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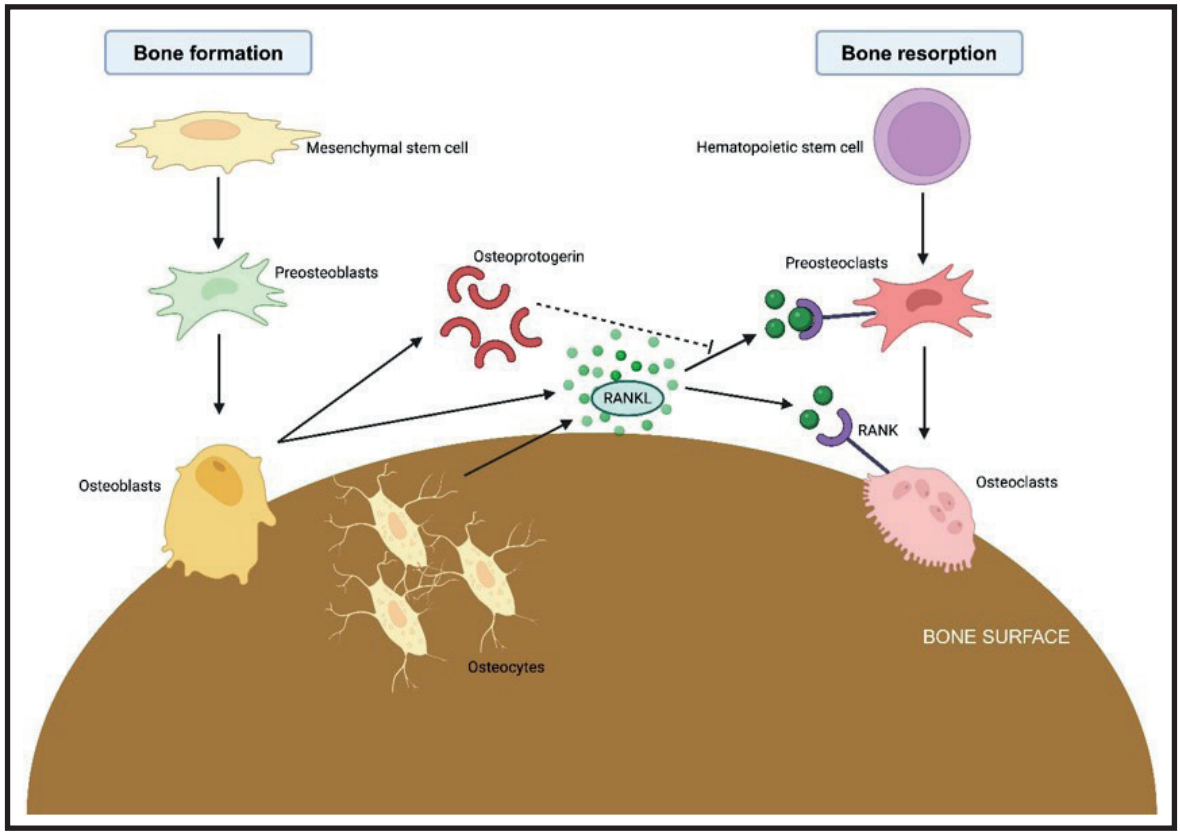

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Phone: +90 (533) 166 80 80
E-mail: bilgi@akdema.com
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Assoc. Prof. Ayşe Anık, MD
E-mail: drayseank@yahoo.com
Department of Pediatrics, Division of Neonatology, Aydın Adnan Menderes University, Medical Faculty, Aydın, Türkiye
ORCID: https://orcid.org/0000-0002-0673-3403

Assoc.Prof. Serkan Fazlı Çelik, MD
E-mail: docser2003@yahoo.com
Department of Pediatrics, Division of Pediatric Cardiology, Aydın Adnan Menderes University, Medical Faculty, Aydın, Türkiye
ORCID: https://orcid.org/0000-0003-1595-802X

Assoc. Prof. Elif Çelik, MD
E-mail: gencelif80@yahoo.com
Department of Pediatrics, Aydın Adnan Menderes University, Medical Faculty, Aydın, Türkiye
ORCID: https://orcid.org/0000-0002-0298-4088

Assoc. Prof. Şükrü Güngör, MD
E-mail: sukru.gungor@yahoo.com
Department of Pediatrics, Division of Pediatric Gestroenterology, Kahramanmaraş Sütçü İmam University, Medical Faculty, Kahramanmaraş, Türkiye
ORCID: https://orcid.org/0000-0002-0433-5970

Research Methods
Prof. Pınar Okyay, MD
E-mail: pinarokyay@hotmail.com
Department of Public Health, Aydın Adnan Menderes University, Medical Faculty, Aydın, Türkiye

Sercan Öztürk, MD
E-mail: dr.sercanozturk@gmail.com
Department of Pediatrics, Aydın Adnan Menderes University, Medical Faculty, Aydın, Türkiye

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Review

Pediatric osteoporosis: An update

Aylin Günay[1], **Serap Turan**[1]

[1]Department of Pediatric Endocrinology, School of Medicine, Marmara University, İstanbul, Türkiye

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ABSTRACT

The diagnosis of childhood osteoporosis is relatively straightforward in primary bone diseases. However, in chronic diseases that can cause osteoporosis, the focus is often on primary treatment, and the risk of osteoporosis is frequently overlooked. Primary bone disease typically presents in infancy or early childhood with multiple fractures of long bones, abnormalities of the sclera or teeth, and an associated family history. On the other hand, secondary osteoporosis is associated with underlying chronic disease and long-term use of medications for these conditions. It may present with vertebral fractures as the only sign. Clinicians must be vigilant in diagnosing it due to its more insidious course. Once diagnosed, diet and lifestyle changes should be made. Also, any vitamin and mineral deficiencies should be replaced. The next step will be the identification of patients who are suitable for medical treatment. In some cases, patients with multiple bone deformities may require corrective surgery. Children diagnosed with osteoporosis should be monitored by a pediatric bone specialist, and their treatment should be coordinated by a multidisciplinary team.

Keywords: osteoporosis, osteogenesis imperfecta, management, treatment, bisphosphonates

INTRODUCTION

Osteoporosis is typically distinguished by a decrease in bone mineral density and the deterioration of bone tissue, leading to an increased probability of fracture and bone deformities.[1] Osteoporosis is a significant health concern among the elderly; however, it is often overlooked in childhood. It is essential to understand how to promote and maintain optimal bone mass from infancy through adulthood.[2]

Bone Development and Pathophysiology of Osteoporosis

Bone mass is regulated through the coordination of osteoblasts, which form new bone tissue; osteoclasts, which cause bone resorption; and osteocytes, which regulate the activity of osteoblasts and osteoclasts in response to mechanical stimuli and aid in bone formation. Bone mineralization commences in the fetal period and attains its peak level during adolescence. Puberty plays a critical role in bone mass, as bone tissue is continuously renewed to achieve maximum size and density. The bone mass acquired during this period serves as a lifelong reserve and determines the risk of osteoporosis in later life. In healthy children, osteoblasts outnumber osteoclasts, resulting in a net increase in bone mass. However, this balance is disrupted in osteoporosis, leading to bone loss.[3–5]

Genetic factors are believed to contribute to 80% of bone mass acquisition, but adequate calcium intake, vitamin D levels, and physical activity are also crucial for bone development. [6] Genetic causes typically involve defects in intercellular signaling pathways, and pharmacotherapy often targets these pathways.

RANK (Receptor Activator of Nuclear Factor Kappa B) is expressed on the surface of osteoclast precursors, while RANK ligand (RANKL) is secreted by osteoblasts and osteocytes. The interaction between RANK and RANKL activates osteoclasts, leading to bone resorption. Osteoprotegerin (OPG), synthesized by osteoblasts, functions as a decoy receptor for RANKL, thereby

Correspondence: Serap Turan **E-mail:** serap.turan@marmara.edu.tr
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inhibiting the RANK-RANKL interaction. The balance between RANKL and OPG is a critical determinant of osteoclast-mediated bone resorption (Figure 1).[7]

Inflammatory mediators, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α), can disrupt this pathway and contribute to osteoporosis by promoting osteoclast activation.[8,9]

The Wnt signaling pathway is also involved in bone modeling and remodeling. It plays a crucial role in the differentiation of mesenchymal stem cells (MSC) into osteoblasts, with β-catenin serving as the core molecule responsible for signal transmission. β-catenin directly affects osteoblastic precursor cells and osteoblasts, enhancing their response to bone morphogenic protein (BMP)-2 and promoting their differentiation into osteoblasts. Several studies have also shown that β-catenin induces OPG activation in osteoblasts. Disruption of β-catenin significantly increases the number of osteoclasts and bone resorption, ultimately leading to osteoporosis. On the other hand, overexpression of β-catenin boosts the amount of osteoblast and bone mass, promoting bone formation. Thus, activating the Wnt/β-catenin signaling pathway might offer a new strategy for managing osteoporosis.[10,11] The Wnt pathway is activated by ligands, such as Wnt1 and Wnt3a, which bind to transmembrane Frizzled receptors and low-density lipoprotein receptor-related protein (LRP)-5 and LRP-6 complexes. Sclerostin, secreted by osteocytes, binds to LRP-5 and LRP-6 and inhibits Wnt signaling (Figure 2).[12]

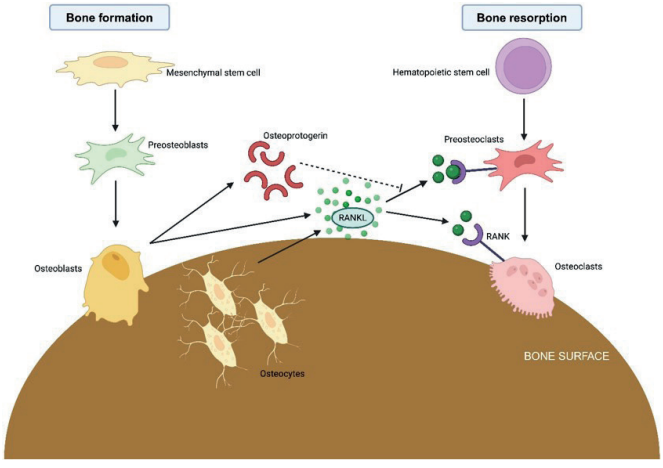

Figure 1. The RANK/RANKL/OPG System in Bone Resorption

RANK (Receptor Activator of Nuclear Factor Kappa B) and RANK ligand (RANKL) play a crucial role in bone resorption. The interaction of RANK, expressed on the surface of osteoclast precursors, with RANKL, which is secreted by osteoblasts and osteocytes, activates osteoclasts. Osteoprotegerin (OPG), synthesized by osteoblasts, functions as a decoy receptor for RANKL, thereby inhibiting the RANK-RANKL interaction.

Transforming growth factor-beta (TGF-β) and BMP signaling play significant roles in both embryonic skeletal development and postnatal bone homeostasis. TGF-β and BMPs transmit intracellular signals through the Smad complex or the mitogen-activated protein kinase (MAPK) cascade, resulting in cell proliferation, differentiation, and migration. Disruptions in TGF-β and BMP signaling can lead to bone disorders. Knockout or mutation of genes associated with TGF-β and BMP signaling in mice results in varying degrees of bone abnormalities.[13] Furthermore, the TGF-β pathway interacts with Wnt signaling by inhibiting sclerostin secretion and modulating different Wnt ligands.[14]

Diagnosis of osteoporosis

The diagnosis of osteoporosis is primarily based on bone mineral density (BMD) measurements using dual-energy X-ray absorptiometry (DXA) in adults. In pediatric patients, clinical

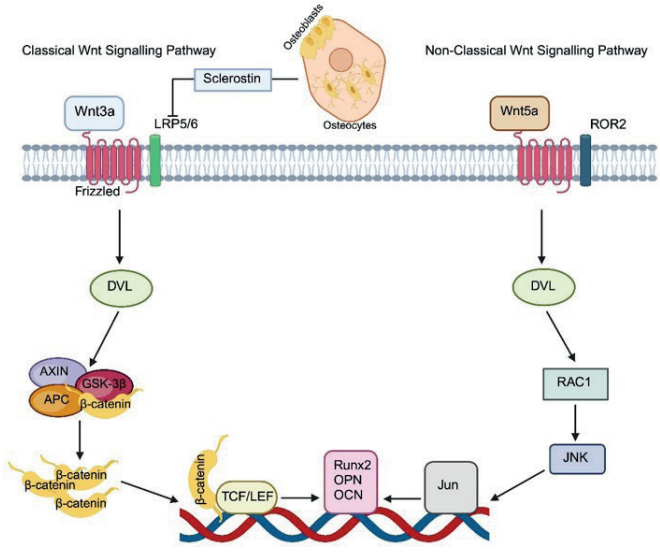

Figure 2. Classical and Non-classical Wnt Signalling Pathways in Bone Metabolism

In the classical pathway, binding of Wnt protein to Frizzled (FZD) and LRP5/6 receptor complex activates DVL. Activated DVL prevents the phosphorylation of β-catenin by inhibiting the AXIN-APC-GSK3β-β-catenin complex. This results in the accumulation of β-catenin, which translocates to the nucleus and binds to osteoblast marker molecules, leading to osteogenic differentiation. Osteocyte-derived sclerostin prevents the binding of Wnt to the receptor complex. In a non-classical pathway, binding of Wnt protein to Frizzled (FZD) and ROR2 receptor complex activates DVL, which in turn activates RAC1. RAC1 activates JNK, and JNK translocates to the nucleus, where it binds the transcription factor c-Jun. Jun binds to osteoblast marker molecules, terminating osteogenic differentiation.

features should also be evaluated alongside densitometric criteria.[9]

Although most childhood fractures are benign, experiencing multiple fractures may suggest primary bone disease or reduced bone mineral density secondary to underlying conditions. Low-trauma fractures are particularly significant for diagnosis.

BMD should be assessed considering the patient's sex, age, and body proportions and is reported as a 'Z-score'. Z-scores below -2 standard deviations (SD) indicate low bone mineral density.[15,16]

The International Society for Clinical Densitometry has set criteria for pediatric osteoporosis:

1. One or more vertebral compression fractures (VCF), irrespective of BMD, in the absence of high-energy trauma* or local disease.

2. A clinically significant fracture history alongside a DXA BMD Z-score ≤ -2 SD (adjusted for age and sex). A significant fracture history is defined as ≥ 2 long bone fractures by age 10 or ≥ 3 by age 19. A BMD greater than -2 SD does not rule out an increased fracture risk.[17]

** High-energy trauma: Significant forces such as motor-vehicle accidents or falls from heights greater than 10 feet (approximately 3 meters). In chronic illness contexts, a more conservative definition is applied, referring to falls from a standing height or higher, occurring at more than walking speed*.[18]

These criteria help prevent overdiagnosis of osteoporosis in children but may not be fully applicable for primary (genetic) and secondary (acquired) bone diseases. If the number of fractures does not meet the existing criteria, diagnosis may be delayed. Diagnosis should consider underlying diseases, risk factors for fractures, characteristics of the fractures (such as location, mechanism, and radiological features), and family history without relying solely on BMD and the number of fractures.[18]

Primary osteoporosis

Primary osteoporosis results from intrinsic defects in bone tissue, leading to hereditary bone fragility. The most common cause of primary osteoporosis in children is osteogenesis imperfecta (OI).

• Osteogenesis imperfecta

OI is a rare skeletal dysplasia with a prevalence of 1:15-20,000, characterized by recurrent fractures, deformities, and growth retardation. The disease is primarily caused by defects in the production of type 1 collagen. Due to the expression of type 1 collagen in different tissues, patients may also exhibit brittle teeth (dentinogenesis imperfecta), blue sclerae, hearing loss, reduced respiratory capacity, and heart valve abnormalities. OI ranges from mild clinical presentations to severe forms with perinatal mortality.[19] The most common mutations are in the COL1A1 and COL1A2 genes, which are inherited in an autosomal dominant pattern. Recently, recessive and X-linked forms have been identified and are associated with several genes (Table 1).[20]

• Other causes of primary osteoporosis

Other rare causes of primary osteoporosis include connective tissue disorders such as Ehlers-Danlos and Marfan syndromes, as well as homocystinuria and osteoporosis-pseudoglioma syndrome (OPPG) which is caused by homozygous inactivating mutations in the LRP5 gene. Patients with OPPG may present with bone fragility, loss of vission due to exudative vitreoretinopathy type 4, learning difficulties, ligament laxity, and muscular hypotonia. Heterozygous LRP5 mutations can also lead to low bone density and increased fracture risk.

Additionally, mutations in WNT-1 and PLS3, along with the conditions such as Bruck syndrome (caused by mutations in the PLOD2 gene), Cole-Carpenter syndrome (associated with P4HB), Hajdu-Cheney syndrome (due to NOTCH2 mutations), geroderma osteodysplasticum (associated with GORAB), RAPADILINO syndrome (linked to RECQL4), gnathodiaphyseal dysplasia (caused by mutation in ANO5 gene), and spondylo-ocular syndrome (linked to XYLT2) are other rare causes of osteoporosis.[21]

• Idiopathic juvenile osteoporosis

In the absence of an underlying cause, the condition is termed idiopathic juvenile osteoporosis. This poorly understood disorder is characterized by widespread pain and difficulty in walking, often occurring during the pre-pubertal period. Vertebral compression fractures and long bone fractures in the metaphyseal regions are common, with the possibility of spontaneous remission after puberty or the development of persistent deformities.[22]

Secondary Osteoporosis

Secondary osteoporosis is more common and often caused by underlying chronic diseases and/or their treatment.[23] Frequent causes include chronic inflammatory diseases, endocrine disorders, immobilization, muscular diseases (especially Duchenne muscular dystrophy), malnutrition, and certain medications, particularly corticosteroids, anticonvulsants, and proton pump inhibitors (Table 2).[24]

Table 1. Types of OI*, Causing Genes, Inheritance Pattern and Mechanism			
OI Type	**Gene**	**Inheritance**	**Mechanism**
I-IV	COL1A1, COL1A2	AD	Defect in type 1 collagen synthesis
V	IFITM5	AD	Defect in mineralization
VI	SERPINF1	AR	Defect in mineralization
VII	CRTAP	AR	Defect in collagen modification
VIII	P3H1 (LEPRE1)	AR	Defect in collagen modification
IX	PPIB	AR	Defect in collagen modification
X	SERPINH1	AR	Defect in collagen folding
XI	FKBP10	AR	Defect in collagen folding
XII	SP7	AR	Defect in osteoblast differentiation and function
XIII	BMP1	AR	Defect in collagen processing
XIV	TMEM38B	AR	Defect in collagen modification
XV	WNT1	AR	Defect in WNT signaling
XVI	CREB3L1	AR	Defect in osteoblast differentiation and function
XVII	SPARC	AR	Defect in collagen processing
XVIII	TENT5A (FAM46A)	AR	Defect in osteoblast differentiation and function
XIX	MBTPS2	XLR	Defect in intramembrane proteolysis
XX	MESD	AR	Defect in WNT signaling
XXI	KDELR2	AR	Defect in retrograde Golgi to ER† transport
XXII	CDC134	AR	Defect in MAPK¥ signaling

*: Osteogenesis Imperfecta, †: Endoplasmic Reticulum, ¥: Mitogen-activated protein kinase

The mechanostat theory points out that bone development and strengthening occur in response to mechanical load. Genetic thresholds determine when osteoblast and osteoclast activities are activated to strengthen bone tissue. This mechanism provides functional adaptation to mechanical load, helping to maintain skeletal stability.[25] Chronic diseases, corticosteroid therapy, and muscle loss can impair the mechanostat, reducing its efficacy.

Proinflammatory cytokines such as TNF-α, IL-1, and IL-6 increase osteoclastogenesis and impair osteoblast function in chronic inflammatory diseases (e.g., Juvenile idiopathic arthritis, Crohn's disease), thereby negatively affecting bone formation. The use of corticosteroids for treatment in these conditions, along with reduced physical activity, delayed puberty, and decreased vitamin D levels, also contribute to the development of osteoporosis.[26,27]

Osteoporosis is a significant morbidity in cerebral palsy, with diagnosis often challenging due to patients' inability to express symptoms adequately. Anticonvulsants, immobility, and prolonged immobilization after surgeries exacerbate the risk of osteoporosis.[28]

The patients with Duchenne Muscular Dystrophy (DMD) are also at an increased risk of osteoporosis due to immobilization and long-term steroid use, which heigthen the risk of vertebral and lower extremity fractures.[29]

Corticosteroids suppress sex steroids and growth factors, increase PTH levels, reduce gastrointestinal calcium absorption, and promote muscle proteolysis, all of which contribute to osteoporosis and an increased risk of fractures.[27] Additionally, corticosteroids negatively impact linear growth, exert direct toxic effects on bone, accelerate osteoblast apoptosis, and prolong the lifespan of osteoclasts, thereby increasing bone resorption.[30]

Studies have shown that children with leukemia, the most common childhood malignancy, experience an increased risk of osteopenia at diagnosis and during treatment, particularly with chemotherapy.[31,32]

Table 2. Common Causes of Secondary Osteoporosis	
Endocrine Disorders	1. Hypercortisolism 2. Diabetes mellitus 3. Hyperthyroidism 4. Hyperparathyroidism 5. Hypogonadism 6. Vitamin D deficiency 7. Hypophosphatemia 8. Hypocalcemia
Haematologic Disorders	1. Leukemia 2. Thalassemia major 3. Bone-marrow transplantation
Medications	1. Anticonvulsants 2. Chemotherapy 3. Corticosteroids 4. Proton-pump inhibitors 5. GnRH analogues 6. Excess levothyroxine 7. Aromatase inhibitors
Chronic Inflammatory Disorders	1. Rheumatic diseases 2. Inflammatory bowel diseases 3. Kidney diseases
Neuromuscular Disorders	1. Duchenne muscular dystrophy 2. Spina bifida 3. Cerebral palsy
Malabsorption/Malnutrition	1. Anorexia nervosa 2. Celiac disease 3. Malnutrition

GnRH: Gonadotrophin-releasing hormone

Conditions that lead to estrogen deficiency, such as hypogonadism, anorexia nervosa, and gonadal failure due to chemotherapy, radiation, and autoimmune diseases, are also known to cause osteoporosis.[33,34]

APPROACH TO SUSPECTED OSTEOPOROSIS IN CHILDREN

The following steps should be considered in the evaluation of children presenting with suspected osteoporosis:

First step: Patient's medical history

1. **History and features of fractures:** Document the location, number, mechanism of injury (low or high energy trauma), the ages at which fractures occurred, and whether any surgical intervention or spontaneous recovery took place.

2. **Symptoms:** Assess for the presence of back pain indicative of vertebral fractures and any complaints related to underlying conditions (e.g., inflammatory bowel disease, leukemia).

3. **Family History:** Inquire about a history of osteoporosis, bone diseases, fractures, hearing loss, or kidney stones.

4. **Dietary Habits:** Evaluate dietary calcium, vitamin D, and protein intake.

5. **Medications:** Review any medications, particularly corticosteroids and anticonvulsants.

6. **Physical Activity:** Assess levels of physical activity.

Second step: Physical examination

1. **Anthropometric Measurements:** Record height, weight, head circumference, and upper-lower segment ratios.

2. **Systemic Examinations:** Conduct an examination of the cardiovascular, respiratory, and gastrointestinal systems, including an assessment of the thyroid gland.

3. **Bone and Joint Examination:** Evaluate for bone deformities, scoliosis, skin-joint laxity, and hypermobility

4. **Ocular Findings:** Note the presence of blue sclerae, myopia, vision defects.

5. **Dental Assessment:** Examine for signs of dentinogenesis imperfecta.

6. **Signs of Underlying Conditions:** Look for features suggestive of Cushing's syndrome, including acne, buffalo hump, moon face, hirsutism, striae, and any systemic diseases such as leukemia or inflammatory disorder.

7. **Pubertal Examination:** Assess for signs of hypogonadism.

Third step: Laboratory work-up

The parameters to be evaluated in the first step, as well as those for the second step, are listed in Table 3. Bone turnover markers should be assessed according to age and sex, as they can be physiologically high in young individuals due to rapid bone formation. Furthermore, it has been observed that BTMs increase during the process of fracture healing.[35,36]

Fourth step: Imaging

• ***Dual-energy X-ray Absorptiometry (DXA)***

DXA is the most commonly preferred method for evaluating bone mineral content (BMC) or BMD in children.[37] DXA measures BMC (in grams) and the projected bone area (in cm^2). These

Table 3. Laboratory work-up	
Key biochemical parameters	**Secondary assessments**
1. Complete blood count 2. BUN, creatinine 3. Transaminases (AST, ALT) 4. ESR* 5. Albumin, calcium, phosphate, ALP† (total and bone-specific), ionized calcium, blood gases 6. Urine calcium/creatinine ratio 7. TRP‡, TmP/GFR§ 8. 25-OH vitamin D 9. Parathormone	1. Bone turnover markers (osteocalcin, beta-crosslaps, P1NP‖) 2. TSH¶, free T4 3. IGFs (if required) 4. Celiac antibodies 5. Gonadotropic hormones, Prolactin 6. Urinary free cortisol/dexamethasone suppression test 7. Consider biochemical testing for inborn error of metabolism

* Eritrocyte sedimentation rate, †Alcaline phosphatase, ‡Tubular reabsorption of phosphate, §The ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate, ‖Serum type 1 procollagen, ¶Thyroid-stimulating hormone

values are subsequently used to calculate areal BMD (aBMD, expressed in g/cm²). The measurements are then converted to age- and sex-specific Z-scores for comparison with normal population. However, DXA is considered unreliable in children under 5 years of age due to motion artifacts and a lack of age-specific reference data.[9]

BMD measurement typically focuses on the posterior-anterior lumbar spine and total body minus head in children. In specific cases, other regions, such as the proximal femur, distal radius, and lateral distal femur, may be utilized for BMD measurement.[35] For instance, imaging may be suboptimal due to spinal rods and plates resulting from scoliosis surgery, evaluating these additional regions valuable for assessment.

In children and young adults, BMD scanning is usually recommended after two or more fractures, fractures occurring in unusual locations (such as the spine or hip), or the presence of chronic diseases or medications that predispose individuals to osteoporosis.[38]

The advantages of DXA include low radiation exposure and rapid application. However, as a two-dimensional measurement, it may yield lower-than-normal results in shorter children or higher-than-normal results in taller children; therefore, height adjustments are necessary.[39] Additionally, vertebral compression fractures and mineral deposits may lead to falsely elevated DXA values.[35]

- ***Radiography***

Radiography is commonly used to detect VCFs and scoliosis. Children with VCFs may not exhibit obvious symptoms, such as back pain, as often seen in adults; therefore, lateral vertebral radiographs should be obtained for all children suspected of having osteoporosis.[14] Standard evaluation typically involves lateral views from the T4 to L4 vertebrae. It is important to distinguish physiological wedging in the mid-thoracic vertebrae (T5-T7) from actual fractures.[40]

- ***Vertebral Fracture Assessment (VFA)***

VFA has been recognized as a suitable alternative for detecting lateral vertebral fractures, particularly due to the potential side effects associated with frequent radiographs in children. VFA utilizes DXA to obtain lateral vertebral images, delivering significantly less radiation than traditional radiography.[41,42]

- ***Bone Biopsy***

Bone biopsies provide valuable information on bone microarchitecture, and dynamic parameters can be assessed through tetracycline labeling. Bone biopsy is especially useful when the diagnosis is unclear, as it aids in distinguishing different types of osteoporosis by analyzing histological features and bone metabolic activity.[9,24]

Fifth step: Genetic investigations

Genetic diagnosis helps confirm clinical suspicion and facilitates the management of osteoporosis. It enables screening for family members of diagnosed individuals, promotes early detection of existing conditions in these individuals, and contributes to preventive treatment and genetic counseling.[43]

Numerous skeletal disorders leading to low and high BMD have been identified, forming an expanding group.[44]

MANAGEMENT OF CHILDHOOD OSTEOPOROSIS

General Advice

Childhood osteoporosis should be managed by a multidisciplinary team comprising pediatric endocrinologists specializing in bone health, orthopedic surgeons, neurosurgeons, physiotherapists, geneticists, dentists, audiologists, and child psychiatrists.

