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Original Research

Evaluation of Patients Diagnosed with Inherited Metabolic Diseases in Adulthood

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Abstract

Objectives: Inherited metabolic diseases (IMDs) arise due to deficiencies in enzymes involved in metabolic pathways or other dysfunctions within these pathways, leading to a deficiency of specific end products or the toxic accumulation of intermediate metabolites. These diseases may present at any age with varying clinical courses. With advances in treatment options and increased awareness, IMDs are increasingly being diagnosed and managed in adulthood. This study aims to understand the clinical features and diagnostic processes of patients diagnosed with IMDs during adulthood and to raise awareness regarding these conditions.

Methods: Medical records of adult patients diagnosed with IMDs between June 2022 and June 2024 were retrospectively reviewed. Patients were included if they were diagnosed with an IMD at or above the age of 18. Those diagnosed during childhood but transitioning to adulthood were excluded.

Results: Twenty patients, aged 19–72 years (11 males, 9 females), were diagnosed with IMDs. The mean age of symptom onset was 30 years (range: 15–70 years), and the mean age of diagnosis was 37 years (range: 18–72 years). Diagnoses included Fabry disease (n=10, 20%), familial hypobetalipoproteinemia (FHBL) (n=3, 15%), and alkaptonuria (AKU) (n=2, 10%). Other diagnoses included Gaucher disease, Niemann-Pick disease type B, glycogen storage disease type IIIa (GSD IIIa), glycogen storage disease type XV (GSD XV), and cerebrotendinous xanthomatosis (CTX). Sixty-five percent of patients were identified via family screening, while 35% were diagnosed based on clinical findings supported by biochemical tests. Misdiagnoses before definitive IMD diagnosis included osteoarthritis, psoriatic arthritis, renal failure, heart failure, proteinuria, interstitial lung disease, hepatosteatosis, and nephrolithiasis. Disease-specific treatments were initiated and follow-ups were conducted.

Conclusion: Chronic and mild phenotypes of certain IMDs may pose diagnostic challenges. Increased awareness among healthcare professionals and further studies focusing on differential diagnoses are critical to improving the detection and management of IMDs.

Keywords: Adult, disease awareness, inherited metabolic disease, treatment

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Inherited metabolic diseases (IMDs) are a group of genetic disorders caused by the deficiency or absence of an enzyme or cofactor involved in a metabolic pathway. This results in either the lack of a specific end product or the excessive accumulation of a potentially toxic intermediate substrate.[1] The term "IMD" was first introduced by Sir Archibald Garrod in reference to alkaptonuria.[2] IMDs are exclusively monogenic disorders, most commonly inherited in an autosomal recessive manner. To date, more than 1,450 IMDs have been identified, and this number continues to grow with advancements in genetic diagnostic methods.[3] Although individually rare, IMDs collectively have an incidence of 1:800 to 1:2.500 live births.[4] Compared to developed countries, the prevalence of IMDs is higher in Türkiye due to the increased rate of consanguineous marriages.

Due to the success of newborn screening programs in treating pediatric patients, many individuals with inherited metabolic diseases (IMDs) now reach adulthood. However, the exact prevalence of these diseases in the adult population remains unclear, as late-onset forms that manifest during adulthood are often underrecognized. It is estimated that 50% of individuals with IMDs are adults.[5,6] Studies have shown that 23–40% of IMD cases are diagnosed in adulthood.[7,8] Diagnosing IMDs in adult patients is challenging due to phenotypic differences from pediatric cases, the influence of factors such as obesity and smoking on clinical presentations, the variability of symptoms across different ages, and the resolution of certain symptoms with supportive therapies.[9] Adult patients with IMDs may present with diverse symptoms or findings, leading them to seek care from specialists in various fields, including neurology, cardiology, gastroenterology, nephrology, and ophthalmology.[10] Awareness of IMDs among clinicians in adult specialties is crucial for early diagnosis and treatment initiation, as well as for providing genetic counseling during pregnancy and protecting at-risk fetuses.[11] Given the increasing recognition of IMDs in adulthood, it is essential for clinicians across specialties, in addition to pediatric metabolic specialists, to acquire more knowledge about this patient population and to identify their characteristic features.

