prompted further metabolic evaluation, ultimately leading to the diagnosis of galactosemia. Early recognition is crucial, as prompt initiation of a galactose-restricted diet can prevent life-threatening complications and improve outcomes.

Limitations

The main limitations of this study include its retrospective and single-center design, potential selection bias due to referral to a tertiary care center, and the limited sample size of individual disease subgroups.

Conclusion

Hepatomegaly and/or splenomegaly are common clinical findings with a broad differential diagnosis, in which metabolic disorders represent an important etiology. Our cohort highlights that normal liver function tests do not exclude metabolic etiologies and that associated features such as cytopenias, neurological manifestations, hypoglycemia, metabolic acidosis, cholestasis, and feeding intolerance can provide essential diagnostic clues. Early recognition and timely metabolic evaluation are crucial. Targeted or dietary interventions can significantly improve clinical outcomes. Increased clinician awareness of these diverse presentations is therefore critical for achieving prompt diagnosis and optimizing patient management.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Adana City Training and Research Hospital (23.10.2025, reference number: 783).

Contribution of the authors

EB: drafted and wrote the manuscript, MYÇ: contributed to data collection and manuscript editing. BK: performed the statistical analysis and assisted with data interpretation. All authors read and approved the final version.

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Conflict of interest

The authors declare that there is no conflict of interest.

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