Effective management of osteoporosis requires lifestyle changes, including increased physical activity and improved nutrition quality. The diet should be rich in calcium and protein. It is recommended that 25-OH vitamin D levels be maintained at or above 50 nmol/L (20 ng/dL). Additionally, zinc, magnesium, copper, and vitamins C and K are also essential for sustaining bone health.[45]

Medication

Pharmacological treatment is not always immediately necessary following the diagnosis of childhood osteoporosis, as children's skeletal systems rapidly repair decreased BMD and remodel vertebral deformities. This capacity for recovery depends on the temporary nature of the risk factor and the remaining growth potential.[18] For instance, approximately 80% of childhood leukemia patients with VFs are able to reshape their vertebral bodies within six years of diagnosis without any treatment.[46] Conversely, in conditions such as corticosteroid-treated DMD, the high incidence of long bone fractures and vertebral fractures, coupled with persistent risk factors, makes spontaneous improvement in BMD and vertebral body reshaping less likely without treatment.[47] Therefore, when deciding to initiate pharmacological treatment, it is essential to consider both the reversibility of risk factors for osteoporosis and the remaining growth potential. Adolescents have more limited bone repair capacity compared to younger children and may require earlier intervention. Early treatment is also recommended for children with primary osteoporosis due to the permanent nature of the underlying issue.[9,18]

Antiresorptive treatment

• Bisphosphonates (BPs)

Bisphosphonates are pyrophosphate analogs that inhibit bone resorption and are considered the first-line treatment for childhood osteoporosis.[6] BP therapy should be considered in children with a history of low-trauma fractures and persistent risk factors that compromise bone health. Common indications for treatment include low-trauma long bone fractures, symptomatic VFs, or moderate-to-severe asymptomatic VFs.[48]

Before initiating BPs, the patient's suitability must be thoroughly assessed. Patients should have normal pre-treatment calcium, phosphate, and 25-OH vitamin D levels, with no evidence of renal insufficiency. Intravenous (IV) zoledronic acid is contraindicated in patients with acute renal insufficiency, and dose adjustments are necessary for those with a glomerular filtration rate of less than 60 ml/min/1.73m².[49]

Pamidronate was first shown to benefit bone health in children with osteoporosis. It is administered at intervals of 2-4 months, with a total annual dose of 6-12 mg/kg.[50] Zoledronic acid is typically administered every 6 to 12 months at doses ranging from 0.0125-0.5 mg/kg, with a maximum annual dose of 4 mg (Figure 3).[51–53] Zoledronic acid is 100 times more potent than pamidronate.[49] Various studies have demonstrated similar long-term effects on BMD for both zoledronate and pamidronate.[54,55]

• Side effects of BPs

The most common side effects of BPs include acute-phase reactions, such as low-grade fever, headache, myalgia, nausea, vomiting, rash, and decreased lymphocyte count.[56] Hypocalcemia and hypophosphatemia have been reported following the first dose of zoledronic acid, although serious cases requiring calcium infusion are rare.[57] Zolendronic acid is more likely to cause hypocalcemia than pamidronate.[56]

Chronic corticosteroid users should receive stress coverage or be closely monitored for signs of adrenal crisis during the first dose of BPs.[49] Osteonecrosis of the jaw is a potential long-term side effect, although it has not been reported in any studies involving children.[51,58] Atypical femur fractures represent another long-term side effect.[59]

Children with moderate to severe OI often require bone correction surgery, and BP treatment has been reported to prolong bone healing at osteotomy sites. Therefore, it is

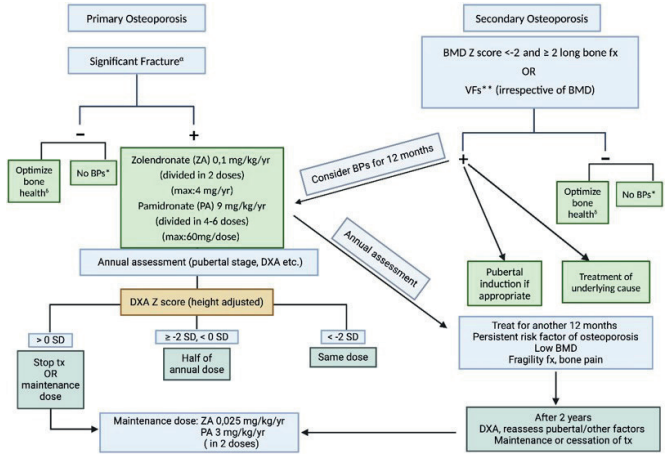

Figure 3. Treatment Algorithm in Primary and Secondary Osteoporosis

[α] Vertebral compression fractures or ≥ 2 long bone fractures caused by low trauma, * Bisphosphonates, ** Vertebral fractures, [δ] Dietary calcium intake, adequate Vitamin D levels, weight-bearing exercises

recommended to withhold BP treatment for at least 4 months post-osteotomy. This issue has not been reported following fractures;[60] thus, the dose of BP treatment should not be omitted due to the presence of fractures.

Oral BPs (e.g., alendronate, risedronate) have been shown to increase BMD in osteopenic children, with studies highlighting their ease of use and tolerability.[61–63] However, some studies suggest that IV BPs may be superior to oral therapy for reducing VF risk, increasing vertebral height and trabecular volumetric BMD. Therefore, intravenous therapy is preferred, while oral BPs may be considered in mild cases or when IV access is unavailable.[49,64]

For children at high risk of osteoporosis, it is recommended that BP therapy continue until the epiphyseal plates are fully closed and the children reach their final height. This is due to the fact that newly formed bone around the growth plate is less dense and may predispose the child to new fractures.[65] The current approach involves administering a high-dose regimen until the patient is clinically stable (at least 2 years from the beginning of treatment), after which treatment may continue at a maintenance dose (half dose or lower) until final height is achieved to avoid over-treatment.[66]

If the risk factor is eliminated in children at temporary risk, treatment discontinuation can be considered after a fracture-free period of 6-12 months (both VF and non-VF), resolution of previous VFs, and normalization of the BMD Z-score.[49]

- ***Denosumab***

Denosumab is a monoclonal antibody developed against RANKL, which regulates osteoclast differentiation and function. It inhibits bone resorption by preventing the binding of RANKL to RANK.[67] Its use has been explored in pediatric patients with conditions such as giant cell bone tumors, aneurysmal bone cysts, fibrous dysplasia, and OI.[68]

In a study comparing the efficacy of denosumab with zoledronic acid in patients with OI, denosumab significantly increased BMD and improved spinal morphometry, demonstrating effects similar to zoledronate. However, denosumab is associated with a risk of severe hypercalcemia following discontinuation or interruption of the treatment, with some cases of hypercalcemic crisis reported. This side effect can be managed by BPs. Therefore, denosumab is not yet recommended as a first-line treatment for OI.[69]

In children with the SERPINF1 mutations (OI Type VI), where the osteomalacic nature of the bone was assumed to reduce the effectiveness of BPs, alternating treatments with denosumab and zoledronate were implemented. This approach mitigated rebound hypercalcemia and utilized the anti-resorptive effect of denosumab.[70]

Anabolic treatments

- ***Testosterone***

Pubertal induction may be recommended if the patient's age is appropriate, particularly in cases of chronic disease associated with delayed puberty, such as prolonged corticosteroid use. In patients with DMD and delayed puberty, testosterone treatment has been administered, resulting in increased BMD.[71]

- ***Teriparatide***

Teriparatide is a recombinant analog of parathyroid hormone that promotes osteoblastogenesis and prevents osteoblast apoptosis.[9] Studies in adults, particularly in postmenopausal women, have demonstrated its ability to reduce the risk of VF and increase BMD.[72] Animal studies have identified a potential risk of osteosarcoma, and until recently, its use in children was not approved.[73] In late 2020, the FDA determined that this side effect is limited to animal studies.[9,49] Clinical trials are needed to evaluate the use of teriparatide in pediatric osteoporosis.

- ***Growth Hormone (GH)***

Growth hormone increases cortical bone thickness and muscle mass.[74] A study in patients with OI type III and IV indicated that GH treatment moderately increased BMD and reduced fracture rates.[75] However, there is insufficient evidence to support the use of GH treatment for osteoporosis.

Anti-Sclerostin Treatment

Sclerostin inhibits bone formation by blocking the Wnt signaling pathway. Anti-sclerostin monoclonal antibody treatments (e.g., setrusumab, romosozumab, blosozumab) counteract this effect. Animal studies have demonstrated increases in BMD and bone formation markers, as well as positive changes in bone geometry.[76] Romosozumab is FDA-approved for the treatment of postmenopausal osteoporosis in women.[77] International clinical phase trials for anti-sclerostin treatment in pediatric patients with OI are currently ongoing.

CONCLUSION

Osteoporosis, caused by both primary and secondary factors, is associated with significant morbidity. In addition to primary

osteoporosis, it is crucial to understand the predisposing conditions that may lead to osteoporosis in patients presenting with features of primary osteoporosis. It is also essential to screen for secondary causes in these patients. Furthermore, early diagnosis and treatment are vital to improve quality of life. While BPs, which inhibit bone resorption, are the preferred agents for treatment, new drugs, and clinical phase trials focusing on reducing bone resorption and promoting bone formation show promise.

Author contribution

Review conception and design: ST, AG; literature review: AG; draft manuscript preparation: AG. 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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Original Article

Evaluation of cardiovascular disease risk in children with type 1 diabetes mellitus by oscillometric method and echocardiography

Gönül Büyükyılmaz[1], Yasemin Özdemir Şahan[2], Ali Kansu Tehçi[3], Emre Özer[1], Nevin Özdemiroğlu[2], Mihriban İnozü[4], İbrahim İlker Çetin[2], Fatih Gürbüz[5], Mehmet Boyraz[5], Umut Selda Bayrakçı[4]

[1]Department of Pediatric Endocrinology, Ankara Bilkent City Hospital, Ankara, Türkiye
[2]Department of Pediatric Cardiology, Ankara Bilkent City Hospital, Ankara, Türkiye
[3]Department of Pediatrics, University of Health Sciences, Ankara Bilkent City Hospital, Ankara, Türkiye
[4]Department of Pediatric Nephrology, Ankara Bilkent City Hospital, Ankara, Türkiye
[5]Department of Pediatric Endocrinology, Ankara Yıldırım Beyazıt University Faculty of Medicine, Ankara, Türkiye

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ABSTRACT

Objective: Type 1 diabetes mellitus (T1DM) patients have an increased risk of developing cardiovascular disease. Our study aimed to compare epicardial fat thickness (EFT), carotid intima-media thickness (cIMT), and arterial stiffness parameters such as pulse wave velocity (PWV), augmentation index (AI), which are well-known early markers of cardiovascular disease in adults, between children with T1DM and healthy individuals.

Methods: One hundred fifteen children with T1DM and 87 age, gender, and anthropometric measurements-matched healthy children were included. The inclusion criteria for patients were having T1DM for at least 2 years and ages 8–18 years. Epicardial fat thickness and cIMT were assessed by the same pediatric cardiologist. Noninvasively, the Mobil-O-Graph® was used to evaluate PWV, AI (normalized to a heart rate of 75 beats/sec: AI@75), and the hemodynamic parameters.

Results: Epicardial fat thickness and cIMT were higher (p<0.001), stroke volume and cardiac index scores were found significantly lower (p<0.001 and p=0.030, respectively) in the patient group compared with the control group. While the AI@75 was significantly higher in the patient group (p <0.01), PWV did not differ between groups (p=0.782). According to the glycated hemoglobin A1c (HbA1c) level, EFT (p=0.015) was significantly higher, and cardiac index score (p=0.030) was significantly lower in the HbA1c >9% group. A strong positive correlation was detected between mean cIMT and microalbuminuria (Rho=,925, p<0.01).

Conclusion: These results support that children with T1DM present significant changes in important subclinical indicators for showing the development of cardiovascular disease. Cardiologic assessment of patients with T1DM can be beneficial for long-term care.

Keywords: arterial stiffness, carotid intima-media thickness, epicardial fat thickness, type 1 diabetes mellitus

INTRODUCTION

Type 1 diabetes mellitus (T1DM), caused by an absolute or relative insulin deficiency due to the destruction of pancreatic beta cells, is a genetic autoimmune condition.[1] Although there has been a decrease in complications as a result of tight glycemic control in recent decades; individuals with T1DM are at an increased risk of developing both acute and chronic complications. Chronic vascular complications are classified as microvascular and macrovascular. Macrovascular complications

Correspondence: Gönül Büyükyılmaz **E-mail:** gonulgulal@hotmail.com
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result in cardiovascular disease (CVD) and stroke.[2] Long duration of DM, poor metabolic control, and coexisting hypertension or dyslipidemia are other risk factors for the development of CVD in T1DM patients.[3,4] Studies have reported that atherosclerotic changes may start in the first two decades of life in patients with T1DM.[5] Even in children and young adults, manifestations of cardiovascular remodeling present early after initial diagnosis. This is found to be related to chronic hyperglycemia, endothelial dysfunction, and chronic inflammation.[6,7] Hyperglycemia leading to an increase in oxidative stress is considered the key pathophysiological factor of both complications.[8]

The main cause of morbidity and mortality in people with T1DM is CVD.[2] Although few data exist on the impact of CVD risk factors in pediatric patients with T1DM, epicardial fat thickness (EFT), carotid intima-media thickness (cIMT), and arterial stiffness (AS) may contribute to the assessment of CVD risk in patients with T1DM. In addition to being a visceral fat depot with protective functions for the heart under physiological conditions, EFT is also the source of several proinflammatory and proatherogenic cytokines that can biologically affect myocardial and epicardial coronary arteries.[9] Studies have shown that increased EFT is a potential indicator of cardiovascular risk factors and coronary calcification.[10] Epicardial fat thickness was found to be an indicator of endothelial dysfunction in T1DM by studies examining the relationship between EFT and endothelial dysfunction.[11] Carotid intima-media thickness is also a structural marker of early atherosclerosis and has been associated with both prevalent and incident CVD.[12]

Arterial stiffness, a biomarker of vascular health, reflects arterial elasticity and compliance and is an index of arterial wall rigidity. Pulse wave analysis (PWA) is used to measure AS. There are various indices to describe the AS. These include pulse wave velocity (PWV), which is accepted as the most simple, noninvasive, robust, and reproducible method to determine AS and augmentation index (AIx).[13,14] Despite the proposed contributions of increased EFT, cIMT, and AS to the atherosclerotic changes in adults with T1DM, studies in children with T1DM are limited.

Early detection of cardiovascular abnormalities in children with T1DM could significantly alter clinical management and improve long-term health outcomes. Given the advancements in T1DM management and the increasing lifespan of patients, understanding and mitigating long-term cardiovascular risks in this population has never been more crucial. Our study aimed to determine EFT, cIMT, and AS in T1DM patients in comparison to healthy control groups and determine the risk factors affecting these.

MATERIAL AND METHODS

Participants

Participants of this cross-sectional, single-center study were recruited from the pediatric endocrinology department of Ankara Bilkent City Hospital. 115 type T1DM patients with a body mass index (BMI) between the -2 and +2 standard deviation scores (SDS) according to age and gender, having this diagnosis for at least 2 years and ages 8–18 years, were consecutively included in the study. Diagnostic criteria for diabetes are based on the American Diabetes Association classification.[15] The T1DM patients were selected from those under an intensive insulin regimen (glargine and rapid insulin (lispro-aspart)) and whose routine clinical and laboratory evaluations were regularly monitored in the pediatric endocrinology clinic. Exclusion criteria for the patient were determined to be having any chronic diseases other than T1DM and the presence of a congenital and/or acquired heart disease, hypertension, etc. This exclusion was necessary to isolate the cardiovascular effects attributable solely to T1DM, though it may limit the applicability to children with comorbid conditions. Healthy adolescents were recruited from those who applied to the pediatric clinic for annual routine child health check-ups and were healthy. The control group consisted of 87 sex, age, Tanner stage, and anthropometric measurements-matched healthy children. Exclusion criteria for the control group were determined to be having any chronic diseases and the presence of a congenital and/or acquired heart disease, hypertension, etc. The study was approved by the clinical research ethics committee of Ankara Bilkent City Hospital with the decision no 23-3128 dated January 04, 2023. Informed consent was obtained from all guardians, and assent was sought from children where appropriate, following a child-friendly explanation of the study's purpose and procedures. Ethical principles were adhered to, and the research was conducted in accordance with the Declaration of Helsinki.

Medical history, as well as age at diagnosis and duration of being a diabetic, were recorded, and physical examinations were performed in all patients and controls. All physical examinations were performed by a single medical doctor. For each participant, weight and height measurements were done, and BMI and SDS were estimated. The BMI was assessed using the weight (kg) ratio to height squared (m^2). We examined anthropometric measurements using an online calculation tool (www.childmetrics.org).[16] Fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG) were measured by enzymatic colorimetric assays (Atellica Solution CH90, Siemens, Germany). For patients, glycated hemoglobin A1c (HbA1c) plasma level, measured within 0 to 14 days from

the measurement of EFT, was determined using capillary electrophoresis on the Capillarys 3 Tera, Sebia (Lisses, France). The arithmetic average of the HbA1c levels in the last two years was taken. The blood pressure (BP) of the participants was categorized by percentiles.[17]

Pulse wave analysis measurement

In our study, a cuff-based validated oscillometric Mobil-O-Graph device (I.E.M., GmbH, Aachen, Germany) was used to PWA. This device is a commercially available brachial oscillometric ambulatory blood pressure monitor approved by the European Society of Hypertension.[18] Measurements were taken from the left arm in a room after a minimum rest of 5 minutes. The cuff size was chosen based on the circumference of the middle upper arm. Data from the Mobil-O Graph device was exported and analyzed using Hypertension Management Software Client-Server version 5.2.3 (I.E.M.). In addition to PWV, other parameters such as AIx, and hemodynamic parameters such as stroke volume, cardiac output, and cardiac index were measured. The PWV is the speed of the pressure wave that passes through the vessels of an organism and is calculated by dividing the distance traveled by the time it takes to travel the distance. A higher PWV indicates increased AS.[19] Augmentation index, a surrogate measure of stiffness in the peripheral arterial resistance, is calculated as the difference between the second and the first systolic peak pressure and is expressed as a percentage of the central pulse pressure. The augmentation index was normalized to a heart rate of 75 beats/sec (AIx@75) for comparison with different heart rates.[20] A higher AIx suggests increased AS.[21] The stroke volume refers to the volume of blood pumped into the body from the left ventricle during a heartbeat. The cardiac index is a parameter for assessing cardiac output and is calculated as the quotient of the cardiac output and the body surface.

Echocardiographic examination

Echocardiographic examinations were performed by using an ultrasound system (iE33, Philips, The Netherlands, Eindhoven) equipped with a broadband (1-5 MHz) X5-1 transducer. Echocardiographic examinations were obtained by a single experienced pediatric cardiologist blind to the diabetes status of participants. Epicardial fat was identified as the echo-free space between the myocardium's outer wall and the pericardium's visceral layer. Measurement of EFT was obtained with the participant in the left lateral decubitus position. The measurements were performed on each parasternal long-axis and short-axis view by directing the ultrasonic beam perpendicular to the right ventricular free wall from the reference point of aortic annulus on the parasternal long axis and from the reference point of interventricular septum and papillary muscle tip on the parasternal short axis section. Epicardial fat thickness was measured from its thickest part in mm at the end of systole due to deformation and pressure on adipose tissue. The average value of three cardiac cycles from each echocardiographic view was considered.

Measurement of cIMT was performed by the same experienced pediatric cardiologist by using a Vivid E95 echocardiography machine (GE Vingmed, Horten, Norway) equipped with a 9L linear probe (2,4-10 Mhz). Carotid intima-media thickness is defined as the distance between the first echogenic line (lumen–intima interface) and the second echogenic line (media–adventitia interface) of the far wall. Measurements were obtained from the far wall of the common carotid artery on both sides at 10–20 mm proximal to the bifurcation at the end-diastole. On the images of the thickest cIMT, measurements were taken with calipers positioned on a zoomed image of the common carotid artery. The mean value of the three measurements on each side was calculated.

Statistical analysis

All analyses were carried out using SPSS 25.0 (IBM, USA). The findings of the study are expressed as frequency and percentages. The normality test was conducted using the Kolmogorov-Smirnov test. Non-normally distributed variables were presented as the median and interquartile range (IQR) with 25^{th}–75^{th} percentiles, while variables with normal distribution are expressed as mean ± standard deviation. Categorical variables were compared using the Chi-square test. Fischer's exact test was applied according to the percentage of expected counts. Numerical variables with and without normal distribution were compared using the independent samples t-test and Mann–Whitney U, respectively. The Kruskal–Wallis test was used to compare numerical variables without normal distribution between more than two groups. Spearman correlation analysis was performed to determine the variables associated with EFT, cIMT, AIx@75, and PWV scores, and $p<0.05$ was considered as a statistically significant value. Multivariable logistic regression analysis was performed to detect associated factors with PWV and AIx@75. Power analysis was conducted using G-power 3.1.9.4. According to the t-test for EFT between T1DM and the control group based on the study conducted by Chambers et al. it was determined that 38 patients should be included in each group for an effect size of 0.767, a margin of error of α:0.05 and a power ratio of 95%.[22]

RESULTS

The demographic, clinical, and laboratory parameters of the participants are presented in Table 1. There were no significant

Table 1. Demographic, clinical findings and laboratory results of the groups				
Variable		**Type 1 DM group (n=115)**	**Control group (n=87)**	**P**
Age (years)		14.0 (11.0-16.0)	14.0 (11.0-16.0)	0.374
Gender (n/%)	Female Male	57 (49.6) 58 (50.4)	46 (52.9) 41 (47.1)	0.672
Weight (kg)		51.0 (38.0-61.0)	48.0 (35.0-57.0)	0.317
Height (cm)		158.00 (144.60-166.00)	155.00 (144.30-166.20)	0.636
BMI		20.16±3.10	19.41±2.8	0.077
BMI SDS		0.01 (-0.64-0.87)	-0.12 (-0.88-0.50)	0.173
Peripheral systolic blood pressure (percentile)		60.5 (36.75-74)	65 (45.5- 74.75)	0.234
Peripheral diastolic blood pressure (percentile)		57 (42-69)	60.5 (44-73.75)	0.198
Duration of tip 1 DM (year)		6.0 (4.0-9.0)	-	
Synchronous HbA1c (%)		8.6 (7.6-9.7)	-	
Average HbA1c in the last two years (%)		8.5 (7.7-9.6)	-	
TG (mg/dl)		84.0 (64.0-129.5)	72.0 (54.5-93.5)	**<0.01**
TC (mg/dl)		156.0 (144.0-180.0)	144.5 (132.3-155.5)	**<0.001**
LDL (mg/dl)		81.0 (69.0-94.5)	74.5 (59.8-85.3)	**<0.01**
HDL (mg/dl)		56.5 (46.8-64.0)	53.0 (44.8-63.3)	0.286
Microalbumiuria (n/%)	Yes	6 (5.2)	-	
Duration of microalbumiuria (mean±SD)		2.83±0.79	-	

BMI: Body mass index, BMI SDS: Body mass index standard deviation score, DM: Diabetes mellitus, HbA1c: Glycosylated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TC: Total cholesterol, TG: Tryglyseride.

differences in age, gender, and BMI SDS between the groups (p>0.05). The median HbA1c of the patient group was 8.6%, and the median HbA1c of the last two years was 8.5%. Total cholesterol, TG, and LDL were higher in the patient group (for TG and LDL p<0.01 and for TC p<0.001); however, HDL levels were similar for both groups (p>0.05). No significant differences were found in the peripheral systolic BP (SBP) percentile and diastolic BP (DBP) percentile (p>0.05).

The PWA device scores, EFT, and cIMT values are shown in Table 2. The stroke volume and cardiac index scores were significantly lower in the patient group (p<0.001 and p=0.036). The AIx@75, EFT, and mean cIMT scores were higher in the patient group (p<0.01 for the AIx@75 and p<0.001 for other variables). There were no significant differences in other variables between the two groups (p>0.05).

When the patient group was divided into three groups according to DM duration as 2-5 years (n=51), 6-10 years (n=44), and >10 years (n=20), stroke volume (p=0.938), cardiac output (p=0.92), AIx@75 (p=0.823), PWV (p=0.774), EFT (p=0.432), and mean cIMT (p=0.782) were similar between groups. Therefore, the cardiac index score was significantly lower in the >10 years of DM group. (p=0.027). According to the HbA1c level three groups were formed: HbA1c <7.5% (n=25), 7.5-9% (n=50), and >9% (n=40). Stroke volume (p=0.882), cardiac output (p=0.657), AIx@75 (p=0.684), PWV (p=0417, and mean cIMT (p=0.582) were similar between groups. Therefore, EFT (p=0.015) was significantly higher, and cardiac index score (p=0.026) was significantly lower in the HbA1c >9% group. Epicardial fat thickness is weakly correlated with BMI and HbA1c in the last two years (respectively, Rho=,214, p=0.022; Rho=,201, p=0.032). There was a strong positive correlation between mean cIMT and microalbuminuria (Rho=,925, p<0.01), a weak positive correlation between mean cIMT and TG (Rho=,217, p=0.021), and a weak negative correlation between mean cIMT and HDL (Rho=-,292, p<0.01). No correlation was found between EFT, mean cIMT, and other variables (p>0.05) (Table 3).

Table 2. Comparison of the pulse wave analysis device scores and echocardiographic assessment of the patient and control groups

	Type 1 DM group (n=115)	Control group (n=87)	p
Hemodynamics			
Stroke volume (ml)	46.30 (41.60-54.40)	49.1 (45.3-62.9)	**<0.001**
Cardiac output (l/min)	4.4 (4.1-4.8)	4.3 (4.0-4.9)	0.496
Cardiac index (l/min/m^2)	2.9 (2.6-3.4)	3.3 (2.8-3.6)	**0.036**
Arterial stiffness			
AIx@75 (%)	33.2±11.5	28.1±11.6	**<0.01**
PWV (m/s)	4.5 (4.3-4.8)	4.6 (4.3-4.7)	0.782
Echocardiographic assessment			
EFT	4.9 (4.2-5.5)	3.10 (2.8-3.5)	**<0.001**
Right cIMT	0.43 (0.40-0.46)	0.40 (0.38-0.41)	**<0.001**
Left cIMT	0.43 (0.41-0.45)	0.40 (0.38-0.41)	**<0.001**
Mean cIMT	0.43 (0.41-0.46)	0.40 (0.39-0.42)	**<0.001**

AIx@75: Corrected augmentation index for heart rate of 75 beats/sec, cIMT: Carotis intima-media thickness, DM: Diabetes mellitus, EFT: Epicardial fat thickness, PWV: Pulse wave velocity. Data are represented as mean ± SD.

