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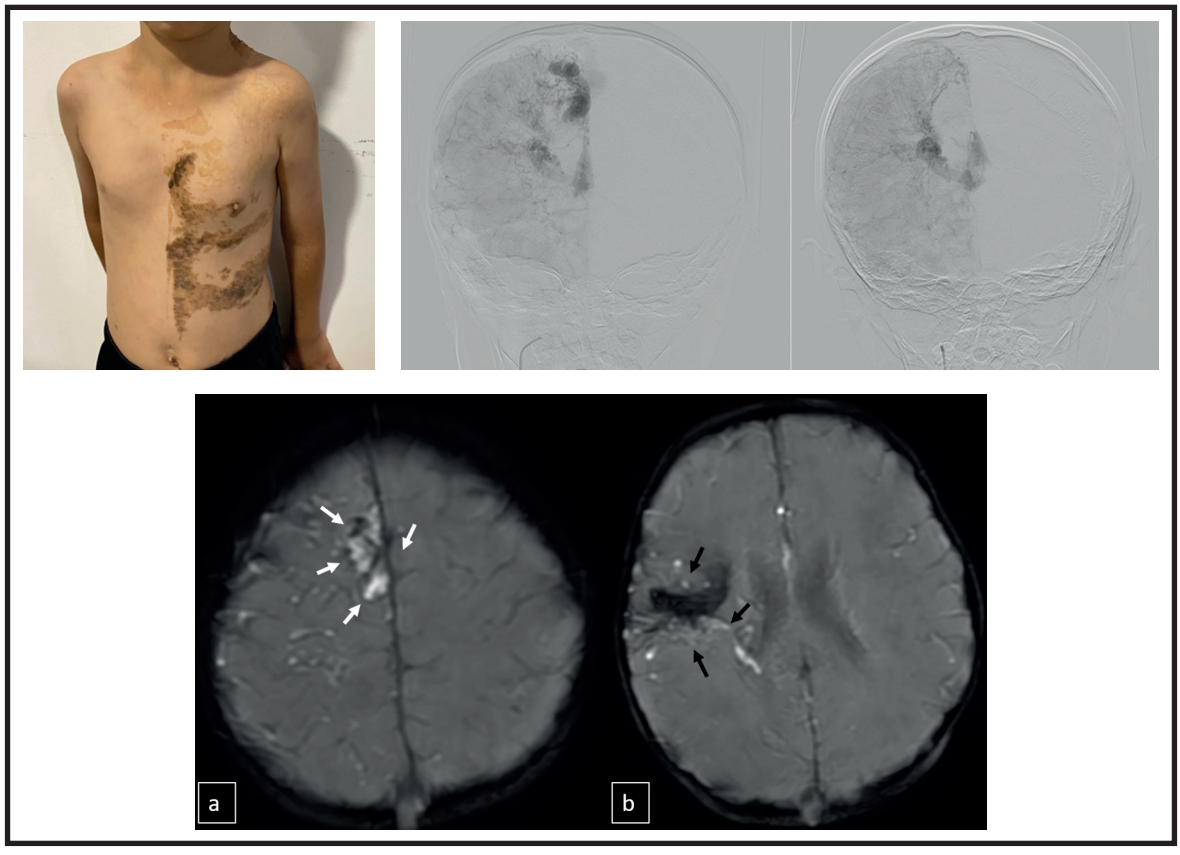

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Review

A new archipelago on the horizon: type 1 interferonopathies

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ABSTRACT

Type 1 interferonopathies are rare genetic disorders characterized by abnormal type 1 interferon (IFN) signaling. They cause chronic inflammation and multisystemic symptoms typically present in early childhood. Neurological, dermatological, and musculoskeletal features are common and often resistant to conventional therapies. Mutations in genes involved in nucleic acid sensing, degradation, proteasome function, and IFN signaling lead to the accumulation of self-deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) in the cytoplasm and a sustained type 1 IFN response, causing tissue damage and autoimmunity. This group includes various syndromes, such as Aicardi-Goutières syndrome (AGS), STING-associated vasculopathy (SAVI), and COPA syndrome. Diagnosis involves clinical evaluation, IFN signature analysis, and genetic testing. Treatment aims to modulate the IFN response by using JAK inhibitors, anti-IFN antibodies, and reverse transcriptase inhibitors. However, these therapies are not curative and have limited efficacy. Further research is needed to develop targeted treatments and improve outcomes, and a multidisciplinary management approach is essential because of the complexity and rarity of these disorders.

Keywords: Aicardi-Goutières syndrome, anifrolumab, baricitinib, interferons, Janus kinases, sifalimumab

INTRODUCTION

Type 1 interferonopathies are a new group of rare and severe multisystemic disorders characterized by abnormal and uncontrolled activation of type 1 interferon (IFNs) signaling pathways caused by specific genetic mutations in the immune system.[1,2] The basic mechanism underlying these diseases is that the immune system mistakenly recognizes its own deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) as a pathogen.[3] This leads to chronic inflammation, resulting in persistently high levels of cytokines, especially IFN-α and IFN-β, and the emergence of autoimmune and autoinflammatory responses.[1,4]

IFNs play a key role in the immune system's defense against viral, bacterial, and tumoral pathogens. Type I IFNs (particularly IFN-α and IFN-β) are produced by almost every nucleated cell, forming the first line of defense in innate immunity and providing a rapid antiviral response.[1] These increase pathogen resistance by regulating cellular functions. Type II IFNs are composed solely of IFN-γ and are secreted by T cells and natural killer cells, supporting adaptive immunity.[3] IFN-γ activates macrophages and potentiates the cytotoxic T-cell response. Type III IFNs (IFN-λ) act at the entry points of infection and induce a localized antiviral response in the respiratory and digestive epithelia.[4] Although IFNs have positive effects on the human body, prolonged IFN exposure in animal models has been linked to growth retardation and organ damage. Interferonopathies often affect the central nervous system, skin, and joint tissues, presenting symptoms from neurological dysfunction to skin lesions.[1,3]

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Type 1 interferonopathies typically begin in early childhood, but the onset age varies depending on the specific disease and genetic mutations.[5] Aicardi-Goutières syndrome (AGS), the first identified Mendelian type I interferonopathy, is a multisystem disorder with neurological symptoms resembling congenital viral infections.[1,4] In AGS, symptoms usually appear in infancy, whereas other interferonopathies may not show symptoms until childhood or, rarely, adolescence.[3]

In recent years, interferonopathies have taken place in modern medicine as rare genetic diseases due to reports of similar cases and an understanding of new genetic mutations and disease mechanisms.[3] This review aims to provide an overview of this rare and current disease group.

PATHOGENESIS

Type 1 interferonopathies occur when endogenous nucleic acids accumulate in the cytoplasm, usually as a result of cellular stress, infections, or genetic mutations.[1] In this process, intracellular DNA and RNA in particular activate cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS) and stimulator of interferon genes (STING) molecules, which act as nucleic acid sensors, leading to excessive production of type 1 IFN.[6] While the cGAS-STING pathway initiates the immune system's natural response to infections and cellular damage, uncontrolled activation of this mechanism leads to chronic production of type 1 IFNs and perpetuation of the inflammatory response.[6] Furthermore, cGAS sensing of mitochondrial DNA and other nucleic acids released from damaged cells promotes sustained activation of the interferon response through STING.[1] Defects in the proteasome and autophagy systems further exacerbate the pathogenesis by increasing the accumulation of these nucleic acids in the cytoplasm. We tried to summarize the overall process of the type I IFN response in Figure 1.

Deoxyribonucleic Acid (DNA) sensing

Normally, most DNA resides in the cell nucleus. The immune system interprets DNA in the cytoplasm as a potential viral or bacterial infection, signaling danger.[7] Type 1 interferonopathies are disorders characterized by excessive activation of the immune system, resulting from viral infections or genetic mutations that cause cellular misidentification of endogenous DNA, termed "self-DNA," as exogenous material.[7] Under normal physiological conditions, exogenous DNA within the cellular environment is eliminated by enzymatic processes, primarily through the action of cytosolic deoxyribonuclease I (DNase I) and DNase II. However, in case of loss of function of enzymes such as Three Prime Repair Exonuclease 1 *(TREX1)*, a cytosolic DNase located in the nuclear membrane, the cell accumulates its own DNA or damaged DNA.[8]

Proper processing of intracellular DNA is ensured by proteins such as DNA Polymerase Alpha 1 (*POL1A*), Sterile Alpha Motif, and Histidine-Aspartate Domain-Containing Protein 1 (SAMHD1), as well as ribonucleotide scavenger enzymes such as Ribonuclease H2 (RNASEH2) A, RNASEH2B, and RNASEH2C.[5] SAMHD1 regulates deoxynucleotide triphosphate (dNTP) levels, keeping DNA synthesis under control and preventing self-DNA accumulation. However, LSM11, U7 Small Nuclear RNA Associated *(LSM11)* and RNA, U7 Small Nuclear 1(*RNU7-1)* mutations resulting from defects in histone pre-mRNA processing can lead to leakage of this DNA into the cytosol.[9] ATPase Family AAA Domain-Containing Protein 3A *(ATAD3A)* mutations can also lead to disruption of the integrity of the mitochondrial membrane and escape of mitochondrial DNA into the cytoplasm.[10]

DNA passing into the cytosol is sensed by the enzyme cGAS, and this sensing initiates the production of the molecule cGAMP, which activates the STING protein in the endoplasmic reticulum (ER).[11,12] The STING protein is located on intracellular membranes and is a critical signaling pathway for initiating the immune response.[13] Mutations in genes such as *coatomer subunit alpha (COPA)*, Transmembrane Protein 173 (*TMEM173),* and *TREX1* lead to abnormal activation of the STING signaling pathway, resulting in sustained and uncontrolled production of type 1 IFN.[14]

Ribonucleic Acid (RNA) sensing

Detection of viral RNA in the cytoplasm signals danger to the immune system and triggers an innate immune response. This process involves two main RNA sensors: *retinoic acid-inducible gene-1 (RIG-1)* and *melanoma differentiation-associated protein (MDA5)*. Both belong to the *RIG-1*-like receptor (RLR) family and initiate IFN production by recognizing viral RNA.[15,16] *RIG-1* (encoded by *DDX58*) detects short double-stranded RNA (dsRNA) and single-stranded RNA (ssRNA) molecules with triphosphate groups at their ends, whereas MDA5 (encoded by *IFIH-1*) binds to longer dsRNA molecules. When both sensors are activated, they transmit the signal to the mitochondrial antiviral signaling protein (MAVS) adaptor protein located in the cytosol.[16,17] MAVS is located on the mitochondrial outer membrane

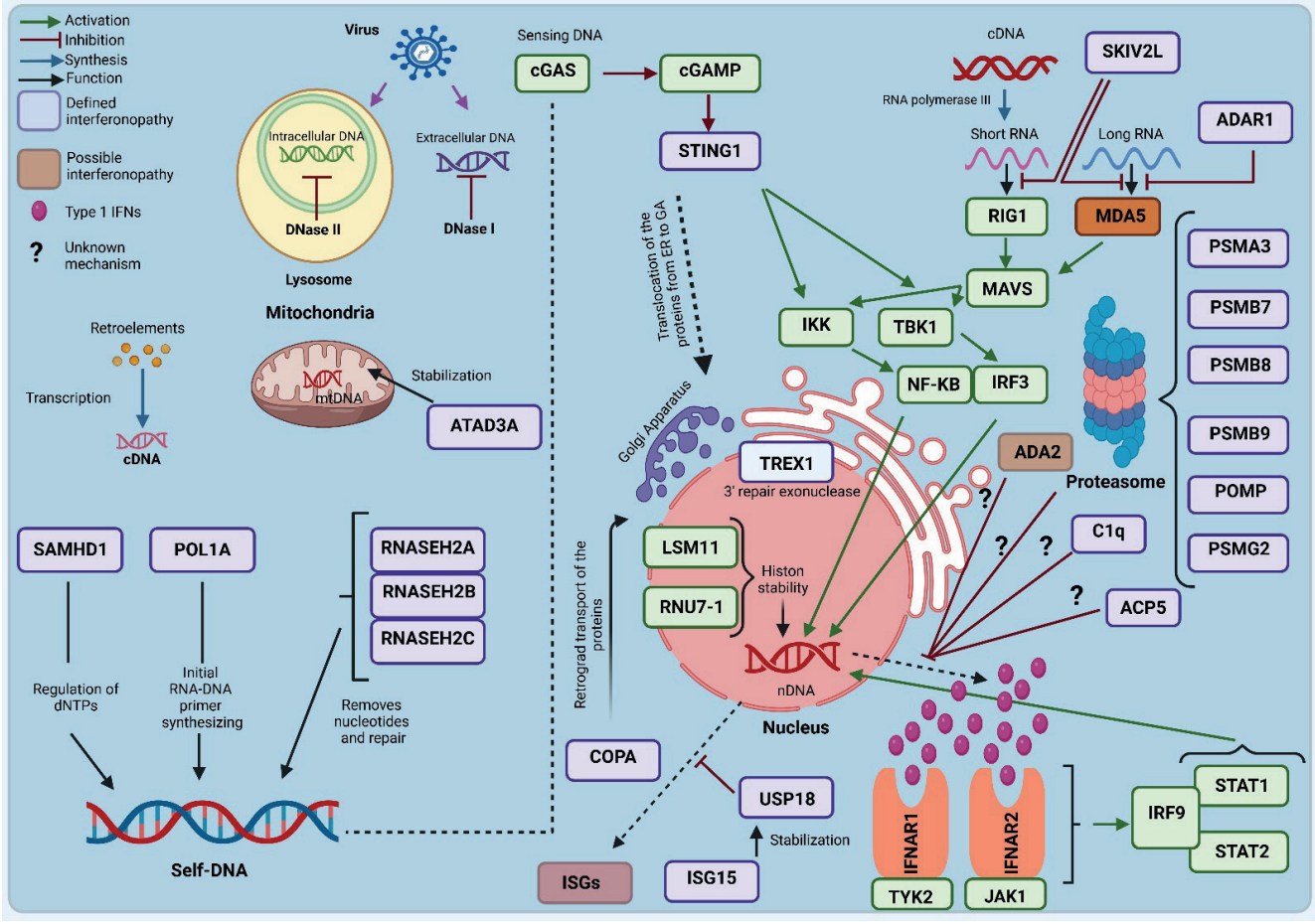

Figure 1. Pathogenesis of type 1 interferonopathies. (cGAS senses cellular and viral DNA and synthesizes cGAMP to activate STING1. STING1 moves to the Golgi, activating IKK and TBK1, which enhances IFN production via NF-κB and IRF3. IFN signaling begins with IFNAR1 and IFNAR2 receptors activating JAK1 and TYK2, continuing through STAT1, STAT2, and IRF9 transcription factor complexes. Enzymes such as TREX1, RNASEH2A, RNASEH2B, and RNASEH2C maintain cellular DNA homeostasis. SAMHD1 regulates dNTP levels, and *POL1A* synthesizes RNA-DNA primers. *ATAD3A* stabilizes mtDNA. RNA sensors *RIG1* and *MDA5* detect short and long viral RNAs, respectively, and this detection activates signaling pathways that trigger antiviral responses through MAVS. Regulation of short viral RNAs is carried out by *ADAR1*, whereas the processing of long viral RNAs is mediated by *SKIV2L* and *ADAR1*. Core histone stability is maintained by LSM11 and RNU7-1. Clearance of aberrant DNA and RNA products is mediated by proteasome components (*PSMA3, PSMB7, PSMB8, PSMB9, POMP,* and *PSMG2*), while *USP18* and *COPA* regulate the IFN response. The roles of *ADA2, C1q,* and *ACP5* in IFN release are not fully understood). (*ACP5:* Acid Phosphatase 5, Tartrate-Resistant, *ADA2:* Adenosine Deaminase 2, *ADAR1:* Adenosine Deaminase Acting on RNA 1, *ATAD3A:* ATPase Family AAA Domain-Containing Protein 3A, *C1q:* Complement Component 1q, *cGAS:* cyclic guanosine monophosphate-adenosine monophosphate synthase, *COPA:* Coatomer Protein Complex Subunit Alpha, *DNA:* Deoxyribonucleic Acid, *DNase I*: deoxyribonuclease I, *DNase II:* deoxyribonuclease II, *dNTP:* Deoxynucleotide triphosphate, *IFNAR1:* Interferon Alpha/Beta Receptor 1, *IFNAR2:* Interferon Alpha/Beta Receptor 2, *IRF3:* Interferon Regulatory Factor 3, *IRF9:* Interferon Regulatory Factor 9, *JAK1:* Janus Kinase 1, *LSM11:* LSM11, U7 Small Nuclear RNA Associated, *MAVS:* Mitochondrial antiviral signaling protein, *MDA5:* Melanoma differentiation-associated protein, *mtDNA:* Mitochondrial DNA, *NF-κB:* Nuclear factor κB, *POL1A:* DNA Polymerase Alpha 1, *POMP:* Proteasome Maturation Protein, *PSMA3:* Proteasome Subunit Alpha Type-3, *PSMB7:* Proteasome Subunit Beta Type-7, *PSMB8:* Proteasome Subunit Beta Type-8, *PSMB9:* Proteasome Subunit Beta Type-9, *PSMG2:* Proteasome Assembly Chaperone 2, *RNA:* Ribonucleic Acid, *RNASEH2A:* Ribonuclease H2 Subunit A, *RNASEH2B:* Ribonuclease H2 Subunit B, *RNASEH2C:* Ribonuclease H2 Subunit C, *RIG1:* Retinoic acid-inducible gene-1, *RNU7-1:* RNA, U7 Small Nuclear 1, *SAMHD1:* Sterile Alpha Motif, and Histidine-Aspartate Domain-Containing Protein 1, *SKIV2L:* Ski2 Like RNA Helicase, *STAT1:* Signal Transducer and Activator of Transcription 1, *STAT2:* Signal Transducer and Activator of Transcription 1, *STING:* stimulator of interferon genes, *IKK:* Inhibitor of κB Kinase, *TBK1:* TANK-binding kinase 1, *IFN:* Interferon, *TREX1:* Three Prime Repair Exonuclease 1, *TYK2:* Tyrosine Kinase 2, *USP18:* Ubiquitin-Specific Peptidase 18).

and interacts with TNF receptor-associated factors (TRAF) proteins and activates downstream kinases.[18]

Common pathway in nucleic acid sensing

Stimulation of the STING pathway by DNA or the MAVS pathway by RNA initiates immune signaling. STING activity is inhibited by enzymes such as cGAMP phosphodiesterase (cGAMP-PDE), while the MAVS signaling pathway is repressed by RNF125 ubiquitin ligase.[19] A defect in the function of these regulatory proteins leads to over-activation of the STING and MAVS signaling pathways, activating the TANK-binding kinase 1 (TBK1) inhibitor and IKKε kinase complex. TBK1 activates IFN regulatory factor 3 (IRF3). Activation of IKKε leads to the activation of the nuclear factor κB (NF-κB) transcription factor.[20]

Proteasomes in this context

Proteasomes maintain intracellular protein balance, clear misfolded proteins, and support immune responses by promoting antigen presentation.[21] Mutations in proteasome-related genes such as *PSMA3, PSMB7, PSMB8, PSMB9, POMP,* and *PSMG2* disrupt the function of the proteasome complex, leading to an uncontrolled type 1 IFN response.[22] This dysfunction causes ER accumulation of misfolded proteins and activates the ER membrane protein Inositol-Requiring Enzyme 1 (IRE1). Activated IRE1 stimulates transcription factors such as IRF3 and NF-κB, triggering the production of proinflammatory cytokines and IFNs.[23]

Nuclear response

The nuclear response begins with the recognition of cytosolic DNA or RNA in immune cells. It proceeds when transcription factors are phosphorylated and transported to the nucleus to initiate the expression of type 1 IFN and proinflammatory cytokines.[24] Factors such as IRF3, IFN regulatory factor 7 (IRF7), and NF-κB play key roles in this process. The cGAS-STING pathway activates IRF3 in response to DNA, while the MAVS pathway activates IRF7 and NF-κB in response to RNA.[12] IRF3 is phosphorylated and transported to the nucleus via TBK1 kinase to initiate the transcription of type 1 IFN and *interferon-stimulated gene (ISG)*. NF-κB enhances inflammatory cytokine production, leading to migration of immune cells to the site of infection.[25] Furthermore, Signal Transducer and Activator of Transcription (STAT) 1 and STAT2 sustain the antiviral response by activating the Janus kinase (JAK) - STAT pathway and potentiate the expression of antiviral proteins such as Interferon-Stimulated Gene 15 (ISG15) and Myxovirus Resistance Protein 1 (MX1). Since excessive nuclear response can trigger autoimmune responses, proteins such as Suppressor of Cytokine Signaling (SOCS) 1 and SOCS3 limit the response by inhibiting the JAK-STAT pathway; Protein Inhibitor of Activated STAT (PIAS) 1 and PIAS3 control STAT1 and STAT3 activity.[26] Ubiquitin-Specific Peptidase 18 (USP18), stabilized by *ISG15*, plays a negative regulatory role in ISG transcription, optimizing the antibacterial response against mycobacteria.[27] Osteopontin (OPN) promotes type I IFN production, whereas this effect is limited by tartrate-resistant acid phosphatase (*ACP5*).[28] Complement proteins such as C1q also contribute to immune balance by inhibiting ISG transcription.