This study aims to document the clinical characteristics of patients diagnosed with IMDs who presented to different specialties in a tertiary care center. Additionally, it seeks to improve understanding of the prognoses of these patients and to raise awareness of IMDs in adult clinical practice.

Methods

A retrospective review was conducted on the medical records of 20 patients diagnosed with IMDs between June 2022 and June 2024 at the Pediatric Metabolic Diseases Clinic of Şişli Hamidiye Etfal Training and Research Hospital, University of Health Sciences. The collected data included demographic and clinical characteristics such as age, sex, diagnosis, age of symptom onset, presenting complaints, initial clinical consultations, physical examination findings, laboratory results, diagnostic tests, and treatments (both disease-specific and symptomatic). Only patients aged 18 years or older at the time of diagnosis were included in the study, while individuals diagnosed during childhood and transitioning to adulthood were excluded.

For Fabry disease, the diagnosis was established through enzymatic analysis, Lyso-Gb3 levels, and genetic testing in males, while Lyso-Gb3 levels and genetic testing were used in females. Glycogen storage diseases were diagnosed using genetic analyses, while Niemann-Pick type B and Gaucher diseases were confirmed through enzyme activity levels and genetic testing. Homogentisic acid in urine was used for diagnosing alkaptonuria (AKU), while low levels of LDL cholesterol and ApoB confirmed familial hypobetalipoproteinemia (FHBL). Elevated cholestanol and 7-dehydrocholesterol levels were used for diagnosing cerebrotendinous xanthomatosis (CTX). Genetic analyses included single-gene sequencing or genetic panels for symptomatic index cases and mutation analysis for family screening.

The data analysis was performed using SPSS version 22.0 (Statistical Package for Social Science, IBM Corp, Armonk, NY, USA). Descriptive statistics were presented as means, minimums, and maximums for continuous variables, and as counts and percentages for categorical variables.

Ethics Committee Approval

Ethics committee approval for the study was obtained from the Non-Interventional Research Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital, University of Health Sciences, on 19/11/2024, with the decision number 4623/2024. All study procedures were in compliance with the principles of the Helsinki Declaration.

Results

During the study period, 20 patients diagnosed with IMDs were included, of whom 11 (55%) were male and 9 (45%) were female. Consanguinity between parents was present in 19 patients (95%). The mean age of the patients was 38 years (range: 19–72 years). The mean age of symptom onset was 30 years (range: 15–70 years), and the mean age at diagnosis was 37 years (range: 18–72 years). Among the cases, 10 (20%) were diagnosed with Fabry disease, 3 (15%) with familial hypobetalipoproteinemia (FHBL), and 2 (10%) with alkaptonuria (AKU). One case each of Gaucher disease, Niemann-Pick disease type B, glycogen storage disease type IIIa (GSD type IIIa), glycogen storage disease type XV (GSD type XV), and cerebrotendinous xanthomatosis (CTX) were also identified. The clinical and demographic characteristics of the patients are shown in Table 1.

Table 1. The clinical and demographic characteristics of the patients in the study