Table 3. Correlation of epicardial fat thickness and mean cIMT with the duration of diabetes mellitus, body mass index, hemoglobin A1c, microalbuminuria, serum lipids, and carotid intima-media thickness

EFT	Duration of DM	BMI	Average HbA1c*	Microalbuminuria	TG	TC	LDL	HDL	Mean cIMT
Rho	,081	**,214**	**,201**	-,016	,067	,025	,026	-,062	,158
P	0.393	**0.022**	**0.032**	0.865	0.486	0.790	0.783	0.517	0.093
Mean cIMT									
Rho	,128	,147	-.050	**,925**	**,217**	-,033	,132	**-,292**	-
P	0.171	0.117	0.595	**<0.01**	**0.021**	0.726	0.163	**<0.01**	

*Average of previous 2 years. BMI: Body mass index, cIMT: Carotis intima-media thickness, DM: Diabetes mellitus, EFT: Epicardial fat thickness, HDL: High-density lipoprotein, HbA1c: Glycosylated hemoglobin, LDL: Low-density lipoprotein, TC: Total cholesterol, TG: Tryglyseride.

Table 4. Correlation analysis of epicardial fat thickness, mean cIMT and pulse wave analysis device scores in the patient group

		Stroke volume	Cardiac output	SBPp	DBPp	Cardiac index	AIx@75	PWV
EFT	Rho	,266	,224	**,348**	**,248**	-,148	-,057	,344
	P	**0.009**	**0.028**	**<0.01**	**0.014**	0.149	0.581	**<0.01**
Mean cIMT	Rho	,150	,059	-,035	-,025	-,099	-,088	-,018
	P	0.139	0.559	0.729	0.219	0.328	0.385	0.856

AIx@75: Corrected augmentation index for heart rate of 75 beats/sec, cIMT: Carotis intima-media thickness, EFT: Epicardial fat thickness, DBPp: Peripheral diastolic blood pressure; SBPp: Peripheral systolic blood pressure; PWV: Pulse wave velocity.

The patient group has a weak correlation between EFT-stroke volume, EFT-cardiac output, and EFT-PWV (p<0.05). The EFT is weakly correlated with SBP and DBP (respectively, Rho=,348, p<0.01; and Rho=,248 p=0.014). No correlation was found between median cIMT and pulse wave analysis device scores (p>0.05) (Table 4).

The correlation analysis of PWV and AIx@75 found no meaningful correlation of these parameters with each other, HbA1c, DM duration, and serum lipids in the patient group. However, a moderate positive correlation was found between PWV and BMI (Rho=,435 p<0.001).

DISCUSSION

Our study demonstrated that EFT, cIMT, and AIx@75 are increased in children with T1DM compared to the healthy control group. In addition, stroke volume and cardiac index were significantly lower in patients with T1DM than the controls. These results support the idea that children with T1DM present significant changes in important subclinical indicators for the development of cardiovascular disease. We also determined the correlation between AS, EFT, cIMT and HbA1c, lipid profile, and diabetes duration in patients. To our knowledge, this is the first clinical study in the literature in which EFT, cIMT, and AS were evaluated together in the same patient group.

The risk of CVD begins in childhood with subclinical abnormalities in patients with T1DM. Epicardial fat thickness is an emerging method for detecting these early changes. In a recent systematic review and meta-analysis, Li et al. reported that EFT was higher in diabetic patients than controls.[23] The reason for the increase in EFT in patients with T1DM is not fully understood. Chambers et al. first showed that youth with T1DM (mean age 12.4 ± 2.9) exhibited significantly higher EFT compared to age, sex, and BMI-matched controls. They found that increased EFT was associated with age, adiposity, and BP but not disease duration, insulin dose, or glycemic control.[22] Another study including T1DM children with a diabetes duration of less than 5 years, with a diabetes duration of 5 years or more, and healthy controls reported that EFT was significantly higher in children with a diabetes duration of ≥5 years. They found a significant positive correlation between EFT and the age of children with diabetes, waist circumference, BMI, and duration of diabetes.[24] In the present study, we demonstrated similar results, with higher EFT in the patients compared to controls. A weak positive correlation of EFT with BMI and average HbA1c in the last two years was found. No significant correlation was observed between EFT and disease duration. Some studies found no relationship between EFT and DM duration when the literature was examined.[22,25-28] These suggest that structural alterations may begin in the early phases of T1DM. There is scarce data about this correlation in the T1DM group.

Recent results from a meta-analysis suggest that there is an association between ultrasonographic parameters of the carotid vessels and both complications of diabetes.[29] It was reported that cIMT is a sign of preclinical atherosclerosis.[30] Several cross-sectional studies have reported greater cIMT in children with T1DM compared to age-matched controls.[31] However, some studies have reported no differences in cIMT between children with T1DM and healthy controls.[32] While some studies reported an association between cIMT and age, blood pressure, lipid levels, HbA1c, or diabetes duration, some studies found no association.[31] Glackin et al. found that children with T1DM who had ambulatory blood pressure monitoring (ABPM) abnormalities had greater cIMT compared to those with normal ABPM. This relationship was found to be positively influenced by BMI.[33] Another study also reported that the mean cIMT was greater in persons with diabetes. Especially they found that the mean cIMT was significantly higher in persons with a diabetic complication (including hypertension, retinopathy, or microalbuminuria). No correlation was detected between cIMT and age, Tanner stage, duration of diabetes, BMI, blood pressure, HbA1C, and lipids.[34] Strong positive correlation between mean cIMT and microalbuminuria, a weak positive correlation between mean cIMT and TG, and a weak negative correlation between mean cIMT and HDL were found in the present study. No correlation was found between mean cIMT and duration of diabetes and HbA1c. These findings suggest that the effects of glycemic control on atherosclerosis progression are a gradual process and may take years.

Arterial stiffness was measured by PWV (a marker of central aortic stiffness) and AIx@75 (a marker of peripheral stiffness) in children and adolescents with T1DM compared to healthy controls in systematic reviews and meta-analyses.[35,36] Results of studies are controversial. This may be due to a lack of data on clinical and biochemical parameters, different sample sizes, different racial populations, and different instruments and techniques used for measuring PWV and AIx@75 in studies. Duarte et al. have reported similar results to our study by using an oscillometric Mobil-O-Graph device. They evaluated 36 children and adolescents diagnosed with T1DM (mean age 12.4 ± 2.9) and 36 control group matched by sex and age. The AIx@75 was found significantly higher in the T1DM group. They did not find any difference between groups regarding PWV.[37] They showed that AIx@75 correlated negatively with age and height. This finding was interpreted as the first signs of vascular dysfunction are more likely to occur in intermediate-sized arteries rather than large arteries.[38] Also, a previous study suggested that AIx might be a more sensitive marker of arterial stiffening in younger individuals and aortic PWV more sensitive in those over 50 years of age.[39] From Turkey, Terlemez et al. evaluated 72 children with T1DM (mean age 12.8 ± 3.7 years). In this study, PWV and AIx@75 levels were significantly higher in T1DM patients than in the control group. They also showed a positive correlation between diabetes duration and HbA1c levels in patients with T1DM with respect to PWV and AIx@75 values.[40] Obermannova et al. found a positive association between PWV and HbA1c but not T1DM duration.[38] Another study indicated that AS was not associated with HbA1c. In this study, it was explained that the effects of hyperglycemia on the vascular system may not be seen with arterial stiffness measurements and that short diabetes durations do not measurably affect vascular structure

and function.[41] Similar to these studies, we also detected that the AIx@75 of the T1DM group was significantly higher than the control group. This finding is important because it indicates that AS increases in children with T1DM. In our study, the correlation analysis of PWV and AIx@75 showed no meaningful correlation of these parameters with each other: HbA1c, DM duration, and serum lipids. This may be related to the short duration of diabetes. These conflicting data highlight the need for comprehensive randomized controlled prospective studies.

Unlike other studies, the correlation between EFT and PWA device scores and between cIMT and PWA device scores was investigated in the present study. We found a weak correlation between EFT-PWV in the patient group. There was no correlation between cIMT and PWA device scores. We found that the stroke volume and the cardiac index of the T1DM group were significantly lower than the control group. These situations may be related to the increase in left ventricular afterload.

The strength of this study is that anthropometric measurements, including weight, height, BMI, and SDSs for all participants were consistent in the study groups. The limitations were as follows: The first was that our sampling method was taken only from a single center, and the second was related to vascular measurements. Pulse wave velocity and AIx were calculated indirectly by a cuff oscillometric method with an algorithm. The third is that the observational design of this study precludes the ability to establish causality between T1DM and cardiovascular risk factors.

CONCLUSION

Significant increase in EFT, cIMT, and AIx@75 suggesting early CVD risk has been demonstrated in children with T1DM. Increased EFT and decreased cardiac index scores with increasing HbA1c levels and a strong positive correlation between mean cIMT and microalbuminuria highlight the importance of poor control in terms of CVD from childhood. Early detection and treatment of risk factors for CVD related to T1DM beginning in childhood are important. Assessment of EFT, cIMT, and AIx@75 can be of benefit to the long-term care of patients with T1DM. This helps to optimize the treatment of youth with T1DM to prevent future CVD.

Ethical approval

This study has been approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee No. 2 (approval date 04.01.2023, number 23-3128). Written informed consent was obtained from the participants.

Author contribution

Study conception and design:GB, YÖŞ, FG, MB, and USB; data collection: GB, YÖŞ, AKT, EÖ, NÖ, and Mİ; analysis and interpretation of results: GB, İİÇ, FG, and USB; draft manuscript preparation: GB, YÖŞ, İİÇ, and USB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of general characteristics of adolescent girls who had ovarian cystectomy (1-year single center experience)

Fatma Özgüç Çömlek[1], Ahmet Fatih Yılmaz[1], Muammer Büyükinan[1], Fuat Buğrul[1], Muslu Kazım Körez[2], Fatma Özcan Sıkı[3], Mehmet Sarıkaya[3]

[1]Department of Pediatric Endocrinology, Faculty of Medicine, Selçuk University, Konya, Türkiye
[2]Department of Biostatistics Endocrinology, Faculty of Medicine, Selçuk University, Konya, Türkiye
[3]Department of Pediatric Surgery, Faculty of Medicine, Selçuk University, Konya, Türkiye

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ABSTRACT

Objective: To evaluate the general characteristics and outcomes of adolescent girls who underwent ovarian cystectomy at our center over a one-year period, emphasizing the importance of conservative surgical approaches and ovarian preservation in this demographic.

Materials and Methods: This retrospective study included 15 adolescent girls who underwent ovarian cyst surgery at our clinic from March 2023 to March 2024. We collected data on age at menarche, menstrual patterns, family history, and preoperative measurements such as height, weight, and various tumor and hormonal markers. Imaging studies before surgery were reviewed.

Results: The median age of the patients was approximately 14.8 years. Most patients presented with abdominal pain, and imaging showed a mix of simple and complex cystic structures. Pathology results revealed a predominance of simple cysts, with a few cases of paratubal serous cysts, endometriomas, serous cyst adenomas, and one juvenile granulosa cell tumor. Surgical treatment was generally indicated by large cyst size, symptoms of torsion, or suspicion of malignancy.

Conclusions: Our findings highlight the varied presentations and surgical needs of adolescent girls with ovarian cysts. Emphasizing conservative surgical strategies that prioritize ovarian preservation is crucial in this age group due to the low malignancy rates and significant potential for future reproductive health implications. The outcomes underscore the necessity for careful preoperative evaluation and tailored surgical approaches based on individual patient characteristics and cyst features.

Keywords: adolescent girls, ovarian cystectomy, ovarian cyst, surgery

INTRODUCTION

It is estimated that pediatric ovarian lesions occur at a remarkable rate of 2–5 cases per 100,000 girls per year.[1–3] These lesions are extremely rare but cover a wide spectrum of pathology, from functional benign ovarian cysts to ovarian torsion and from benign tumors to highly aggressive neoplasms. Functional ovarian lesions (FOL), such as follicular and corpus luteum cysts, are the most common abnormalities in both adults and children, representing approximately 45% of all ovarian pathologies.[4] The clinical appearance of patients with adnexal masses varies depending on the underlying cause. The majority of diagnosed patients present with pelvic or lower abdominal pain, often due to torsion of the adnexa or hemorrhage into

Correspondence: Fatma Özgüç Çömlek **E-mail:** fatmaozguc@gmail.com
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the lesion.[5] Ovarian cyst treatment varies depending on the cyst type, size, and imaging findings (ranging from surveillance to surgery).[6] Laparoscopic cystectomy is a treatment method that has become the gold standard in the surgical treatment of persistent adnexal masses due to the presence of ovarian cysts and potential risks of rupture or malignancy.[7] In our study, we aimed to present the general characteristics of adolescent girls who had cystectomy for various reasons and applied to our outpatient clinic within the last year.

MATERIAL AND METHOD

We included in our study 15 adolescent girls who underwent ovarian cyst surgery for various reasons and applied to our polyclinic between March 2023 and March 2024. Ages at first menarche, menstrual patterns, and family history of cystectomy were questioned and recorded. A single trained nurse carried out height and weight measurements. Tumor marker and hormone test results were noted from the patients' files (Luteinizing hormone (LH), Follicular stimulating hormone (FSH), estradiol (E2), total testosterone (TT), thyroid stimulating hormone (TSH), free T4 (fT4), glucose, insulin, chorioembryonic antigen (CEA), beta-human chorionic gonadotropin (beta HCG), lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), C-125) Additionally, 17OH progesterone, Dehydroepiandreosterone-sulfate (DHEA-S), ACTH and cortisol hormones were examined in 3 patients with hirsutism. Preoperative imaging and abdominal/pelvic USG were recorded from the patient's files. Approval for the study was received from the Ethics Committee Unit of Selçuk University Faculty of Medicine (Protocol No:2024/242).

Statistical analysis

The study was descriptive, and descriptive statistics for the variables were presented as mean ± standard deviation, frequency (n), and percentage (%).

RESULTS

General characteristics of the patients are given in Table 1. The median age of our patients was 14.8 ± 1.15 years. The mean SD of the patient's body weight was 0.5± 1.35, and the body mass index SD was 0.63± 1.36. Obesity was detected in only one patient with a body mass index (BMI) SD of 2.65, but this patient had a regular cycle and did not have hirsutism. The mean age at menarche was 12.3± 1.13 years, but one patient had an early age at menarche at 9.8 years, and all the others had menarche older than 11 years.

Laboratory results of the patients are given in Table 1. In the results, no hormonal disorders or pathological findings were detected. According to the Ferriman Gallwey score, only three patients were diagnosed with mild/moderate hirsutism, and ACTH, 17OHP, and DHEA-S tests were performed, but the results were normal. In one patient who was obese, the Homo IR value was borderline high at 3.9, but the values of the other patients were normal. Cyst sizes could not be evaluated because two patients were admitted to our hospital with the clinic of acute abdomen (cyst rupture). However, in the preoperative imaging of the other 13 patients, the mean long axis of the cyst was 75± 55 mm. In preoperative USG imaging, septate cyst structure was observed in 4 patients, and the presence of a solid component was observed in 2 patients, while the cyst morphology of the other patients was pure cystic.

While 2 (13.3 %) patients were diagnosed incidentally through imaging performed for other reasons, 2 (13.3 %) patients presented with acute abdomen due to ovarian torsion; the complaints of all 11 (73.3%) patients were abdominal pain. Patients with incidentally detected cysts were operated on because their cyst sizes were large (80 mm and 100 mm), and there was no resolution within one month of follow-up.

According to the pathology results, simple cysts were observed in 7 (46.6 %) patients, paratubal serous cysts in 4 (26.6 %) patients, endometrioma in 2 (13.3 %) patients, serous cyst adenoma in 1 patient, and juvenile granulosa cell tumor in 1 (6.6 %) patient (Table 2). There was no family history of ovarian cystectomy in the patients.

DISCUSSION

In this study, we present 15 patients who applied to our outpatient clinic for ovarian cystectomy for 1 year. Although most were simple cysts, granulosa cell tumors and cystadenoma were detected in the ovaries of 2 of our patients. Although the reason for admission mainly was abdominal pain, acute abdominal clinic due to cyst rupture was observed in 2 (13.3 %) patients.

Ovarian cysts are common during adolescence but rare during pre-adolescence.[8] The common cause of cyst formation during the pubertal period is dysfunctional ovulation: maturing follicles fail to ovulate and remain simple ovarian cysts. These follicular cysts develop in the first half of the menstrual cycle and resolve in the second half. They are fluid-filled and can grow to enormous sizes under hormonal stimulation. Persistence of the corpus luteum formed from the ruptured follicle may also cause functional ovarian cysts. These cysts can grow up to 10 cm, be filled with fluid and/or blood, and may rupture during menstruation, causing bleeding. During the prepubertal period, follicular ovarian cysts might develop in response to

Table 1. General characteristics of the patients

								Percentiles	
	N	Missing	Mean	Median	SD	Minimum	Maximum	25th	75th
Age (month)	15	0	177.733	183	21.063	144	204	162.000	192.000
Weight	15	0	59.367	55.000	10.776	47.000	80.400	51.350	68.500
Weight (SD)	15	0	0.549	0.440	1.350	-1.130	3.040	-0.465	1.550
Height	15	0	160.520	161.500	6.956	147.900	170.000	156.150	165.850
Height (SD)	15	0	-0.015	0.140	1.155	-2.370	1.980	-0.890	0.695
BMI	15	0	22.900	21.200	4.157	18.300	32.700	20.250	24.650
BMI (SD)	15	0	0.632	0.550	1.363	-1.090	3.040	-0.550	1.650
Menarche age	15	0	148.000	148	13.670	118	168	144.000	156.000
LH mIU/ml	15	0	10.724	9.670	6.481	1.530	24.600	6.420	13.950
FSH mIU/ml	15	0	5.371	5.100	2.300	1.120	9.830	3.825	6.880
LH/FSH	15	0	2.292	1.680	1.662	0.590	6.740	1.175	3.140
E2 pg/ml	15	0	79.300	65.300	64.672	11.400	275.000	42.200	90.700
T. testosterone ng/dl	15	0	25.613	30.200	11.999	8.650	47.600	14.300	33.950
TSH mIU/ml	15	0	1.783	1.500	0.843	0.800	3.200	1.070	2.455
F t4 ng/dl	15	0	1.199	1.190	0.164	0.930	1.620	1.095	1.280
Beta HCG mIU/ml	15	0	0.200	0.200	0.000	0.200	0.200	0.200	0.200
AFP ng/ml	15	0	1.529	1.160	0.854	0.900	3.260	0.920	1.590
CEA ng/ml	15	0	0.937	0.770	0.494	0.400	2.170	0.565	1.235
CA-125 U/ml	15	0	23.771	16.600	20.010	2.100	81.300	13.100	33.150
LDH U/L	15	0	172.067	173	30.767	135	260	152.500	181.000
Glukoz mg/dl	15	0	89.067	88	11.139	78	109	79.000	95.500
Insulin mIU/ml	15	0	13.550	6.170	16.355	3.900	65.000	5.100	13.400
Homo IR	15	0	3.201	1.470	4.248	0.840	17.000	1.000	3.295
ACTH pg/ml	3	12	18.033	19.000	6.504	11.100	24.000	15.050	21.500
Cortizol mcg/dl	3	12	7.233	7.000	0.777	6.600	8.100	6.800	7.550
DHEAS mcg/dl	3	12	174.667	182	24.826	147	195	164.500	188.500
17OHP ng/ml	3	12	0.977	1.030	0.225	0.730	1.170	0.880	1.100
preop cyst long axis (mm)	13	2	75.154	66	55.287	35	247	44.000	76.000

SD: Standard Deviation, BMI: Body mass index, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, E2: Estradiol, TSH: thyroid stimulating hormone, Ft4: free T4, beta HCG: human gonadotropic gonadotropin, AFP: alpha fetoprotein, LDH: Lactate Dehydrogenase, ACTH: Adrenocorticotropin Hormone, CEA: Carcino embryogenic antigen, CA-125: carbohydrate antigen-125, DHEA-S: Dehydroepiandrosterone sulfate, 17OHP: 17-Hydroxyprogesterone.

stimulation caused by intermittent gonadotropin release from the developing pituitary.[9] None of our patients were in the prepubertal period.

The most common symptoms of functional ovarian cysts are menstrual irregularity due to anovulation (70%) and lower abdominal pain.[10] Similarly, the most common presenting complaint of our patients was abdominal pain at 73.3%.

Table 2. Histopathological findings of ovarian cyst materials

Histopathological findings	Counts	% of Total	Cumulative %
Simple cyst	7	46.7%	46.7%
Para tubal serous cyst	4	26.7%	73.3%
Endometrioma	2	13.3%	86.7%
Serous cystadenoma	1	6.7%	93.3%
Juvenile granulosa cell tumor	1	6.7%	100.0%

The ovaries can sometimes experience torsion, which initially disrupts venous and lymphatic circulation, causing ovarian obstruction, and may ultimately progress to arrest of arterial circulation and ovarian necrosis. Ovarian torsion is primarily related to an ovarian mass or cyst but can also occur in normal ovaries (idiopathic, 16% of cases).[11,12] The most apparent symptom of ovarian torsion is the acute onset of sharp right- or left-sided lower abdominal pain. Vomiting caused by the pain-induced vagal reflex is present in 73% of cases and typically occurs as soon as after the onset of pain.[13] It was stated in the files that two patients with torsion had severe sharp abdominal pain accompanied by vomiting.

Mixed solid and cystic component masses and completely solid masses seen in the ovary have a higher neoplasm and malignancy rate than simple cysts. The presence of solid ingredients has the highest predictive value for malignancy.[14] In two of our patients in whom adenoma and tumor were detected, the solid component image was tested by ultrasonography. In addition, the smallest cyst we detected in our patients was 35 mm. However, due to severe abdominal pain, septa formation in ultrasound imaging, and leveling within the cyst, the patient was taken to surgery, and pathology evaluation was reported as endometrioma.

Ultrasonography is the initial imaging modality of choice, and further imaging is usually unnecessary. It provides information about the nature of the mass (cystic or solid), its dimensions, its place of origin, and its relations with neighboring organs.[9] Simple cysts: They present as fluid-filled functional cysts, which are monocular, anechoic, thin, and smooth-walled. Hemorrhagic functional cysts seem complex and multilocular, with lace-like reticular inner echoes corresponding to thin fibrin strands and/or containing a solid clot inside. Doppler ultrasound typically shows peripheral blood flow (“ring of fire”) at the cyst border, but no passage is seen at the internal septation.[8] Septa formations were seen within the cyst in the preoperative ultrasound images of 3 patients with simple cysts and one with paratubal serous cysts. Additionally, the presence of a solid component was reported in a patient diagnosed with endometrioma.

Surveillance is recommended for both simple and hemorrhagic functional ovarian cysts. As a rule, both follicular and corpus luteum cysts dissolve.[15] Cysts up to 8 cm in size heal in an average of 4-5 weeks, while larger cysts may take up to 3 months to heal.[16] In girls diagnosed with ovarian cysts before puberty, puberty praecox should be excluded as the cause of the cyst.[15] Surgery is indicated in the presence of complications such as ovarian torsion or cyst rupture with persistent intra-abdominal bleeding, as well as in cases of concern for malignancy or failure to provide resolution during follow-up.[11,15]

There is no agreement on the timing of surgery for ovarian cysts in adolescents, but there are some recommendations. If a simple cyst less than 3 cm in diameter is identified (a large follicle), no further imaging is required. For cysts measuring 3–5 cm in diameter, a follow-up scan should be scheduled after three months to check for resolution. If the cyst is 5–7 cm in diameter, a surveillance ultrasound after three months or laparoscopic ovarian cystectomy if symptomatic should be offered. If a hemorrhagic cyst is identified, another scan should be conducted after 6–8 weeks to check for resolution.[17] In this study, patients were evaluated according to recommendations for surgical indications.

Although the general opinion is that the treatment of ovarian lesions in children should be based on a minimally invasive approach depending on the patient’s age and ultrasound findings, there is no clear algorithm on when surgery should be performed.[18] Berger-Chen et al.[19] showed that in the approach to benign ovarian masses, in addition to patient characteristics, the characteristics of both the physician and the hospital strongly affect the decision on the treatment method of these patients. Since our hospital is a surgical center, cases from surrounding provinces with suspected surgical requirements are referred to our hospital. It can be speculated whether the decision to undergo surgery might have been made more quickly.

A study conducted by Seckin et al.[20] reported the rates of simple cysts in 40.5%, para ovarian/para tubal cysts in 25.3%, endometriomas in 11.4%, and malignancy in 1.3% of adolescent girls aged 12-18 years, which is very similar to our results.

The lack of a precise algorithm for deciding on surgery for adolescents with ovarian cysts makes management difficult. Although the exact duration is not clear for patients with ovarian cysts whose complaints have resolved, most authors recommend a waiting period of 3-6 months.[9] Similarly, another study showed that although most pediatric ovarian neoplasms are benign and can be treated with ovarian-sparing surgery (OSS), there is no consensus on the optimal surgical approach. In particular, younger patients, those presenting from the emergency department, and those treated by pediatric surgeons (compared to pediatric and adolescent gynecologists) were less likely to have OSS.[21]

Evaluation of serum tumor markers is recommended if malignancy is suspected regarding the nature of the cyst or before scheduled or urgent surgery. Although it is recommended to check some tumor markers for preoperative risk classification and surgical planning, especially in ovarian masses with high suspicion of malignancy, it has been stated that it would be more

appropriate to look at many markers together as a panel with no findings. Only one sign is meaningful.[22] In addition, although only 1% of simple cysts are reported to be malignant, some studies recommend evaluating tumor marker levels in persistent simple cysts.[23] We evaluated many tumor markers in our study, but we could not evaluate their sensitivity and specificity due to our limited number of patients and the majority of simple cysts.

Knaus et al.[24] showed that routine imaging did not provide significant results in detecting malignancy and recommended imaging based on evaluation in symptomatic cases in their study for postoperative follow-up of benign ovarian masses. We planned to evaluate our patients in 3-month periods in the first postoperative year according to the menstrual cycle and presence of complaints. No recurrent cysts were observed in any patient during the approximately 9-month postoperative follow-up.

The most important limitation of our study is the small sample size. This reduces the study's power and limits the generalizability of the data.

In conclusion, ovarian cysts are seen with high frequency in the pediatric age group. Since there are no standard protocols for managing ovarian cysts in this age group, patients are usually managed according to the knowledge and experience of an individual clinician and surgeon. The contribution of clinical expertise to the literature will undoubtedly alleviate management difficulties.

In addition, our experience in this field, combined with our hospital's easy access to surgery, will contribute to establishing management protocols.