Type I IFN activity

During infection, recognition of viral RNA and DNA in the cell cytoplasm initiates type I IFN production via RLRs and cGAS-STING, activating transcription factors such as IRF3 and NF-κB.[29] This, in turn, leads to the production of IFN-α and IFN-β, resulting in the secretion of these molecules. IFN-α and IFN-β bind to IFN-alpha/beta receptors (IFNAR) consisting of IFNAR1 and IFNAR2 subunits on the cell surface by autocrine or paracrine action.[30] This binding activates the JAK-STAT pathway; IFNAR-bound Tyrosine Kinase 2 (TYK2) and JAK1 kinases are activated through phosphorylation and subsequent phosphorylation of STAT1 and STAT2 proteins.[31] Phosphorylated STAT1 and STAT2 combine with *IRF9* to form the *Interferon-Stimulated Gene Factor 3 (ISGF3)* complex. The ISGF3 complex then enters the nucleus and initiates ISG transcription. ISGs encode proteins that inhibit viral replication and exert antiviral effects. Antiviral proteins, such as Protein Kinase R (PKR), 2'-5'-Oligoadenylate Synthetase (OAS), and Myxovirus Resistance Protein A (MxA), stop virus replication in infected cells, limiting the spread of infection. Thus, the type I IFN signaling pathway provides the immune system's initial response by creating a strong antiviral environment in both infected cells and surrounding cells.[32] Negative regulatory proteins such as SOCS1 and SOCS3 fail to inhibit the JAK-STAT pathway, and proteins such as USP18 fail to suppress the sustained activation of IFNAR, resulting in prolonged type I IFN activation and tissue damage.[33]

CLINICAL FEATURES

Type 1 interferonopathies are autoinflammatory and autoimmune disorders characterized by onset in early childhood due to genetic alterations. Neurological manifestations include microcephaly, seizures, spasticity, and intracranial calcification, while dermatological findings encompass livedo reticularis, lupus-like rashes, and ulceration. Additional common features include retinal vasculopathy, acrocyanosis, finger necrosis, interstitial lung diseases (ILD), bone marrow depression, growth retardation, hepatosplenomegaly, and arthritis.[1,5] The general genetic and clinical features of these diseases are summarized in Table 1.

Table 1. Summary of Inheritance, Genetic, and Clinical Characteristics of Type I Interferonopathies

	Inheritance	Gene	Clinical Features
AGS	AR/AD	*SAMHD1, ADAR1, RNASEH2A, RNASEH2B, RNASEH2C, TREX1, IFIH1*	mental-motor retardation, developmental delay, spasticity, dystonia, ataxia, peripheral neuropathy, epilepsy, brain atrophy (cortical and subcortical), leukodystrophy, intracranial calcification, anemia, thrombocytopenia, chilblain, livedo, HSM
COPA	AD	*COPA*	peripheral arthritis, interstitial lung disease, diffuse alveolar hemorrhage, glomerulonephritis, oral ulcer, livedo
DADA2	AR	*ADA2/CECR1*	Growth retardation, recurrent fever, livedo, digital gangrene, stroke, epilepsy, peripheral neuropathy, pancytopenia, hemolytic anemia, mesenteric ischemia
FCL	AD	*TREX1, SAMHD1*	Early-onset, cold-induced chilblains in acral sites, arthralgia, lymphopenia, myalgia, conjunctivitis
FSLE	AR/AD	*TREX1, SAMHD1, ACP5, DNASE1, DNASE1L3, PRKCD, C1Q/R/S, C2, C3, C4*	Arthritis, lupus nephritis, malar rash, discoid rash, photosensitivity, chilblain, pancytopenia, pericarditis, myocarditis, intracranial calcification, leukodystrophy, vision loss, stroke, seizure, psychosis
ISG15	AR	*ISG15*	increased susceptibility to bacterial and viral infections, mycobacterial infections, seizures, developmental delay, muscle weakness, skin rash
PRAAS	AR	*PSMA3, PSMB7, PSMB8, PSMB9, POMP, PSMG2*	recurrent episodes of fever from infancy, neutrophilic dermatosis, lipodystrophy, bone tenderness, muscle weakness
SAVI	AD	*TMEM173/STING1*	cold-induced livedo, ulceration, necrosis of fingertips, short fingers, interstitial lung disease, arthritis, fever, myalgia
SMS	AD	*IFIH1, DDX58*	early tooth loss starting in childhood, enamel hypoplasia, skeletal dysplasia, deformity of the hands and feet, calcification and bone hardening, vascular calcification
SPENCD	AR	*ACP5*	developmental defects in the spine (spondylo-) and long bones (endochondro-), growth retardation, short stature, muscle weakness, spasticity, autoimmune thyroid diseases
THES	AR	*SKIV2L, TTC37*	severe and treatment-resistant diarrhea, malabsorption, growth retardation, hepatosplenomegaly, cirrhosis, trichorexis nodosa, dry skin, skin hyperpigmentation, eczematous rash, pancytopenia
USP18	AD	*USP18*	severe skin rashes, fever, muscle weakness, respiratory distress, seizures, starting in the neonatal period
RVCL	AD	*TREX1*	retinal vasculopathy, cerebral leukoencephalopathy, hypertension, renal failure, difficulty speaking and walking
XLRPD	AR	*POLA1*	reticular hyperpigmentation, photophobia, corneal opacity, recurrent pneumonia, nephritis, renal failure

AD: autosomal dominant; **AGS:** Aicardi-Goutières syndrome; **AR:** autosomal recessive; **DADA2:** adenosine deaminase 2 deficiency; **FCL:** familial chilblain lupus; **FSLE:** familial systemic lupus erythematosus; **HSM:** hepatosplenomegaly; **ISG15:** interferon-stimulated gene 15 deficiency; **PRAAS:** proteasome-associated autoinflammatory syndrome; **SAVI:** STING-associated vasculopathy with onset in infancy; **SLE:** systemic lupus erythematosus; **SMS:** singleton–Merten syndrome; **SPENCD:** spondyloenchondrodysplasia; **THES:** trichohepatoenteric syndrome; **USP18:** ubiquitin-specific protease 18 deficiency; **RVCL:** retinal vasculopathy with cerebral leukodystrophy; **XLRPD:** X-linked reticulate pigmentary disorder.

Aicardi-Goutières Syndrome (AGS)

AGS is a rare autoinflammatory disease in patients with type 1 interferonopathies and is characterized by neurological symptoms in early childhood. Mutations in genes such as *TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1,* and *IFIH1* lead to the accumulation of DNA or RNA in the cytoplasm, triggering the continuous production of type 1 IFN and causing the body to attack its own tissues.[1,5,34]

In the neonatal period, AGS presents clinical features resembling congenital infections, including TORCH. During this period, cerebral calcifications, particularly in the basal ganglia and other cerebral regions, are often accompanied by microcephaly and are crucial for diagnosing the condition. Cerebral white matter damage and encephalopathy symptoms resulting from elevated type 1 IFN levels are also characteristic findings. Furthermore, hepatosplenomegaly, increased leukocyte levels, and febrile episodes frequently accompany the disease presentation.[5]

The most prominent findings that shape the clinical picture of AGS in the infantile period include developmental delay, spasticity, increased muscle tone, and seizures. In addition to severe motor and mental retardation, significant neurologic symptoms, such as limitation of limb movements and inadequate head control, are observed in children during this period. Magnetic resonance imaging (MRI) findings reveal basal ganglia calcifications and white matter damage.[5] In addition, livedo reticularis, lace-like bruises on the skin such as acrocyanosis and hair loss, are among the autoinflammatory manifestations specific to the infantile phase of AGS.[4]

In late childhood, AGS is characterized by marked autoimmune and neurological disorders, as well as exacerbated autoinflammatory symptoms. Later in life, sustained immune system activation may cause autoimmune responses such as lupus-like skin lesions, lace-like rashes, and arthritis. Some patients develop permanent neurological damage, such as intellectual disability, vision, and hearing loss.[1,5] Especially in those with *IFIH1* mutation, autoimmune findings are more prominent, and clinical features such as skin atrophy and hair loss are frequently seen during this period.[1]

STING-Associated Vasculopathy with Onset in Infancy (SAVI)

Gain-of-function (GOF) mutations in *STING1*, which encodes a protein called STING, underlie the disease. These mutations lead to sustained activation of STING and consequent chronic stimulation of type 1 IFN production.[35] SAVI causes severe inflammation of the skin, lungs, and vascular system, usually starting in childhood, and can lead to permanent tissue damage.[36]

The most characteristic findings of SAVI include livedo reticularis, ulcerations, and necrosis of the fingertips, which are particularly severe in cold weather. These findings usually begin shortly after birth and can lead to tissue loss, shortening, and deformation of the fingers.[37] A large proportion of patients develop ILD, which can lead to severe respiratory failure and a marked decrease in quality of life. Early onset of pulmonary involvement is a factor that adversely affects the prognosis of the disease; therefore, close monitoring of pulmonary findings is important.[37] Fever, musculoskeletal pain, arthritis, anorexia, growth, and developmental delay may also be observed.[35,36] Rare cases of alopecia, short stature, epilepsy, intracranial calcification, pulmonary hypertension, and spastic diplegia have also been reported.[37]

COPA syndrome

Heterozygous mutations in the *COPA* gene constitute the basic mechanism of the disease by disrupting the function of the COPA protein, which regulates intracellular protein transport and the return of proteins between the endoplasmic reticulum and the Golgi body. This dysfunction leads to intracellular accumulation of misfolded or mutated proteins, resulting in increased production of type 1 IFN.[38]

COPA syndrome is one of the most common diseases with lung involvement and is characterized by inflammatory conditions, particularly ILD, and alveolitis. These patients usually present with symptoms such as shortness of breath, cough, and breathing difficulties, which usually begin at an early age.[39] It is characterized by joint involvement, usually presenting as symmetrical polyarthritis and morning stiffness. In some cases, signs of vasculitis, such as lupus-like skin rashes, livedo reticularis, and ulceration, have also been reported.[38] Fever, growth retardation, and glomerulonephritis may also be seen.[38]

Familial Systemic Lupus Erythematosus (SLE)

Familial SLE is an autoimmune disease that affects multiple family members owing to a genetic predisposition, with early onset and severe progression. Key mutations increasing SLE susceptibility are found in *TREX1, DNASE1L3, BLK, IRAK1, SAMHD1, ACP5, DNase1, protein kinase C δ (PRKCD)*, and early complement proteins (C1q/r/s, C2, C3, and C4).[40,41] Specifically, *TREX1* and *DNASE1L3* mutations lead to DNA accumulation in the cytosol, stimulating type 1 IFN production and causing skin, joint, and kidney damage.[42] Skin manifestations include malar rash and chilblain lesions, worsened by sun exposure.[40] Joint symptoms include symmetrical pain, morning stiffness, and arthritis, impacting quality of life despite not causing permanent deformity. Lupus nephritis, which is common in early-onset familial SLE, can result in permanent kidney damage.[42] Rarely, retinal vasculopathy, leukodystrophy, vision loss, stroke, and mental retardation may occur. It is highly resistant to standard SLE treatments due to the constant activation of the immune system.[42]

Familial Chilblain Lupus (FCL)

FCL is caused by heterozygous mutations in *TREX1* or *SAMHD1*, resulting in intracellular DNA accumulation.[1,5] The hallmark of FCL is red-purple skin lesions on the fingertips, hands, feet, nose, and ears, which typically intensify in cold weather. These painful lesions can result in ulceration, necrosis, and tissue loss after prolonged exposure to cold.[8] Phenotypic diversity should be indicated in FCL patients since patients with the same mutations may result in different severities of clinical features.[43] Arthralgia and myalgia may also be seen but are usually less severe than skin symptoms. Lymphopenia and anti-nuclear antibody (ANA) positivity have been observed in some cases.[1]

Spondyloenchondrodysplasia (SPENCD)

SPENCD is a clinical entity characterized by autoimmune disorders and skeletal dysplasia caused by mutations in *ACP5*. This gene encodes tartrate-resistant acid phosphatase (TRAP), which is found in osteoclasts and is crucial for bone metabolism and immunity. Reduced TRAP activity impairs osteoclast function, affecting bone growth and the immune response.[9,44] Short bones, metaphyseal dysplasia, platyspondyly, and developmental defects of the spine and long bones can be seen and can cause growth retardation and short stature.[44,45] The disease is often linked to autoimmune conditions such as autoimmune thyroid diseases, SLE, Sjögren's syndrome, and vasculitis. Headaches, spasticity, muscle weakness, and motor disorders may also occur.[45]

Deficiency of Adenosine Deaminase 2 (DADA2)

The literature does not definitively classify DADA2 as a type 1 interferonopathy, but it is believed to trigger a type 1 IFN response via STING, sustaining the immune response.[46] DADA2 is an autosomal recessive (AR) inherited immunodeficiency syndrome caused by mutations in the *ADA2* or *CECR1* gene.[9]

One of the most characteristic features of DADA2 is the presence of vasculitis affecting small- and medium-sized vessels. This can lead to the development of livedo reticularis of the skin, ulceration, and gangrene of the fingers and toes. If vascular inflammation involves brain vessels, recurrent episodes of ischemic stroke may occur. Stroke, especially in childhood, is one of the remarkable clinical manifestations of DADA2.[47]

The inflammatory response triggered by ADA2 deficiency can lead to the development of hematologic abnormalities such as autoimmune hemolytic anemia, thrombocytopenia, and neutropenia. Systemic manifestations such as pancreatitis, hepatosplenomegaly, and arthritis are also included in the clinical spectrum of the disease.[48] MRI findings of our patient with DADA2 are shown in Figure 2.

Trichohepatoenteric Syndrome (THES)

THES is a rare AR disease that occurs in early childhood and affects multiple organs, including the digestive system, liver, and skin.[49] Mutations in the *SKIV2L* and *TTC37* genes disrupt proteins that regulate intracellular mRNA turnover, causing multisystemic symptoms.[50] Key characteristics of THES include severe, treatment-resistant diarrhea, malabsorption, and growth retardation, accompanied by nutritional deficiencies that manifest from infancy. Many patients also exhibit liver dysfunction, characterized by hepatomegaly, elevated liver enzyme levels, and, in some cases, cirrhosis-related splenomegaly. A hallmark feature of the syndrome is thin, brittle, and slow-growing hair, often associated with trichorexis nodosa, along with dry skin, eczematous rashes, and a texture prone to bruising. Recurrent infections due to immunodeficiency are common, while bone marrow suppression frequently results in anemia, thrombocytopenia, and leukopenia, further contributing to the clinical complexity of the disorder.[49]

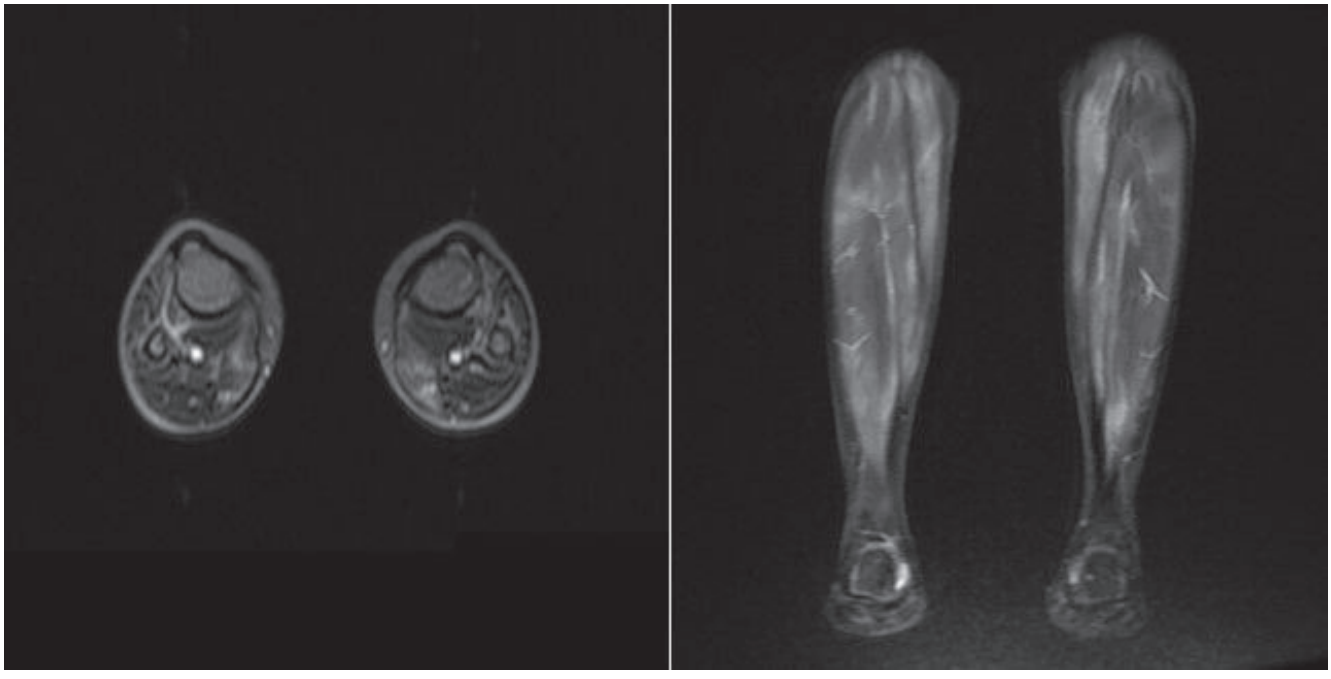

Figure 2. Edematous changes in the skin, subcutaneous tissue, and muscle tissues at both cruris on Magnetic Resonance Imaging of a 9-year-old boy with Deficiency of Adenosine Deaminase 2