Patient No	Age/ Gender	Symptoms/Findings	Mode of Diagnosis	Diagnostic Approach (Biochemical/ Genetic)	Genetic	Diagnosis	Treatment
1	49/F	Osteoarthritis	Clinical	Urine organic acid (↑Homogentisic acid)	*HGD* Homozygous	Alkaptonuria	Nitisinone + Tyrosine-restricted diet
2	36/M	Joint pain, Kidney stones	Family screening	Urine organic acid (↑Homogentisic acid)	*HGD* Homozygous	Alkaptonuria	Nitisinone + Tyrosine-restricted diet
3	51/M	Renal failure, Kidney transplant, Hypertrophic cardiomyopathy Hearing loss	Clinical	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Declined enzyme replacement therapy due to surgeries
4	72/F	Heart failure	Family screening	Genetic analysis	*GLA* Heterozygous	Fabry Disease	Declined enzyme replacement therapy due to old age
5	46/M	Hypertension, Hypertrophic cardiomyopathy, Proteinuria	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
6	40/M	Renal failure, Hearing loss, Angiokeratoma	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
7	33/M	Proteinuria, Acroparesthesia	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
8	37/M	Angiokeratoma, Acroparesthesia, Increased vascular tortuosity in eyes	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
9	45/F	Renal failure, Heart failure, Acroparesthesia	Family screening	Genetic analysis	*GLA* Heterozygous	Fabry Disease	Enzyme replacement therapy (ERT)
10	19/M	Proteinuria, Hypertrophic cardiomyopathy	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
11	48/F	Hypohidrosis, Hypertrophic cardiomyopathy, Increased vascular tortuosity in eyes	Family screening	Genetic analysis	*GLA* Heterozygous	Fabry Disease	Enzyme replacement therapy (ERT)
12	22/M	Hypertrophic cardiomyopathy, Difficulty gaining weight	Family screening	↓Alpha-galactosidase, ↑Lyso Gb3	*GLA* Hemizygous	Fabry Disease	Enzyme replacement therapy (ERT)
13	34/F	Abdominal swelling, Joint pain	Family screening	↓Beta-glucosidase, ↑Lyso Gb1	*GLA* Compound Heterozygous	Gaucher Disease	Enzyme replacement therapy (ERT) + Vitamin D supplementation
14	43/F	Joint pain, Iron deficiency anemia, Hepatosplenomegaly, Interstitial lung disease	Clinical	↓Sphingomyelinase, ↑Lyso SM, Lyso SM-509	*SMPD* Homozygous	Niemann-Pick Disease Type B	Applied for enzyme replacement therapy
15	31/M	Chest pain, Hypertrophic cardiomyopathy	Clinical	Genetic analysis	*GYG1* Homozygous	Glycogen Storage Disease Type XV	Symptomatic treatment
16	55/F	Xanthomas, Depression	Clinical	↑Cholestanol, ↑7-dehydrocholesterol	*CYP27A1* Homozygous	Cerebrotendinous Xanthomatosis	Chenodeoxycholic acid therapy
17	38/F	Ataxia, Hepatosteatosis	Clinical	↓Apo B, ↓LDL Cholesterol, ↓Vitamin E	*APOB* Homozygous	Hypobetalipoproteinemia	MCT-supported fat-restricted diet + Fat-soluble vitamins

Table 1. The clinical and demographic characteristics of the patients in the study (Cont.)

Patient No	Age/ Gender	Symptoms/Findings	Mode of Diagnosis	Diagnostic Approach (Biochemical/ Genetic)	Genetic	Diagnosis	Treatment
18	19/F	Asymptomatic, Hepatosteatosis	Family screening	↓Apo B, ↓LDL Cholesterol	*APOB* Heterozygous	Hypobetalipoproteinemia	Fat-soluble vitamins
19	21/M	Asymptomatic, Hepatosteatosis	Family screening	↓Apo B, ↓LDL Cholesterol	*APOB* Heterozygous	Hypobetalipoproteinemia	Fat-soluble vitamins
20	27/M	Fatigue, Hypoglycemia, Muscle weakness	Clinical	↓Glucose, ↑ALT, ↑AST, ↑Triglycerides, ↑Creatine Kinase	*AGL* Homozygous	Glycogen Storage Disease Type IIIa	Modified Atkins diet

M: Male; F: Female; Glu: Glucose; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Tg: Triglyceride; CK: Creatine kinase; Apo B: Apolipoprotein B.