Ethical approval

This study has been approved by the Selcuk University Faculty of Medicine Dean's Office Local Ethics Committee (approval date 07.05.2024, number 2024/242). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: FÖÇ, FÖS, MS, AFY ; Concept: FÖÇ, FB, MB; Design: FÖÇ, AFY; Data Collection or Processing: AFY FÖS MS Analysis or Interpretation: MKK, FÖÇ Literature Search: FÖÇ, MB, FB; Writing: FÖÇ. 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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Original Article

Use of serum biomarkers in the diagnosis of traumatic brain injury

Nadira Nabiyeva Çevik[1], Ali Korulmaz[2], Mehmet Alakaya[3], Barış Ten[4], Çağrı Eroğlan[5], Mehmet Burak Yavuz Çimen[5], Ali Ertuğ Arslanköylü[3]

[1]Department of Allergy and Immunology, Hacettepe University Medical School, İhsan Doğramacı Children's Hospital, Ankara, Türkiye
[2]Department of Pediatric İntensive Care Unit, Kocaeli Derınce Educatıon and Research Hospıtal, Kocaeli, Türkiye
[3]Department of Pediatric Intensive Care, Mersin University Faculty of Medicine, Mersin, Türkiye
[4]Department of Radiology, Mersin University Faculty of Medicine, Mersin, Türkiye
[5]Department of Medical Biochemistry, Mersin University Faculty of Medicine, Mersin, Türkiye

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ABSTRACT

Objective: Traumatic brain injury (TBI) is a leading cause of death and disability in the pediatric age group. This study aimed to investigate the effectiveness of serum S100 calcium-binding protein B (S100b), ubiquitin carboxyterminal hydrolase-like1 (UCH-L1), glial fibrillary acidic protein (GFAP), and neurofilament (NF) protein levels in predicting the diagnosis and prognosis of traumatic brain injury.

Methods: The research comprised head trauma patients aged 1 month to 18 years hospitalized at Mersin University Faculty of Medicine between October 2018 and November 2019. We recorded the demographic data of the patients, the type of trauma, the treatments administered in the pediatric intensive care unit (PICU), the Glasgow Coma Scale (GCS), the Pediatric Trauma Score (PTS), and the computed cerebral tomography (CT) reports. S-100b protein, UCHL-1, GFAP, and NF levels of the patients and control group were checked. The correlation between serum levels of biomarkers and GCS, CT findings, Rotterdam score, and Glasgow Outcome Scale-Extended (GOS-E) score of the patients was analyzed statistically.

Results: The study included 73 patients, 49 males and 24 females. Comparing the groups revealed no statistically significant correlation between GFAP and TBI ($p>0.05$). However, the correlation between S-100b, UCHL-1, and NF and patient groups was statistically significant ($p<0.05$). The NF level was statistically higher in the PICU 24-hour group than in the control and pediatric emergency groups but statistically lower compared to the PICU 48-hour group ($p<0.05$). UCHL-1 levels in the PICU 24-hour group were statistically higher than those in the control group ($p<0.05$). The inverse correlation between GOS-E and UCHL-1 in the PICU 24-hour group was statistically significant ($p<0.05$). Patients with CT findings had a higher UCHL-1 level than those without ($p<0.05$).

Conclusion: S-100b, UCHL-1, and NF may be used for the diagnosis of TBI and evaluation of its severity. Furthermore, UCHL-1 has the potential to be useful in forecasting patients' prognoses.

Keywords: traumatic brain injury, biomarkers, glial fibrillary acidic protein, ubiquitin carboxyterminal hydrolase-like1

Correspondence: Nadira Nabiyeva Çevik **E-mail:** nadiyanabiyeva@gmail.com
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INTRODUCTION

Traumatic brain injury (TBI) is defined as the disruption of brain functions caused by a physical force applied to the head. There may be cases of isolated head trauma, but there are also cases of trauma accompanied by head trauma in which multiple organ systems are affected.[1] Injury mechanism can be defined as the relation of physical and physiological effects resulting from mechanical forces on the head with the brain.[2] Hypoxia, hypotension, cerebral edema, and increased intracranial pressure over the initial injury cause the secondary damage.

With cell death on the first day after TBI and disruption of the blood-brain barrier, proteins that can trigger the immune response and their degradation products (biomarkers) are released from damaged cells into the cerebrospinal fluid (CSF) and blood.[3] Neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100b), myelin essential protein (MBP), ubiquitin carboxyterminal hydrolase-like 1 (UCH-L1), and neurofilament (NF) proteins are some of the biomarkers that have been found in human biofluids after TBI.[4,5] The Rotterdam score, Glasgow Coma Scale (GCS), Pediatric Trauma Score (PTS), and Glasgow Outcome Scale-Extended (GOS-E) are used to evaluate and follow-up patients with TBI. GOS-E is a scoring system used in regular neurological examinations of patients with head trauma and in monitoring their recovery levels. This assessment score evaluates the patient's activities of daily living, social relationships, and professional performance. It is scored from 1 to 8, from worst to best.[6] Serum-based TBI biomarker tests can assess the degree of TBI severity and predict patient prognosis by correlation with other neurological measures (neuroimaging). There is a need for rapid and straightforward diagnostic serum markers that can reduce the use of CT and may be used for the diagnosis and follow-up of patients with TBI. An appropriate marker should be readily available, increase the severity of trauma in the acute phase compared to the control group, be at basal levels in the healthy control group, originate mainly from the damaged brain, and be easily identified and measured using available tests. It should also be sensitive to TBI severity defined by GCS and CT abnormalities, allowing repeated detections within 48 hours of brain injury.[7] Our knowledge about serum biomarkers in the diagnosis and follow-up of TBI in children is minimal. Our study aims to demonstrate the effectiveness of S-100b protein, UCHL-1, GFAP, and NF levels in diagnosing TBI and predicting the prognosis of TBI patients admitted to the pediatric emergency department and pediatric intensive care unit (PICU).

MATERIAL and METHODS

Sample size calculation was performed prior to the study. Using a significance level (α) of 0.05, power (1-β) of 0.80, and expected difference in biomarker levels between TBI and control groups of 40% based on previous studies, the minimum required sample size was calculated as 53 patients and 20 controls. In this prospective study, 53 children with head trauma aged one month to 18 years who were admitted to the pediatric emergency room and PICU of Mersin University Medical Faculty Hospital between October 2018 and November 2019 were included, along with 20 healthy children in the same age group as the control group. The participants were divided into two groups: those monitored in the PICU (n = 15) and those attended to in the emergency department (n = 38). The age, gender, physical examination findings, laboratory parameters, kind of trauma, length of hospital stay, need for mechanical ventilation, blood transfusion, therapies, and radiological results of the patients were recorded. The Rotterdam score, GCS, and PTS of the patients were calculated. The GOS-E scale was calculated and recorded 12 months after the discharge of the patients hospitalized in the PICU. Blood samples were taken from the patients at admission to measure serum S-100b protein, UCHL-1, GFAP, and NF biomarker levels. The measurement of biomarkers was repeated at 48 hours of trauma in patients followed up in the PICU. A group named "PICU 48-hour" was created from these measurements. The patients in the control group were composed of healthy individuals who do not have a history of smoking, alcohol, or drug use, have no acute traumatic injury, have not followed a special diet in the last three months, have not had a critical illness in the previous month, have not undergone radiological examination such as x-ray or tomography, and have not been vaccinated. The study patients underwent cerebral CT procedures based on their clinical indications. The same radiologist who performed the Rotterdam scoring also evaluated the cerebral CTs and recorded the results.

5 ml of venous blood samples taken from the patients and the control group to measure S-100b protein, UCHL-1, GFAP, and NF levels were placed in the EDTA tube for hematological examination. In contrast, gel tubes were used for biochemical analysis. S-100b protein, UCHL-1, GFAP, and NF biomarkers were placed into gel tubes in the first 24 hours and 48 hours of our study, and the samples were centrifuged for 15 minutes, and their serums were separated. The serum samples were stored in the biochemistry laboratory of our hospital under specific conditions, at a temperature of -80 ºC, until the start of the research. The samples were analyzed using human NEFL (neurofilament light polypeptide) (lab science, catalog no. E-EL-H0741), human GFAP (glial fibrillary acidic protein) (lab science, catalog no. E-EL-H6093), human S100B (S100 calcium-binding protein B) (lab science, catalog no. E-EL-H1297), and human UCHL1 (ubiquitin carboxyterminal hydrolase L1) (lab science, catalog no. E-EL-H2377) using the Sandwich-ELISA method on an automated ELISA analyzer (DSX, Dynex Technologies, USA).

Statistical analysis

The SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the data. Categorical measurements were expressed as numbers and percentages, and continuous measurements were expressed as mean and standard deviation (median and minimum-maximum, where necessary). The Shapiro-Wilk test was applied to determine whether the parameters in the study showed a normal distribution. Independent student t-tests and one-way ANOVA tests were used for normally distributed parameters, while Mann-Whitney U and Kruskal-Wallis tests were used for non-usually distributed parameters. The Bonferroni test, one of the post-hoc tests, was used to determine the source of the difference between the groups. In all tests, the accepted level of statistical significance was 0.05. This study was authorized by the Mersin University Ethics Committee on November 7, 2018, with the decision numbered 2018/452, and was financed by the Scientific Research Projects Coordination Unit of Mersin University, under project number 2019/-1-TP3-3347.

RESULTS

The study included 73 cases, 53 in the patient and 20 in the control groups. There were 15 patients in the PICU group and 38 patients in the pediatric emergency group. It was determined that there was no statistically significant difference between the ages and genders of the patients included in the study and the control group (p > 0.05) (Table 1).

Table 2 shows the mechanical ventilator (MV), inotrope and transfusion requirement, length of stay in the PICU, length of MV, and 24-hour and 48-hour GCS and GOS-E values of the patients followed in the PICU. The majority of patients in the PICU received MV, inotropic, and transfusion support.

No statistically significant difference was found between the trauma causes and survival rates of the PICU and pediatric emergency group patients (p> 0.05). However, the differences between the two groups in terms of antiedema and antiepileptic treatment, surgery, length of hospital stay, and additional disease presence were statistically significant (p<0.05). All patients hospitalized in the PICU received antiedema treatment, but only 7.9% of patients in the pediatric emergency department received it. Falling (33.3%) and road traffic accidents (33.3%) were the most common causes of trauma among the patients in the PICU. In comparison, the majority of the patients in the pediatric emergency room were found to be falling (73.7%) (Table 3).

There was no statistically significant difference between the patients in the PICU and pediatric emergency in C-reactive protein (CRP), platelet, sodium, and potassium values (p > 0.05). It was found that patients who followed up in the PICU had statistically significantly higher leukocyte and blood glucose levels and statistically considerably lower hemoglobin and hematocrit levels compared to the patients in the pediatric emergency department (p<0.05). The information is shown in Table 4.

The cerebral CT findings and consciousness status of the PICU patient group were compared with those of the emergency patient group. A cerebral CT evaluation was performed according to the Rotterdam scoring. The study detected pathological findings in cerebral CT in 58.5% (n = 31) of the patients. The incidence of pathological cerebral CT findings was 93.3% in the PICU group and 44.7% in the pediatric emergency group, and this difference was statistically significant (p<0.05). The ratio of patients with moderate and severe TBI was statistically significantly higher in the PICU group than in the pediatric emergency group (p<0.05).

Similarly, the difference between both groups regarding PTS was statistically significant (p<0.05). While PTS was <8 in the majority of patients (71.4%) in the PICU group, PTS was >8 in the majority of pediatric emergency patients (92.1%). In addition, when the mean values of GCS, PTS, and Rotterdam scoring were examined, the difference between the two groups was

Table 1. Patient age and gender distribution by group

		PICU (n: 15)		Control (n: 20)		Pediatric Emergency (n: 38)		Total (n: 73)		p*
		n	%	n	%	n	%	n	%	
Gender⁺	Female	3	20.0	10	50.0	11	28.9	24	32.9	0.132
	Male	12	80.0	10	50.0	27	71.1	49	67.1	
Age (month) (x^2)		Mean±SD (min-max)		Mean±SD (min-max)		Mean±SD (min-max)		Mean±SD (min-max)		p*
		137.26±72.55 (9-204)		84.55±72.32 (7-215)		95.21±63.21 (3-204)		100.93±69.45 (3-215)		0.145

x^2: Kruskal-Wallis test; ⁺: Chi-square; PICU; Pediatric Intensive Care Unit; min: minimum; max: maximum, *p<0.05

Table 2. Clinical parameters of patients admitted to the PICU			
		Number (n)	**Percent (%)**
Mechanical Ventilator Support	no	10	66.7
	yes	5	33.3
Inotrope	no	13	86.7
	yes	2	13.3
Transfusion	no	11	73.3
	yes	4	26.7
GCS at 24th hour× (TBI level)	severe	5	33.3
	moderate	5	33.3
	mild	5	33.3
GCS at 48th hour× (TBI level)	severe	5	33.3
	moderate	1	6.7
	mild	9	60.0
		Mean±SD	**min-max**
Length of stay in the PICU (hours)		179.20±159.67	24-624
Mechanical Ventilator Support (day)		2.73±4.14	0-10
GOS-E		6.00±1.81	1-8

GCS; Glasgow Coma Scale, GOS-E; Glasgow Outcome Scale Extended, MV; Mechanical ventilator, PICU; Pediatric
Intensive Care Unit, TBI; traumatic brain injury ×: Severe;8 and below, Moderate;9-13, Mild;14-15; min: minimum; max: maximum

statistically significant (p<0.05). The mean Rotterdam score was higher in the PICU patient group, but the mean GCS and PTS were higher in the pediatric emergency patient group (Table 5).

When the relationship between the presence of cerebral CT findings and the mean values of UCHL-1, GFAP, S100b, and NF in the patients in intensive care and emergency groups was investigated, a statistically significant relationship was found between patients with pathological findings on cerebral CT and a high mean value of UCHL-1 (p<0.05), on the other hand, no correlation was found with GFAP, S-100b, and NF and CT findings. Although the mean values of NF and S-100b were higher in patients with cerebral CT findings than those without, the difference was not statistically significant (Table 6). It was also found that there was an inverse correlation between GOS-E results and all biomarkers in PICU patients in the 24-hour group. However, only the inverse correlation with UCHL-1 was statistically significant among these parameters (p<0.05). However, we found no statistically significant correlation between GOS-E findings and biomarkers in the PICU 48-hour patient group.

The correlation between S-100b protein, UCHL-1, GFAP, and NF parameters of the PICU patients at 24 hours and 48 hours in the pediatric emergency and control groups was examined. Differences between groups in GFAP levels were not statistically significant (p > 0.05). On the other hand, the differences between the groups in S-100b protein, NF, and UCHL-1 values were statistically significant (p<0.05). S-100b protein and UCHL-1 were highest in the PICU 24-hour patient group, while NF was highest in the PICU 48-hour patient group (Table 7).

DISCUSSION

This prospective study is one of the few investigations to simultaneously evaluate multiple serum biomarkers (S-100b, UCH-L1, GFAP, and NF) in pediatric TBI patients. Our primary objective was to assess the effectiveness of these biomarkers in diagnosing TBI and predicting patient outcomes. The main outcomes indicate that S-100b and UCH-L1 reach their peak within 24-hours following damage, whereas NF levels persist in ascending for up to 48 hours. UCH-L1 had a substantial connection with CT results and GOS-E scores, indicating its potential utility as a diagnostic and prognostic instrument in pediatric TBI.

TBI may result in both temporary and chronic deficits in cognitive, physical, and psychosocial functioning. These impairments are often accompanied by a reduction or alteration in the state of awareness.[8] Impaired cerebral perfusion after TBI leads to disturbed cerebral oxygenation, causing brain hypoxia. Hypoxia occurs when there is a disequilibrium between the amount of oxygen being delivered to the brain and the amount of oxygen being used by the brain.

We investigated gender and trauma type as factors affecting TBI severity. A study that included 59 children aged 0–19 years found that the differences in terms of age and gender were not statistically significant.[9] Also, our study determined that the gender and age differences between the patient groups were not statistically significant. However, the mean age of the patients followed in the PICU was higher than the patients followed in the emergency department, which was attributed to the increased risk of exposure to severe trauma with age. When the types of trauma-causing TBI were examined, it was reported that the most common cause of trauma in the current population was a road traffic accident, followed by falling.[10] In our study, unlike the literature, fallings (62.3%) were in the first place, followed by motor vehicle accidents (28.3%) and other causes. The location, socioeconomic status, and lifestyle differences may explain this inconsistency with the literature.

Table 3. Comparison of clinical features of PICU and Pediatric Emergency Group patients								
		PICU (n:15)		Pediatric Emergency (n:38)		Total (n:53)		p
		n	%	n	%	n	%	
Cause of trauma	Road traffic accident (RTA)	8	53.3	7	18.5	15	28.3	0.031
	Trauma	5	33.3	30	79	35	66.1	
	Brunt	0	0.0	1	2.6	1	1.9	
	Work accident	1	6.7	0	0.0	1	1.9	
	Suicide	1	6.7	0	0.0	1	1.9	
Survival	Non-survival	1	6.7	0	0.0	1	1.9	0.108
	Survive	14	93.3	38	100.0	52	98.1	
Anti-edema treatment	no	0	0.0	35	92.1	35	66.0	**0.000**
	yes	15	100.0	3	7.9	18	34.0	
Antiepileptic drug	no	1	6.7	36	94.7	37	69.8	**0.000**
	yes	14	93.3	2	5.3	16	30.2	
Surgery	no	8	53.3	38	100.0	46	86.8	**0.000**
	yes	7	46.7	0	0.0	7	13.2	
Comorbidities	no	6	40.0	29	76.3	35	66.0	**0.012**
	yes	9	60.0	9	23.7	18	34.0	
		Mean±SD (min-max)		Mean±SD (min-max)		Mean±SD (min-max)		p
Length of hospital stay (hours)[u]		244.0±178.31 (48-708)		18.84±29.11 (4-120)		82.56±140.17 (4-708)		**0.000**

*p<0.05, u: Mann-Whitney U test, PICU; pediatric intensive care unit; min: minimum; max: maximum

Table 4. Comparison of Laboratory Findings of the PICU and Pediatric Emergency Group				
	PICU (n:15)	Pediatric Emergency (n:38)	Total (n:53)	p
	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)	
Leukocyte	19.55±7.88	10.73±3.86	13.23±6.59	**0.000**
($x10^3$/µL) (u)	(8.48-33.64)	(4.46-23.59)	(4.46-33.64)	
CRP	4.25±9.96	8.46±16.68	7.27±15.11	0.053
(mg/L) (u)	(0.1-38.5)	(0-98)	(0-98)	
Hgb	10.41±2.35	12.23±1.32	11.72±1.85	**0.002**
(g/dL) (t)		(9.5-14.5)	(6.9-15.7)	
Hct	30.26±7.13	35.52±3.95	34.03±5.52	**0.001**
(%) (t)		(25-42)	(20-48)	
Platelet	288.8±101.79	291.84±88.27	290.98±91.30	0.629
(x103/µL) (t)	(152-542)	(100-457)	(100-542)	
Sodium	137.86±3.46	137.70±3.03	137.75±3.12	0.524
(mmol/L) (u)	(129-143)	(130-145)	(129-145)	
Potassium	3.98±0.48	3.99±0.44	3.99±0.45	0.843
(mmol/L) (t)	(2.76-4.82)	(3.16-4.74)	(2.76-4.82)	
Serum glucose levels	207.13±137.52	129.32±51.10	151.34±90.56	**0.017**
(mg/dL) (u)	(99-592)	(83-380)	(83-592)	

* p<0.05, t: independent student test, u: Mann- Whitney U test, PICU: Pediatric Intensive Care Unit, CRP: C-reactive protein, Hgb: Hemoglobin, Hct: Hematocrit; min: minimum; max: maximum

Table 5. Comparison of cerebral CT findings and GCS, PTS, and Rotterdam CT scoring results in PICU and Pediatric Emergency Group patients

		PICU (n:15)		Pediatric Emergency (n:38)		Total (n:53)		p
		n	%	n	%	n	%	
CT finding (k)	no	1	6.7	21	55.3	22	41.5	**0.001**
	yes	14	93.3	17	44.7	31	58.5	
GCS (k)	severe	5	33.3	0	0.0	5	9.4	**0.000**
	moderate		5	33.3	3	7.9	8	
	mild	5	33.3	35	92.1	40	75.5	
PTS (k)	< 8	10	71.4	3	7.9	13	25.0	**0.000**
	> 8	4	28.6	35	92.1	39	75.0	
		Mean±SD (min-max)		Mean±SD (min-max)		Mean±SD (min-max)		p
Rotterdam CT scoring (u)		1.40±0.73 (0-3)		0.97±0.28 (0-2)		1.09±0.49 (0-3)		**0.005**
GCS (u)		10.46±5.13 (3-15)		14.44±0.82 (11-15)		13.32±3.29 (3-15)		**0.001**
PTS (u)		5.40±3.56 (0-11)		10.5±1.08 (8-12)		9.05±3.10 (0-12)		**0.000**

*p<0.05, u: Mann-Whitney U test, k: Chi-square, PICU: Pediatric Intensive Care Unit, PTS: Pediatric Trauma Score, GCS: Glasgow Coma Score, Severe; 8 and below; Moderate; 9–13, Mild; 14–15; CT: computer tomography

Table 6. Correlation of biomarkers with cranial CT and GOS-E

Biomarker(s)	Cerebral CT finding			GOS-E			
	no (n: 23)	yes (n:30)	p	PICU-24		PICU-48	
	Mean±SD	Mean±SD		r	p	r	p
GFAP (pg/ml)	360.96±160.32	319.28±210.61	0.434	-0.226	0.419	0.334	0.224
S-100b (pg/ml)	755.32±560.96	1011.66±605.19	0.121	-0.116	0.680	-0.361	0.186
NF (pg/ml)	2.79±9.72	4.25±8.48	0.564	-0.245	0.380	-0.356	0.193
UCHL-1 (pg/ml)	323.07±1032.7	1467.76±2190.46	**0.025**	-0.633	**0.011**	0.146	0.603

GFAP: glial fibrillary acidic protein; S-100β: S100 calcium-binding protein B, UCHL-1; Ubiquitin carboxy-terminal hydrolase L1, NF; Neurofilament protein, GOS-E; Glasgow Outcome Scale Extended, PIC-24; Pediatric intensive care 24-hour patient group, PIC-48; Pediatric intensive care 48th hour patient group

Radiological imaging techniques and a neurological examination of the patient are the main methods used to diagnose TBI. The GCS is the most commonly used scale for evaluating neurological tests. A GCS score of 13–15 defines mild TBI, 9–12 moderate TBI, and 3–8 severe TBI.[11] A study examined the GCS and found that 26% of the patients had moderate or severe TBI, while 74% had mild TBI.[12] Şimşek et al. reported a rate of moderate and severe head trauma at 29.9% in their study.[13]

Most patients in our study had mild TBI, accounting for 75.5% of the cases, which aligns with the findings reported in existing literature. Recent enhancements in PICU infrastructure and a greater supply of trained healthcare workers, especially pediatric emergency and intensive care experts, have led to decreased fatality rates from TBI. The mortality rate of our study, 1.9%, is consistent with the current literature's reported figure of 3.8%.[12,14] A research conducted by Lazar et al. revealed that children with mild TBI had lower levels of serum sodium and potassium and greater levels of serum glucose and leukocytes compared to healthy individuals.[15] In our study, the leukocyte and serum glucose levels of the patients admitted to the PICU were higher than those followed in the pediatric emergency room. Both our study and the study of Lazar et al. show an increase in leukocyte and serum glucose levels as the severity of TBI increases. In other words, hyperglycemia and leukocyte levels are essential parameters in identifying the severity of TBI. When planning follow-up and treatment for trauma patients, these factors should be considered. In addition, since hyperglycemia is associated with increased mortality after TBI, it is crucial to keep blood glucose within physiological limits in these patients. PTS and GCS are valuable tools for evaluating the severity of trauma in pediatric patients. GCS is the most widely used scale to measure the severity of TBI in adults and children after a modification.[16,17] A study investigating the

Table 7. Investigation of the correlation of biomarkers between PICU, pediatric emergency, and control groups

	GFAP (pg/ml)	S100b (pg/ml)	NF (pg/ml)	UCHL1 (pg/ml)
	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)	Mean±SD (min-max)
PICU 24th hour (n:15), (1)	380.67±255.71	1291.55±619.24	5.67±10.30	1518.27±2203.81
	(12.75-720.52)	(247.30-3163.04)	(0.00-27.73)	(0.00-5000.0)
Control (n:20), (2)	348.99±196.55	925.67±552.48	1.07±1.84	57.92±130.75
	(41.33-651.33)	(101.82-1781.29)	(0.03-5.49)	(0.01-472.01)
Pediatric Emergency (n:38) (3)	320.28±157.67	746.03±515.45	2.80±8.41	754.99±1687.65
	(39.46-659.60)	(25.60-1689.25)	(0.18-47.01)	(0.00-5000.0)
PICU 48th hour (n:15), (4)	380.35±214.83	719.44±544.76	63.79±95.56	422.34±1269.60
	(12.78±654.77)	(25.72-1731.73)	(0.37- 284.21)	(0.01-5000.0)
Total (n: 88)	347.34±194.05	875.31±575.38	13.29±45.27	669.97±1574.76
	(12.75-720.52)	(25.6-2163.05)	(0.0-284.21)	(0.0-5000.0)
P	0.663	**0.021**	**0.000**	**0.027**
Post-hoc significance p	No significant difference between groups	1-4; p=0.032 1-3; p=0.009	4-1; p=0.001 4-2; p=0.000 4-3; p=0.000	1-2; p=0.038

* p<0.05, x2: Kruskall-Wallis test, F: one-way Anova, Post Hoc: Bonferroni, PICU: Pediatric Intensive Care Unit, GFAP: glial fibrillary acidic protein, S-100β: S100 calcium-binding protein B, UCHL-1: ubiquitin carboxy-terminal hydrolase L1, NF: neurofilament protein

effectiveness of PTS and GCS in predicting mortality in children injured by trauma reported that the mean GCS and PTS were higher in children who were non-survival.[10] Since the mortality rate was not sufficient for statistical evaluation in our study, this comparison was performed between the pediatric emergency group and the PICU group with different TBI severity. In our study, the mean GCS and PTS were found to be 10.4 and 5.4 in the PICU group and 14.4 and 9.05 in the pediatric emergency group, respectively. Both in the literature study and our study, we observed that scores in both scoring methods decreased as the severity of TBI increased. In Papa et al.'s investigation, it was shown that patients with TBI who had intracranial lesions on a cranial CT scan had substantially elevated levels of UCH-L1 in their blood, compared to individuals without lesions[18] Consistent with previous research, our study found that serum UCH-L1 levels were significantly elevated in individuals with CT results compared to those without CT findings. Our investigation revealed a negative association between the GOS-E results and the UCH-L1 level of the patients in the PICU. This finding indicates that the neurological outlook of patients may be anticipated by assessing the UCH-L1 levels of patients who are monitored in the PICU for TBI. Furthermore, based on the findings of our research and the study conducted by Papa et al.[18] it can be concluded that UCH-L1 serves as a reliable indicator for detecting TBI during the first 24-hour period. GFAP, which Eng described in 1971, is a monomeric small and acidic intermediate protein found in the astroglial skeleton and is a brain-specific marker after cell death.[19] In a study conducted in patients with and without head trauma, serum GFAP, S100b, and NSE levels were evaluated, and it was shown that GFAP has higher specificity in head trauma than other biomarkers (S100b, NSE).[20] Lei et al. reported that GFAP peaked at 0.5–4 hours after injury.[21] Similarly, Papa et al. observed that GFAP was detected in the serum immediately after injury, distinguishing patients with head trauma from others. The serum GFAP level was higher in patients with mild TBI who had lesions on CT than in those without.[22] Our research did not detect any statistically significant difference in the GFAP values between PICU and pediatric emergency patients, regardless of whether they had CT results or not. The explanation for this was hypothesized to be the potential oversight of the peak phase of GFAP in our investigation since some blood samples were collected more than 4 hours after the incident. S100b is a serum biomarker that has been extensively researched in TBI. It is a protein that binds to calcium channels and is found in high levels in astroglial cells in brain tissue.[23] A previous investigation revealed that the average blood S100b level in patients with severe TBI was considerably greater than that in individuals with mild TBI.[24] In our study, the differences between the groups were found to be statistically significant. This difference was because the biomarker level in the PICU 24-hour group was higher than the pediatric emergency, control, and PICU 48-hour groups. This finding indicates that the S100b concentration increases during the first 24-hours after a severe head injury and returns to a normal level after this period. Both our research and the study

conducted by Abbasi et al.[24] corroborate the notion that S100b may serve as a reliable indicator for the diagnosis of TBI during the first 24 hours after the trauma.