Singleton-Merten Syndrome (SMS)

SMS is usually associated with GOF mutations in *IFIH1*. However, an atypical form caused by the *DDX58* mutation has also been described.[51] Characteristic features of SMS include dental abnormalities such as early tooth loss and enamel hypoplasia, which may provide important clues to the diagnosis. In addition, skeletal dysplasia, osteoporosis, and growth abnormalities in long bones have been observed in patients. Calcifications are common, especially in the hands and feet, and can lead to severe finger and spinal deformities.[52] One of the hallmarks of SMS is vascular calcifications that progress with age. These calcifications, especially in the aorta and other heart valves, are common and often lead to serious cardiovascular complications.[1] In addition, symptoms such as myalgia, skin rashes, growth retardation, and glaucoma have also been reported in cases.[52]

Interferon-Stimulated Gene 15 (ISIG15) Deficiency

ISG15 deficiency is an AR disorder caused by mutations in *ISG15*. This leads to impaired production of ISG15, a ubiquitin-like protein. ISG15 is an important molecule that enhances the immune response to viral infections through post-translational modification of intracellular proteins.[53] Symptoms usually appear in the newborn or early childhood, including clinical signs such as fever, skin rashes, and recurrent lung infections. Patients become more susceptible to mycobacterial infections, especially tuberculosis.[27] Seizures, psychomotor retardation, and developmental delays may also occur.[54]

Ubiquitin-Specific Protease 18 (USP18) Deficiency

USP18 deficiency results from heterozygous GOF mutations in the *USP18* gene.[53] The USP18 protein, in conjunction with ISG15, negatively regulates the type 1 IFN response.[1] This condition typically manifests in the neonatal period, with symptoms such as severe skin rashes, fever, muscle weakness, and respiratory issues. Chronic CNS inflammation can lead to severe neurological symptoms, including seizures and developmental delays.[1] It is termed "pseudo-TORCH syndrome" due to features like microcephaly, ventriculomegaly, and intracranial calcification without congenital infection.[53]

Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL)

RVCL is an autosomal dominant (AD) disorder resulting from mutations in the TREX1 gene. This mutation results in the loss of function of the TREX1 protein, which is responsible for DNA fragmentation.[55] Consequently, this leads to

intracellular DNA accumulation and chronic inflammation, thereby triggering an autoimmune response that damages vascular and nerve tissues. Symptoms typically appear between the ages of 30 and 50 and include blurred vision, vision loss, cognitive impairment, headaches, seizures, and progressive dementia.[56] Hypertension and renal failure have also been reported.[55]

X-linked Reticulate Pigmentary Disorder (XLRPD)

XLRPD occurs due to mutations in the *POLA1* gene.[57] Patients with XLRPD often experience photophobia and sometimes corneal opacities. Corneal thickening and reduced transparency may progress to the point where vision loss may occur. These symptoms usually appear early and may progress over time.[58] One of the hallmarks of the disease is diffuse reticular hyperpigmentation that begins shortly after birth and affects the trunk, extremities, and face. Patients may also experience dry skin and eczematous rashes. Males with XLRPD often have additional manifestations such as recurrent respiratory and gastrointestinal infections, facial dysmorphia, corneal dyskeratosis, and hypohidrosis. Female carriers usually only exhibit cutaneous manifestations.[58]

Proteasome-associated Autoinflammatory Syndromes (PRAAS)/Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE)

PRAAS/CANDLE is an AR disease caused by mutations in the *PSMB8, PSMB4, PSMB9, PSMB10, PSMA3, PSMB7, POMP*, and *PSMG2* genes.[59] Patients with CANDLE syndrome frequently experience recurrent fevers from infancy, accompanied by neutrophilic dermatitis, characterized by purple plaques, swelling, painful rashes, and ulcerations on the skin.[59] They exhibit significant facial and arm lipodystrophy, leading to both aesthetic and metabolic issues.[60] Musculoskeletal symptoms such as arthralgia and muscle weakness are common.[59] Due to chronic inflammation, visceral functions are negatively affected in these patients. Growth retardation, hepatosplenomegaly, lymphadenopathy, and hematologic disorders may be observed.[60]

DIAGNOSIS

Due to their rarity, type 1 interferonopathies necessitate thorough clinical evaluation, laboratory analysis, and genetic testing.[1] A chronic and progressive inflammatory presentation may indicate interferonopathies, typically manifesting in childhood with unusual symptoms and resistance to conventional therapies.[3] A wide range of symptoms are observed, including skin rashes, neurological findings due to central nervous system involvement, pulmonary symptoms, and musculoskeletal problems.[5] Symptoms such as vasculitic skin changes, panniculitis, ILD, basal ganglia calcifications, neuromotor disorders, epilepsy, and recurrent fever are particularly common in these diseases.[53] Since it has a Mendelian inheritance pattern, risk factors such as family history and consanguineous marriage are also taken into account in the diagnostic process.[2]

Diagnosing type 1 interferonopathies necessitates demonstrating an elevated type 1 interferon response; however, low blood levels present a challenge in measurement.[1] The IFN signature method is an approach to assess ISG expression. Increased expression of genes such as *IFIT1, IFI27, IFI44L, ISG15, RSAD2*, and *SIGLEC1* are important biomarkers supporting interferonopathies. Although a positive IFN signature is observed in most patients, results may be negative in some cases, especially AGS patients with *RNASEH2B* mutations.[5] Positive results can also occur in viral infections or SLE, limiting specificity and risking false positives.[2] Thus, combining the IFN signature with clinical findings and genetic analysis improves diagnostic accuracy.[53]

Genetic analysis is crucial for confirming the diagnosis and distinguishing interferonopathies from other diseases, as most gene mutations affect the interferon pathways. Identifying gene mutations like *IFIH1, TREX1, TMEM173*, and *ADAR1* clarifies the diagnosis.[3] Next-generation sequencing, such as whole-exome sequencing (WES) or whole-genome sequencing (WGS), is recommended for definitive diagnosis.[61]

In which patients should we suspect Type I interferonopathies?

Type I IFNs should be suspected in the presence of chronic autoinflammatory or autoimmune diseases resistant to conventional therapies, usually starting in early childhood, especially in the presence of unexplained neurologic or dermatologic symptoms.[2] Findings such as livedo reticularis, ulceration or necrosis of the extremities, basal ganglia calcifications, treatment-resistant seizures, and unexplained musculoskeletal symptoms strongly support the possibility of Type I IFNs.[5] In addition to these symptoms, factors such as family history, consanguinity, and genetic predisposition are also important clues that increase suspicion for the diagnosis.[2]

How should we approach the diagnosis in patients suspected of having interferonopathies?

The diagnosis of type 1 IFN starts with a high clinical suspicion, followed by a demonstration of an IFN response.[1] For this, the IFN signature test is used, which measures ISG expression in the peripheral blood. Although the IFN signature is positive in most patients, it can be confused with other diseases owing to its low specificity.[5] WES is preferred to clarify the diagnosis; however, it has limitations, such as its high cost and inability to detect intronic mutations. The most accurate diagnosis is made using WGS; however, it is rarely used because of its high cost.[61] Therefore, an accurate diagnosis requires a multidisciplinary approach using clinical, laboratory, and genetic testing.

TREATMENT

Treating type 1 interferonopathies aims to alleviate symptoms and modulate the interferon response. Although no definitive cure exists, current strategies focus on suppressing IFN signaling. JAK inhibitors (ruxolitinib, tofacitinib, and baricitinib) block the JAK-STAT pathway, reducing inflammation and symptoms in conditions such as AGS. However, they are not fully curative and may not reverse lung involvement.[62] Side effects include BK virus viremia and respiratory infections. Anti-inflammatory and immunosuppressive drugs (corticosteroids, methotrexate, mycophenolate mofetil) reduce general inflammation but do not directly target interferon signaling, thus offering a limited response.[3]

Anti-IFN antibodies (sifalimumab and anifrolumab) specifically neutralize interferon molecules and have shown promise in phase 2-3 trials.[63] Reverse transcriptase inhibitors (abacavir, lamivudine, and zidovudine) provide short-term improvement in some patients but lack long-term efficacy.[5] Gene therapy may offer future solutions but remains in the research phase.[4] Due to their experimental nature, these treatments require monitoring by a multidisciplinary team and an individualized approach.

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Author contribution

Review conception and design: EK, FH; literature review: EK, FH; draft manuscript preparation: EK, FH. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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Original Article

Is chronotype a risk factor for nocturnal non-dipping hypertension in children?

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ABSTRACT

Objectives: Chronotype is an individual circadian rhythm pattern affecting vascular tone and blood pressure. We aimed to investigate the effect of chronotype on nocturnal dipping in children with essential hypertension. This study was conducted considering that the habit of sleeping late at night has become widespread in children, especially during adolescence, potentially leading to the non-dipping phenomenon. With this study, we wanted to draw attention to the importance of sleep patterns and quality.

Material and Methods: This is a cross-sectional study, which was performed at Adiyaman University Faculty of Medicine between July 15, 2022, and March 15, 2023. All patients received 24-hour ambulatory blood pressure (BP) monitoring with essential hypertension based on the American Academy of Pediatrics guidelines. A chronotype questionnaire was administered to collect data from the participants.

Results: A total of 49 patients were included in the study, comprising 14 (29%) girls and 35 (71%) boys. The mean age of the patients was 13.9±2.3 years. Based on the chronotype questionnaire, 2 (4%) patients were identified as morning type, 23 (47%) as evening type, and 24 (49%) as intermediate type. Chronotype was not significantly associated with hypertension stage (p = 0.88) or the dipping phenomenon. In the intermediate type group, nighttime systolic BP dipping was 9.9±6% and in the evening type group, nighttime systolic BP dipping was 9.8±4.9% (p = 0.88). In the intermediate type group, nighttime diastolic BP dipping was 12.7±7.3% whereas in the evening type group it was 14.4 ± 6.4% (p = 0.58). Chronotype was not significantly associated with hypertension type [(p = 0.95) for systolic hypertension, (p = 0.58) for diastolic hypertension].

Conclusion: Chronotype affects nocturnal dipping in essential hypertensive children. In our study, the very low number of the morning type suggests that there are problems with sleep patterns and quality, especially late falling asleep, among adolescents. Sleep health, quality, and average daily sleep duration, and how they affect blood pressure levels in children, are a public health problem.

Keywords: children, chronotype, dipping phenomenon, hypertension

INTRODUCTION

Hypertension (HT) is a major health concern due to its high prevalence in the general population. In childhood, the prevalence of HT ranges from 4.9% to 7%, although regional and genetic differences exist.[1-3] The suprachiasmatic nucleus of the hypothalamus, also known as the biological clock, regulates the circadian rhythm. The circadian rhythm is involved in the regulation of the sleep-wake cycle, body temperature, and the release of hormones such as melatonin and cortisol. Chronotype represents individual circadian preferences that affect our physiology and psychology. Several modifiable and non-modifiable determinants that affect chronotype include genetics, family structure, environmental, social, and cultural factors, dietary habits, and urban lifestyle. Generally, humans can be categorized into three chronotypes: morning (preferring to go to bed earlier), evening (preferring to go to bed

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later), and intermediate (falling between morningness and eveningness) chronotypes.[4-6]

Healthy and sufficient sleep is crucial for the neurocognitive, cognitive, and emotional development of children and adolescents.[7] Circadian rhythm is a reflection of changes in vascular tone, blood pressure (BP), and coagulation balance, hunger-satiety cycles, and physical activity rhythms. Circadian rhythm disorders are known to be a risk factor for the development of cardiovascular disease (CVD).[8] In healthy individuals, arterial blood pressure typically decreases by approximately 10% at night compared to daytime, although this variation differs from person to person. Known as the "dipping phenomenon", this condition is associated with blood pressure variability regulated by neuroendocrine factors acting on the sympathetic nervous system and baroreceptors. A decrease in nighttime arterial BP is a normal part of circadian rhythm, and its absence is called the "non-dipping phenomenon". Abnormal parasympathetic and increased sympathetic nervous system activities have been implicated in this phenomenon.[9-11] In children, sleep health (sleep duration, timing, and efficiency) is one of the key family-level factors influencing hypertension.[12] However, limited data are available on the daytime course of blood pressure in relation to chronotype profiles. This study aimed to determine the relationship between chronotype and nocturnal BP dipping in children with essential hypertension. To the best of our knowledge, this is the first study to investigate whether blood pressure levels differ among chronotypes (morningness, intermediate, and eveningness) using 24-hour ambulatory BP monitoring (ABPM).

MATERIALS AND METHODS

Research and Publication Ethics: The study received the appropriate Institutional Review Board (IRB) approval. This study was conducted with the approval of the Ethics Commission of the Firat University Hospital, No. 17.07.2022-9571. Informed consent was obtained from the participants and the parents of the participants under 18 years of age.

Definitions

After obtaining ethics committee approval, patients diagnosed with essential hypertension at the Pediatric Nephrology outpatient clinic of Adıyaman University Faculty of Medicine were prospectively evaluated between July 15, 2022, and March 15, 2023. The diagnosis of HT was based on the American Academy of Pediatrics (AAP) guidelines, which define HT as blood pressure values of ≥130/80 mmHg in individuals aged ≥13 years.[13,14] For children under 13 years, HT is defined as blood pressure at or above the 95th percentile for age, height, and sex. Children aged 11-18 years were included in the study, and all participants underwent 24-hour ambulatory blood pressure monitoring (ABPM). Patients with known chronic conditions that could cause hypertension and/or a history of drug use were excluded from the study. To assess individual sleep-wake cycles, the Turkish version of the Children's Chronotype Questionnaire (CCTQ), validated by Dursun et al., was administered.[15] Demographic characteristics, serum biochemical parameters, thyroid function tests, fasting lipid profiles, renin and aldosterone levels, eye examination findings, echocardiography, renal doppler ultrasonography findings, and 24-hour ABPM data were recorded.

Children's Chronotype Questionnaire (CCTQ)

CCTQ was created as an adaptation of the Morningness-Eveningness Scale for Children developed by Werner et al. and the Munich Chronotype Questionnaire developed by Zavada et al. and validated by Dursun et al. The CCTQ is a 10-item, parent-reported tool for children. Sleep/wake parameters, including sleep latency, bedtime, lights-off, wake-up time, daytime naps for scheduled days, and free days, are questioned. The scores for 10 questions are summed up to obtain an overall score, which is interpreted as follows: 23 or less, morning type; 24 to 32, intermediate type; 33 or higher, evening type. This questionnaire also allows for determining the average duration of sleep per day by noting the exact times the child sleeps and wakes up. If the child takes a nap during the day, that time is added to the sleep time to find out the total sleep time. The same calculation is made for both scheduled and free days. Average daily total sleep time was calculated as follows: total sleep time on scheduled days x 5 plus total sleep time x 2 on free days divided by 7.[12, 15,16]

Statistical analysis

IBM SPSS (Statistical Package for the Social Science) 26.0 software was used for statistical analysis. Descriptive statistics, numbers, and percentages for categorical variables, mean, and standard deviation for numerical variables were presented. The normal distribution for numerical variables was evaluated with the Shapiro-Wilk test. The Mann-Whitney U Test was used in the analysis of non-normally distributed variables, and the Independent Samples T-Test was used in the analysis of normally-

distributed variables. The Pearson Chi-square Test was used in the analysis of categorical data. In all statistical analyses, the significance value of $p<0.05$ was accepted.

RESULTS

A total of 49 patients were included in the study, comprising 14 (29%) girls and 35 (71%) boys. The mean age of the patients was 13.9±2.3 years. The mean body mass index (BMI) of the patients was 26.8±6.5 kg/m^2. Thirty-four (70.4%) of the patients were overweight, obese, or morbidly obese. The most common presenting symptom was headache (n=28, 57.1%), and 17 (34.8%) patients were asymptomatic. Hepatosteatosis was detected in 12 (24.5%) patients, and 6 (12.2%) patients had hyperlipidemia. Uric acid elevation was not found in any of the patients, and all had normal thyroid function tests and serum renin aldosterone levels. Renal Doppler ultrasound examinations were normal in all patients. Hypertensive retinopathy was identified in 8 (16.3%) patients, while 9 (18.4%) patients had microalbuminuria. Among the hypertensive patients, 29 (59.2%) had systolic HT, 3 (6.1%) had diastolic HT, and 17 (34.7%) had systolodiastolic HT. Stage 1 HT was diagnosed in 24 (49%) patients, while Stage 2 HT was diagnosed in 25 (51%) patients. Additionally, 23 (46.9%) patients exhibited nighttime systolic BP drops, and 34 (69.4%) patients had nighttime diastolic BP drops, categorizing them as nocturnal dippers. Considering the echocardiographic findings of the patients, left ventricular hypertrophy was detected in 2 (4.1%) patients. Based on the chronotype questionnaire, 2 (4%) of the patients were identified as morning type, 23 (47%) as evening type, and 24 (49%) as intermediate type. The average sleep duration did not have a significant effect on nocturnal systolic and diastolic blood pressure dipping ($p = 0.65$, $p = 0.55$, respectively). Clinical and demographic characteristics of the study population are presented in Table 1. Being a dipper or non-dipper was not significantly associated with age, BMI percentile, sleep time, neutrophil/lymphocyte ratio, and blood pressure measurements during sleep and wakefulness.