In our cohort includes 8 unrelated families. 65% of patients (13 cases from four families; 9 Fabry, 2 FHBL, 1 AKU, 1 Gaucher) were diagnosed through family screening. The remaining 7 patients (35%) were diagnosed based on clinical findings supported by biochemical and genetic tests. These included 1 case each of Niemann-Pick disease type B, CTX, FHBL, GSD type IIIa, GSD type XV, Fabry disease, and AKU. The index case of Fabry disease was diagnosed through selective screening in the cardiology department, while one GSD type XV patient, who could not be diagnosed biochemically, was identified through clinical exome sequencing. Some phenotypic features of adult patients diagnosed with inherited metabolic diseases are presented in Figure 1 (a-d).

Symptomatic patients primarily presented to internal medicine (30%), gastroenterology (10%), nephrology (10%), cardiology (10%), and orthopedics (10%), as well as hematology and physical therapy departments. Prior to diagnosis, these patients had been misdiagnosed with conditions such as osteoarthritis, psoriatic arthritis, renal failure, heart failure, proteinuria, interstitial lung disease, hepatosteatosis, and nephrolithiasis. Among Fabry disease patients, organ screenings revealed ocular and cardiac involvement in asymptomatic women. In men, hypertrophic cardiomyopathy was detected in three cases, while two cases showed ocular involvement and proteinuria. A total of 11 patients (60%) presented with involvement of two or more organs at the time of diagnosis. This group included 8 Fabry patients, and one patient each with AKU, Niemann-Pick disease type B, CTX, and GSD type IIIa.

Disease-specific treatments were initiated for the IMD patients. Two Fabry patients declined treatment (one due to advanced age and social reasons, and the other due to surgical considerations). Enzyme replacement therapy was administered to 8 Fabry and 1 Gaucher patient. Additionally, 2 AKU patients received nitisinone (NTBC) and a specialized diet, while the CTX patient was treated with chenodeoxycholic acid. A patient with GSD type IIIa was managed with a modified Atkins diet, and the homozygous FHBL patient was treated with fat-soluble vitamin supplementation and a fat-restricted diet. Heterozygous FHBL patients were also managed with fat-restricted diets.

Discussion

Inherited metabolic diseases (IMDs) are a group of genetic disorders that typically present acutely in childhood or, more commonly, progress insidiously in adulthood.[12] Diagnosing IMDs in adults is rare, and these conditions are often overlooked in clinical practice.[7] This study presents the clinical