NFs are a kind of protein that is located in the axons and dendrites of neurons. They belong to the category of intermediate filament proteins. NFs are intermediate filament proteins found in the axons and dendrites of neurons. Gatson et al. investigated serum NF levels on the first and third days after injury to predict injury severity in patients with TBI. According to their study, patients with pathological CT findings had significantly higher NF levels than those without, and there was an inverse correlation between NF levels and GCS.[25] According to the results of the post hoc analysis performed to determine the source of the difference between the groups in the NF biomarker value in our study, it was found statistically significant that the NF biomarker level in the PICU 24-hour group was higher than that of the patients in the control and pediatric emergency groups. Still, it was lower than the patients in the PICU 48-hour group. This result shows that the NF level increases in the first 24 hours after TBI, and this level continues to increase until 48 hours. Therefore, it suggests that NF level may be an important parameter that can be used in the first 24 hours after trauma to reveal TBI and in the diagnosis and follow-up of TBI after 24 hours. This study has several notable limitations. First, as a single-center study, the sample size was limited, particularly for severe TBI cases (n=5), which restricted the generalizability of our findings. Second, the timing of sample collection posed a methodological challenge, as some blood samples were obtained more than 4 hours post-trauma, potentially missing the peak GFAP levels that typically occur within 0.5-4 hours after injury. The limited incidence of severe TBI cases restricted our capacity to thoroughly assess biomarker patterns across varying severity levels. These constraints highlight the necessity for forthcoming extensive, multi-center investigations with an equitable distribution of TBI severity cases and uniform biomarker-gathering techniques.

In conclusion, our data indicate that S-100b protein, UCHL-1, and NF are significant biomarkers for evaluating TBI severity. Each biomarker exhibits a unique temporal profile: UCHL-1 and S-100b reach their peak during the initial 24 hours post-TBI, whereas NF peaks on the second day. UCHL-1 is significantly important, exhibiting strong correlations with both CT results and patient outcomes. The inverse correlation between UCHL-1 levels and GOS-E scores suggests its potential as a predictive biomarker. These biomarkers, especially UCHL-1, may reduce reliance on repeated CT scans and facilitate earlier diagnosis and improved monitoring of TBI patients.

Ethical approval

This study has been approved by the Mersin University Ethics Committee (approval date November 7, 2018, number 2018/452). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: NNÇ, AEA; data collection: NNÇ, AK, BT, ÇE; analysis and interpretation of results: NNÇ, AEA, MA, BT, MBYÇ, AK; draft manuscript preparation: NNÇ, AEA, MA, MBYÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Does previous tuberculosis increase the risk of functional gastrointestinal disorders in children?

Hatice Uygun[1], Sibel Yavuz[2], Nurettin Erdem[3], Saniye Başak Oktay[4], Seval Özen[5], Mehmet Turgut[6]

[1]Department of Pediatric Infectious Diseases, Faculty of Medicine, Gaziantep University, Gaziantep, Türkiye
[2]Department of Pediatric Gastroenterology, Adana Training and Research Hospital, Adana, Türkiye
[3]Department of Pediatric Infectious Diseases, Şanlıurfa Training and Research Hospital, Şanlıurfa, Türkiye
[4]Department of Medical Biochemistry, Faculty of Medicine, Alanya Alaaddin Keykubat University, Antalya, Türkiye
[5]Department of Pediatric Infectious Diseases, Ankara Bilkent City Hospital, Ankara, Türkiye
[6]Department of Pediatric Infectious Disease, Adana Training and Research Hospital, Adana, Türkiye

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ABSTRACT

Objective: Functional gastrointestinal disorders (FGIDs) encompass a range of chronic conditions of unknown etiology, including functional dyspepsia, irritable bowel syndrome, functional abdominal pain, and functional constipation. The exact pathogenic mechanisms behind tuberculosis (TB) are unclear. This study aimed to investigate whether children with previous TB are at an increased risk of developing FGIDs after completion of TB treatment.

Materials and **Methods:** A total of 35 patients diagnosed with TB (age range, 24 to 216 months) and 49 age- and sex-matched healthy controls were included in this retrospective study. Patients were evaluated for the presence of FGID symptoms after at least 6 months had passed after cessation of TB treatment, while the control group was assessed at the time of their first examination according to the Rome IV criteria.

Results: The overall prevalence of FGIDs was 42.9% (n=15) in the patient group versus 12.2% (n=6) in the control group. A significant difference was found between the groups in terms of the frequency of FGIDs and the diagnosis of functional abdominal pain ($p = 0.001$ and $p < 0.001$, respectively).

Conclusions: This study demonstrated a higher prevalence of FGIDs in children with a history of TB compared to healthy controls, supporting the hypothesis that FGIDs are more common in children with previous TB. Children with previous TB may be at an increased risk for FGIDs, possibly due to chronic inflammation and immune system alterations associated with TB, highlighting the need for ongoing assessment of GI health in this population.

Keywords: children, functional gastrointestinal disorders, tuberculosis.

INTRODUCTION

Functional gastrointestinal disorders (FGIDs), also known as disorders of gut-brain interaction, encompass a range of chronic, relapsing conditions of unknown etiology. The most common subtypes include functional dyspepsia, irritable bowel syndrome (IBS), functional abdominal pain, and functional constipation. Diagnosis and treatment of FGIDs are challenging because they do not cause any obvious structural or biochemical changes in the gastrointestinal (GI) system.[1] Low-grade inflammation plays a role in the pathogenesis of FGIDs. Disruption to the gut-brain axis, associated changes in GI microbiota and mucosal permeability, as well as abnormalities in mucosal defense mechanisms, are also involved in the disease process.[2-4]

Correspondence: Hatice Uygun **E-mail:** ozhanhatice@hotmail.com
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Tuberculosis (TB) is a preventable, chronic, inflammatory, and infectious disease caused by the *Mycobacterium tuberculosis (M. tuberculosis)* complex. After exposure to *M. tuberculosis* and subsequent deposition in the lungs, one of the following outcomes may occur: immediate clearance of the organism, immediate onset of active disease (primary disease), latent infection, and reactivation disease (onset of active disease years after a period of latent infection).[5] In children, TB most commonly manifests as pulmonary disease and/or intrathoracic adenopathy. Sites of extrapulmonary involvement include the lymph nodes, central nervous system (CNS), abdomen, and bones/joints.[6]

The exact pathogenic mechanisms behind TB are unclear. The time between aerosol droplets containing *M. tuberculosis* entering the body and disease onset varies among individuals. Studies have shown that *M. tuberculosis* causes persistent infection due to persistent inflammation, chronic antigen exposure, and chronic antigenic stimulation despite the induction of adaptive immune responses.[5] Low-grade, chronic inflammatory process induced by the inhalation of the aerosol droplets permanent or temporary changes in the gut microbiota following the development of TB, and GI changes associated with the therapeutic agents used suggest that FGID symptoms may be triggered in children with TB.[7-9]

The aim of this study was to investigate whether children with previous TB are at an increased risk of developing FGIDs after completion of TB treatment.

MATERIALS AND METHODS

This study has a retrospective design.

Sample selection

Forty-eight patients who received treatment for tuberculosis at our department between January 1, 2017, and November 1, 2021, were evaluated for FGID symptoms after at least six months had passed since the cessation of the TB treatment. For each patient, relevant information was obtained by reviewing their medical records retrieved from the hospital database and questioning their parents.

Inclusion and exclusion criteria

Patients with symptoms of organic GI disorders such as involuntary weight loss, significant vomiting, chronic diarrhea, bloody stools, fever, or a family history of inflammatory bowel disease, as well as those previously diagnosed with FGID were excluded from the study. Individuals with a history of any chronic rheumatic or endocrinological disease and/or those currently receiving any medications were also excluded.

A total of 13 patients who did not attend follow-up examinations regularly, had chronic diseases, and were diagnosed with and treated for any FGID were excluded from the study. None of the TB patients in the study had FGID symptoms or follow-up before TB treatment. The control group consisted of children without any health problems as reported by their parents and did not meet the aforementioned exclusion criteria. Ultimately, the study population consisted of 35 patients with TB, aged between 24 and 216 months, and 49 age- and sex-matched healthy controls. The study flow diagram is presented in Figure 1.

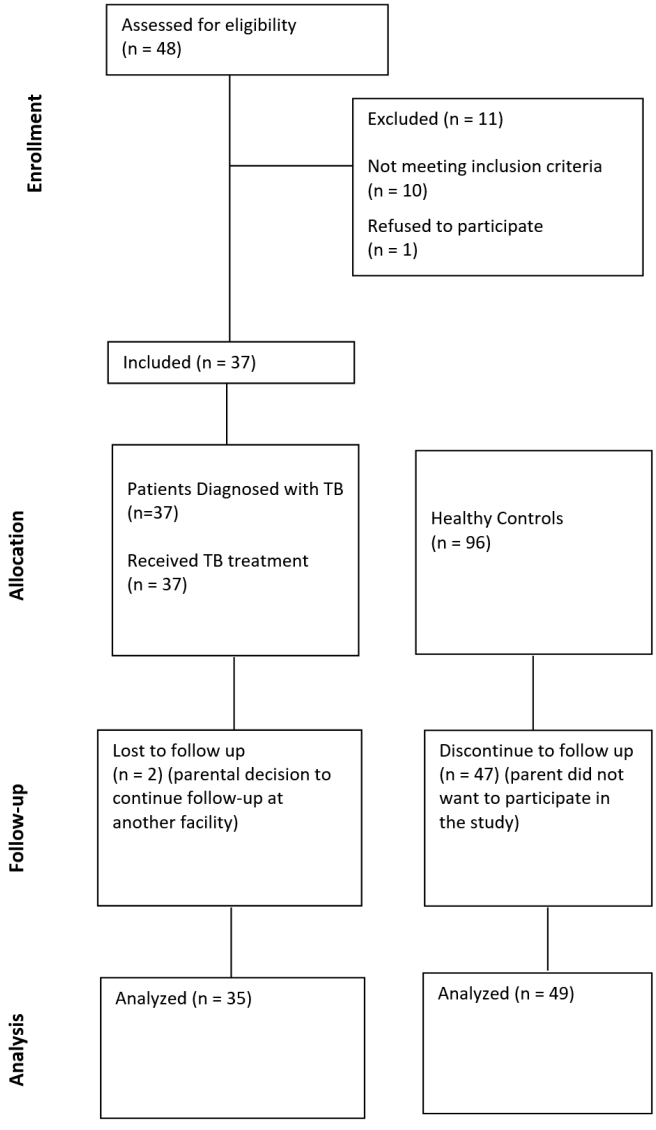

Figure 1. Flow diagram showing participants through each stage of the study

Patients were evaluated for the presence of FGID symptoms after at least 6 months had passed after completing TB treatment, while the control group was assessed at the time of their first examination according to the Rome IV criteria by experienced pediatricians.[10] The diagnosis of tuberculosis was established by reviewing the results of clinical, radiological, bacteriological, and histopathological examinations in patients suspected of having TB based on their history, physical examination, laboratory workup, and chest X-ray findings.[11] Among the laboratory parameters of the patients, white blood cell (WBC), platelet (PLT), lymphocyte and neutrophil counts, hemoglobin concentration, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level were noted. Data on patient sex, age at diagnosis, symptoms such as cough, fever, weight loss, areas of involvement, medications used for TB treatment, and total duration of treatment were also noted.

Diagnosis of Functional Gastrointestinal Disorders

We used the Rome IV criteria to diagnose FGIDs at study enrollment and at least six months after completing TB treatment. FGIDS were simply classified into three subcategories: functional nausea and vomiting disorders, functional abdominal pain disorders, and functional defecation disorders. These conditions were identified in both patient and control groups using specific diagnostic criteria for the subcategories, including functional dyspepsia, IBS, functional abdominal pain, and functional constipation.

For the diagnosis of functional dyspepsia, one or more of the following symptoms must be observed at least 4 times a month in the last 2 months: postprandial fullness, early satiety, epigastric pain, or burning not associated with defecation. Patients are diagnosed with IBS if they experience recurrent abdominal pain at least 4 days per month, associated with two or more of the following: symptoms related to defecation, changes in the frequency and appearance of stools, and symptoms that persist even after resolution of constipation. According to the Rome IV criteria, episodic or persistent abdominal pain must occur at least 4 times per month for at least 2 months in the absence of sufficient criteria for other functional abdominal pain disorders. Additionally, functional constipation is diagnosed when a patient meets two or more of the following criteria at least once a week for at least one month, with insufficient criteria for IBS: two or fewer defecations per week, fecal incontinence more than once a week, retentive posturing, history of painful or hard bowel movements, large fecal mass in the rectum, and large diameter stools.

For all FGID diagnoses, symptoms must not be attributable to any other medical condition after appropriate evaluation.[10]

Statistical analysis

All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY). Categorical variables were reported as numbers and percentages, while continuous variables were summarized as median and interquartile range (IQR). Chi-square and Fisher's exact tests were used to compare categorical variables between the groups. The between-group age difference was analyzed using the Mann-Whitney U test among continuous variables. The statistical significance level was set at 0.05 for all tests.

Ethics statement

This study has been approved by the Adıyaman University Non Interventional Clinical Research Ethics Committee (approval date 24.05.2022, number 2022/5-16). Written informed consent was obtained from the participants.

RESULTS

The patient group comprised 35 children with a median age of 11.5 years (IQR,5.75-14). Among them, 42.9% (n=15) were male and 57.1% (n=20) were female. The control group consisted of 49 children with a median age of 8 years (IQR, 3-12.2), 57.1% (n=28) of whom were male and 42.9% (n = 21) were female. No significant difference was found between the groups in terms of age (p = 0.115) or sex (p = 0.197).

Of the patients diagnosed with TB, 65.7% (n=23) had pulmonary tuberculosis, 22.9% (n = 8) had tuberculous lymphadenitis, 8.6% (n = 3) had gastrointestinal tuberculosis, 2.9% had (n = 1) had tuberculous meningitis. TB treatment was completed in all patients at least six months prior to the study. None of the patients had laboratory and/or clinical findings suggesting relapse or treatment failure during post-treatment follow-up. The patients' Laboratory workup results and clinical characteristics are shown in Table 1.

Initial TB treatment was administered as a combination of three (RHZ) or four (RHZE) drugs, including rifampin, isoniazid, and pyrazinamide, with or without ethambutol. After two months of initial treatment, maintenance treatment with rifampin and isoniazid was commenced. For each patient, the duration of treatment was determined based on the area and extent of involvement, as well as the results of clinical, radiological, and bacteriological examinations. The minimum duration of treatment for all patients was six months.

In the patient group (n=35), the median (IQR) time elapsed since the cessation of TB treatment was 8 (6-12) months. When the

Table 1. Laboratory and clinical data of the patient group at the time of diagnosis	
Variables	
CRP** (mg/dL)	39 (20-68)
ESR** (mm/h)	37 (27.5-59)
WBC** (103/uL)	14,500 (9675-18,100)
Hb** (g/dL)	11 (10-12)
Neutrophils** (103/uL)	9745 (5450-13,000)
Lymphocytes** (103/uL)	4670 (2975-5600)
Presence of cough, n (%)	23 (65.7%)
Presence of fever, n (%)	27 (77.1%)
Presence of weight loss, n (%)	27 (77.1%)
Pulmonary tuberculosis, n (%)	23 (65.7%)
Tuberculous lymphadenitis, n (%)	8 (22.9%)
Gastrointestinal tuberculosis, n (%)	3 (8.6%)
Tuberculous meningitis, n (%)	1 (2.9%)
Treatment duration (months)*	8.57 ± 1.65
Type of treatment	
Triple treatment, n (%)	8 (22.9%)
Quadruple treatment, n (%)	27 (77.1%)

* mean± SD (standard deviation)
** median (IQR)
WBC: White Blood Cell, Hb: Hemoglobin, PLT: Platelet Count, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein.

TB patients were divided into two subgroups, those with or without a FGID, the median time elapsed since TB treatment discontinuation was 9 (6-12) and 8 (7-11) months, respectively. No significant difference was observed between the subgroups (p = 0.973).

The frequencies of FGIDs and their subtypes in the study population are shown in Table 2. The overall prevalence of FGIDs was 42.9% (n=15) in the patient group and 12.2% (n=6) in the control group. A significant difference was found between the groups with respect to the overall frequency of FGIDs (p = 0.001). The frequency of functional abdominal pain was higher among the patients (34.3%, n=12) versus controls (2%, n=1), with a significant difference between the groups (p<0.001). There was no statistically significant difference between groups for other FGID subtypes.

DISCUSSION

In this study investigating whether children diagnosed with TB show an increased frequency of FGIDs after cessation of treatment, it was found that FGIDs were more common in patients with previous TB than in healthy controls.

In TB, phenotypic and genetic variation of the bacteria, as well as the interaction between the bacteria and their hosts, can affect the disease progression.[12] Although TB typically affects the lungs, abdominal TB accounts for about 5 percent of all TB cases. Clinical signs of abdominal TB may include fever, weight

Table 2. Frequency of functional gastrointestinal disorders in patient and control groups			
	Patients (n=35)	**Controls (n=49)**	**p**
Age (years)-median (IQR)	11.5 (5.75-14)	8 (3-12.2)	p = 0.115
Sex, n (%)			p = 0.197#
Male	15 (42.9%)	28 (57.1%)	
Female	20 (57.1)	21 (42.9%)	
FGID, n (%)			p = 0.001#
Yes	15 (42.9%)	6 (12.2%)	
No	20 (57.1%)	43 (87.8%)	
Cyclic vomiting, n (%)	1 (2.9%)	0 (0.0%)	p = 0.417*
Functional dyspepsia, n (%)	2 (5.7%)	2 (4.1%)	p = 0.556*
Irritable bowel syndrome, n (%)	2 (5.7%)	0 (0.0%)	p = 0.171*
Functional abdominal pain, n (%)	12 (34.3%)	1 (2%)	p <0.001*
Functional constipation, n (%)	4 (11.4%)	3 (6.1%)	p = 0.316*

FGID: Functional gastrointestinal disorders
Using Chi-square test, *Using Fisher's exact test.

loss, abdominal pain, bloating, ascites, hepatomegaly, diarrhea, intestinal obstruction, and abdominal mass.[13]

FGIDs are a collection of chronic or recurrent gastrointestinal symptoms that occur in the absence of a known underlying structural or biochemical abnormality. Currently, it is believed that low-grade and/or chronic inflammation, disruptions to the GI microbiota, changes in mucosal permeability, and impaired mucosal defense mechanisms are responsible for the pathogenesis of FGID.[2-4,14]

Although the reported prevalence of FGIDs varies across studies, Vernon-Roberts et al.[15] found a median prevalence of 22.2% (range 5.8-40%) in children up to four years of age and 21.8% (range 19-40%) in children aged four to eighteen years. In a study, Alonso-Bermejo et al.[16] reported that the annual frequency of FGIDs based on the Rome IV criteria was 32.4% in children under 16. In our study, the median frequency of FGIDs was higher compared to previous reports, with 42.9% (n=15) of the patients and 12.2% (n=6) of the controls being diagnosed with an FGID, and the difference between the groups was significant (p=0.001).

In many parts of the world, the prevalence of TB is much higher in males than in females.[17] On the other hand, FGIDs are more common in females than in males.[18] Our study findings show both similarities and contrasts with the existing literature in terms of sex distribution in TB and FGIDsin terms of sex distribution. Contrary to the literature, 42.9% (n = 15) of the patients diagnosed with TB were male, and 57.1% (n = 20) were female. However, consistent with the literature, 40% (n = 6) of the patients who developed any FGID were male and 60% (n =9) were female.

Functional dyspepsia, IBS, functional constipation, and functional abdominal pain are the most common manifestations of FGIDs in children.[19] In our study, among FGIDs, functional abdominal pain was the most common in the patient group (34.3%, n=12), while cyclic vomiting was the least frequent (2.9%, n=1). By comparison, functional constipation was the most prevalent FGID in the control group, diagnosed in 6.1% (n=3) of the controls. Statistical analysis revealed a significant difference in the frequency of functional abdominal pain between the patients and controls (Table 2).

Our study demonstrated that both the overall frequency of FGIDs and the prevalence of functional abdominal pain were higher in TB patients than in controls. Additionally, our study diagnosed 3 (8.6%) patients with gastrointestinal TB. Considering that there is some overlap in symptoms of gastrointestinal TB and FGIDs, especially concerning abdominal discomfort and changes in bowel movements, these three patients were evaluated more attentively for proper differentiation. One of these patients did not have any FGID symptoms, the second patient had IBS and cyclic vomiting, and the third patient had functional constipation. These patients were evaluated approximately one year after completion of TB treatment. Of note, after TB treatment, these three patients no longer exhibited any symptoms or signs present at the time of diagnosis. Based on these results, we concluded that the observed conditions were more likely associated with FGIDs rather than the residual effects of previous TB. Our findings support the hypothesis that FGIDs are more common in patients with a history of TB than in healthy controls.

Studies have shown that infections of the GI tract, nonspecific inflammation, exacerbations of IBD, celiac disease, rheumatic, autoimmune, and some inflammatory diseases may cause FGIDs.[20-22] Paula et al. showed that extra-intestinal infections may also trigger FGIDs. They suggested that this could be due to changes in the GI tract induced by a previous GI infection (e.g., alterations in cytokine production) and/or the use of antibiotics that modify the gut microbiota, both of which can trigger symptoms .[23]

In many countries, patients with TB are not followed for extended periods after treatment, resulting in limited data on the extent of long-term complications of the disease and their impact on children. In a study by Igbokwe et al.[24], it was reported that a small number of patients receiving conservative treatment for GI TB may experience permanent sequelae, such as recurrent adhesive obstructions, in the following years. However, the same study also noted that none of the long-term and/or permanent sequelae caused by other types of TB were related to the gastrointestinal system. This information is crucial for differentiating between GI TB and FGIDs to avoid confusion due to overlapping symptoms of these conditions.

A review of the literature revealed that the relationship between previous TB and FGIDs has not been thoroughly investigated. At present, it is not known exactly how long the inflammatory state and the changes in the immune system associated with TB persist or when they subside or resolve. Moreover, long-term antibiotic treatment for TB can lead to changes such as immune system dysregulation, altered mucosal permeability, abnormal mucosal defense mechanisms, inappropriate activation of the host immune system, and microbiota plasticity.[23] Due to the interaction of all these TB-related factors with host-related factors, patients with a history of TB may be susceptible to the development of FGIDs. To our knowledge, there is no other study in the literature focusing on the relationship between previous TB and susceptibility to FGIDs.

While attributing FGID symptoms to TB or its treatment after 6 months might seem indirect, several plausible mechanisms exist. Firstly, TB treatment often involves a prolonged course of antibiotics. Antibiotics can disrupt the normal gut flora, potentially leading to conditions like antibiotic-associated diarrhea or IBS. Disruptions in the microbiome can last long after the antibiotics have been stopped, contributing to FGID symptoms. Secondly, some of the drugs used to treat TB, such as rifampin or isoniazid, can cause GI side effects like nausea, diarrhea, or abdominal pain. Even after the drugs are discontinued, there might be lingering effects or sensitivity. Also, TB can cause significant inflammation in the GI tract, especially if the infection was extrapulmonary or gastrointestinal involvement. After the treatment, residual inflammation or immune system changes might contribute to ongoing FGID symptoms. Some GI symptoms might not appear immediately after the treatment but could develop over time as the body continues to recover and adjust from the effects of the illness and its treatment.

Limitations

The main limitations of this study are the relatively small sample size and its retrospective design. Future studies should investigate the underlying mechanisms linking TB with FGIDs and explore potential preventive or therapeutic strategies.

CONCLUSION

Our study supports the hypothesis that patients with previous TB are more likely to develop FGIDs than healthy controls. Children with previous TB may be at an increased risk for FGIDs, possibly due to chronic inflammation and immune system alterations associated with TB, highlighting the need for ongoing assessment of GI health in this population. Healthcare providers should be aware of the increased risk of FGIDs in children with a history of TB and implement appropriate monitoring and management strategies.

Ethical approval

This study has been approved by the Adıyaman University Non-Interventional Clinical Research Ethics Committee (approval date 24.05.2022, number 2022/5-16). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: HU, SY; Concept: HU, SY, SO; Design: HU, MT, SBO; Data Collection or Processing: HU, SO, NE; Analysis or Interpretation: HU, NE, MT; Literature Search: HU, SBO; Writing: HU, SY, NE. 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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Original Article

Assessment by neo-CIAF formula predicts contrast occurrence of overweight and undernourishment in preschool children of Jangalmahal districts, India

Baibhab Mahanti[1], Subham Chowdhury[2], Soham Paul[2], Debjani Adak[3], Subhajit Mahanty[1], Rama Das[4], Surajit Majumder[1], Smarajit Maiti[5], Nirmalya Kumar Sinha[3,6]

[1]Department of Zoology, Bankura Sammilani College, Bankura, West Bengal, India
[2]Department of Paediatrics, Midnapore Medical College & Hospital, Midnapore, West Bengal, India
[3]Department of NSS, Raja Narendralal Khan Women's College, Midnapore, West Bengal, India
[4]Department of Food & Nutrition (U.G. & P.G.), Barrackpore Rastraguru Surendranath College Barrackpore, West Bengal, India
[5]Department of MLT, Haldia Institute of Health Sciences, Haldia, West Bengal, India
[6]Department of Nutrition, Raja Narendralal Khan Women's College, Midnapore, West Bengal, India

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ABSTRACT

Objective: Overweight/obesity among preschool children has become an alarming phenomenon in low to middle-income countries, including India. This cross-sectional study aimed to assess the prevalence of overweight and underweight among children aged 2-6 years in Paschim Medinipur and Bankura districts, West Bengal, India.