Chronotype was not significantly associated with hypertension stage ($p = 0.88$) or the dipping phenomenon. In the intermediate type, nighttime systolic BP dipping was 9.9 ± 6%, while in the evening type, it was 9.8 ± 4.9% ($p = 0.88$). In the intermediate type, nighttime diastolic BP dipping was 12.7 ± 7.3%, whereas in the evening type, it was 14.4 ± 6.4% ($p = 0.58$). Chronotype and systolic/diastolic/dipper blood pressures, hypertensive retinopathy, and microalbuminuria relationships are given

Table 1. Demographic and clinical features of the study population

Parameter	**Patients** (n=49)
Demographic parameters	
Sex (female/male)	14/35
Age (years)	13.9 ± 2.3
Height (cm)	165.4 ± 12.1
Body weight (kg)	74.1 ± 22.1
Nutritional parameters	
Body mass index (kg/m^2)	26.8±6.5
Distribution by BMI percentile	Lean: 0 (0.0%) Normal: 15 (30.6%) Overweight: 8 (16.4%) Obese: 11 (22.4%) Morbidly Obese: 15 (30.6%)
Presenting Symptom	
Nosebleed	1(2%)
Dizziness	1(2%)
Chest pain	2(4.1%)
Asymptomatic	17(34.8%)
Headache	28(57.1%)
Number of children per family	3.3±1.1
Intermediate type	3.5±1.0
Evening type	3.0±1.2
Chronotype	
Morning type	2(4%)
Evening type	23(47%)
Intermediate type	24(49%)
Average Sleep Time (hours)	8.5±1.2
Intermediate type	8.1±1.1
Evening type	9±1.3
Blood Pressure Parameters	
Daytime Systolic BP (SBP) (mmHg)	126 ±8.2
Daytime Diastolic BP (DBP) (mmHg)	74.2 ±8
Nighttime Systolic BP (mmHg)	114 ±10.2
Nighttime Diastolic BP (mmHg)	64.2 ±6.7
Nighttime Systolic BP Dippers (%)	9.6 ±5.5
Nighttime Diastolic BP Dippers (%)	13.2 ±7
Stage 1 HT (n)	
Intermediate type	11/23
Evening type	12/24
Stage 2 HT Intermediate type Evening type	 12/23 12/24

BMI: Body mass index, BP: Blood Pressure, HT: Hypertension

in Table 2. Chronotype was not significantly associated with hyperlipidemia, microalbuminuria, the presence of hypertensive retinopathy, or hypertension stage (p = 1.00, p = 0.701, p = 0.63, p = 0.88, respectively). The number of children per family was not associated with sleep duration or chronotype (p = 0.13, p = 0.96, respectively). The number of siblings had no effect on nighttime systolic dipper BP and nighttime diastolic dipper BP (p = 0.49, p = 0.14, respectively).

DISCUSSION

In this study, we aimed to investigate whether chronotype (morningness, intermediate type, and eveningness) has an impact on the expected physiological drop in nocturnal blood pressure. Although it is more commonly reported in adults, the relationship between sleep duration and blood pressure has also been demonstrated in childhood.[17] To the best of our knowledge, this is the first study to evaluate the effects of chronotype on nocturnal blood pressure fluctuations in hypertensive children by means of 24-hour ABPM. There are studies reporting that chronotype affects cardiovascular health by modulating physiological processes such as heart rate and blood pressure, and therefore, may predispose the individual to CVD.[17-19] In our study, we expected to see a decrease in physiologic BP drops in evening-type hypertensive children compared to their intermediate-type counterparts. However, we did not find a significant difference in terms of the effect of chronotype on nocturnal BP drops. We found no significant impact of chronotype on the nocturnal dipping phenomenon. Chronotype was not significantly associated with hypertension stage (p = 0.88) or the dipping phenomenon. In the intermediate type, nighttime systolic BP dipping was 9.9 ± 6%, while in the evening type, it was 9.8 ± 4.9% (p = 0.88). In the intermediate type, nighttime diastolic BP dipping was 12.7 ± 7.3%, whereas in the evening type, it was 14.4 ± 6.4% (p = 0.58). Previous studies have shown that obese children and adolescents sleeping less than 6 hours per day are at an increased risk of hypertension.[20,21] As reported in many studies, shorter sleep duration is associated with an increased likelihood of obesity and cardiovascular disease.[22] A link between habitual short sleep and increased body fat composition has been demonstrated in adolescents and adults.[23] Each one-hour increase in total sleep time has been shown to reduce the risk of obesity by 9.0%.[21,24] It was shown that insufficient, poor-quality sleep can lead to the development of HT and CVD by causing endothelial dysfunction and increasing the secretion of proinflammatory cytokines.[25] There are studies reporting a strong negative correlation between short sleep duration and elevated blood pressure.[26-29] In contrast to these reports, we did not observe any relationship between sleep duration and nocturnal dipping/non-dipping or blood pressure changes in our study. This may be related to the small sample size of subgroups. Since there were only two morning-type children in our study, all comparisons were made between evening-type and intermediate-type children. This may also be another reason for the dissimilar findings. Further studies involving a larger cohort that specifically compares morning-type and evening-type pediatric patients may yield statistically significant findings. Our results contradict some of the previous reports. In a study by Navarro-Solera et al., short sleep duration was found to be significantly associated with higher pulse pressure and mean arterial pressure in children aged 7 to 16 years.[30] Similarly, Peach et al. demonstrated that short sleep duration is a risk factor for HT.[29] Previous studies have shown that both sleep quality and duration are associated with systolic BP[26-31] and diastolic BP.[30] Contrastingly, in our study, systolic and diastolic blood pressures did not show any relationship with chronotype (Table 2). The CARDIA

Table 2. Chronotype and systolic/diastolic/dipper blood pressures, hypertensive retinopathy, and microalbuminuria relationships

	Intermediate type	Evening type	p
Daytime systolic BP (mmHg)	127.9±9.3	124.4±6.7	0.14
Daytime diastolic BP (mmHg)	74.8±8.9	73.8±7.4	0.70
Nighttime systolic BP (mmHg)	115.4±12.3	112.4±7.8	0.33
Nighttime diastolic BP (mmHg)	64.7±7.8	63.5±5.8	0.57
Nighttime systolic BP Dippers (%)	9.9±6	9.8±4.9	0.88
Nighttime diastolic BP Dippers (%)	12.7±7.3	14±6.4	0.58
Hypertensive retinopathy (+) (n)	3/23	5/24	0.63
Microalbuminuria (+) (n)	3/23	5/24	0.70

BP: Blood Pressure

sleep study has shown that not only reduced sleep duration but also poor sleep quality were associated with increased systolic and diastolic BPs.[32]

In our study, we also examined whether an increasing number of siblings negatively impacts sleep quality and nighttime blood pressure. Our findings indicated no significant association between the number of siblings and either sleep quality or nighttime blood pressure. Bal et al.[33] examined sleep duration and its effect on BP in 2.860 patients aged 11 to 17 years and showed that a sleep duration of 8 hours or less is an independent risk factor for pre-HT and HT. The consensus statement issued by the American Academy of Sleep Medicine recommends that adolescents 13 to 18 years of age sleep 8 to 10 hours per day.[34] In our study population, the average sleep time was 8.5±1.2 hours daily, and we did not observe a relationship between sleep time and BP variations. Again, this may be due to the insufficient number of morning-type children included in this study, which led to their exclusion from any comparative analyses. If there had been more morning-type children, we could have compared the evening-type and morning-type children and potentially found significant differences in blood pressure fluctuations at night. However, these findings suggest that adolescents may not have a morning-type chronotype due to their lifestyles. In our study, chronotype profile was not significantly associated with indicators of the clinical course of HT such as the presence of hypertensive retinopathy and microalbuminuria (p=0.63, p=0.70, respectively).

CONCLUSION

Our findings show that morning type chronotype is less common among children. The lack of an association between chronotype and dipper/non-dipper hypertension was attributed to the very low prevalence of the morning chronotype in our cohort. If the number of morning chronotypes had been sufficient, the effect of morning and evening chronotypes on dipper/non-dipper hypertension might have been more significant. On the other hand, this situation suggests that late falling asleep is a common problem among adolescents, which may have a negative impact on health in the long term. This indicates that sleep patterns in children are becoming disrupted. We believe our study will provide valuable insights for future research, as no similar studies exist in the pediatric age group. Multicenter, large-sample studies are needed in childhood. Further studies involving a larger cohort will be helpful for understanding the relationship between chronotypes and blood pressure changes.

Ethical approval

This study has been approved by the Ethics Commission of the Firat University (approval date 17.07.2022, number 9571). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: GI, EA; data collection: GI, EA ; analysis and interpretation of results: GI and EA; draft manuscript preparation: GI. 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

The prediction of outcomes for pediatric traumas: a local single-center study

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ABSTRACT

Objective: Trauma is defined as a life-threatening condition and the leading cause of death in children. The present study aimed to investigate the relationship between clinical findings documented at admission and the interventions implemented in relation to patient outcomes, with the goal of determining the benefits of multidisciplinary treatment in a pediatric intensive care unit (PICU) for patients with trauma.

Method: A retrospective single-center study was conducted, including patients aged 1 month to 18 years who were treated for trauma between March and September 2022 in the PICU. The demographic characteristics, traumatic brain injury/multi-traumas, length of stay, Pediatric Risk of Mortality Score III (PRISM III), neurological findings, laboratories, radiological imaging, mortality, and outcomes were evaluated. Pediatric Trauma Score (PTS), Shock Index (SI), and Shock Index Pediatric Adjusted (SIPA) were calculated. These scores are evaluated for length of stay, transfusions, head injury, and mortality. In addition, the Vasoactive Intotropic Score (VIS), Rotterdam Computed Tomography Score (RCTS), and Functional Status Scale (FSS) were analysed to determine outcomes and effect on mortality.

Results: This study included 55 patients with a mean age of 73.95 (IQR:63.00) months. The mean PRISM III score was 24.95 (IQR:14.00) and the length of stay was 13.27 (IQR: 4.00) days. The most prevalent type of injury was falls from a height, accounting for 47.3% of cases. Furthermore, 28 subjects (50.9%) exhibited brain trauma, while a total of 30 subjects (54.5%) had multiple injuries. Surgery was performed on 21 (38.2%) cases. The mortality rate was 12 (21.8%). The requirement for inotropes (p=0.001), transfusions (p=0.004), and abnormal findings in brain computed tomography (CT) (p=0.036) have been demonstrated to have a significant impact on mortality, with intracranial hemorrhage having a substantial effect on the sequelae (p=0.019). In patients exhibiting elevated risk scores for predicting mortality and protracted PICU admission, PTS (p=0.001; p=0.001), SI (p=0.001; p=0.022), and SIPA (p<0.001; p<0.001) were identified as statistically significant. Despite the absence of a statistically significant relationship between the presence of head trauma and high risk (p>0.05), the need for transfusion was found to be associated with high SIPA (p=0.013). A positive and statistically significant correlation was identified between VIS (r= 0.914), RCTS (r= 0.751), and FSS (r= 0.946) and mortality (p<0.001).

Conclusion: The study demonstrates a statistically significant correlation between PTS, SIPA, VIS, RCTS, FSS, and mortality, as well as length of stay and outcomes. Children who have suffered a serious traumatic injury must be examined using age-based evaluation systems in a timely manner and be transferred to centres that can provide them with appropriate treatment as soon as possible.

Keywords: trauma, children, mortality, intensive care, outcome

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INTRODUCTION

Trauma is a considerable and life-threatening condition that is the most common cause of mortality and morbidity in pediatric ages.[1-4] Trauma can be classified into four types: physical, chemical, psychological, and thermal. In Turkey, traffic accidents are the leading cause of mortality among children; however, it is important to note that these incidents are preventable.[3,5,6] Physical trauma represents a significant health concern, particularly in children over the age of one year. The mechanisms by which these traumas are realized determine the primary risk factors and may result in multiple traumas in children. The increasing mortality and morbidity rates associated with multi-trauma cases are a matter of particular concern. To mitigate the adverse consequences of such traumas, patients must be managed in specialised trauma centers.[7,8] It is crucial to meticulously monitor these seriously unwell children in the pediatric intensive care units (PICU) both before and after surgery to avoid complications.

The severity of the trauma and multisystem involvement are the primary determinants of mortality in children who have experienced trauma. In addition to the severity of the trauma, the duration of exposure, the time to access treatment, and the effectiveness of the treatment all have a role. Due to their physiology, children develop shock clinic earlier than adults. The survival probability increases with early intervention, rapid stabilisation, and treatment in a facility equipped with trauma teams. In addition to new imaging techniques, the advantages of being able to perform emergency surgical and interventional procedures quickly when necessary, as well as easily obtaining medicines, supplies, and blood products, are significant.

In our study, we evaluate demographic data and clinical, laboratory, and imaging methods used in the follow-up and treatment of trauma patients in our PICU. The objective of the study was to determine the status of consultation and surgery, the duration of intensive care stay, the need for respiratory support and mechanical ventilation, the requirement for inotropic agents and blood products, mortality and morbidity, and short-term outcomes. For predicting outcomes in pediatric trauma, the Pediatric Trauma Score (PTS), Shock Index (SI), and Shock Index Pediatric Adjusted (SIPA) were used to categorize patients as high risk or low risk based on clinical findings at the time of admission. These scores were evaluated for length of stay, transfusions, head injury, and mortality. In addition, the inotropic using score, Vasoactive Inotropic Score (VIS), was calculated, along with radiological results for the Rotterdam Computed Tomography Score (RCTS) and clinical evaluations for Functional Status Scale (FSS) scores. The relationship between these scores and mortality was evaluated.

Furthermore, the study investigated the success rate of therapy in accordance with the guidelines, utilising data from our center. The hospital is situated in a socioeconomically and culturally disadvantaged region, but it is a tertiary treatment center that offers pediatric intensive care and also features surgical units. In addition to the effect of reaching the trauma center and the initial trauma, the impact of starting early and effective treatment on this situation has also been investigated. The follow-up of PICU-based pediatric trauma patients was investigated with a multidisciplinary approach.

MATERIALS AND METHODS

We conducted a retrospective, single-center study of pediatric patients aged 1 month to 18 years who were admitted to the pediatric intensive care unit (PICU) with trauma between March and September 2022. The study was conducted in a tertiary-care referral hospital with 800 beds and a 52-bed PICU that admits approximately 1,400 patients annually, providing comprehensive surgical services.

Demographic characteristics, type of trauma, indication for PICU admission, past medical history, comorbidities, presence of traumatic brain injury or polytrauma, length of PICU stay, Glasgow Coma Scale (GCS) score, Pediatric Risk of Mortality III (PRISM III) score, pupillary reactivity, occurrence of brain death, post-resuscitation status, need for invasive mechanical ventilation, laboratory and radiologic findings, in-hospital morbidities, and mortality were obtained from electronic medical records. The Pediatric Trauma Score (PTS), Shock Index (SI), and Shock Index Pediatric Age–adjusted (SIPA) were calculated from admission data and analyzed in relation to length of stay, transfusion requirements, head injury, and mortality. In addition, vasoactive-inotropic score (VIS), revised computed tomography score (RCTS), and functional status scale (FSS) were evaluated to assess clinical outcomes.

Vital signs have long been used to predict outcomes in trauma patients, although the prognostic value of systolic blood pressure (SBP), heart rate (HR), and respiratory rate (RR) alone is limited. The SI, defined as HR/SBP, and the SIPA, an age-adjusted modification of the SI, have been investigated as outcome predictors in children. High-risk

thresholds are generally defined as SI >0.9 for all ages and SIPA >1.2 for ages 1–6 years, >1.0 for ages 7–12 years, and >0.9 for adolescents. The PTS, based on six clinical parameters, was among the first tools developed and demonstrated high sensitivity and specificity for triage purposes, whereas SIPA has more recently been shown to identify severely injured children with moderate accuracy.

The VIS, which integrates the doses of dopamine, dobutamine, adrenaline, noradrenaline, milrinone, and vasopressin, was calculated as previously described.[9] Initially developed to quantify the intensity of vasoactive support in children after congenital cardiac surgery, VIS has been validated as a predictor of adverse outcomes and was applied in this study to critically ill pediatric patients beyond the postoperative cardiac setting.

In children with traumatic brain injury (TBI), the RCTS evaluates radiologic findings, including the status of basal cisterns, presence of midline shift, epidural mass lesion, intraventricular hemorrhage, and subarachnoid hemorrhage.[10] The total score reflects the severity of cranial injury and stratifies mortality risk in moderate-to-severe TBI. Higher RCTS values are associated with increased mortality and worse functional outcomes, whereas lower scores are correlated with improved survival.

Because mortality alone does not fully capture clinical outcomes in pediatric trauma, functional morbidity was also assessed. The FSS was developed through a consensus process among pediatric health professionals to standardize the evaluation of long-term sequelae.[11] It measures six domains—mental status, sensory function, communication, motor function, feeding, and respiratory status—with scores ranging from 6 to 30, where lower scores indicate better function.

In accordance with current guidelines, prophylactic antiepileptic therapy was initiated in patients with TBI and a GCS score <8. Levetiracetam was administered intravenously at a dose of 20 mg/kg/day. Antiepileptic treatment was also initiated in patients with a history of cardiopulmonary resuscitation or in those who developed new seizures. For patients presenting with active seizures, intravenous midazolam (1–2 mg/kg per dose) was given as a loading treatment, followed by intravenous levetiracetam at 20 mg/kg/day.

All patients were managed in the PICU under the supervision of pediatric intensive care specialists with continuous monitoring. Multidisciplinary consultations were obtained as needed for comprehensive evaluation and organ-specific management. Patients requiring urgent surgical or minimally invasive intervention upon presentation to the emergency department were stabilized post-procedure and subsequently admitted to the PICU for further care. Treatments were continued in the PICU both before and after definitive interventions. Neurosurgery, pediatric surgery, orthopedics, plastic and reconstructive surgery, otolaryngology, and pediatric neurology teams were actively involved in the management of these patients.

Patient data were extracted from electronic medical records and entered into a standardized database. Before study initiation, ethical approval was obtained from the institutional ethics committee (HRÜ/22.18.04), in accordance with the principles of the Declaration of Helsinki.

Statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, version 26.0; IBM Corp., Armonk, NY, USA). The normality of distribution was assessed with the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation (SD) when normally distributed, and as median with interquartile range (IQR) when non-normally distributed. Categorical variables are expressed as frequencies and percentages. Comparisons of categorical variables were made using Pearson's chi-square test or Fisher's exact test, as appropriate. Correlations between continuous variables were examined with Pearson's correlation analysis. To determine the factors influencing the mortality status of patients included in the study, multiple regression analysis was performed. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 55 pediatric patients with trauma were included in the study, of whom 38 (69.1%) were male and 17 (30.9%) female. The median age was 74 months (IQR, 63). The mean PRISM III score at admission was 24.9 (IQR, 14), and the median length of PICU stay was 13 days (IQR, 4).

Falls from height were the most common cause of trauma (n=26, 47.3%), followed by traffic accidents and other mechanisms (Figure 1). The highest rate of admissions occurred in June (23.6%). Twenty-eight patients (50.9%) sustained traumatic brain injury, and 30 (54.5%) had multiple injuries involving other organs or systems. Twenty-one patients (38.2%) underwent surgery, most commonly neurosurgical (n=18, 85.7%) or pediatric surgical procedures

(n=6, 28.6%). The majority of patients (n=53, 96.4%) had no significant comorbidities.