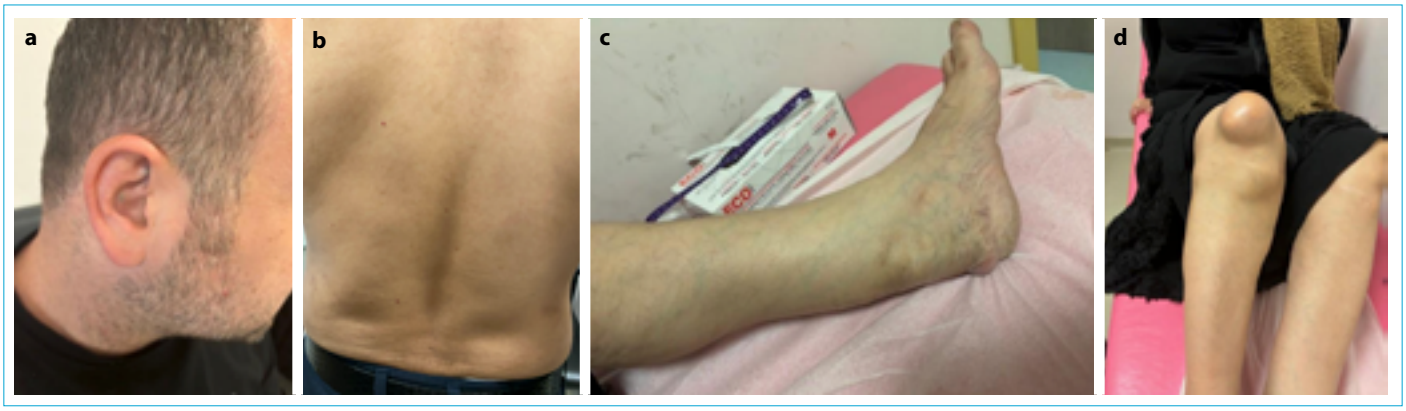

Figure 1. Images of cases. **(a)** Patient no 2- Ear ochronosis. **(b)** Patient no 6- Anjiokeratoma of Fabry disease. **(c)** Patient no 16- Xanthoma in the left achilles tendon. **(d)** Patient no 16- Xanthoma in the right knee.

features, diagnostic processes, and treatment pathways of 20 adult patients diagnosed with IMDs. It aims to increase awareness of these conditions among healthcare professionals.

Timely diagnosis of IMDs is essential for initiating treatment, determining prognosis, and conducting family screening. A study conducted in Spain reported that the average age of diagnosis in adult patients was 39 years, with a mean diagnostic delay of 8.6 years from the onset of symptoms.[8] Similarly, one study found that adult patients were diagnosed, on average, 15 years after the appearance of their initial symptoms.[9] In our cohort, the mean age of the patients was 38 years, and the average diagnostic delay was 7 years. This delay may be attributed to insufficient recognition of the chronic and mild phenotypes of IMDs by adult specialists and limited access to biochemical tests necessary for diagnosis.

A study from Saudi Arabia showed that the most frequent specialties visited before IMD diagnosis were neurology, ophthalmology, nephrology, pulmonology, and gastroenterology.[10] Similarly, in our study, the most common specialties patients consulted were internal medicine, gastroenterology, nephrology, cardiology, and orthopedics. Until receiving a definitive diagnosis, these patients were often misdiagnosed with conditions such as osteoarthritis, psoriatic arthritis, renal and heart failure, proteinuria, interstitial lung disease, and hepatosteatosis. Given the broad clinical heterogeneity of IMDs and their multisystemic nature, it is essential to recognize that patients may present to a variety of medical specialties. Clinicians should be vigilant for symptoms or findings suggestive of disorders outside their primary specialty and refer patients for further metabolic and genetic testing when necessary.

In our study, Fabry disease was the most frequently diagnosed condition (20%). Reports indicate that Fabry disease and mitochondrial disorders are commonly diagnosed in adulthood.[5] A five-year study from Italy identified Fabry disease, urea cycle defects, and glycogen metabolism disorders as the most common IMDs diagnosed after the age of 16.[13] Similarly, a study conducted in Türkiye reported that Fabry disease, along with citrullinemia type 2, multiple acyl-CoA dehydrogenase deficiency, alkaptonuria, and adrenoleukodystrophy, were the most frequent diagnoses in adult IMD patients.[14] These findings align with our results.

Conclusion

In conclusion, the significant increase in the number of adults diagnosed with IMDs suggests that many adult IMD patients remain undiagnosed. To establish the most effective diagnostic approach for adults presenting with diverse symptoms and suspected IMDs, it is crucial to first identify the clinical and biochemical phenotypes of patients and then select and sequence appropriate metabolic and genetic tests. Clinicians should recognize that the majority of IMDs are treatable, and early diagnosis allows some patients to live unaffected or minimally affected by their condition and its complications. While the chronic and mild phenotypes of certain IMDs may pose diagnostic challenges, increasing awareness among healthcare professionals and conducting further research are critical steps toward improving detection and management.

Disclosures

Ethics Committee Approval: The Non-Interventional Research Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital, University of Health Sciences Ethics Committee granted approval for this study (date: 19/11/2024, number: 4623/2024).

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