Methods: We selected 497 children using systematic random sampling. The weight and height of each child was measured. BMI and Z-scores (WAZ, HAZ, WHZ) were calculated following standard techniques. Stunting, wasting, underweight, and composite index of anthropometric failure (CIAF) were evaluated. Data analysis included Student's t-test and one-way ANOVA. Bibliometric analysis was conducted to evaluate the trends of research in this field.

Results: Height and weight increased with age, indicating growth, but BMI declined slightly in older age groups. WAZ scores indicated prevalent underweight across all ages, with significant stunting observed in children aged 48-59 months. WHZ scores showed consistent negative values, suggesting ongoing wasting. The CIAF revealed that 50.91% of children experienced anthropometric failure, predominantly stunting and underweight. The study also revealed that 4.63% of the child suffer from overweight. Girls showed slightly higher rates of anthropometric failure than boys.

Conclusion: This study underscores the significant prevalence of the double burden of malnutrition among young children in Paschim Medinipur and Bankura. Effective interventions are urgently needed to address these challenges, including improving food security, enhancing healthcare services, promoting nutritional education, and ensuring sanitation facilities. Tailored strategies considering local socio-economic contexts are crucial for improving child health outcomes and mitigating the long-term effects of malnutrition in these districts.

Keywords: malnutrition, children, stunting, wasting, CIAF

Correspondence: Nirmalya Kumar Sinha **E-mail:** nksinhakgp@gmail.com
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INTRODUCTION

The double burden of malnutrition among children remains a critical public health challenge in many developing countries, resulting in both immediate and long-term adverse health effects.[1,2] It negatively impacts children's health and development, increases their vulnerability to illnesses, and significantly raises child morbidity and mortality rates.[3,4] Key measures of a child's nutritional health include indicators such as being underweight, experiencing wasting, and suffering from stunting.[5] Wasting and stunting are particularly significant as they directly indicate undernutrition.[6] Malnutrition, including undernutrition and overnutrition, is a major factor in the global burden of many diseases.[7]

According to the World Bank Report, the under-five mortality rate in India is 34 per 1,000 live births, whereas in West Bengal, it is somewhat lower at 25 per 1,000 live births.[8] Data from the National Family Health Survey (NFHS 5) for 2020-2021 show that in India, 35.5% of children suffer from stunting, 32.1% are underweight, and 19.3% experience wasting. In comparison, the figures for West Bengal are slightly different, with 33.8% of children stunted, 32.2% underweight, and 20.3% wasted.[9]

The prevalence of malnutrition in specific regions of West Bengal, such as Paschim Medinipur and Bankura, underscores the importance of localized studies to identify and address the unique challenges these communities face. These districts, characterized by their diverse socioeconomic conditions and cultural practices, exhibit varying nutritional outcomes among children.[10] For instance, factors such as food insecurity, limited access to healthcare services, inadequate maternal education, and poor sanitation significantly contribute to malnutrition in these areas.[11]

The regions encompassing Bankura, Purulia, Paschim Medinipur, and Jhargram districts in West Bengal are traditionally known by the colloquial term 'Jungle Mahal'. Paschim Medinipur, with its predominantly rural population, often struggles with issues related to agricultural dependency and seasonal variations in food availability, which directly affect children's nutritional intake.[12] Similarly, Bankura, known for its tribal communities, faces challenges such as poverty, illiteracy, and cultural barriers to accessing health services.[13] These socioeconomic determinants play a crucial role in shaping children's health and nutritional status in these districts.

The implications of malnutrition are far-reaching. Children who are malnourished in early life are more likely to suffer from impaired cognitive and physical development, which can hinder their educational performance and productivity in adulthood.[14] Furthermore, malnutrition can lead to a weakened immune system, making children more susceptible to infectious diseases, thereby exacerbating the cycle of poverty and poor health.[15] Addressing malnutrition in Paschim Medinipur and Bankura requires a multifaceted approach that includes improving food security, enhancing maternal and child healthcare services, promoting nutritional education, and ensuring clean water and sanitation facilities.[16] Targeted interventions that consider the local socioeconomic and cultural contexts are essential for effectively combating malnutrition and improving the health outcomes of children in these districts. There is limited data concerning the health profiles and nutritional statuses of preschool children in Paschim Medinipur and Bankura districts. This study aims to assess levels of undernutrition, stunting, wasting, and overweight among preschoolers in these districts of West Bengal, India.

MATERIALS & METHODS

Study location and human participants

A community-based cross-sectional study was conducted from February 2024 to April 2024 among preschool children between the ages of 2 and 6 who resided in Paschim Medinipur and Bankura districts.

Minimal sample size calculation

The minimal estimated sample size was calculated using the standard formula[17]: $n=(z^2pq)/d^2$. The calculation $\{(1.96^2\times0.388\times0.662)/ (0.05^2)\}$ was based on 33.8 % of prevalence (P) of stunting at the age of under five years children according to the recent report of the fifth National Family Health Study (NFHS-5) conducted during 2019-2021 in India (NFHS-5)[9], where z=1.96, q=p-1 and the desired precision (d) was ±5. Thus, the estimated sample size was 344 with a dropout rate of 10% was 378. The study focused on children aged between 2 and 6 years. Researchers conducted several visits to the study area within a specific period. Using a systematic random sampling method outlined by Das and Das[18], we selected a sample of 497 children, comprising 263 boys and 234 girls.

Ethical issues

The study was approved by the Institutional Ethics Committee/ Institutional Review Board. Written informed consent was obtained from the respective mothers of the children before the study was conducted.

Anthropometric measurements

Each child's name, age, and sex were recorded, and birth certificates were used to verify their birth dates for data accuracy. Height and weight measurements were taken using standard techniques, accurate to the nearest 0.1 cm and 0.5 kg, respectively.[19] Instruments were properly calibrated before use. Body Mass Index (BMI) was calculated using Quetelet's Index. The nutritional status was evaluated using age- and sex-specific height and weight data from the National Centre for Health Statistics (NCHS) reference.[20] Researchers assessed indices of undernutrition, such as stunting, underweight, and wasting, by calculating Z-scores from height-for-age, weight-for-age, and weight-for-height reference values. The formula for Z-score calculation was applied such as:

$$Z\ Score = \frac{X - Median\ of\ NCHS}{Standard\ Deviation\ of\ NCHS}$$

Where X represents an individual measurement. Z-scores for height-for-age (HAZ), weight-for-age (WAZ), weight-for-height (WHZ), and BMI-for-age (BAZ) were computed. Undernutrition was defined as a Z-score below -2 for any index. The WAZ>+1 was considered as overweight. The composite index of anthropometric failure (CIAF) was calculated using the recently developed equation given by Mahapatra and Bose.[21]

Statistical analysis

Statistical analyses were carried out using the IBM SPSS statistics 25 (2017, IBM Corporation, USA) for Windows. The anthropometric data was analyzed using a software package based on the NCHS database provided by ENA. Continuous variables were analyzed using Student's t-test or one-way analysis of variance (ANOVA) while applicable. If the F value was significant ($p < 0.05$), Dunnet's post hoc test was performed to determine the differences between the pairs of means. Statistical results were considered to be significant at $p < 0.05$.

RESULTS

Demographic and anthropometric profile

Figure 1 analyzes the demographic and anthropometric parameters of 497 children separated by sex (boys and girls). The circular plot (Figure 1a) represents the distribution of age in months. The radial lines appear to correspond to data points, and the numbers around the plot (0/6.28, 1.57, 3.14, 4.71) represent angles in radians. This format indicates the spread of ages across the sample, with the densest data points around the ages of 1.57 and 4.71 radians (approximately 15 months and 45 months, respectively). The scatter plot (Figure 1b) shows the relationship between weight and age. The data points for boys (blue) and girls (orange) show that weight increases with age. The trend lines for boys and girls indicate a similar pattern of weight gain over time, with slight differences between the sexes. Boys tend to have a slightly higher weight trajectory than girls. The violin plots at the top and sideshow that the weight distribution is slightly broader for boys, with most children falling within a weight range of approximately 10 to 20 kg between the ages of 30 and 70 months.

Figure 1c shows that height increases with age, with boys generally being taller than girls at most ages. The violin plots suggest that the height distribution is more varied, especially for boys, with most children falling within the height range of 80 to 120 cm between 30 and 70 months of age. Histogram of BMI (Figure 1d) indicates the mean BMI is 14.86±2.063 kg/m^2. The distribution is roughly normal, as indicated by the overlaid black curve. Most children have a BMI between 13 and 17 kg/m^2, with a few outliers at lower and higher values.

Influence of demographic profile on anthropometric indices

Table 1 explains the impact of the age of the children on the anthropometric parameters. Height measurements showed a significant increase with age, ranging from 86.19 cm (24-35 months) to 105.58 cm (60-71 months) ($F=130.588$, $P<0.001$). Weight also increased significantly across age groups, from 11.58 kg (24-35 months) to 16.10 kg (60-71 months) ($F=57.273$, $P<0.001$). BAZ declined slightly from -0.20 (24-35 months) to -0.82 (60-71 months) ($F=2.926$, $P<0.05$).

WAZ scores ranged from -1.22 to -1.53 across age groups, indicating the tendency towards underweight, but differences were not statistically significant ($F=1.142$, $P>0.05$). HAZ scores showed significant variation ($F=4.482$, $P<0.01$), with the lowest average (-1.70) observed in children aged 48-59 months, indicating the tendency towards stunting. WHZ scores did not vary significantly with age ($F=0.535$, $P>0.05$), hovering around -0.68 to -0.87, indicating consistent levels of wasting. The BAZ shows a significant decline ($F = 2.926$, $P < 0.05$) with increasing age, with mean values of -0.20 ± 1.42, -0.59 ± 1.80, -0.51 ± 1.67 and -0.82 ± 1.43 for the age groups 24–35 months, 36–47 months, 48–59 months, and 60–71 months, respectively. The Dunnett post hoc analysis indicated that the youngest age group (24–35 months) had significantly higher BAZ values while comparing among the age groups.

The distribution of z-scores for weight-for-height, height-for-age, and weight-for-age for the preschool children compared with the international reference values is presented in Figure 2. This figure

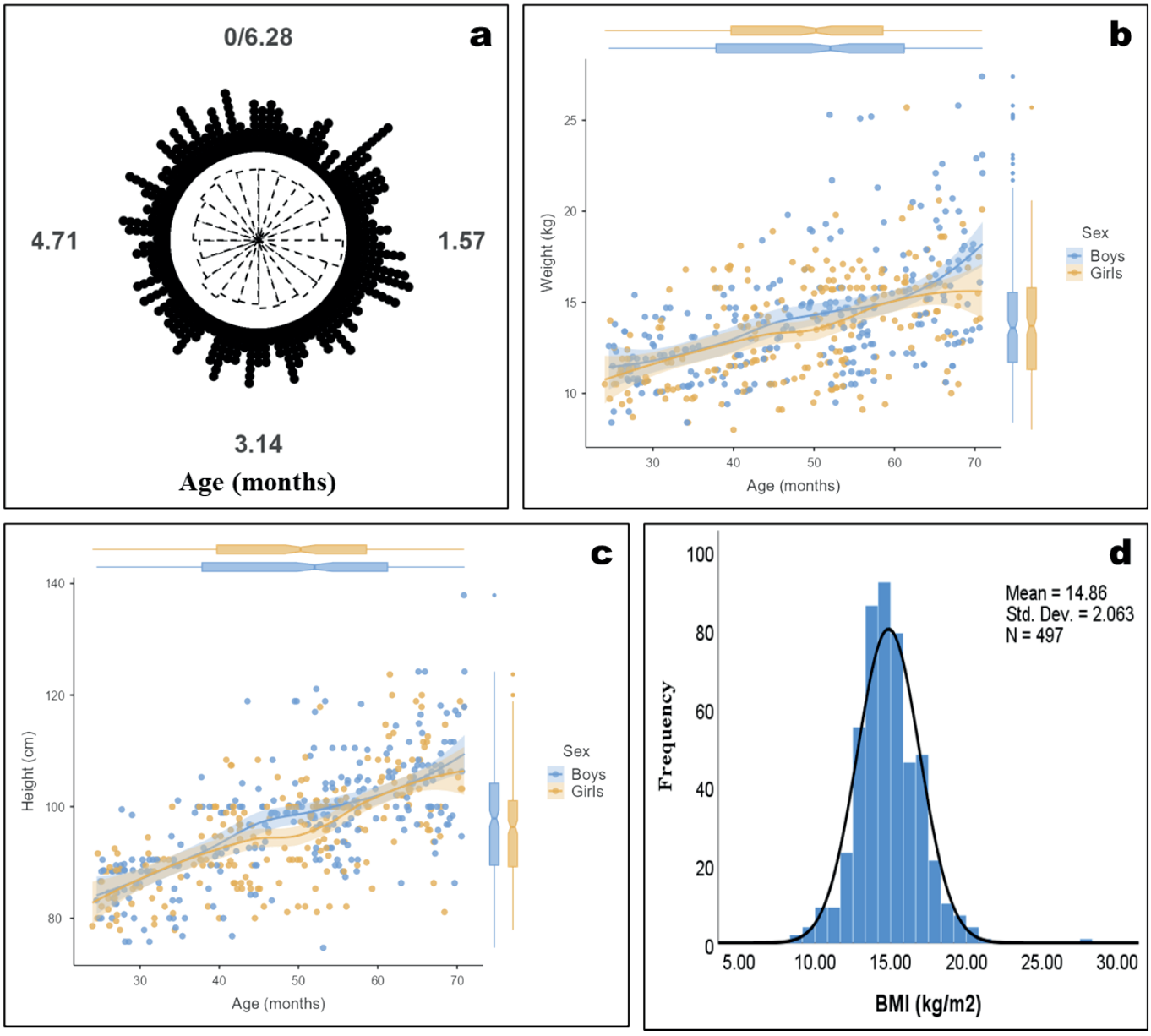

Figure 1. Distribution of the demographic and anthropometric parameters of the children

BMI-Body Mass Index

indicates the negative tendency of WAZ (Figure 2a), HAZ (Figure 2b), and WHZ (Figure 2c), which denotes the undernourishment among the children of Jangalmahal areas. Figure 2d shows the distribution of BAZ for boys and girls. The distributions for both sexes are centered around a z-score of approximately -1 to -2, further highlighting that the children in this study have lower BMI-for-age compared to the reference population. The distribution for boys appears slightly broader, with a notable peak around a z-score of -2.5, while the distribution for girls is narrower, with a peak between -1.5 and -2.0.

Figure 3 presents anthropometric parameters for boys and girls aged 24 to 71 months, including height, weight, BMI, WAZ, HAZ, and WHZ. The results are categorized into four age groups (24-35 months, 36-47 months, 48-59 months, 60-71 months) and a combined age group. For boys, the average height increases with

Table 1. Influence of age (month) of the children on the anthropometric parameters					
Parameters	**24-35 months**	**36-47 months**	**48-59 months**	**60-71 months**	**F**
Height	86.19±5.34	94.05±7.48‡	98.25±7.76‡	105.58±8.82‡	**130.588****
Weight	11.58±1.66	13.12±2.41‡	14.31±2.91‡	16.10±3.29‡	**57.273****
BAZ	-0.20±1.42‡	-0.59±1.80	-0.51±1.67	-0.82±1.43	**2.926***
WAZ	-1.22±1.19	-1.36±1.38	-1.53±1.47	-1.43±1.41	1.142
HAZ	-0.96±1.57	-1.10±1.87	-1.70±1.79‡	-1.39±1.89	**4.482***
WHZ	-0.68±1.06	-0.85±1.42	-0.74±1.44	-0.87±1.22	0.535

P<0.001 (**); P<0.05(*); Post Hoc= P (<0.05) ‡
BAZ: Z-scores for BMI-for-age; WAZ: Z-scores for weight-for-age; HAZ: Z-scores for height-for-age; WHZ: Z-scores for weight-for-height

age: 86.36±5.53 cm for 24-35 months, 94.69±7.91 cm for 36-47 months, 100.02±8.13 cm for 48-59 months, and 105.65±9.11 cm for 60-71 months. The combined age group's average height is 97.29±10.53 cm. The weight shows a similar trend, with means of 11.76±1.58 kg, 13.15±2.24 kg, 14.69±3.21 kg, and 16.40±3.62 kg for the respective age groups, and a combined mean of 14.16±3.33 kg. BMI was relatively decreased with increasing age groups, with values of 15.81±1.94, 14.74±2.27, 14.64±2.42 and 14.58±1.84, resulting in an overall mean of 14.92±2.19. WAZ shows consistent negative values across age groups: -1.24±1.14, -1.46±1.20, -1.50±1.56, and -1.51±1.50, with a combined mean of -1.44±1.39. HAZ decreases slightly over age groups such as -1.05±1.63, -1.11±1.90, -1.46±1.88, and -1.57±1.88, with a combined mean of -1.33±1.39. WHZ values also show negative means: -0.65±1.13, -1.05±1.39, -0.93±1.48, and -0.83±1.28, resulting in a combined mean of -0.86±1.34. For girls, the average height increases from 85.95±5.12 cm for 24-35 months to 105.49±8.52 cm for 60-71 months, with an overall average height of 95.84±9.53 cm. The average weight progresses from 11.31±1.75 kg for 24-35 months to 15.71±2.79 kg for 60-71 months, with an overall average of 13.64±2.86 kg. The BMI values are 15.27±1.44, 14.94±2.17, 14.94±1.99, and 14.09±1.70 for the respective age groups, with a combined mean of 14.81±1.92. WAZ shows negative averages across all groups: -1.20±1.26, -1.28±1.53, -1.57±1.37, and -1.34±1.29, resulting in a combined mean of -1.37±1.37. HAZ values are -0.82±1.48, -1.09±1.87, -1.96±1.65, and -1.17±1.90, with a combined mean of -1.35±1.78. WHZ values for girls are -0.73±0.94, -0.68±1.43, -0.55±1.37, and -0.93±1.15, resulting in a combined mean of -0.70±1.27. Overall, both boys and girls show an increase in height and weight with age. BMI remains relatively stable, while WAZ, HAZ, and WHZ indicate negative trends across all age groups, reflecting potential nutritional or growth challenges.

Nutritional status of the children and its determinants

Table 2 shows the prevalence of underweight, stunting, wasting, and Composite Index of CIAF across different age groups (24-71 months) among boys, girls, and the combined group. Among boys, the prevalence of underweight is highest in the 48-59 months group at 39.02%, with an odds ratio (OR) of 1.656, while for girls, it peaks at 44.07% in the 36-47 months group (OR = 1.818). Stunting is most prevalent in boys aged 60-71 months (37.68%, OR = 1.854) and girls aged 48-59 months (39.74%, OR = 2.886). Wasting is notably higher in girls aged 36-47 months at 23.73% (OR = 4.148) compared to boys in the same age group, who have a prevalence of 21.57% (OR = 1.589). The CIAF, which captures multiple forms of malnutrition, is particularly high in the 36-47 months age group for girls (67.80%, OR = 3.220) and boys (52.94%, OR = 1.514), with the combined prevalence in this age group reaching 60.91% (OR = 2.210). This data highlights the significant burden of undernutrition in these specific age groups, particularly among girls.

Table 3 presents the distribution of the CIAF among boys, girls, and combined sexes in Paschim Medinipur and Bankura districts. The CIAF categorizes children based on anthropometric indicators, including wasting, stunting, underweight, and overweight. Most children in Group A (49.09%) showed no anthropometric failure, with similar proportions between boys (50.95%) and girls (47.01%). Group B, characterized by wasting only, comprised 2.82% of children overall, with a slightly higher prevalence among girls (3.85%) compared with boys (1.90%). Group C included children who were both wasting and underweight (7.65%), with comparable distributions across sexes. Group D, involving wasting, stunting, and underweight, accounted for 6.04% of children, with a higher proportion among boys (7.60%) than girls (4.27%). Group E, characterized

Table 2. Influence of age and sex on the nutritional status of the children

	Boys				Girls				Sex combined			
Age (months)	**N**	**Underweight**	**χ^2**	**OR [95%CI]**	**N**	**Underweight**	**χ^2**	**OR [95%CI]**	**N**	**Underweight**	**χ^2**	**OR [95%CI]**
24-35	61	17 (27.87)®			43	13 (30.23)®			104	30 (28.85)®		
36-47	51	18 (35.29)	0.713	1.412 [0.633-3.148]	59	26 (44.07)	2.016	1.818 [0.793-4.167]	110	44 (40.00)	2.940	1.644 [0.930-2.909]
48-59	82	32 (39.02)	1.933	1.656 [0.811-3.384]	78	29 (37.18)	0.590	1.366 [0.616-3.029]	160	61 (38.13)	2.402	1.520 [0.894-2.584]
60-71	69	26 (37.68)	1.408	1.565 [0.745-3.286]	54	13 (24.07)	0.463	0.732 [0.297-1.802]	123	39 (31.71)	0.218	1.145 [0.648-2.024]
		Stunting				**Stunting**				**Stunting**		
24-35	61	15 (24.59)®			43	8 (18.60)®			104	23 (22.12)®		
36-47	51	13 (25.49)	0.012	1.049 [0.445-2.475]	59	19 (32.20)	2.363	2.078 [0.810-5.333]	110	32 (29.09)	1.362	1.445 [0.778-2.684]
48-59	82	29 (35.37)	1.907	1.678 [0.802-3.510]	78	31 (39.74)	5.671*	2.886 [1.183-7.041]	160	60 (37.50)	6.921**	2.113 [1.203-3.710]
60-71	69	26 (37.68)	2.570	1.854 [0.868-3.963]	54	16 (29.63)	1.563	1.842 [0.702-4.835]	123	42 (34.15)	3.992*	1.826 [1.008-3.309]
		Wasting				**Wasting**				**Wasting**		
24-35	61	9 (14.75)®			43	3 (6.98)®			104	12 (11.54)®		
36-47	51	11 (21.57)	0.879	1.589 [0.601-4.202]	59	14 (23.73)	5.026*	4.148 [1.111-15.492]	110	25 (22.73)	4.680*	2.255 [1.066-4.768]
48-59	82	14 (17.07)	0.139	1.190 [0.478-2.961]	78	11 (14.10)	1.376	2.189 [0.576-8.321]	160	25 (15.63)	0.873	1.420 [0.679-2.968]
60-71	69	10 (14.49)	0.002	0.979 [0.370-2.595]	54	10 (18.52)	2.748	3.030 [0.778-11.800]	123	20 (16.26)	1.037	1.489 [0.690-3.212]
		CIAF				**CIAF**				**CIAF**		
24-35	61	26 (42.62)®			43	17 (39.53)®			104	43 (41.35)®		
36-47	51	27 (52.94)	1.186	1.514 [0.717-3.200]	59	40 (67.80)	8.058**	3.220 [1.419-7.309]	110	67 (60.91)	8.190**	2.210 [1.279-3.819]
48-59	82	45 (54.88)	2.101	1.637 [0.839-3.194]	78	42 (53.85)	2.272	1.784 [0.838-3.801]	160	87 (54.85)	4.281*	1.691 [1.026-2.785]
60-71	69	31 (44.93)	0.070	1.098 [0.548-2.200]	54	25 (46.30)	0.446	1.318 [0.585-2.971]	123	56 (45.53)	0.401	1.186 [0.700-2.009]

Significance level at P<0.001 (**); P<0.05(*). ®: Reference
CIAF: Composite Index of Anthropometric Failure

Table 3. Influence of sex on the composite index of anthropometric failure (CIAF)				
Group	**Categories**	**Boys**	**Girls**	**Sex Combined**
A	No failure	134 (50.95)	110 (47.01)	244 (49.09)
B	Wasting only	5 (1.90)	9 (3.85)	14 (2.82)
C	Wasting and underweight	19 (7.22)	19 (8.12)	38 (7.65)
D	Wasting, stunting and underweight	20 (7.60)	10 (4.27)	30 (6.04)
E	Stunting and underweight	43 (16.35)	42 (17.95)	85 (17.10)
F	Stunting only	20 (7.60)	22 (9.40)	42 (8.45)
G	Stunting and overweight	-	-	-
H	Overweight only	11 (4.18)	12 (5.13)	23 (4.63)
I	Stunting and wasting only	-	-	-
Y	Underweight only	11 (4.18)	10 (4.27)	21 (4.23)
	Total CIAF (B-Y)	129 (49.05)	124 (52.99)	253 (50.91)

Data presented as N (%)
CIAF: Composite Index of Anthropometric Failure

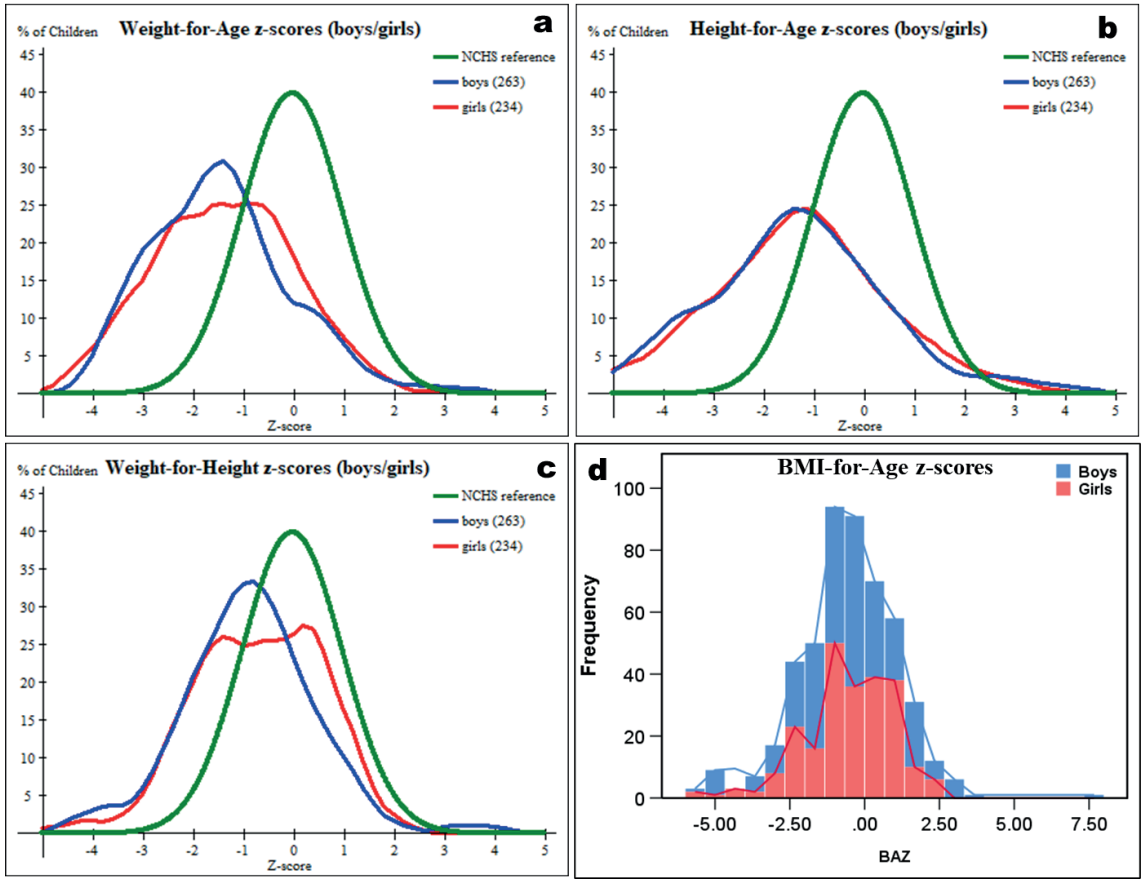

Figure 2. Z-score of the weight for age, height for age, weight for height, and BMI for age among the children

NCHS-National Center for Health Statistics, BAZ-BMI-for-Age z-score

by stunting and underweight, represented 17.10% of children, again showing similar distributions between boys (16.35%) and girls (17.95%). Group F, stunting only, comprised 8.45% of children, with a slightly higher prevalence among girls (9.40%) than boys (7.60%). Group H, overweight only, represented 4.63% of children, with a slightly higher prevalence among girls (5.13%) compared with boys (4.18%). Group Y, underweight only, accounted for 4.23% of children, with similar distributions between boys (4.18%) and girls (4.27%). Overall, the combined CIAF (sum of Groups B-Y) indicated that 50.91% of children in the study area experienced some form of anthropometric failure. There was a slight predominance among girls (52.99%) compared to boys (49.05%). These results underscore the multifaceted nature of malnutrition among children in Paschim Medinipur and Bankura districts, with significant proportions experiencing various combinations of wasting, stunting, underweight, and overweight.