At presentation, 23 patients (41.8%) had a GCS score <8, 11 (20.0%) lacked pupillary light reflex, 15 (27.3%) required cardiopulmonary resuscitation, and 9 (16.4%) had clinical signs of brain death. Most patients were admitted to the PICU after initial stabilization in the emergency department (n=30, 54.5%). During the PICU stay, 21 patients (38.2%) did not require respiratory support, 41 (74.5%) required inotropic therapy, and 19 (34.5%) received blood or blood product transfusion (Table 1). Multidisciplinary management was provided with consultations from neurosurgery, pediatric surgery, orthopedics and traumatology, otolaryngology, and pediatric neurology (Figure 2). Pathological findings on initial radiologic examinations are summarized in Table 2.

Twelve patients (21.8%) died during their PICU stay. Of the survivors, 43 (74.5%) were discharged to pediatric wards, and 2 (3.6%) were discharged to the palliative care unit. Prophylactic antiepileptic medication was administered to 23 patients (41.8%), and seizure therapy was required in 3 (5.5%). At discharge, four patients (7.3%) required nasogastric tube feeding, 2 (3.6%) had tracheostomies with home ventilator support, and central nervous system (CNS) sequelae were documented in 3 (7%).

No significant associations were observed between month of trauma (p=0.942), trauma type (p=0.471), or the presence of brain trauma (p=0.217), multiple trauma (p=0.436), or surgical intervention (p=0.288) and mortality. In contrast, the need for inotropic support (p=0.001), transfusion of blood products (p=0.004), and abnormal cranial CT findings (p=0.036) were significantly associated with increased mortality. Although brain trauma and surgical intervention were not significantly correlated (p=0.066), the presence of intracranial hemorrhage on CT was significantly associated with the development of CNS sequelae (p=0.019).

High-risk scores on the Pediatric Trauma Score (PTS), Shock Index (SI), and Shock Index Pediatric Age–adjusted (SIPA) were significantly associated with both mortality (PTS, p=0.001; SI, p=0.001; SIPA, p<0.001) and prolonged PICU stay (PTS, p=0.001; SI, p=0.022; SIPA, p<0.001) (Table 3). There was no significant association between the presence of head trauma and high-risk scores (p>0.05). However, the need for transfusion was significantly associated with high

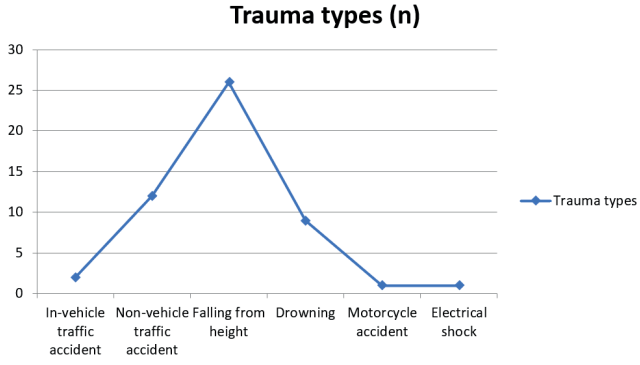

Figure 1. The reasons for hospitalization

Table 1. The distribution of transfusion types and intracranial traumas

		n (%)
Transfusion types	None	18 (32.7)
	Erythrocyte suspension	7 (12.7)
	Platelet suspension	0 (0)
	Fresh frozen plasma	8 (14.5)
	Erythrocyte & Platelet suspension	0 (0)
	Erythrocyte suspension & Fresh frozen plasma	11 (20)
	Erythrocyte & Platelet suspension & Fresh frozen plasma	9 (16.3)
Intracranial traumas	Normal	27 (49)
	Epidural hemorrhage	5 (9)
	Subdural hemorrhage	6 (10.9)
	Subaracnoidal hemorrhage	10 (18.1)
	Intraparenchymal hemorrhage	6 (10.9)
	Diffuse parancimal edema	9 (16.3)

SIPA scores (p=0.013). In contrast, when cranial pathologies and transfusion types were analyzed separately, no significant relationships were observed (p>0.05).

Among patients with critical trauma, VIS scores ranged from 0 to 220 (median, 0). RCTS values based on cranial CT findings ranged from 1 to 6 (median, 1). Functional assessment of survivors yielded FSS scores ranging from 1 to 30 (median, 6). Multiple regression analysis revealed that VIS (r=0.914, p<0.001), RCTS (r=0.751, p<0.001), and FSS (r=0.946, p<0.001) were independently and significantly associated with mortality, indicating that each parameter contributed as a strong predictor of adverse outcomes beyond the effects of the others.

DISCUSSION

Trauma is reported as the second most frequent cause of death among children aged 1-4 years after infections from underdeveloped and developing countries. It is the most common cause of death in developed countries for those aged 1 to 14.[8,12] Physical traumas in childhood increase mortality, morbidity, and health expenditures in countries. As observed in our study, in research examining childhood traumas in Turkey, Öztan et al. (2-11) found that 0.5-17 (6.3) years was the age range of children with trauma.[13] Tambay et al. reported a mean hospital stay of 5.54 ± 6.42 days, while Mısırlıoğlu et al. recorded an average of 11.8 ± 8.2 days. The mean duration of PICU stay was 4.4 ± 2.9 days.[7,14] While the majority of trauma patients were found to be healthy in this study, the period of hospitalization in the PICU was found to be longer than in other studies. This is likely due to the fact that the hospital is the only pediatric trauma center in the city and has high PRISM III scores.

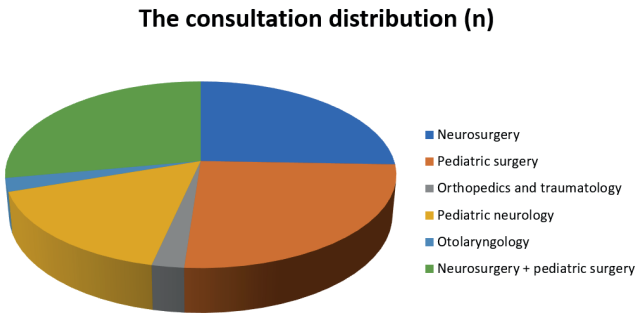

Figure 2. The distribution of consultations

Falling from height is the most common cause of trauma in all age groups following motor vehicle accidents, and it is the most prevalent cause of trauma in childhood.[15] Similar to the literature, falling from a height was the most often cause of trauma in this study. The month of June, which corresponds with the commencement of the school holidays in this country, exhibits a marked increase in the number of trauma patients, attributable to the warming of the weather. This month is thus identified as the most significant month in terms of trauma admissions in our study.

Head trauma and/or brain injury are the most common form of pediatric trauma and are the most common cause of trauma-related mortality and morbidity.[16] Doğan et al. in their study of pediatric traumas found that the most common region was the head and neck region, with a rate of 41.9%. Extremity traumas were observed in 33.4%

Table 2. Radiological findings

Radiological imagings	Findings	n (%)
PAAG*	Normal	44 (80)
	Pathological findings (pneumothorax, hemothorax)	11 (20)
Cranial CT*	Normal	27 (49.1)
	Intracranial hemorrhage	18 (32.7)
	Diffuse parenchymal edema	9 (16.4)
	Collapse fracture	1 (1.8)
Thorax CT*	Normal	45 (81.8)
	Pathological findings (pneumothorax, hemothorax)	10 (18.2)
Abdomen CT*	Normal	43 (78.2)
	Pathological findings (perforation, hemorrhage)	12 (21.8)

*PAAG: posteroanterior chest X-ray, CT: Computed tomography

Table 3. Distribution of SI, SIPA, and PTS at the time of admission, and these high and low-risk scores for the length of stay, transfusions, head injury, and mortality relationships

		SI		SIPA		PTS	
		Low-risk	High-risk	Low-risk	High-risk	Low-risk	High-risk
Mortality (n)	No	22	21	34	9	35	8
	Yes	0	12	0	12	4	8
	p value	**0.001**		**<0.001**		**0.001**	
Intracranial pathology (n)	Normal	9	18	20	7	22	5
	p value	0.595		0.237		0.597	
	Epidural hemorrhage	4	1	5	0	3	2
	p value	0.695		0.794		0.897	
	Subdural hemorrhage	2	4	2	4	3	3
	p value	1.000		0.894		0.897	
	Sub-arachnoidal hemorrhage	3	7	3	7	4	6
	p value	1.000		0.794		0.796	
	Intra-parancimal hemorrhage	0	6	0	6	0	6
	p value	1.000		0.965		0.747	
	Diffuse edema	6	3	6	3	3	9
	p value	0.794		0.895		0.847	
Transfusion types (n)	None	10	8	16	2	16	2
	p value	0.782		0.412		0.344	
	Erythrocyte suspension	2	5	4	3	6	1
	p value	0.633		0.118		0.576	
	Platelet suspension	0	0	0	0	0	0
	p value	-		-		-	
	Fresh frozen plasma	1	7	3	5	6	2
	p value	0.683		0.788		1.000	
	Erythrocyte & Platelet suspension	0	0	0	0	0	0
	p value	-		-		-	
	Erythrocyte suspension & Fresh frozen plasma	5	6	6	5	7	4
	p value	0.722		0.957		0.344	
	Erythrocyte & Platelet suspension & Fresh frozen plasma	2	7	3	6	3	6
	p value	0.766		0.433		0.766	
Length of stay (day)	Median (IQR)	4 (6)	19 (21)	4 (4)	28 (47)	9 (7)	23 (35)
	p value	**0.022**		**<0.001**		**0.001**	

* PTS: Pediatric Trauma Score, SI: Shock Index, SIPA: Shock Index Pediatric Adjusted

of cases.[17] The present study provides support for these rates, and it was found that the rate of consultation with neurosurgeons and pediatric surgeons was higher than that of other specialists.

It is known that 30-50% of trauma-related deaths occur at the accident site, and 30% of them occur in the hours and days after the accident, usually in the first hours.[18] The high PRISM III scores of the patients included in the study, which evaluates the data of the first 24 hours of PICU admission, the presence of a high rate of head trauma, and the high rate of multiple trauma, describe the fact that the mortality rate is higher compared to literature data. Mortality rates can be reduced by prompt recognition of patients who require appropriate and rapid transport, urgent evaluation and resuscitation, and necessary surgical

intervention. In addition, it is essential to reduce mortality and morbidity through effective management, treatment, and a multidisciplinary approach in pediatric emergency care and the PICU.

In the study by Embleton et al., only traffic accident traumas were examined, with a mean age/gender of 11.2 years/60.1% male, respectively. Accidents occurred at 45.6% in the summer, the mortality rate was 3.8%, and CNS sequelae were 1.9% reported.[19] In the PICU treatment study, Misirlioglu et al. followed up and treated 49 pediatric trauma patients, but no mortality was detected during this process.[14] On the contrary, at the end of our study, the mortality rate was higher, and it was associated with patients' first clinical scores at admission. This underscores the significance of scoring systems such as the SI, SIPA, and PTS, which are utilized in the preliminary assessment of critically ill trauma patients, in predicting mortality. Additionally, we examined 55 patients over only 6 months. The high rate is due to the high number of pediatric patients in our region and the high incidence of physical trauma because of weak socioeconomic and sociocultural conditions. Additionally, our facility is the only trauma center in the region with a pediatric intensive care physician. Our patients, unlike other study results, showed a newly developed high rate of central nervous and respiratory system support needs at the end of the study. This situation is associated with the severity of the primary trauma etiology of our patients and the high rate of patients with severe shock in the clinic. This condition shows that the duration of hypoxemic and hypotensive stay is prolonged due to difficulties in reaching our center for various reasons.

In Özcan et al., the factors affecting mortality in pediatric severe TBI study, it was observed that CPR was applied in patients who lost their lives, the need for inotropes and the need for erythrocyte transfusion were statistically significantly higher.[20] Our study identified a statistically significant relationship between the necessity for inotropic agent administration and blood product transfusions and the mortality rate. Furthermore, the presence of hemorrhage, diffuse edema, and fractures on brain CT scans was found to have a statistically significant impact on mortality.

In pediatric TBI patients, the most common findings at cranial brain CT imaging are diffuse axonal injury, edema, midline shift, and subdural and intraparenchymal hemorrhage.[21] Our critically ill trauma patients had similar rates of pathologies. Interestingly, we detected that while there was no significant relationship between the presence of brain trauma and the need for an operation, the presence of hemorrhage on brain CT significantly affected the development of CNS sequelae. This situation demonstrates the significant impact of primary injury caused by trauma and its severity on mortality and morbidity. Moreover, the higher final mortality rate compared to other studies may be attributed to the sociocultural and socioeconomic weakness of the region where the study was conducted. Additionally, trauma patients took longer to reach our center, and transportation systems were difficult due to physical reasons in our region. There is evidence to suggest that delayed initial treatment of patients can affect their prognosis.

The Injury Severity Score (ISS) is the most commonly utilised injury scoring system in the domains of trauma research and benchmarking. An ISS>15 is conventionally used to define severe injury. In a study by Brown et al., the relationship between ISS scoring and mortality in children was examined. The study suggests that ISS>25 may be a more appropriate definition of severe injury in paediatric trauma patients. However, it is important to note that in paediatric patients with single-system injury, mortality is primarily driven by head and chest injuries. This suggests that the specific pattern of injury may be more significant than the overall ISS score. The assumption that adult injury metrics can be applied to pediatric patients with adequate performance must be robustly evaluated to ensure the best care for the injured child.[22] In light of the findings that different scores would be more appropriate than the ISS used in adults, the mortality rate was evaluated with scores such as PTS, SI, and SIPA in the present study. Pediatric outcomes were also examined with FSS.

In a study published in 2023, where 750 pediatric trauma patients were examined retrospectively, predictive outcomes (length of stay, disposition, ventilator use, Index Severity Score, and spleen/liver injury) data of patients with high-risk scores in the PTS and SIPA scoring were analyzed, and odds ratios were associated with increased risk for both scores. When the PTS and SIPA were compared, it was determined that the odds ratio was higher in the PTS, while the need for urgent fluid replacement was higher in the SIPA score.[23] In our study, we found that pediatric trauma patients with high-risk scores for predicting mortality and prolonged PICU stay were statistically significant. This finding lends further support to the hypothesis that these scoring systems are effective in predicting length of stay, mortality, and outcomes in paediatric trauma patients.

The American College of Surgeons Pediatric Trauma Quality Improvement Program database compared SIPA scores in patients with and without TBI. Higher blood transfusion requirements and increased mortality rates were found in patients with TBI. Isolated TBI and those with multisystem injury, suggesting its utility in the prediction of outcome in TBI patients with elevated SIPA regardless of the presence of concomitant injuries. For this reason, it has been suggested to develop scoring systems that include the status and severity of TBI in the analysis of trauma patients.[24] In our study conducted without isolating TBI, there was no statistically significant relationship between the presence of head trauma and high-risk scores at PTS, SI, and SIPA. Similarly, in those with high-risk SIPA scores, the need for blood transfusion was found to be statistically significantly higher.

The three-year study of pediatric sepsis patients in the PICU examined the association between VIS scores and mortality. In addition to mortality, it was also found to be associated with PICU length of stay, mechanical ventilator days, cardiac arrest, and extracorporeal membrane oxygenation.[9] In a study examining sepsis patients in adult intensive care over an 11-year period, the VIS score was calculated at 2-hour intervals for a 72-hour period. Inotrope treatment was evaluated according to the VIS score. The relationship between the VIS score and mortality was examined. The study concluded that the VIS score was both a reliable predictor of 28-day mortality and a valuable tool in clinical decision-making processes within intensive care management.[25] Although the VIS score is primarily a predictor of mortality in sepsis and cardiac surgery patients, it has also been shown to be a predictor of mortality in TBI patients in the Adult TBI Study.[26] A study on the use of RCTS as a predictor of mortality in pediatric TBI patients found that the use of validated RCTS, especially in patients with moderate or severe TBI, provides accurate data and can be used for risk stratification.[10] The FSS is a tool for producing a functional status result at the end of a major intervention. As it provides clear, non-subjective data, it provides standardisation in patient assessment. When evaluated using the Adaptive Behaviour Assessment System (ABAS) II, the study assessing its feasibility and effectiveness reported that it was quick, reliable, and suitable for use in hospitalized pediatric patients.[11] This study found a positive and statistically significant correlation between VIS, RCTS, and FSS and mortality, similar to the results of mortality and outcome prediction evaluations reported in the literature.

A retrospective cohort study was published in 2021, using data from 2012 to 2017, and was conducted in 832 emergency departments (EDs) across the United States of America (USA), located in all 50 states and the District of Columbia. The study focused on admission, transfer, or injury-related death at a participating trauma centre. The objective of the study was to evaluate the relationship between pediatric ED preparation, in-hospital mortality, and in-hospital complications in injured children admitted to USA trauma centres. The study compared injured children treated in high-prepared EDs with those treated in low-prepared EDs. The mortality rate was lower in the former group, but no fewer complications were observed.[27] This finding underscores the significance of multidisciplinary management of pediatric trauma patients in reducing mortality in centres with teams with expertise in trauma surgery, such as the hospital where our study was conducted.

This study was conducted retrospectively at a single center. Nevertheless, the clinic and interventions for trauma patients during admission to the PICU were performed by the same group of physicians and surgeons. Intracranial pressure and continuous electroencephalography monitoring could not be applied due to a lack of equipment. Although the admission indications and severity of traumas were heterogeneous, this study center was the only pediatric intensive care specialist clinic in this city. Patients with severe or moderate physical traumas were treated in a multidisciplinary manner by a team of neurosurgeons, pediatric surgeons, orthopedists, traumatologists, otolaryngologists, and pediatric neurologists.

CONCLUSION

In conclusion, the results of our single-centre study demonstrate a statistically significant correlation between PTS, SIPA, VIS, RCTS, FSS, and mortality, as well as length of stay and outcomes. These results are analogous to those reported in the literature regarding mortality and outcome prediction evaluations. Children who have suffered a serious traumatic injury should be quickly recognized, examined with clinical findings and age-based evaluation systems/scoring tools, and taken as soon as possible to centers that can provide them with appropriate treatment. Although this study population showed some results, multi-center prospective studies are needed to obtain clear data and develop the first recognition charts and transfer conditions on the management and mortality of pediatric trauma patients.

Ethical approval

This study has been approved by the Harran University Clinical Research Ethics Committee (approval date 19.09.2022, number HRÜ/22.18.04). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: HFA; data collection: HFA, AD; analysis and interpretation of results: HFA, AD, BE, GG; draft manuscript preparation: HFA. All authors reviewed the results and approved the final version of the article.

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The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The clinical and genetic spectrum of ınfantile osteopetrosis: a single-center experience ıncluding a novel TCIRG1 mutation

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ABSTRACT

Background: Osteopetrosis (OP) is a rare, severe inherited disorder of bone metabolism caused by impaired osteoclast function. The most severe form, malignant infantile osteopetrosis (MIOP), presents in early life with bone abnormalities, neurologic issues, and often hypocalcemia and carries a high mortality rate if left untreated. This study aimed to define the molecular spectrum and delineate genotype-phenotype correlations in a cohort of patients from a single pediatric hematology center.

Methods: We retrospectively reviewed the medical, laboratory, radiological, and genetic data of 12 children with OP followed between 2012 and 2022. Whole-exome sequencing was used for genetic analysis.

Results: The median age at diagnosis was three months. The most frequently mutated gene was *TCIRG1* (n=7, 58.3%), followed by *OSTM1* (n=3, 25%), and *CLCN7* (n=2, 16.7%). A novel homozygous deletion in *TCIRG1* was identified. A strong genotype-phenotype correlation was observed. Patients with *TCIRG1* mutations predominantly presented with severe bone marrow failure and osteopetrorickets. In contrast, all patients with *OSTM1* and *CLCN7* mutations exhibited significant neurodegenerative changes. Two patients received hematopoietic stem cell transplantation (HSCT), with one survivor.

Conclusion: This study highlights the distinct clinical and genetic heterogeneity of MIOP. Our findings reinforce that the specific genetic mutation is critical for predicting the disease course—hematological complications for *TCIRG1* versus primary neurodegeneration for *OSTM1* and *CLCN7*. This genetic diagnosis is essential for counseling families and determining eligibility for curative therapies like HSCT.

Keywords: malignant infantile osteopetrosis, *TCIRG1*, *OSTM1*, *CLCN7*, genotype-phenotype correlation, marble bone disease

INTRODUCTION

Osteopetrosis (OP), also known as “marble bone disease,” is a group of rare, heritable skeletal disorders characterized by increased bone mass resulting from defective osteoclast development or function. This failure of bone resorption leads to generalized skeletal sclerosis, which paradoxically increases the risk of fractures.[1-3] Consequently, overly dense bones may compress the cranial nerves, potentially resulting in irreversible nerve damage. Additionally, expansion of bone into the marrow cavities can lead to bone marrow failure.[4]

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OP is classified into three clinical subtypes based on age of onset, severity, and inheritance patterns:

Autosomal recessive osteopetrosis (ARO) severe malignant infantile and intermediate form, and autosomal dominant osteopetrosis (ADO) late-onset form.[2,5-7]

Malignant infantile osteopetrosis (MIOP) represents the most severe form of osteopetrosis and is inherited in an autosomal recessive pattern. This form is genetically heterogeneous. Mutations in the *TCIRG1* gene are the most common cause, accounting for over 50% of ARO cases.[8-10] Biallelic mutations in T cell immunoregulator 1 (*TCIRG1*), chloride channel 7 (*CLCN7*), sequence nexin 10 (*SNX10*), osteopetrosis-associated transmembrane protein 1 (*OSTM1*), TNF receptor superfamily member 11a (*TNFRSF11A/RANK*), TNF Receptor Superfamily Member 11 (*TNFSF11/RANKL*), pleckstrin homology domain-containing family M -with RUN domain-member 1 (*PLEKHM1*), lead to ARO.[11-15]

The incidence of MIOP is 1/250,000 live births.[8-10]In individuals with MIOP, clinical manifestations typically appear shortly after birth and are associated with various systemic abnormalities.[12,15] Common symptoms include recurrent infections, unusual bruising, and bleeding disorders.[16]Affected patients also experience frequent pathological fractures. Other symptoms include macrocephaly and hepatosplenomegaly, hearing loss, vision impairment, and hypocalcemia.[17]

Osteopetrosis is primarily diagnosed based on the presence of characteristic clinical and radiographic features. Genetic mutations can be identified in approximately 90% of patients with OP.[2,11]

Radiographic examinations typically reveal generalized osteosclerosis throughout the skeleton, characterized by a “marble bone” appearance. The notable radiologic findings are: “Erlenmeyer flask” deformity, “bone-in-bone” or “endobone” appearance, and the “sandwich vertebrae” or “rugger jersey spine”.[5]

Genetic testing provides critical insights into prognosis and clinical correlates, which significantly influence management decisions.

HSCT is the treatment of choice for patients with OP. Clear indications for HSCT include progressive bone marrow failure or the imminent risk of vision loss due to optic nerve compression. However, HSCT is not suitable for all patients.[18,19]

The rarity of the disease, particularly in developing countries, often results in diagnostic delays that preclude timely intervention. This study aims to characterize the molecular spectrum and clinical features of 12 children with MIOP from a single center to better understand the genotype-phenotype correlations and highlight the diagnostic journey.

MATERIALS AND METHODS

Study design

This retrospective study included 12 children with osteopetrosis who were followed at a single pediatric hematology center between 2012 and 2022. Data on family history, physical examination findings, complete blood counts, serum biochemistry (25-hydroxyvitamin D, calcium, phosphorus, alkaline phosphatase, and parathyroid hormone), imaging results, and genetic analyses were retrieved from medical records. This study was approved by the Gaziantep University University Non-Interventional Clinical Research Ethics Committee (Date: 4 October 2023, Number: 2023/316), and written informed consent was obtained from the participants’ parents.

Genetic analysis

Genomic DNA was extracted from peripheral blood leukocytes of the patients and parents. Whole-exome sequencing libraries were prepared using the Twist Human Core Exome Kit and NovaSeq system (Illumina, USA). The variant interpretation followed a structured analysis algorithm. Sequence data were analyzed using SOPHIA DDM software. Variants were first filtered based on their frequency in the Genome Aggregation Database (gnomAD) to exclude common polymorphisms. The potential pathogenicity of remaining rare variants was assessed using multiple *in silico* prediction tools (e.g., LRT, CADD, EIGEN, BayesDel). Variants were then cross-referenced with public databases (ClinVar, HGMD) and literature sources before being classified according to the American College of Medical Genetics and Genomics (ACMG) 2015 guidelines. Segregation analysis was performed using Sanger sequencing to confirm that variants were inherited from the parents.

Statistical analysis

Data were examined utilizing SPSS version 24 (IBM Corp., Armonk, NY). Quantitative (numerical) variables were displayed as mean, standard deviation, median, maximum,

and minimum, whereas qualitative (categorical) variables were summarized in terms of frequency and percentage

RESULTS

Cohort characteristics

A total of 12 patients (7 female, 5 male) from ten distinct families were included. All patients were born to consanguineous parents. The median age at diagnosis was three months (range, 1 to 36.5 months). The most common presenting symptoms were nasal congestion and difficulty sucking (n=4) (Table 1). Radiographic assessments in all 12 patients revealed features typical of osteopetrosis, including diffuse bone sclerosis, thickened skull bones, a "sandwich vertebrae" appearance, and a "bone-within-bone" sign (Figure 1 and Figure 2).

Molecular findings

Genetic analysis identified pathogenic or likely pathogenic variants in all 12 patients (Table 2). The most frequently affected gene was *TCIRG1* in seven patients (58.3%), followed by *OSTM1* in three patients (25%), and *CLCN7* in two patients (16.7%). All mutations were homozygous. A novel homozygous deletion in *TCIRG1*, c.936_963del (NM_006019.4), which causes a frameshift leading to a premature stop codon, was identified in Patient 4. This variant was absent from the gnomAD database and was classified as "likely pathogenic." Other identified variants have been previously reported.

Clinical and laboratory findings by genotype

Clinical features varied significantly according to the underlying genetic defect (Table 1).

TCIRG1-related osteopetrosis (n=7)

This group comprised Patients 1, 2, 3, 4, 5, 6, and 7. Bone marrow failure was the predominant clinical feature. Six of the seven patients (85.7%) had anemia and/or thrombocytopenia at presentation or during follow-up. All patients in this group, except one, required transfusions, with six becoming transfusion-dependent. All seven patients had hepatosplenomegaly, indicative of extramedullary hematopoiesis. Vision loss was present in three patients, and pale optic discs were noted in six. Osteopetrorickets was diagnosed in six of the seven patients (85.7%). Neurodegenerative changes were not a feature in this group. At the time of the study, four patients in this group had died, two were alive under supportive care, and one was alive and well post-HSCT.

OSTM1-related osteopetrosis (n=3)

This group included Patients 8, 9, and 10, all of whom carried the same homozygous splice site mutation in *OSTM1*. These patients presented with a severe neurodegenerative phenotype. All three exhibited neurodegenerative changes on cranial imaging, including diffuse cerebral atrophy and a thin corpus callosum, and had a history of seizures. Two patients died during the study period.

Table 1. Molecular findings of patients with osteopetrosis

Patient No.	Gene	Zygosity	Variant	Protein alteration	Location	Mutation type	ACMG classification
1	TCIRG1	Homozygous	-	-	Exon 11-12	Large deletion	Pathogenic
2	TCIRG1	Homozygous	c.2236C>T (NM_006019.4)	p.Q746* p. Gln746*	Exon 18	Nonsense	Pathogenic
3	TCIRG1	Homozygous	c.2236+1G>A (NM_006019.4)	-	Intron 18	Splice site	Pathogenic
4	TCIRG1	Homozygous	c.936_963del (NM_006019.4)	p.Ser312ArgfsTer25	Exon 9	Indel	Likely pathogenic
5	TCIRG1	Homozygous	c.2236+1G>A (NM_006019.4)	-	Intron 18	Splice site	Pathogenic
6	TCIRG1	Homozygous	-	-	Exon 11-13	Large deletion	Pathogenic
7	TCIRG1	Homozygous	-	-	Exon 11-13	Large deletion	Pathogenic
8	OSTM1	Homozygous	c.402+1G>T (NM_014028.3)	-	Intron 1	Splice site	Likely pathogenic
9	OSTM1	Homozygous	c.402+1G>T (NM_014028.3)	-	Intron 1	Splice site	Likely pathogenic
10	OSTM1	Homozygous	c.402+1G>T (NM_014028.3)	-	Intron 1	Splice site	Likely pathogenic
11	CLCN7	Homozygous	c.1576C>T (NM_001287)	p.(Arg526Trp)	Exon 17	Missense	Pathogenic
12	CLCN7	Homozygous	c.746C>G (NM_001287.5)	p.Pro249Arg	Exon 9	Missense	Pathogenic

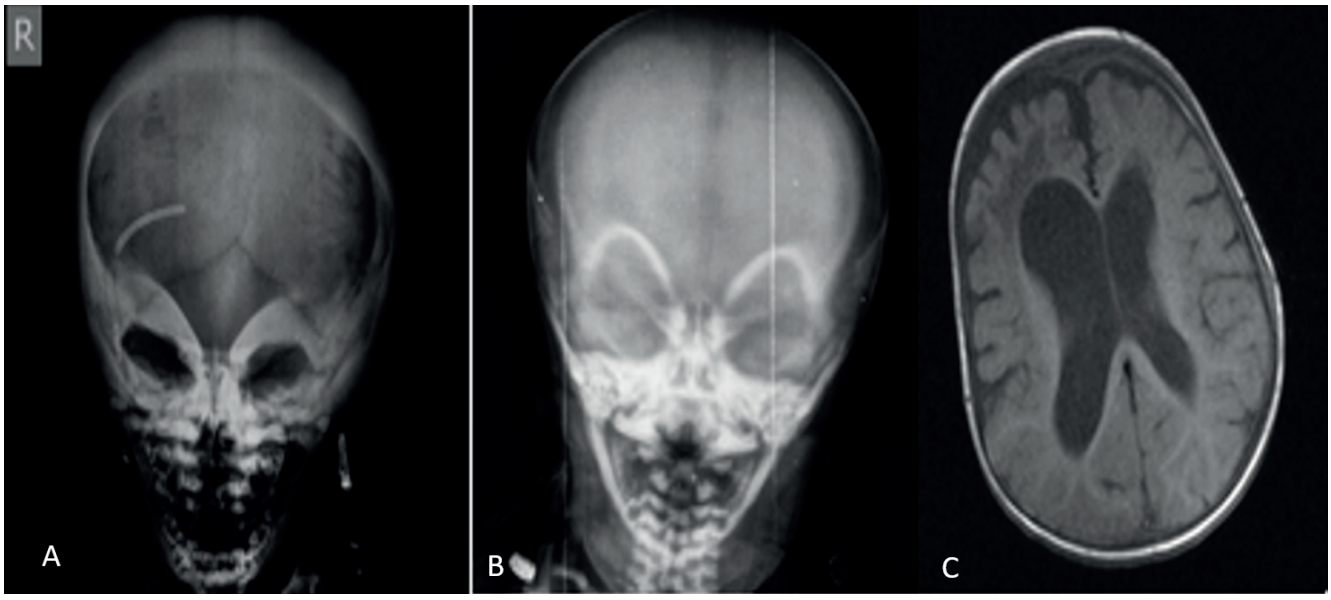

Figure 1. Representative cranial X-ray and computerized tomography findings of our patients

A. Diffuse sclerosis and thickening of skull and orbital bone structures are evident, with the presence of a ventriculoperitoneal shunt catheter; **B.** Marked sclerosis of the orbit, midface, skull vault and cervical spine, and mandible. Note the sclerotic inner table, the widened and radiolucent diploic space, and the less sclerotic outer table of the skull; **C.** Enlarged lateral ventricles, more pronounced on the right side. Note the prominent extra-axial CSF space in the right frontal region. There is a suspected thin subdural hemorrhage on the left frontal region.

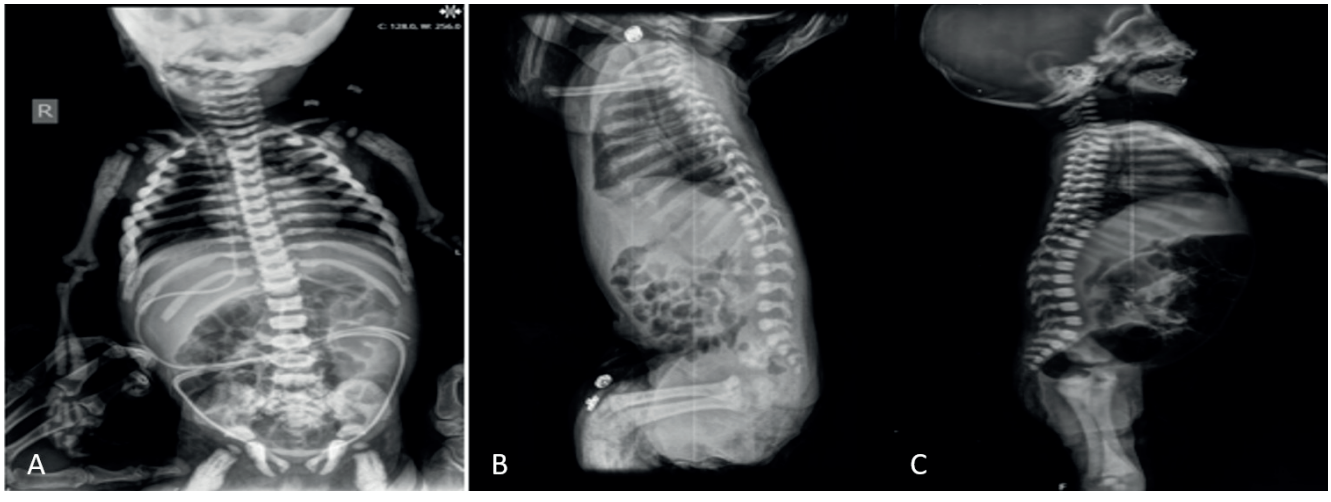

Figure 2. Representative vertebral X-ray findings of our patients with osteopetrosis

A. Generalized skeletal sclerosis, with broad and thickened ribs. Bilateral humeral shaft fractures are also notable; **B.** Lateral radiograph of the whole spine showing the characteristic "sandwich vertebra" appearance, defined by pronounced sclerosis of the superior and inferior endplates of the thoracic and lumbar vertebral bodies; **C.** Lateral radiograph of the whole spine showing "bone-within-bone" appearance of the lumbar vertebral bodies and posterior elements, a hallmark radiographic feature of osteopetrosis.

CLCN7-related osteopetrosis (n=2)

Patients 11 and 12 had homozygous missense mutations in *CLCN7*. Both patients presented with a severe phenotype that included neurodegenerative changes. Patient 11 had hydrocephalus and seizures, while Patient 12 had vision loss and hepatosplenomegaly. Both patients in this group died.

Table 2. Clinical, laboratory and radiologic findings of patients with osteopetrosis

Genetic mutation	**TCIRG1**							**OSTM1**			**CLCN7**	
Patient Number	1	2	3	4	5	6	7	8	9	10	11	12
Sex	F	F	M	F	M	M	M	F	F	M	F	F
Age at diagnosis (months)	6.5	36.5	1	2	3.5	3	4	6	2	1.5	2	3
Presenting symptom	Pneumonia	Pallor	Bleeding	Vision loss	Pneumonia	Bone fracture	Nasal congestion, difficulty sucking	Nasal congestion, difficulty sucking	Pallor	Nasal congestion, difficulty sucking	Nasal congestion, difficulty sucking	Bone fracture
Nystagmus	+	-	-	-	-	-	-	-	-	-	+	-
Strabismus	-	-	-	-	-	-	+	-	-	-	-	-
Vision loss	-	+	-	+	-	+	-	+	+	-	-	+
Pale optic disc	+	+	-	+	-	+	+	+	+	-	+	+
Hydrocephaly	+	+	-	-	-	-	-	+	-	-	+	-
Neurodegenerative changes	-	+	-	-	-	-	-	+	+	+	+	+
Hepatosplenomegaly	+	+	+	+	+	+	+	+	+	+	+	+
Bone fracture	+	+	-	-	-	+	-	-	+	-	-	+
Hearing loss	+	N/A	+	-	-	+	+	N/A	+	N/A	-	-
Seizures	-	+	-	-	-	-	-	+	-	-	+	-
Anemia	+	+	-	+	+	+	+	-	+	+	+	-
Thrombocytopenia	+	+	+	+	+	-	+	-	+	+	+	-
Leukocytosis	+	+	-	-	-	+	+	-	+	+	+	-
Hypocalcemia	+	+	-	-	+	+	+	+	+	-	+	+
HSCT	-	-	+	-	+	-	-	-	-	-	-	-
Death	+	+	-	-	+	-	+	+	+	-	+	+

F: Female, M:Male, HSCT: Hematopoietic stem cell transplantation, N/A: Not available

Patient outcomes

Overall, eight of the twelve patients (66.7%) died during the study period. Four patients were still alive. Two patients underwent HSCT. Patient 3 (*TCIRG1* mutation), who underwent HSCT, died from sepsis one month post-transplant. The other patient who received HSCT (Patient 5, *TCIRG1* mutation) survived and remains in good health.

DISCUSSION

This study describes the clinical and genetic landscape of 12 children with MIOP from a single center, highlighting distinct genotype-phenotype correlations and identifying a novel pathogenic mutation. Our findings confirm that MIOP is a heterogeneous disorder where the underlying gene defect is a major determinant of the clinical course and prognosis.

In our cohort, *TCIRG1* variants were identified as the likely causative gene for ARO in seven cases (58.3%), consistent with previous research indicating that *TCIRG1* is the pathogenic gene in over 50% of ARO cases.[8,10] In one patient (Patient 4), we identified a novel homozygous mutation in *TCIRG1*, while all other mutations had been previously reported.