DISCUSSION

The findings of this cross-sectional study reveal significant variations in the anthropometric parameters of children aged 2 to 6 years in Jangalmahal areas of West Bengal, highlighting the complex nature of malnutrition in these regions. The results illustrate the impact of age on height, weight, BMI, WAZ, HAZ, WHZ, and BAZ, providing critical insights into the prevalence and distribution of undernutrition among these children. The data showed a clear trend of increasing height and weight with age, reflecting expected growth patterns. This growth trajectory indicates that, on average, children in the study population are experiencing linear growth and weight gain appropriate for their age groups. Such patterns align with established growth standards, suggesting that while overall growth is occurring, underlying issues need to be addressed.[22] Despite the increase in height and weight, the slight decline in BMI as children age suggests that their weight gain is not keeping pace with their height growth. This trend could be indicative of emerging nutritional and health issues, where children may be growing taller but not gaining adequate weight. The persistent negative WAZ scores across all age groups point to a widespread issue of underweight, indicating that undernutrition is a significant concern for these children. Consistent negative WAZ scores across age groups suggest that underweight remains a persistent problem, necessitating targeted nutritional interventions. The variation in HAZ scores, with the lowest values observed in a particular age group, signals a notable incidence of stunting, indicative of chronic malnutrition. Stunting reflects long-term nutritional deficits, which could have lasting impacts on

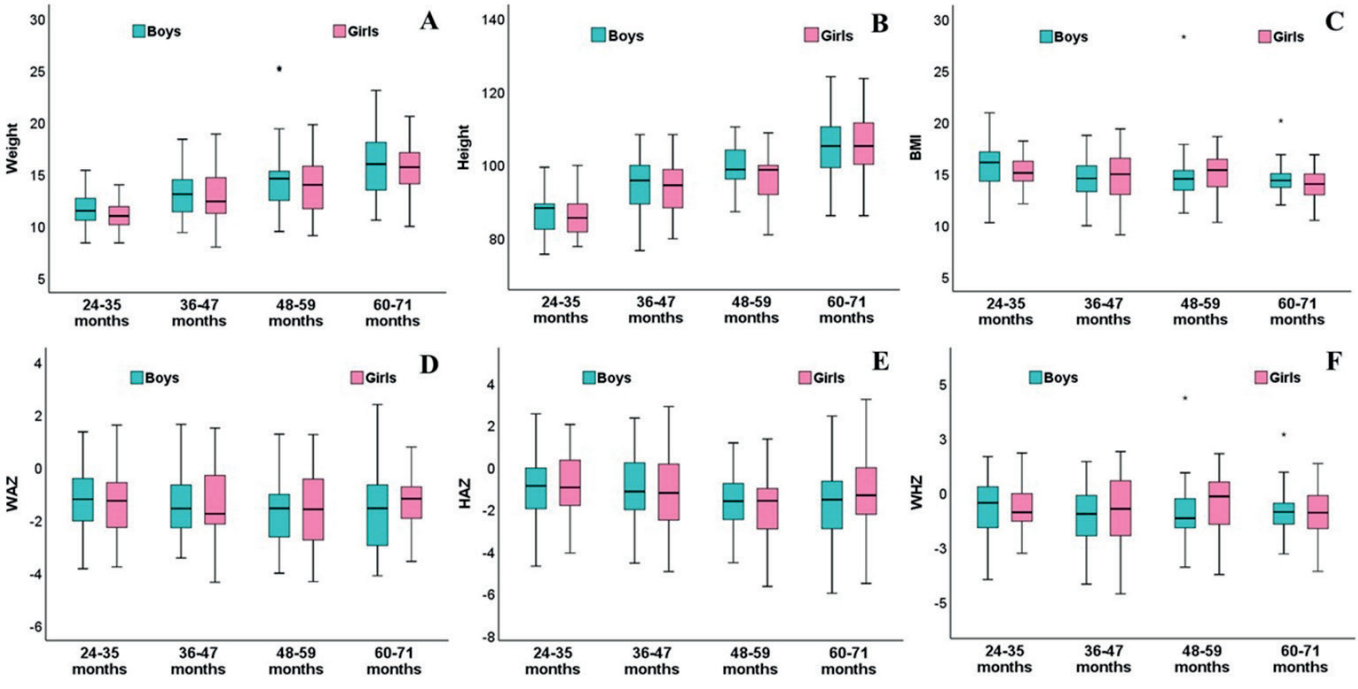

Figure 3. Influence of age and gender on different anthropometric indices

BMI-Body Mass Index; WAZ-Weight-for-Age z-score; HAZ-Height-for-Age z-score; WHZ- Weight-for-Height z-score

children's physical and cognitive development. These findings align with other studies that report high stunting prevalence in similar contexts, highlighting the need for sustained nutritional support.[23] Notably, the children were not meeting the typical weight and height benchmarks as defined by the NCHS standards. It was noted that both boys and girls are below the expected weight and height compared to the NCHS reference data (Figure 2). Additionally, the data shows that boys and girls have very similar measurements in terms of height and weight. Similar kinds of results were reported earlier by Sinha et al.[24]

Figure 3 provides an overview of nutritional status indicators among children aged 24-71 months, categorized by gender and age groups. It outlines prevalence rates of underweight, stunting, and wasting across different periods. The findings highlight varying degrees of malnutrition across age and gender categories. For instance, underweight prevalence is highest among boys aged 48-59 months (39.02%) and girls aged 36-47 months (44.07%). Stunting rates are notably high among boys aged 60-71 months (37.68%) and girls aged 48-59 months (39.74%). Wasting rates are relatively lower but show a consistent pattern across age groups and genders. This study also provides a detailed analysis of the relationships between various anthropometric indices in children, highlighting significant trends and correlations that are crucial for understanding childhood growth patterns. Younger children exhibit a wider range of HAZ based on their WHZ, with this variability decreasing as they age, indicating that early nutritional status has a profound impact on linear growth.[25] A strong positive correlation between Weight and Height ($r = 0.79$, $p < 0.001$) and between BMI and both BAZ ($r = 0.97$, $p < 0.001$) and WHZ ($r = 0.92$, $p < 0.001$), underscoring the importance of BMI as a reliable indicator of nutritional status in children.[26] Age also correlates moderately with Weight ($r = 0.51$, $p < 0.01$) and Height ($r = 0.66$, $p < 0.01$), suggesting that as children grow older, their weight and height generally increase, consistent with typical growth trajectories.[26] These insights underscore the necessity of early and continuous nutritional interventions to mitigate the risk of long-term growth impairments and emphasize the value of using multiple anthropometric measures to accurately assess and address malnutrition in pediatric populations.

WHZ scores, which remained consistently negative and did not show significant variation with age, indicate ongoing levels of wasting among the children. Wasting is often a result of acute nutritional deficiencies and underscores the immediate need for nutritional interventions and healthcare support to address this acute form of undernutrition. These results are consistent with global wasting patterns in regions facing nutritional challenges.[27]

It is probably the first study in Paschim Medinipur and Bankura district where we have considered the newly developed formula for evaluating CIAF in which the overweight is also included, along with stunting, wasting, and underweight. The prevalence of stunting, wasting, underweight, overweight, and CIAF among preschool children in this locality was 31.59%, 16.50%, 35.01%, 4.63%, and 50.91%, respectively.

The CIAF analysis revealed that a significant proportion of children experienced some form of anthropometric failure, with a slightly higher prevalence among girls compared to boys. The majority of children showed no anthropometric failure, but a substantial number were affected by various forms of undernutrition. This finding indicates diverse patterns of malnutrition, necessitating comprehensive and multifaceted intervention strategies to address the specific combinations of wasting, stunting, and underweight observed.

In addition to nutritional factors, various socioeconomic elements significantly contribute to malnutrition. Poor hygienic conditions, inadequate sanitation, lifestyle factors, and low levels of education play crucial roles. Infections, cultural practices related to childcare, breastfeeding, weaning, and superstitions also impact the nutritional status of certain communities. The children included in this study were randomly selected from marginalized or underprivileged groups. Previous research on similar populations indicates that many children do not complete their immunization schedules due to parental ignorance and lack of health awareness. Moreover, these children often face poor hygiene, detrimental household practices, infectious diseases, and malnutrition.[24,28]

This study provides robust evidence of the varying impacts of age on anthropometric parameters and underscores the prevalence of malnutrition among young children in Paschim Medinipur and Bankura districts. The significant findings regarding height, weight, BMI, WAZ, HAZ, and WHZ highlight the urgent need for targeted nutritional and health interventions to address the complex nature of undernutrition in these regions. Future research should focus on understanding the underlying causes of these nutritional deficits and developing effective strategies to combat them.

Strengths and limitations of this study

The strength of this work is that it briefly outlines the occurrence of malnutrition in the rural forest-based area in the southern part of West Bengal state. This place is comparatively more eco-restored and environmentally rich territories where migrated populations and industrial/commercial activities are scanty. In

this community, children are found to have diverse nutritional status, both malnutrition and overnutrition. This indicates the infiltration of multicultural practices in the community, which may be due to the advancement of information technology, digitization, and tourism-related activities. The attributing factors related to our present findings have not been well-focused in the current study and might be the topic of future research. Other environmental and confounding factors have not been discussed in the current study. Considering that under and over-nutrition develops adverse physiological status and may even create pathological conditions in association with other factors, multidimensional strategies are required for better health interventions in these communities.

CONCLUSION

In conclusion, the study underscores the pervasive issue of malnutrition among children aged 2 to 6 years in Paschim Medinipur and Bankura districts, revealing significant variations in anthropometric parameters such as height, weight, BMI, WAZ, HAZ, WHZ, and BAZ. Probably, it was the first study to evaluate the nutritional status of children using the recently developed CIAF by Mahapatra and Bose, where overweight is also included while calculating CIAF. This also emphasized the double burden of malnutrition. While children generally exhibit expected growth patterns in terms of height and weight, persistent underweight, stunting, and wasting indicate ongoing challenges in nutritional status. These findings necessitate targeted interventions addressing both immediate nutritional deficiencies and underlying socioeconomic factors contributing to malnutrition. Effective strategies should focus on improving health awareness, promoting hygienic practices, and ensuring access to nutritious diets to mitigate the complex impacts of undernutrition on child development and well-being in these regions.

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Ethical approval

This study has been approved by the Institutional Ethics Committee of Raja Narendralal Khan Women's College (Autonomus) [approval date 07.02.2024, number 03/IEC/RNLKWC/2024]. Written informed consent was obtained from the parents/care givers of the participants.

Author contribution

Study Concept: RD, SM, SM, NKS; Design: SM, SM, NKS; Data Collection or Processing: SC, SP, DA, BM; Analysis or Interpretation: SM, NKS; Literature Search: RD, SC, SP; Writing: BM, SM, SM. 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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Original Article

Clinical features and long-term follow-up of patients with West syndrome: 5-year developmental outcomes

Yiğithan Güzin[1], Serdar Pekuz[2], Pakize Karaoğlu[2], İpek Burcu Parlak İbiş[2], Hatice Hilal Kırkgöz[2], Merve Yavuz[2], Aycan Ünalp[2], Ünsal Yılmaz[2]

[1]Department of Pediatric Neurology, University of Health Sciences Tepecik Training and Research Hospital, İzmir, Türkiye
[2]Department of Pediatric Neurology, Dr. Behçet Uz Child Disease and Surgery Training and Research Hospital, İzmir, Türkiye

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ABSTRACT

Objectives: West syndrome (WS) is an early childhood epileptic encephalopathy characterized by spasms, typically occurring within the first year of life. The International League Against Epilepsy reclassified WS as "infantile epileptic spasm syndrome" to enhance early diagnosis and treatment. It is marked by a triad of epileptic spasms, psychomotor retardation or regression, and hypsarrhythmia on EEG. The prognosis and response to classical anti-epileptic treatments are often poor, and factors influencing prognosis remain unclear.

Methods: This study retrospectively analyzed 75 patients with WS over five years, assessing etiology, MRI findings, and neurodevelopmental outcomes according to ILAE guidelines.

Results: The cohort comprised 35 females (46.7%) and 40 males (53.3%). The most common etiology was structural, observed in 41 patients (54.7%), followed by unknown causes in 19 patients (25.3%). Genetic, metabolic, and infectious causes were less common. Brain MRI findings were normal in 23 patients (30.7%). Treatment primarily involved Vigabatrin, which was used in 54.7% of cases, followed by Adrenocorticotropic hormone (ACTH) in 25.3%. Seizure control improved over time, with 24% of patients fully controlled at one year and 42.8% at five years. However, 28% showed no change in seizure frequency. The presence of structural abnormalities correlated with a poorer prognosis, while early and complete seizure control was associated with better outcomes. Mortality was 5.3%, with four patients passing away during the follow-up period.

Conclusion: The study highlights that while the etiology remains a significant factor in the prognosis of WS, early intervention and effective seizure management are crucial for improving long-term outcomes.

Keywords: west syndrome, long-term prognosis, development delay

INTRODUCTION

West syndrome (WS) is an early epileptic encephalopathy of childhood, which was first described by William West in 1841. This disease mostly affects infants in the first year of life, and its characteristic feature is spasms.[1] The terms infantile spasms, epileptic spasms, and infantile spasm syndrome (WS, IS, ES, and ISs) are still used interchangeably.[2] In 2022, The International League Against Epilepsy classified all patients with infantile spasm and epileptic activity on electroencephalography (EEG) as "infantile epileptic spasm syndrome (IESS)" in addition to typical WS patients for early diagnosis and treatment.[3]

Correspondence: Yiğithan Güzin **E-mail:** yguzin@hotmail.com
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Infantile spasms have been evaluated for more than 170 years in terms of etiology, pathogenesis, clinical features, and diagnosis. It is a rare disease that occurs in 1.6% to 4.5% of 10,000 live births.[4-6] The clinical triad of WS is an epileptic spasm, psychomotor retardation or regression, and hypsarrhythmia pattern on EEG. It is one of the epileptic encephalopathy syndromes seen in early childhood.[7] The classical anti-epileptic treatment response and long-term prognosis are often poor.[8] The long-term overall prognosis for patients with infantile spasm is directly related to its etiology.[9] Although psychiatric problems such as autism and attention deficit are common, severe mental retardation is seen in 70% of patients together with psychiatric problems.[10] Current knowledge of the factors affecting the prognosis of WS is still limited. Therefore, the aim of this study was to determine the prognosis and factors affecting the prognosis of WS.

METHOD

A retrospective examination was conducted on the files of patients diagnosed with WS who were followed up for at least five years. The etiology of the patients was classified for the ILAE classification.[11] Magnetic resonance imaging (MRI) of the brain was performed in all patients. Chromosome analysis was performed. Urine and serum amino acid, organic acid in the urine, biotinidase, lactate, and pyruvate levels were examined. Psychomotor development steps were evaluated using the Denver II Developmental Screening Test, and the 5-year development milestones were examined.

Neurodevelopmental milestones were classified as normal, mild, moderate, or severe retardation. Developmental delay was categorized as mild for deficits less than 50%, moderate for deficits between 50% and 70%, and severe for deficits greater than 70%.

Patients with normal and mild retardation of neurodevelopmental milestones were classified as good prognosis, and those with moderate and severe retardation as poor prognosis. EEG hypsarrhythmia and modified hypsarrhythmia on admission were classified as normal or other. Hypsarrhythmia is an EEG pattern characterized by random, high-voltage spikes and slow waves. Key features include high-voltage slow waves of varying amplitude, multifocal spikes, and a lack of synchrony, resulting in a chaotic appearance. It is defined as random high-voltage (>200 µV) slow waves with intermixed multifocal spikes.[12] Modified hypsarrhythmia refers to variations of the classic hypsarrhythmia pattern seen on EEG that differ from the typical chaotic appearance. These variations may include more organized features, such as hemispheric synchronization, a consistent focal point, reduced overall voltage, or a lower frequency of spikes and sharp waves.[13]

The follow-up EEG findings were recorded in cases with normal EEG at the time of admission. The EEG findings were recorded after treatment per year. The efficacy of treatment and the factors affecting psychomotor retardation were investigated.

Approval for the study was granted by the Non-Pharmaceutical Clinical Research Ethics Committee of Dr. Behçet Uz Children's Health and Diseases Training and Research Hospital. (Date: 26.05.2021 Issue: E-13399118-799)

Statistical analysis

Data was analyzed using SPSS (Statistical Package for the Social Sciences) software. The Shapiro-Wilk test was used to determine whether the data followed a normal distribution. Mean and standard deviation were calculated for data that followed a normal distribution, whereas median and interquartile range were computed for data that did not follow a normal distribution.

The chi-square test or Fisher's exact test was used for categorical data. Independent samples t-test or Mann-Whitney U test was applied for differences between groups in continuous variables. For comparing more than two groups, ANOVA or Kruskal-Wallis test was utilized. Post-hoc tests were performed to identify differences between specific groups. Statistical significance was set at $p < 0.05$.

RESULTS

The records of 103 patients diagnosed with WS were retrospectively examined. A total of 28 patients who did not attend follow-up appointments regularly were excluded from the analyses. Evaluation was made of 75 patients, comprising 35 (46.7%) females and 40 (53.3%) males with a mean age of 5.5±3.6 months (median 5 months, min 0-max 20 months) at seizure onset. The age at seizure onset was 5.5±3.8 months in females and 5.6 ±3.4 months in males. No significant difference was found between the two groups ($p = 0.864$).

When the birth histories were examined, there was seen to be perinatal asphyxia in 13 patients (17.3%), premature birth in 14 (18.7%), hypoglycemia in 2 (2.7%), and intrauterine growth retardation in 2 (2.7%). There was a history of parental consanguinity in 12 (16%) patients. According to the ILAE, the etiology of WS was classified as genetic in 10 patients, structural in 41 patients, metabolic in 2 patients, infectious in 3 patients, and unknown cause in 19 patients (Table 1). All patients diagnosed with tuberous sclerosis complex (TSC) were genetically confirmed. All patients had mutations in the TSC1 gene.

Table 1. Etiology of West syndrome	
	n (%)
Genetics	10 (13.3)
MTHFR mutation	1 (1.3)
Merosin-deficient congenital muscular dystrophy	1 (1.3)
Rett syndrome	1 (1.3)
Prader Willi syndrome	1 (1.3)
TSC	6 (8.0)
Structural	41 (54.7)
Hypoxic ischemic encephalopathy	13 (17.3)
Periventricular leukomalacia	14 (19.7)
Others	14 (19.7)
Metabolic	2 (2.7)
Nonketotic hyperglycinemia	1 (1.3)
Possible metabolic disease	1 (1.3)
Infectious	3 (4.0)
Congenital CMV infection	1 (1.3)
Meningococcal meningitis	1 (1.3)
Herpes encephalitis sequelae	1 (1.3)
Unknown	19 (25.3)
Total	75 (100)

MTHFR: Methylenetetrahydrofolate reductase, TSC: Tuberous sclerosis complex, CMV: Cytomegalovirus.

The most common type of spasm in patients was flexor spasm. Two patients with flexor spasms had focal spasms. All patients had a history of more than one type of seizure. Seizure types were classified according to the ILAE. One patient had a focal clonic seizure in which awareness was maintained, and all other types of additional seizures were generalized (Table 2).

Brain MRI examination was performed in all the patients, and the findings were normal in 23 patients. The MRI findings of the patients are summarized in Table 3.

In the analysis of the patients' EEGs, hypsarrhythmia was identified in follow-up EEGs within a median of 14 days (min 7 - max 21 days) in eight patients who did not exhibit hypsarrhythmia at the time of admission.

Hypsarrhythmia was detected in 33 patients (44%), and modified hypsarrhythmia was detected in 42 (56%) patients.

B6 (pyridoxine) treatment was started orally at 30 mg/kg/day (maximum 300 mg/day) in all patients and discontinued within 2 weeks in patients with no change in seizure frequency.

Table 2. Seizures types in West syndrome	
	n (%)
Epileptic spasm	
Flexor spasm	42 (56)
Extensor spasm	6 (8)
Mixed spasm	27 (36)
Generalized tonic-clonic	65 (86.6)
Generalized myoclonic	22 (29.3)
Generalized Tonic	11 (14.7)
Generalized clonic	5 (6.7)
Focal clonic	2 (2.7)

Table 3. MRI findings in West syndrome	
	n (%)
Normal	23 (30.7)
Periventricular leukomalacia	25 (33.3)
Cerebral atrophy	7 (9.3)
Cortical tubers	5 (6.7)
Encephalomalacia	5 (6.7)
Cortical dysplasia	3 (4)
Corpus callosum dysplasia	3 (4)
Lissencephaly	2 (2.7)
Congenital CMV infection-related findings	1 (1.3)
Neurometabolic disorders-related findings	1 (1.3)

CMV: Cytomegalovirus.

The most commonly used anti-epileptic drugs in the treatment were vigabatrin (VGB) in 41 (54.7%) patients and ACTH in 19 (25.3%) patients.

VGB treatment was started at a dose of 50 mg/kg/day. The VGB dose was gradually increased in patients whose spasms could not be controlled (max150mg/kg/day). Tetracosactide (ACTH) was used at a dose of 0.02 mg/kg daily for two weeks and tapered over 6 weeks. Other anti-epileptic drugs were used by 15 patients (20%). VGB was started as the first treatment in 6 patients with TSC. All patients receiving VGB were examined for visual evoked potential (VEP) at 6-month intervals. The first positive waveform (P100) was defined as delayed when it was above 115 ms. P100 wave latency was prolonged in 5 patients. In 13 of the 19 patients administered ACTH in the first treatment, there was a decrease in the frequency of seizures in the 1st year of follow-up, while there was no change in the frequency of seizures in 6 patients. Four patients in the first year and eight patients in the 5th year were seizure-free. During the follow-up

Table 4. Seizure frequency and number of anti-epileptic drugs					
	1st year	2nd year	3rd year	4th year	5th year
Seizure free	18 (24%)	13 (17.3%)	21 (28%)	28 (37.3%)	32 (42.8%)
50%-99% decrease in seizure frequency	2 (2.7%)	8 (10.7%)	10 (13.3%)	14 (18.7%)	14 (18.7%)
< 50% decrease in seizure frequency	13 (17.3%)	14 (18.7%)	7 (9.3%)	5 (6.7%)	4 (5.3%)
No change in seizure frequency	42 (55%)	38 (49.7%)	33 (44.4%)	24 (32%)	21 (28%)
Number of anti-epileptic drugs	2±0.9	2.1±1	2.1±1.1	1.9±1.2	1.8±1.2

AEDs: anti-epileptic drugs

period, 65 patients (86.7%) required two or more anti-epileptic therapies. When the patients' seizure frequency was examined, 18 (24%) patients were fully controlled in year 1 and 32 (42.8%) in year 5. There was no change in the frequency of seizures in 21 (28%) patients (Table 4).

The most effective treatment for seizure control (50% or more decrease in seizure frequency and intensity) was VGB in 21 patients (28%), valproic acid in 13 patients (17.3%), clobazam in 11 patients (14.7%), and ketogenic diet in 7 patients (9.3%).

Mortality developed in 2 patients during the first year and in 2 patients during the second year of follow-up. The mortality rate was determined to be 5.3%. No statistically significant relationship was found between mortality and developmental delay (p=0.289).

The neuromotor development of the patients is summarized in Figure 1.

Complete remission was achieved in 7 patients (9.3%), with seizure freedom occurring after a median of 12 months (min 3– max 36 months) following seizure onset. EEG normalization was attained after a median of 36 months (min 12– max 60 months).

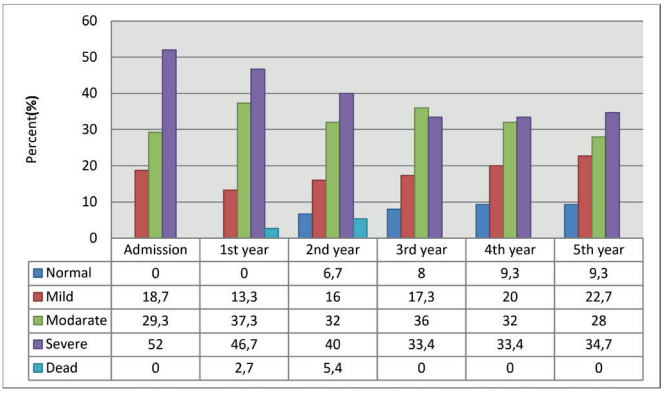

Figure 1. Neuromotor development from admission to 5 years

Age, gender, type of spasm, and choice of anti-epileptic treatment did not affect prognosis. The prognosis was worse in patients with structural etiology. In particular, complete seizure control was found to be associated with a good prognosis (Table 5).

In this study, in which the results of a 5-year follow-up were evaluated, important findings were obtained about the long-term prognosis of patients with WS.

Of the patients included in this study, 53% were male, which is consistent with the literature, which has shown mild male predominance.[7] WS is an age-related epileptic encephalopathy that typically begins around 6 months of age.[14] In the current study, the median age of seizure onset was 5 months, similar to the literature.[4,5] All patients had neuromotor growth retardation at the time of diagnosis.

In a 1993 study by Ohtahara et al.[15], 42.8% of patients had a prenatal history, while Osborne et al.[16] reported prenatal history in 36 of 208 patients. HIE is known to be one of the most common causes of WS etiology. In the UK Infantile Spasm study, the most common etiology of WS was HIE (10%), followed by chromosomal abnormalities (8%), complex malformation syndromes (8%), perinatal stroke (8%), TSC (7%), periventricular leukomalacia (5%), and intracranial hemorrhage (5%).[16]

In a cohort followed up in China, 70 of 541 patients were reported with HIE in the etiology.[17] In another study of 208 patients with HIE, Inoue et al. reported that 8 (4.9%) patients were diagnosed with WS.[18] Similarly, in the current study, HIE was determined in 13 (17.3%) patients as one of the most common causes.