The clinical presentation of our *TCIRG1* patients was dominated by severe hematological complications and osteopetrorickets, which aligns with existing literature.[20] This is biologically plausible, as the *TCIRG1* gene encodes a crucial subunit of the proton pump necessary for osteoclasts to acidify the bone-resorption lacuna. Its dysfunction directly cripples bone resorption, leading to marrow cavity obliteration and subsequent bone marrow failure.

In stark contrast, all patients with *OSTM1* and *CLCN7* mutations exhibited a severe neurodegenerative phenotype. This finding highlights the broader physiological roles of the proteins encoded by these genes. Unlike *TCIRG1*, which is primarily expressed in osteoclasts, *CLCN7* (a chloride channel) and *OSTM1* (its beta-subunit) are also vital for the proper function of the endolysosomal system in various cell types, including neurons. Disruption of this pathway is thought to cause lysosomal storage defects within neurons, leading to the observed cerebral atrophy, seizures, and progressive neurological decline, which are absolute contraindications for HSCT.[21,22]

The prevalence of *OSTM1* mutations in our cohort (25%) is significantly higher than the ~5% reported in broader studies, which may suggest a founder effect within our population, especially since all three affected patients carried the same homozygous mutation.[12,15]

Mutations in the CLCN7 gene are the second most common cause of ARO, accounting for 17% of cases.[2,5,20,22,23] In the current study, we identified CLCN7 mutations in 16.7% of the patients, which aligns with previous reports. However, this mutation was the third most prevalent in our cohort. Our patients with biallelic *CLCN7* mutations also exhibited neurodegenerative features, consistent with reports that approximately half of such cases involve neurological decline.[21]

For many patients with MIOP, hematopoietic stem cell transplantation (HSCT) is the only curative treatment option, particularly in cases of progressive bone marrow failure or optic nerve compression. However, the suitability of HSCT is highly dependent on the specific underlying genetic mutation and the patient's clinical presentation, making early and accurate genetic diagnosis crucial for management decisions. Absolute contraindications include extrinsic osteoclast defects caused by *RANKL* mutations and the severe neurodegenerative forms of OP associated with all known *OSTM1* mutations and about half of biallelic *CLCN7* mutations. In osteopetrosis, the conditioning regimen must strike a delicate balance between achieving sufficient myeloablation and immunosuppression while minimizing regimen-related toxicity.[18,19]

TCIRG1 mutations, who underwent HSCT, with starkly different outcomes. Patient 5 received an HSCT and is alive and in good health. Patient 3, however, died from sepsis one month post-transplant.

While a detailed analysis is limited by the small sample size, this highlights the critical challenges of HSCT in this population. Patients with MIOP are often malnourished and have recurrent infections, making them highly susceptible to regimen-related toxicity and post-transplant complications like severe infections. The choice of conditioning regimen, donor source, and the timing of the transplant before irreversible organ damage occurs are paramount for success. These cases underscore the need for early genetic diagnosis to identify suitable candidates (i.e., those without primary neurodegeneration) and to proceed with HSCT under optimal clinical conditions to minimize the risk of fatal complications.

CONCLUSION

This study underscores the significant clinical and genetic heterogeneity of Malignant Infantile Osteopetrosis (MIOP) and reinforces the critical role of genotype-phenotype correlations in clinical management. Our findings confirm that hematological and skeletal symptoms should raise suspicion for TCIRG1-related osteopetrosis, while early and severe neurological decline is characteristic of forms caused by OSTM1 and some CLCN7 mutations. The identification of a novel pathogenic *TCIRG1* mutation contributes to the growing catalog of variants for this disease. Ultimately, a timely and comprehensive assessment that combines clinical, radiological, and genetic data is essential for accurate diagnosis, prognostication, and guiding crucial therapeutic decisions, particularly regarding the feasibility and timing of curative therapies like HSCT.

Ethical approval

This study has been approved by the Gaziantep University University Non-Interventional Clinical Research Ethics Committee (approval date 04.10.2023, number 2023/307). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: EPS, SA, ACO, MK; data collection: EPS, ACO, SA; analysis and interpretation of results: EPS, UG, CD, BS; draft manuscript preparation: EPS, ACO, SA. 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

Prevalence, incidence, mortality attributed to HIV in children under 5 years of age, and comparative analysis of health expenditure in central Asian countries

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ABSTRACT

Background and Aim: Despite progress in HIV prevention and treatment in many regions, Eastern Europe and Central Asia continue to experience a rising epidemic, with a 20% increase in new HIV cases since 2010. Pediatric HIV remains a significant concern, with 13,000 children (0–14 years) living with HIV in Eastern Europe and Central Asia. Mother-to-child transmission (MTCT) rates in the region stand at 10%, far exceeding the global elimination targets of 2% (for non-breastfeeding mothers) and 5% (for breastfeeding mothers). However, country-specific, age-disaggregated data on pediatric HIV (prevalence, incidence, mortality, and ART coverage) remain scarce, hindering targeted interventions. This study aimed to assess the prevalence, incidence, and mortality of HIV among children under 5 years in Central Asia and evaluate health expenditures related to pediatric HIV treatment in the region.

Methods: This descriptive study includes prevalence, incidence of HIV, and all deaths of children under 5 years of age living with HIV, in different regions covered by Central Asia during the years 1990 to 2021. Information was collected from the mortality registration system. Financial data on HIV-related health spending for each country of interest were gathered through the Development Assistance to Health (DAH) database. The model framework was based on the Global Burden of Disease (GBD) protocol.

Results: There is a dramatic surge in HIV prevalence across Central Asia, from 4,776 cases in 1990 to over 1.5 million in 2019. Kazakhstan and Uzbekistan faced the most significant increases, while Georgia showed progress in reducing new infections, and Mongolia remained the least affected. Male children consistently had higher rates of HIV-related incidence and mortality. Notably, Uzbekistan experienced a rise in under-5 HIV-related mortality, from 10.06 per 100,000 in 1990 to 11.52 in 2019. Disparities in healthcare spending were evident, with Kazakhstan and Kyrgyzstan demonstrating more substantial investments, in contrast to lower per capita spending in Uzbekistan and Turkmenistan.

Conclusion: Overall, the Central Asian region is experiencing a surge in HIV cases among children under 5 years of age, which contrasts with global trends. This may be attributed to disparities in healthcare spending, access to care, prevention efforts, and the stigma associated with HIV in Central Asia.

Keywords: children living with HIV, human immunodeficiency virus (HIV), central Asian countries

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INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is a severe, life-threatening condition caused by the Human Immunodeficiency Virus (HIV).[1] HIV is the most common viral infection worldwide, according to the World Health Organization (WHO), and is increasing in high-risk groups, reaching more than 5 percent of the population.[2] Currently, there is no vaccine for this disease, and prevention is considered the most important and effective method of combating the HIV epidemic in the world.[3] The number of HIV-infected patients is declining in numerous African countries[4], but in Eastern Europe and Central Asia, the number of new HIV cases acquired has increased by 20% since 2010. The region is not on track to meet the 2030 targets for ending AIDS. Moreover, Central Asian countries account for a significant portion of these cases, with four countries (Kazakhstan, the Russian Federation, Ukraine, and Uzbekistan) reporting 92% of all new registered HIV cases in the region, according to published case reports from 15 of 16 countries.[5] This alarming trend extends to pediatric HIV, where significant challenges persist. While global efforts have reduced mother-to-child transmission (PMTCT) rates in many parts of the world, Eastern Europe and Central Asia still face hurdles. In Eastern Europe and Central Asia, an estimated 13,000 children aged 0-14 were living with HIV at the end of 2023, with 1,400 newly infected children in this age group in 2023.[6]

Currently, the main pattern of HIV in Central Asia includes transmission through injection drug users (IDUs). However, it seems that, like other parts of the world, these countries are rapidly moving towards a pattern of sexual transmission, which will also increase the perinatal risk of acquiring HIV.[7] In developed countries, mother-to-child HIV transmission has decreased from 25% at the beginning of the epidemic to less than 2% in 2008.[8,9] However, in Central Asia, mother-to-child transmission is still a significant concern. In 2023, the overall global mother-to-child transmission rate for Eastern Europe and Central Asia was 10%, which is still far from the 2% elimination threshold for non-breastfeeding countries and 5% for breastfeeding countries, indicating a critical need for intensified efforts in the region.[10] While regional data exist, precise, country-specific, disaggregated data on pediatric HIV (prevalence, incidence, mortality, and ART coverage) for all Central Asian nations, particularly for specific age subgroups (e.g., 0-1 year, 1-5 years), are often limited or not publicly available.

Understanding HIV prevalence, incidence, and mortality in wider Central Asian countries is crucial, particularly given the region's growing child population.[11] Analyzing HIV dynamics in children under 5 in this region can inform targeted policies to support this vulnerable population.

The present study aimed to assess the prevalence, incidence, mortality, and health expenditures for HIV treatment in children under 5 years of age from 9 Central Asian countries (Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan) and compare these findings with a global picture.

METHODS

Study design and population

This descriptive study includes prevalence, incidence and all deaths of children under 5 years of age attributed to HIV (ICD-11 codes B20-B24, C46-C469, D84.9; ICD-11 codes are 042-044, 112-118 (after 1980), 130 (after 1980), 136.3-136.8 (after 1980), 176.0-176.9 (after 1980), 279 (after 1980); and ICD-11 BTL codes are B184-B185), during the years 1990 to 2021 in 9 countries covered by Central Asia: Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, and Uzbekistan. Since most of the Central Asian countries in this study were part of the Soviet Union before 1991, we analyze trends.

Input data

The data collection protocol was described in detail in Figure S1.

Household seroprevalence surveys

Geographically representative HIV seroprevalence survey results were used as inputs to the model for countries with generalized HIV epidemics where available.

GBD demographic inputs

Location-specific population, fertility, migration, and HIV-free survival rates from GBD 2020 were used as inputs in modelling all locations.

Data from countries

The files compiled by the Joint United Nations Programme on HIV/AIDS (UNAIDS) for their HIV/AIDS estimation process were one of our sources of data for producing estimates of the HIV burden. The files are often built by within-country experts with the support of UNAIDS, which publishes estimates annually on behalf of countries and only shares

their files when permission is granted. The files contain HIV-specific information needed to run the Spectrum1, Estimation and Projection Package-Age Sex2 (EPP-ASM) models. Spectrum and EPP-ASM require the following input data: AIDS mortality among people living with HIV with and without ART, CD4 progression among people living with HIV not on ART, ART coverage among adults and children, cotrimoxazole coverage among children, coverage of breastfeeding among women living with HIV, prevention of mother-to-child transmission coverage, and CD4 thresholds for treatment eligibility. EPP-ASM additionally uses HIV prevalence data from surveillance sites and representative surveys. Antenatal care (ANC), incidence, prevalence, and treatment coverage data from UNAIDS were used in modelling for all locations. We extracted all of this data from the proprietary format used by UNAIDS.

Vital and civil registration

We utilized all available sources of vital and civil registration, as well as sample registration data, from the GBD Causes of Death database, following the redistribution of garbage codes and the correction of HIV/AIDS mis-coding in Group 2A countries from the Central Asian region. Both systems are administered by the Centers for Disease Control and Prevention, of which the reported number of deaths due to HIV is archived.

Case notifications data

We searched for case notification data using the ECDC database and the country reports series in countries with four- and five-star vital registration data. We identified all nine countries for which information was available.

Prevalence Data

Geographically representative HIV seroprevalence survey results were used as inputs to the model for countries with generalized HIV epidemics where available. From these surveys, we used age- and sex specific prevalence data.

Data from countries

The files compiled by UNAIDS for their HIV/AIDS estimation process served as our primary source of data for producing estimates of the HIV burden. The files are often built by within-country experts with the support of UNAIDS, which publishes estimates annually on behalf of countries and only shares their files when permission is granted. The files contain HIV-specific information necessary to run the Spectrum4 Estimation and Projection Package-Age Sex (EPP-ASM)5 models. We extracted all of this data from the proprietary format used by UNAIDS. The EPP-ASM and Spectrum models used for GBD estimation vary slightly from those used by UNAIDS, with details on this variation included below. In addition to the differences in model structure, we integrate our estimates of input model parameters, including new transition parameters and demographic rates. The differences between our estimates and UNAIDS' estimates reflect differences in model structure, model parameters, and the location-specific data used to calibrate our models.

Modelling strategy

The conceptual and analytical framework of the model was based on the Global Burden of Disease protocol (https://www.healthdata.org/sites/default/files/2024-06/GBD%20Protocol%20060424.pdf), a causal hierarchy, and detailed methods have been previously published by us.[12-14] We used two different components to derive year-, age-, and sex-specific estimates of HIV incidence, prevalence, and mortality depending on the locations' availability of data and extent of HIV burden, as described below:

1. EPP-ASM was used to estimate incidence, prevalence, and mortality that are consistent with serosurveillance data from antenatal care clinics and/or prevalence surveys.
2. Spectrum is a compartmental HIV progression model used to generate age-sex-specific incidence, prevalence, and death rates from input incidence and prevalence curves and assumptions about intervention scale-up and local variation in epidemiology. This model was used in conjunction with EPP-ASM for India and for all Group 2A countries.

Statistical analysis

The data were analyzed using SPSS version 21 software. The data were reported as numbers, percentages, mean, and standard deviation. The data were separated by gender and place of residence. The mortality rate was calculated per 10,000 live births. To visually represent the mortality rate of children under 5 years of age attributed to HIV, we used ArcGIS software (version 1.10). These maps highlight areas within the studied regions and countries. Distinct colors were employed to differentiate areas based on their varying mortality rates.

RESULTS

Global and national scenario (Overall estimates)

The global HIV burden has grown significantly over the past three decades. HIV-related deaths rose nearly threefold, from 305,944 in 1990 to 863,837 in 2019, while prevalence increased from 7.93 million to 36.85 million cases during the same period. In Central Asia, the epidemic escalated sharply. HIV-related deaths rose from 401 in 1990 to 27,715 in 2019—a 69-fold increase. Prevalence also surged from 4,776 to 1.54 million cases. Kazakhstan and Uzbekistan were the most affected. In Kazakhstan, deaths increased from 96 to 261; Uzbekistan recorded the highest rise in deaths, from 120 to 585 (a 385% increase), and in new cases, from 804 to 2,537 (Table 1). In contrast, Georgia showed a decline in new HIV cases, dropping from 477 in 1990 to 269 in 2019. Kyrgyzstan and Tajikistan experienced moderate increases in deaths—Kyrgyzstan's rose more than fourfold, and Tajikistan's by 41%. Mongolia remained the least affected, with a minimal rise in deaths (from 8 to 15) and new cases (from 35 to 39) over the same period.

Sex difference

Across all three metrics, males consistently demonstrate higher numerical values than females. The line graphs suggest that over time, the number of deaths attributable to HIV has been increasing for both sexes, but the escalation is more pronounced in males. Correspondingly, the number of newly acquired HIV cases has been growing, with men experiencing a more precipitous rise compared to women. The prevalence of HIV, denoting the total population living with the virus, also follows this pattern, with a steeper upward trend in males than in females (Figure 1).

Under 5 years of age children scenario

The scenario for children under 5 years of age is presented in Table 2. The data on HIV-related deaths, incidence cases, and prevalent cases from 1990 to 2019 reveal significant trends in the global and Central Asian contexts. In 1990, the number of deaths due to HIV globally was 43,744.40 (95% CI: 38,062.46 - 48,832.55), but by 2019, this figure significantly decreased to 20,594.30 (95% CI: 15,723.78 - 27,328.31), reflecting a significant reduction in mortality. In Central Asia, however, the number of deaths remained relatively stable, increasing slightly from 24.70 (95% CI: 24.69 - 24.71) in 1990 to 25.80 (95% CI: 25.75 - 25.85) in 2019, indicating persistent challenges in this region. Among individual Central Asian countries, Kazakhstan, Kyrgyzstan, and Uzbekistan exhibited variations in mortality trends (Figure S2). Kazakhstan's HIV-related deaths increased slightly from 2.15 (95% CI: 2.14 - 2.15) in 1990 to 2.42 (95% CI: 2.41 - 2.42) in 2019. In Kyrgyzstan, the death toll also rose from 1.73 (95% CI: 1.73 - 1.74) in 1990 to 2.25 (95% CI: 2.25 - 2.26) in 2019. Meanwhile, Uzbekistan experienced a more noticeable increase, from 10.06 (95% CI: 10.05-10.07) in 1990 to 11.52 (95% CI: 11.49-11.55) in 2019.

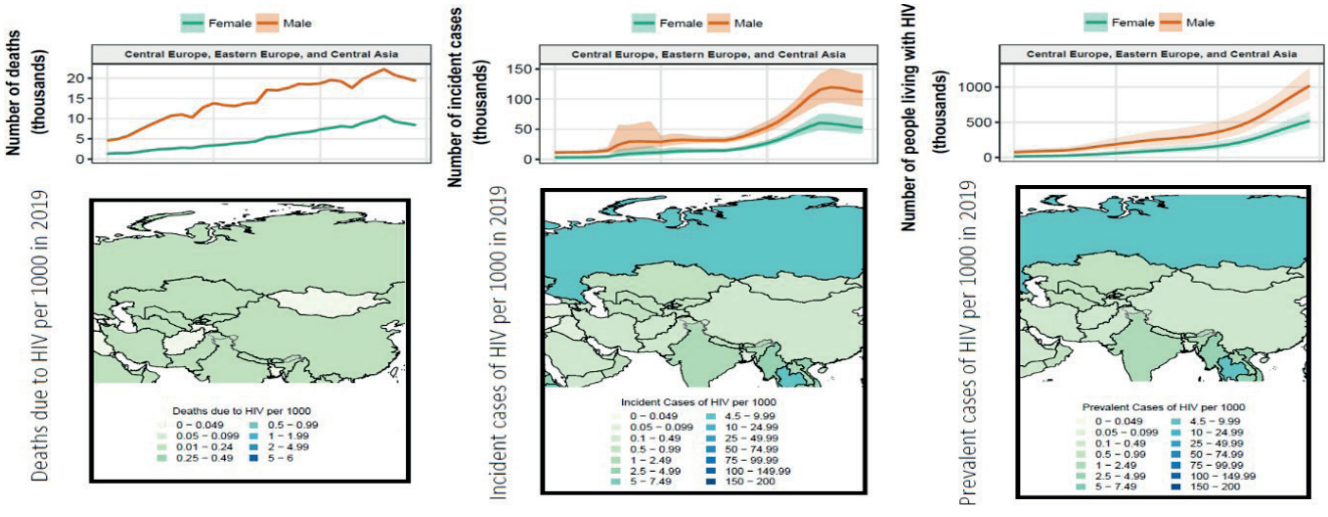

Figure 1. Upper figures from left to right: Deaths due to HIV (in thousands), Incidence cases of HIV (in thousands), and prevalent cases of HIV (in thousands) from 1990 to 2019 by super region; lower figures from left to right: Deaths due to HIV per 1000, incidence cases of HIV per 1000, and prevalent cases of HIV per 1000 in 2019.