In 5-35% of patients, the underlying cause cannot be determined.[4,19] It is thought that this rate will decrease with the widespread use of imaging examinations and advances in genetics and metabolism analyses.[20-22] In the current study, no cause could be determined in 19 patients (25.3%).

Table 5. Factors affecting the prognosis of WS			
	Good Prognosis (n=24)	**Poor Prognosis (n=51)**	**p**
The first month of the seizure			
Age (<3 months)	5 (20.8%)	20 (39.2%)	0.115
Gender (female)	11 (45.8%)	24 (47.1)	0.921
Etiology			
Genetic	6 (25%)	4 (7.8%)	0.049
Structural	8 (19.8%)	33 (64.7%)	0.011
Metabolic	1 (2%)	1 (1.9%)	0.593
Infectious	-	3 (5.9%)	0.123
Unknown	9 (19.6%)	10 (37.5%)	0.097
Type of spasm			
Flexor spasm	14	28	0.083
Extensor spasm	-	6	
Mixed type	10	17	
Cranial MRI (Normal)	11 (45.8%)	12 (23.5%)	0.051
First treatment			
ACTH	5	11	0.541
Vigabatrin	16	24	
Seizure Free			
1st year	9 (37.5%)	9 (17.6%)	0.060
2nd year	8 (33.3%)	5 (10.2%)	**0.015**
3rd year	14 (58.3%)	7 (14.9%)	**0.001**
4th year	17 (70.8%)	11 (23.4%)	**0.001**
5th year	17 (70.8%)	15 (31.9%)	**0.002**

MRI: Magnetic resonance imaging, ACTH: Adrenocorticotropic hormone.

TSC is an autosomal dominant inherited disease that affects multiple organs.[23] Due to TSC-specific MRI findings, patients can be divided into both structural and genetic categories.[24] Of the 6 TSC patients included in the genetic etiology group in the current study, 5 had cortical tubers. These five patients can also be classified in a structural subcategory due to genetic disease, as in the study by Peng et al.[17]

Spasms may be flexor, extensor, or mixed axial jerks, and crying or screaming attacks may be seen before or after. The spasms often occur in a rapid sequence and commonly occur just before sleep or upon waking. In the most severe ictal phenotypes, spasms may also be noticed during sleep. Deviation in the eyes may occur during attacks, and cardiac and respiratory involvement may occur.[4,7] Flexor spasm was determined to be present in 56% of the current study patients, extensor spasm in 8%, and mixed-type spasms in the remaining patients.

Hypsarrhythmia, first described by Gibbs in 1953, is a chaotic interictal pattern in which normal background rhythm elements are not observed, involving a diffuse, irregular, high-voltage multifocal spike and multiple spike activity discharges.[25] Hypsarrhythmia with increased interhemispheric synchrony, asymmetric hypsarrhythmia, hypsarrhythmia with abnormal focal focus, hypsarrhythmia with generalized, focal, or localized voltage attenuations, and hypsarrhythmia including bilateral asynchronous slow activity with high voltage are considered modified hypsarrhythmia.[26] Of the patients in the current study, 56% had signs of modified hypsarrhythmia.

MRI is recommended for all patients to clarify the etiology of WS. Early imaging is essential for etiological differential diagnosis.[27] In addition, if the patient does not respond to treatment or does not follow the expected course associated with the etiological diagnosis and there is clinical deterioration, MRI repetition is recommended. In infants with incomplete myelination, some abnormalities, such as focal cortical dysplasia, may be overlooked.[28] In a study by Aydinli et al. in 1998, the findings of 14 of 78 children who underwent MRI were normal.[29] Brain MRIs were performed on all patients included in the current study, and the MRI findings of 24 patients (32%) were normal. No correlation was found between MRI findings and prognosis (p=0.051) (Table 5). It was thought that this might be due to the small number of patients.

Data on the treatment of infantile spasms are limited, as most studies are retrospective or small prospective studies. ACTH, corticosteroids, and VGB are the main recommended drugs in the treatment.[30,31]

While VGB is the first choice in patients with tuberous sclerosis, hormonal therapy is the first treatment option for other patients.[32] In the current study, 41 (54.7%) of the patients were started with VGB, and 19 (25.3%) with ACTH anti-epileptic as the first option.

One of the most well-known side effects of VGB is visual field defects[33], which manifests as visual field loss in 34% of children treated with VGB.[34] Visual field test follow-up is required at regular intervals before and after treatment. In a study conducted in 2014, retinal toxicity was detected in 21% of 146 patients using VGB.[35] Since a visual field test was not performed in our center, a VEP examination was performed on the patients. An abnormal finding was detected in the VEP test in 12% of the patients. VGB use for more than 6 months is thought to increase retinal toxicity.[35] In the current study, abnormality in VEP examination was observed in the median 1st year. At the end of 5 years of follow-up, there was no clinical vision loss in any patient.

In line with the literature, 8 of the 19 patients (42.1%) who underwent ACTH treatment achieved complete seizure control in the 5th year.[32]

In the current study, VGB was identified as the most effective anti-epileptic drug for seizure control, aside from ACTH therapy. This finding has been attributed to the initiation of treatment tailored to the underlying etiology.

While ketogenic diet therapy (KDT) is the first treatment option for GLUT-1 deficiency, it is also one of the alternative treatment methods that can be used in nonketotic hyperglycinemia (NKH) and drug-resistant epilepsy, and there have been reports that it is effective in infantile spasm.[36–39] The most effective treatment method in the current study was seen to be KDT in a total of 7 patients, one of whom was NKH.

The long-term prognosis of WS is poor, and prognostic outcomes and data are still limited. Etiology is recognized as the most important prognostic factor.[40] Generally, the prognosis is better in patients of unknown etiology than in patients of known etiology.[41,42] Similarly, the prognosis was found to be poor in patients with structural etiology and good in patients with unknown etiology. The developmental delay occurs in the majority of patients with infantile spasms, and the rate of complete remission is generally low.[40,43] In a study conducted by Güveli et al. 8 of 109 patients had complete remission.[44] This rate was 15% in a study by Yuskaitis et al.[22] and 28% in a study by Camfield et al.[45] In the current study, complete remission was obtained in 7 (9.3%) patients. It was thought that this difference may be related to the underlying etiology. Early initiation of treatment and good treatment response in WS is also known to affect the prognosis positively.[46] In the current study, it was seen that patients who were seizure-free in year 2 and later had better neuromotor development (Table 5). Mortality in WS ranges from 3-30%.[47–49] In the current study, the mortality rate was 5.4%, similar to the literature.

In conclusion, although the underlying etiology is the most important determinant in the long-term prognosis of WS, early and complete seizure control is just as important. Therefore, etiological diagnosis and treatment are necessary.

Ethical approval

This study has been approved by the Non-Pharmaceutical Clinical Research Ethics Committee of Dr. Behçet Uz Children's Health and Diseases Training and Research Hospital (approval date 26.05.2021, number E-13399118-799).

Author contribution

Study conception and design: YG, PK, SP; data collection: YG, MY, HHK; analysis and interpretation of results: İBPİ, ÜY; draft manuscript preparation: YG, AÜ, ÜY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

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Case Report

Two variants of the ferredoxin reductase (FDXR) causing isolated retinitis pigmentosa

Fayize Maden Bedel[1], **Müşerref Başdemirci**[2]

[1]Department of Pediatric Genetics, Genetic Diseases Diagnostic Center, Erzurum City Hospital, Erzurum, Türkiye
[2]Department of Medical Genetics, Konya City Hospital, Konya, Türkiye

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ABSTRACT

Objective: The FDXR gene encodesferredoxin reductase, which is a mitochondrial membrane protein and plays a role in Fe-S cluster synthesis. Loss of function in this gene causes intracellular iron accumulation, leading to dysfunction, especially in nervous system cells. To date, 46 patients with biallelic FDXR variants have been reported. While optic atrophy was a common finding in most of the patients, it was found that many neurological findings were also accompanied.

Method: Two siblings from an unrelated Turkish family and their parents were included. DNA was isolated from the patient's blood sample. Whole exome sequencing was performed using next-generation DNA sequencing.

Results: We described two siblings with the same compound heterozygous variants, but with phenotypically different characteristics. While ataxia, opticatrophy, and minor dysmorphic findings were present in one sibling, we did not detect any finding other than subclinical retinal dystrophy in the other sibling.

Conlusion: Many patients described in the literature have also been reported to show wide phenotypic variability. We would like to report these patients to contribute to the genotype phenotype relationship of the disease and to create resources for future gene therapies.

Keywords: FDXR gene, optic atrophy

INTRODUCTION

Iron is required as an enzymatic cofactor to synthesize many protein complexes, including Fe-S clusters. Incorrect biosynthesis of Fe-S aggregates creates iron overload in tissues and cells. Excessive iron accumulation also causes pathological changes and dysfunction in cells. Due to a decrease in Fe-S clusters, this accumulation is responsible for the pathogenesis of mitochondrial diseases. Ferredoxin Reductase (FDXR) encodes flavoprotein, a mitochondrial membrane protein involved in the biosynthesis of Fe-S clusters and the transfer of electrons from NADPH to the cytochrome p450 system. The flavoprotein interacts with ferredoxin 1 (FDX1) and ferredoxin 2 (FDX2). FDX1 plays a critical role in the steroid biosynthesis pathway, while FDX2 plays a critical role in the biosynthesis of Fe-S aggregates.[1,2] When FDXR activity decreases, the synthesis of Fe-S clusters decreases, and iron overload occurs, resulting in multiorgan dysfunction, especially in the neurons. FDXR is a gene with 12 exons localized at 17q25 and has three main domains: two NAD(P) binding domains and the FAD/NAD(P) binding domain in the middle. FDXR plays a role in the pathogenesis of mitochondrial myopathy, auditory neuropathy, and optic atrophy. It was first

Correspondence: Fayize Maden Bedel **E-mail:** drfmaden@hotmail.com
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described by Paul et al.[3] in patients with hereditary auditory neuropathy and optic atrophy. It is among the ten most common genes that cause hereditary optic neuropathy. In this study, we report the different phenotypic features in two siblings with the same variants.

MATERIAL AND METHODS

Subjects

Two siblings from an unrelated Turkish family and their parents were included. The study was approved by the Necmettin Erbakan University Faculty of Medicine Ethics Committee (2023/4118) and performed in accordance with the ethical standards of the Declaration of Helsinki. The parents signed a written informed consent form.

Genetic Studies

The number of GAA repeats for Freidrich's ataxia was evaluated and found to be <33. Mitochondrial sequence analysis revealed no pathogenic variant in Patient 1. DNA was isolated from the patient's blood sample. Whole exome sequencing was performed using next-generation DNA sequencing (NextSeq, Illumina). The data obtained was analyzed using the Franklin Genoux database. Homozygous and heterozygous variants with high sequence read quality were filtered out.

RESULTS

Patient 1

A 5-year-old male patient presented to us with a complaint of walking disorder. The patient's walking had gradually deteriorated over the previous year, resulting in an unbalanced gait. According to the patient's medical history, he was hospitalized because of a walking disorder that developed suddenly when he was 2.5 years old. He was diagnosed with Gullian-Barre and received immunoglobulin treatment for the same. The walking disorder partially improved after the treatment, but it worsened when he was approximately four years old. A pediatric neurology check-up was performed because the patient had frequent falls and an unbalanced gait. The patient's electromyography and electroencephalography were evaluated as normal. Cranial magnetic resonance imaging (MRI) was reported as normal. The patient's nystagmus, which started two weeks after his first hospitalization, continues, and visual field loss and optic atrophy were detected during an ophthalmology check-up. The patient's visual loss was progressive. A hearing test and brainstem auditory-evoked potentials (BAEP) were performed and evaluated as normal. The following findings were reported upon physical examination: body weight – 24 kg (75–90 p), height – 127 cm (99p, +2.4 SDS), head circumference – 51 cm (25–50 p). Other than dysmorphic findings, such as downward slanting palpebral fissures, ptotic eyelids, drooping ears, no eye tracking, and weak deep tendon reflexes were found (Figure 1).

Patient 2

A 9-year-old female patient was born to the same unrelated parents at 40 weeks gestational age. It was learned from the patient's medical history that she had completed her neurodevelopmental milestones without delay and had no disease. An eye examination was performed since optic atrophy was detected in her brother. Retinal dystrophy and optic atrophy were detected in the concerned patient. However, the patient had no complaints about vision. BAEP was evaluated as normal. Cranial MRI was reported as normal. The hearing test was assessed as normal. The following findings were noted upon physical examination: body weight – 35 kg (75–90 p), height – 137 cm (75–90 p), head circumference – 52 cm (25–50 p). Systemic examination revealed no significant finding examination.

Molecular Findings

FDXR c.235C>T, p.Arg79Cys (NM_024417.5), c.980G>A, p.Arg327His variants were detected, which are compatible with the patient's clinical findings. These variants were deemed likely pathogenic based on the American College of Medical Genetics 2015 (ACMG) criteria. According to the ACMG criteria, the FDXR c.235C>T variant is of uncertain clinical significance (VUS), and when evaluated together with family segregation data, it is classified as likely pathogenic (PP1, PM2). In addition, this variant has been reported as deleterious by in silico prediction programs (MT, DANN, SIFT). The DNA was obtained from the blood samples of the family members, after which the PCR product prepared with the target region primers was sequenced. The FDXR c.980G>A variant was detected in the mother, and the FDXR c.235C>T variant was detected in the father. His older sister also had compound heterozygote FDXR variants (Figure 2).

DISCUSSION

Here, we present a case study of a male patient with optic atrophy and ataxia and his sister, who had the same variants but presented with no clinical findings. The literature has reported 46 such patients so far. The most common finding in these patients is optic neuropathy, observed in 93.2% of the cases.[4] The second most common finding reported is acoustic neuropathy, found in 50% of the cases. Developmental delay, developmental regression, peripheral neuropathy, and hypotonia are among the less common findings reported. The rate of ataxia seen in our

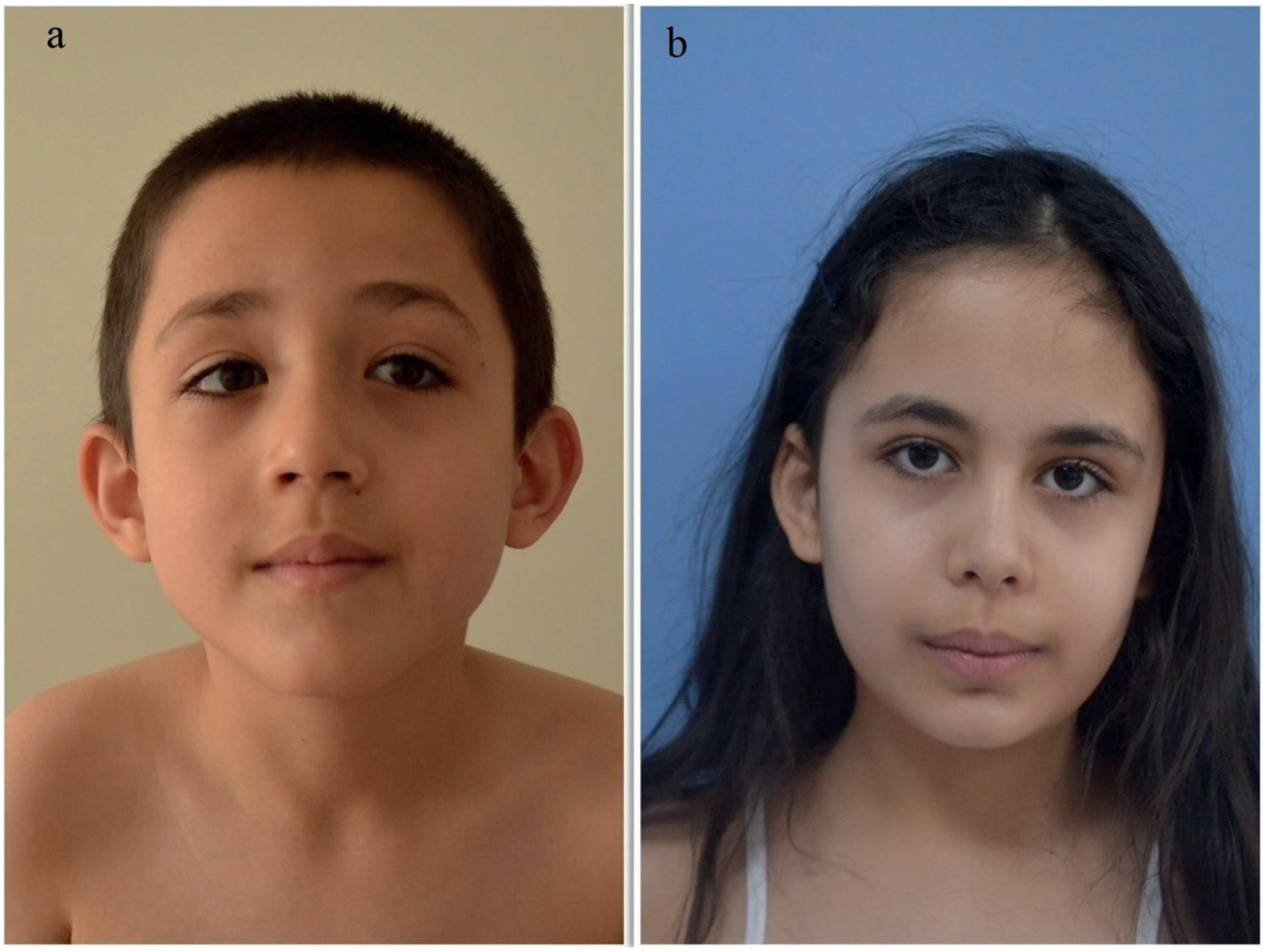


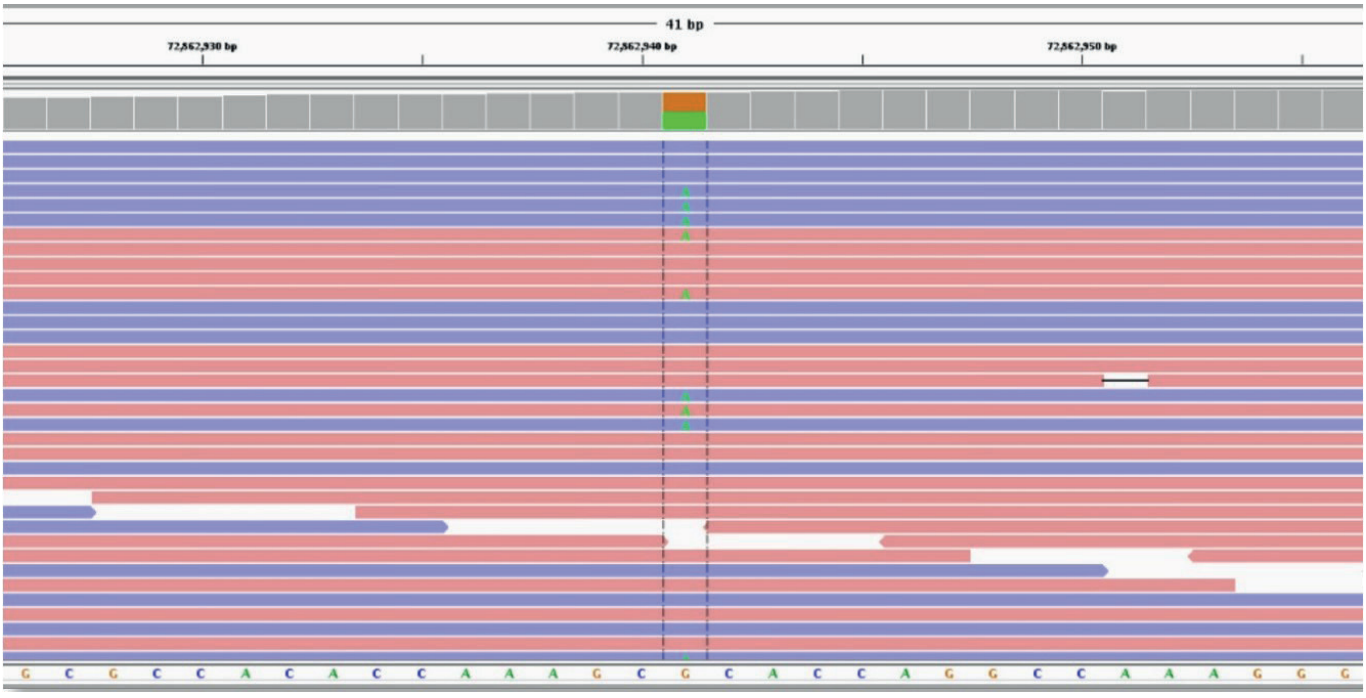
Figure 1. a. Patient 1: Downslanting palpebral fissures, ptotic eyelids, and drooping ears **b. Patient 2:** No dysmorphic features.

Patient 1 was 43.9%. When the genotype of the patients with ataxia was examined, it was determined that the most common variant was c.1115C>A. However, in most of these patients, a compound heterozygous variant was detected.[4] In addition, the rate of retinal dystrophy was reported as 30.4% in this study, and no patient with isolated retinal dystrophy was identified. In our Patient 2, there was no finding other than infraclinical retinal dystrophy.

Dramatic amounts of iron accumulation have been detected in FDXR mutant mice.[3] This accumulation has also been found in the nervous system. Because of the FDX2 median pathway component, it has been thought that pathophysiology similar to Friedrich's ataxia may also occur in FDXR mutants.[5] Therefore, the occurrence of ataxia in Patient 1 was expected.

The literature describes a case involving the FDXR biallelic variant with only optic atrophy but no neurological deficit. It is reported that this patient's symptoms appeared at the age of 12 years, and his visual acuity gradually decreased in 6 months without any apparent trigger.[6] Another study on ten patients did not show retinal dystrophy alone. Optic atrophy was present in all patients, while retinal dystrophy was found in 6 patients. Cataracts, nystagmus, and ophthalmoplegia were among the ocular findings.[7] In the last published study by Jurkute et al.[7], retinal dystrophy was reported in 30.4%, nystagmus in 17.4%, cataracts in 10.9%, and ophthalmoplegia 4.3% (Table 1).[4] Mutant mice retinal cells were functionally reduced.

Further, a reduction in the number of cells in the visual cortex of mutant mice has been observed even at eight weeks of age,



FDXR c.235C>T heterozygous variant above, and below FDXR c.980G>A heterozygous variant below.

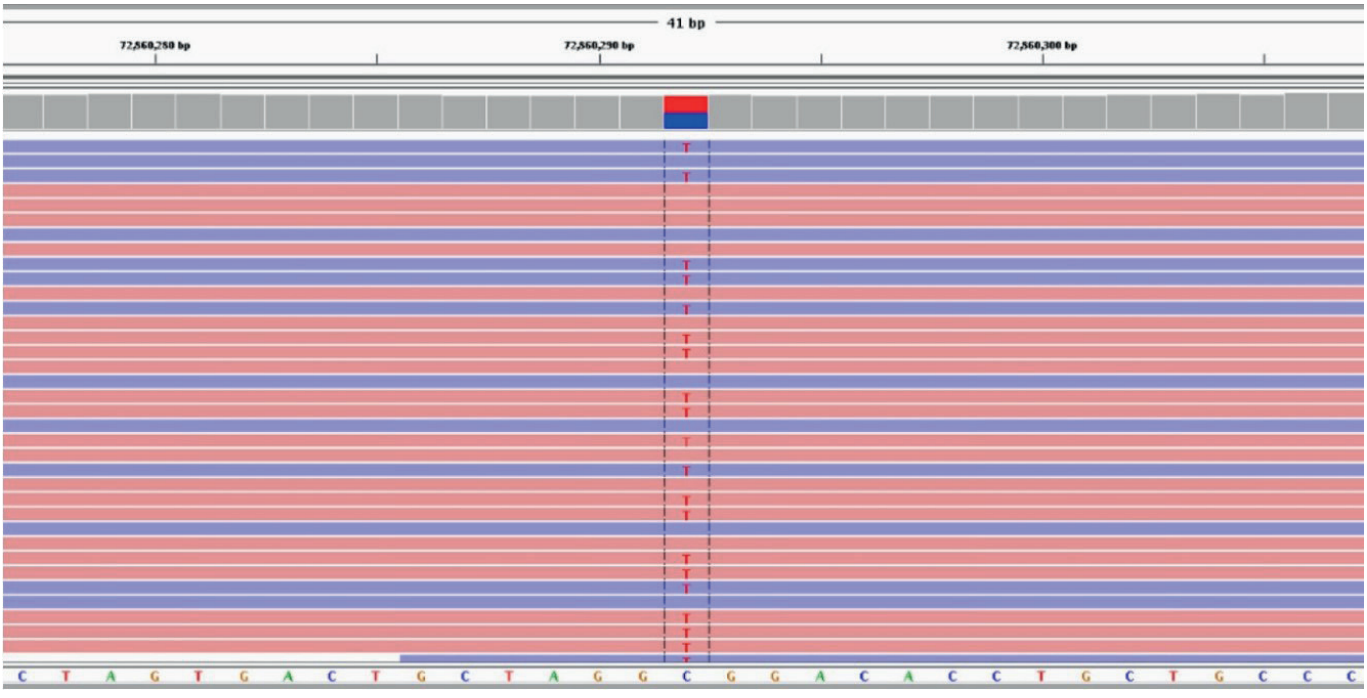


Figure 2. IGV image of variants

suggesting worsening of optic atrophy.[5] Despite this, although retinal dystrophy and optic atrophy were present in Patient 2, no clinical findings were detected. No additional findings were found during the follow-up eye examinations.

In many FDXR mutant patients, an MRI of the brain revealed

Table 1. Clinical findings of patients and literature review

Clinical findings	Patient 1	Patient 2	Review of the literature
Optic neuropathy	+	+	%93,5
Acoustic neuropathy	-	-	%50
Ataxia	+	-	%43.9
Hypotonia	-	-	%41.3
Developmental delay	-	-	%39.1
Developmental regression	-	-	%34.8
Retinal dystrophy	+	+	%30.4
Peripheral neuropathy	+	-	%23.9
Pyramidal signs	-	-	%23.9
Speech issues	-	-	%23.9
Nystagmus	+	-	%17.4
Loss of deambulation	-	-	%15.2
Microcephaly	-	-	%15.2
Cataract	-	-	%10.9
Encephalopathic episodes	-	-	%10.9
Dystonia	-	-	%8.7
Seizures	-	-	%6.5
Ophthalmoplegia	-	-	%4.3
Tremor	-	-	%4.3

findings such as delayed myelination, cerebellar atrophy, cerebral atrophy, and corpus callosum anomalies. Nevertheless, the MRI was normal in many of the other patients.[8] In our patients, both orbital and brain MRI were normal.

CONCLUSION

As the relationship between variants in the FDXR gene and the phenotype is defined, which makes it easier to study it on a molecular level. The FDXR gene may also have an essential role in the genetic etiology of patients with only ophthalmic findings and no additional neurological anomalies. This will increase the number of defined variants, which can guide suitable gene therapy development.

Ethical approval

This study has been approved by the Necmettin Erbakan University Non-Drug and Non-Medical Device Research Ethics Committee (approval date 06.01.2023, number 167). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: FMB; data collection: FMB, MB; analysis and interpretation of results: MB; draft manuscript preparation: FMB, MB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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