Table 1. Number of deaths due to HIV, number of new HIV acquired cases, number of prevalent cases due to HIV between 1990 and 2019 for GBD super-regions and nine countries in the Central Asian region

GBD super-regions	Number of deaths due to HIV		Number of HIV incidence cases		Number of prevalent cases	
	1990 (95%CI)	2019 (95%CI)	1990 (95%CI)	2019 (95%CI)	1990 (95%CI)	2019 (95%CI)
Global	305,944.92 (234,538.17 – 404,774.04)	863,837.35 (786,074.86 – ;996,044.87)	2,008,915.56 (1,843,346.1 – 2,181,339.29 7)	1989282.21 (1760906.83 – 2259348.18)	7,934,076.57 (7,417,414.38 – 8,495,409.73)	36,848,153.96 (35,149,001.88 – 38,856,666.01)
Central Asia	400.89 (400.59 – 401.15)	27,715.47 (27352.19 – 28093.88)	2,890.91 (1,993.00 – 4,057.82)	165,005.29 (133488.11 – 206380.51)	4,776.60 (3,397.03 – 6,416.14)	1,539,667.32 (1,267,868.51 – 1,893,286.31)
Armenia	4.75 (4.75 – 4.76)	19.08 (18.11 – 20.13)	85.3 (62.81 – 115.16)	127.9 (101.33 – 166.94)	10.44 (0.00 – 18.01)	1,389.42 (1,111.43 – 1,824.16)
Azerbaijan	27.96 (27.95 – 27.98)	37.11 (29.86 – 42.38)	159.77 (103.12 – 205.25)	304.82 (204.41 – 490.6)	352.19 (223.61 - 489.82)	3,355.87 (2,490.91 – 4,697.71)
Georgia	11.85 (11.79 – 11.87)	23.28 (22.19 – 24.5)	477.14 (327.89 – 697.13)	269.12 (174.56 – 460.87)	40.35 (20.56 - 78.46)	4,510.62 (3,074.2 – 6,794.12)
Kazakhstan	96.44 (96.22 – 96.65)	260.54 (246.37 – 276)	694.41 (541.63 – 878.53)	2381.56 (1571.7 – 3192.79)	1,336.40 (911.51 - 1,888.77)	16,742.87 (13,231.76 – 21,456.06)
Kyrgyzstan	38.56 (38.51 – 38.62)	170.04 (162.07 – 177.8)	458.45 (321.18 – 651.19)	932.01 (614.89 – 1375.89)	342.83 (204.57 - 543.19)	6191.71 (4,364.42 – 9,005.16)
Mongolia	8.12 (3.7 – 14.86)	15.03 (1.78 – 38.02)	35.39 (13.1 – 74.8)	38.97 (10.86 – 80.37)	0.21 (0.10 – 0,25)	418.59 (163.84 – 836.54)
Tajikistan	42.55 (42.51 – 42.58)	60.02 (45.02 – 87.39)	243.91 (183.86 – 293.38)	527.35 (276.94 – 735.1)	369.49 (245.28 - 556.69)	4,528.95 (3,441.58 – 5,548.36)
Turkmenistan	56.66 (56.57 – 56.75)	105.37 (99.05 – 112.62)	158.41 (135.87 – 184.05)	270.07 (214.51 – 332.48)	1,013.42 (722.49 - 1,337.44)	3755.76 (2,978.44 – 4,963.33)
Uzbekistan	120.43 (120.31 – 120.57)	584.56 (553.98 – 617.1)	803.64 (120.97 – 1292.08)	2536.9 (841.7 – 4197.25)	1,311.28 (791.75 - 1,899.30)	22,344.82 (13,096.14 – 31,621.82)

The global number of new HIV-acquired cases decreased substantially, from 256,869.86 (95% CI: 232,181.80-280,576.59) in 1990 to 101,273.76 (95% CI: 84,106.23-126,532.44) in 2019. In contrast, Central Asia saw an increase in incidence cases from 82.55 (95% CI: 53.41 - 123.31) in 1990 to 128.36 (95% CI: 77.12 - 280.88) in 2019, suggesting ongoing transmission despite global progress. Notably, Kazakhstan's incidence cases surged from 26.27 (95% CI: 16.03 - 39.22) in 1990 to 41.59 (95% CI: 26.38 - 67.70) in 2019, while Kyrgyzstan experienced an alarming rise from 2.63 (95% CI: 1.48 - 4.61) in 1990 to 33.21 (95% CI: 11.77 - 141.28) in 2019 (Figure S3).

HIV prevalence, reflecting the total number of living cases, slightly increased globally from 290,331.34 (95% CI: 265,698.46 - 316,063.71) in 1990 to 294,367.71 (95% CI: 251,093.66 - 357,920.66) in 2019. In Central Asia, however, prevalence nearly doubled from 55.83 (95% CI: 38.25 - 77.53) in 1990 to 103.88 (95% CI: 53.13 - 267.47) in 2019, indicating persistent transmission and an increasing number of people living with HIV. Countries such as Kazakhstan and Kyrgyzstan showed a sharp rise in prevalence, with Kazakhstan increasing from 7.35 (95% CI: 4.87 - 10.40) in 1990 to 24.51 (95% CI: 12.18 - 70.48) in 2019, and Kyrgyzstan from 2.51 (95% CI: 1.47 - 4.01) in 1990 to 20.19 (95% CI: 5.93 - 74.93) in 2019 (Figure S4).

Figure 2 illustrates the HIV-related deaths, incidence cases, and prevalent cases among children under 5 years old per 1,000 individuals globally. In 1990, the highest prevalence of HIV in children under five was concentrated in Sub-Saharan Africa, with some countries experiencing over 500 cases per 100,000. By 2021, the prevalence had significantly declined globally, yet Sub-Saharan Africa remained the most heavily impacted region. The incidence of new HIV acquired cases in 1990 followed a similar pattern, with the highest rates in Sub-Saharan Africa, as well as some cases in parts of South America and Southeast Asia. By 2021, there was a substantial decrease in new cases globally, with improvements in regions that had previously experienced high burdens. Mortality rates due to HIV in children under five were also highest in Sub-Saharan Africa in 1990. However, by 2021, there was a notable reduction in child deaths from HIV, reflecting advancements in treatment, prevention, and intervention programs. Whereas in Central Asian countries, there was a surge in HIV incidence in children under 5 years of age.

Overall, the comparison of these maps indicates that while the global burden of HIV in children under five has declined significantly from 1990 to 2021, Sub-Saharan Africa

Table 2. Number of deaths due to HIV, number of new HIV acquired cases, number of prevalent cases due to HIV between 1990 and 2019 for GBD super-regions and nine countries in the Central Asian region in children under 5 years of age

GBD super-regions	Number of deaths due to HIV		Number of HIV incidence cases		Number of prevalent cases	
	1990 (95%CI)	2019 (95%CI)	1990 (95%CI)	2019 (95%CI)	1990 (95%CI)	2019 (95%CI)
Global	43,744.40 (38,062.46 - 48,832.55)	20,594.30 (15,723.78 - 27,328.31)	256,869.86 (232,181.80 - 280,576.59)	101,273.76 (84,106.23 - 126,532.44)	290,331.34 (265,698.46 - 316,063.71)	294,367.71 (251,093.66 - 357,920.66)
Central Asia	24.70 (24.69 - 24.71)	25.80 (25.75 - 25.85)	82.55 (53.41 - 123.31)	128.36 (77.12 - 280.88)	55.83 (38.25 - 77.53)	103.88 (53.13 - 267.47)
Armenia	0.17 (0.17 - 0.17)	0.06 (0.06 - 0.07)	0.14 (0.00 - 0.25)	0.75 (0.46 - 1.21)	0.06 (0.00 - 0.13)	0.39 (0.25 - 0.61)
Azerbaijan	1.48 (1.48 - 1.48)	0.85 (0.85 - 0.86)	1.46 (0.85 - 2.23)	0.58 (0.34 - 0.94)	1.71 (0.70 - 2.72)	0.82 (0.48 - 1.30)
Georgia	0.26 (0.25 - 0.26)	0.11 (0.11 - 0.11)	0.63 (0.27 - 1.40)	0.53 (0.27 - 0.97)	0.13 (0.04 - 0.33)	0.64 (0.33 - 1.17)
Kazakhstan	2.15 (2.14 - 2.15)	2.42 (2.41 - 2.42)	26.27 (16.03 - 39.22)	41.59 (26.38 - 67.70)	7.35 (4.87 - 10.40)	24.51 (12.18 - 70.48)
Kyrgyzstan	1.73 (1.73 - 1.74)	2.25 (2.25 - 2.26)	2.63 (1.48 - 4.61)	33.21 (11.77 - 141.28)	2.51 (1.47 - 4.01)	20.19 (5.93 - 74.93)
Mongolia	0.18 (0.18 - 0.18)	0.09 (0.08 - 0.09)	0.00 (0.00 - 0.00)	0.09 (0.03 - 0.17)	0.00 (0.00 - 0.00)	0.38 (0.09 - 1.29)
Tajikistan	5.30 (5.30 - 5.31)	5.98 (5.96 - 6.02)	11.14 (5.98 - 19.46)	9.83 (6.64 - 13.83)	13.55 (7.75 - 22.22)	12.38 (8.33 - 17.49)
Turkmenistan	3.36 (3.36 - 3.37)	2.51 (2.50 - 2.53)	12.09 (8.06 - 17.05)	13.19 (8.25 - 22.06)	12.35 (6.57 - 17.88)	21.58 (14.26 - 36.90)
Uzbekistan	10.06 (10.05 - 10.07)	11.52 (11.49 - 11.55)	28.19 (14.90 - 44.70)	28.59 (16.22 - 49.39)	18.18 (8.55 - 27.55)	22.99 (7.27 - 89.46)

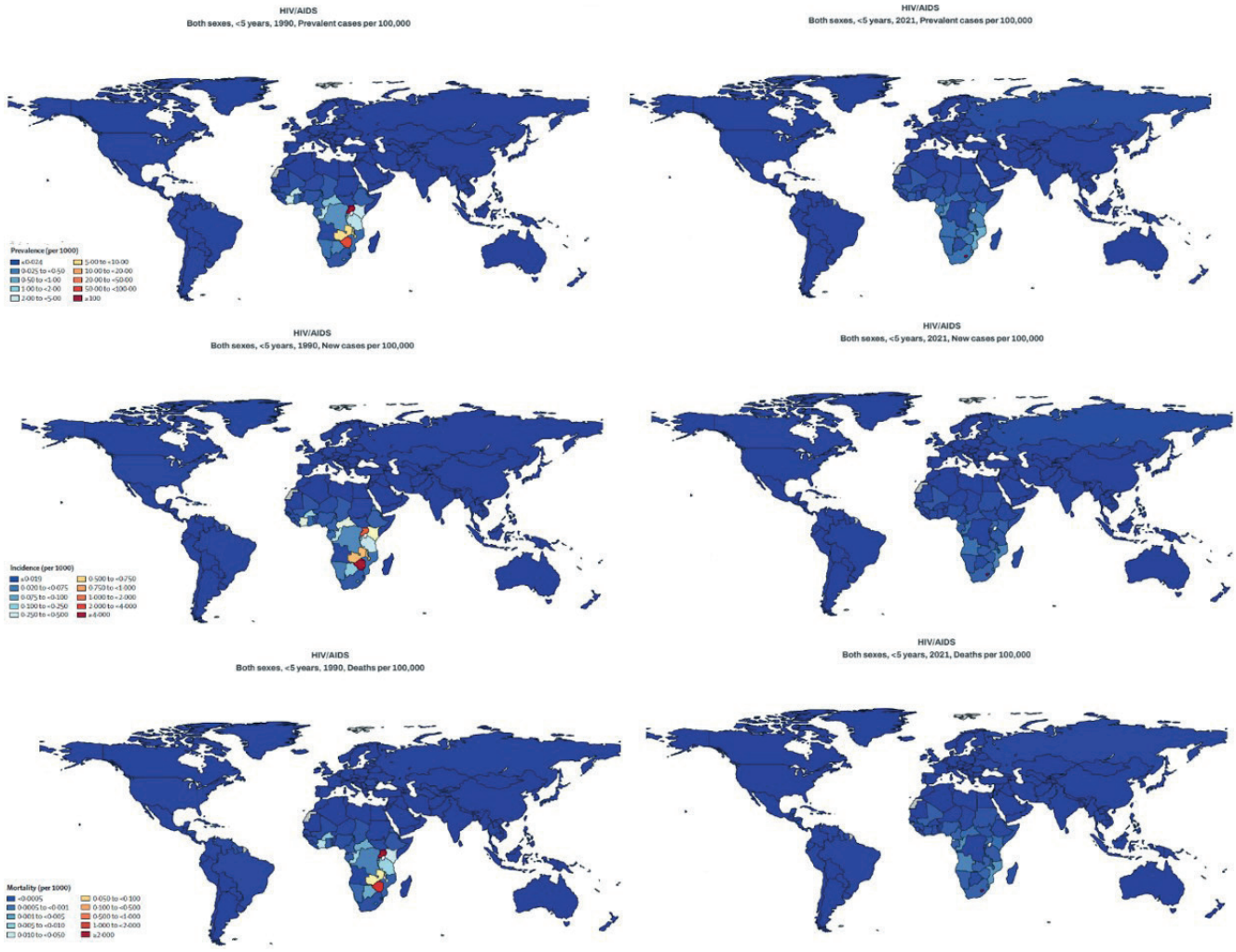

Figure 2. Comparing deaths due to HIV per 1000, incidence cases of HIV per 1000, and prevalent cases of HIV per 1000 among children aged under 5 years

remains the most affected region. The improvements seen over time are likely due to the expansion of HIV treatment, prevention of mother-to-child transmission, and public health initiatives aimed at reducing HIV-related mortality among young children.

Sex difference in the under-5-year age group

The data presented in Figure 3 highlight notable sex-based disparities in HIV-related mortality, incidence, and prevalence among children under 5 years of age across global and regional levels, particularly in Central Asia. Overall, HIV-related deaths among young boys have consistently been higher than in girls, both globally and in Central Asia. In terms of prevalence in 2021, the highest burden is observed in Kyrgyzstan, Tajikistan, and Uzbekistan for both males and females. These countries exhibit significantly higher prevalence rates compared to other nations in the dataset. The broader regional estimates indicate that Sub-Saharan Africa has the highest prevalence, followed by lower-middle-income countries, while high-income countries have the lowest rates. The incidence of new cases of HIV per 100,000 in 2021 displays a similar pattern. Countries such as Kyrgyzstan, Tajikistan, and Uzbekistan report the highest rates for both males and females. In the regional estimates, Sub-Saharan Africa again records the highest incidence rates, with lower-middle-income countries following closely behind. Regarding mortality, the death rates per 100,000 in 2021 suggest that Kyrgyzstan and Tajikistan have the highest mortality burden among the selected countries.

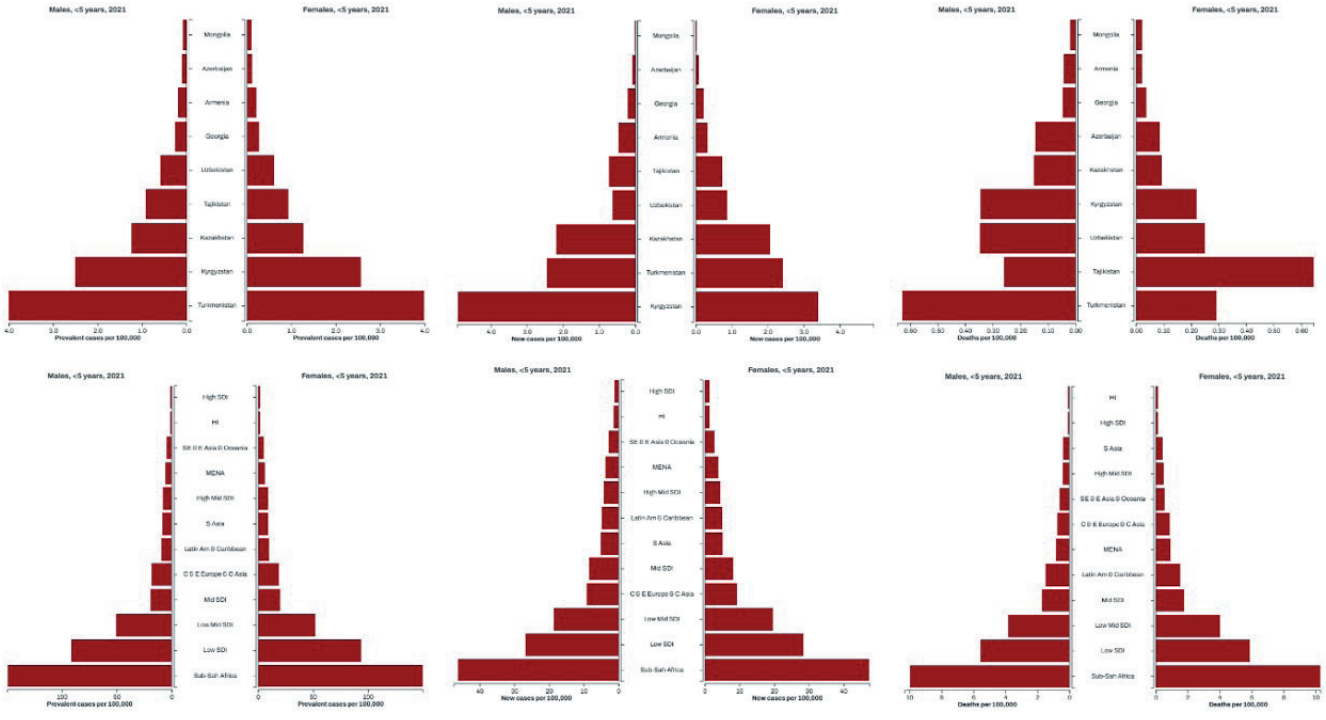

Figure 3. Subgroup estimates about deaths due to HIV per 1000, incidence cases of HIV per 1000, and prevalent cases of HIV per 1000 in children aged under 5 years in different sex groups

HIV total health spending

Figure 4 illustrates the trends in HIV total health spending in Central Asian countries from 2000 to 2017, expressed in 2022 US dollars. The data indicate that HIV healthcare expenditures have risen across the board, demonstrating a heightened commitment to combating the epidemic. Nevertheless, spending levels have experienced notable variations for certain countries. Kazakhstan consistently had the highest spending among the countries shown. The spending saw steady growth, with sharp increases around 2004–2006 and another significant rise after 2012. By 2017, Kazakhstan's spending had exceeded $40 million, making it the dominant country in terms of financial commitment to HIV/AIDS healthcare. Mid-tier spending countries such as Georgia, Kyrgyzstan, and Uzbekistan have relatively higher spending than others, although their trends are more volatile. Georgia experienced notable peaks around 2012 and 2016, while Kyrgyzstan maintained a moderate level of spending despite some fluctuations. In contrast, lower spending countries, including Armenia, Azerbaijan, Mongolia, Tajikistan, and Turkmenistan, have consistently allocated less to HIV healthcare. Their spending remained below $10 million for most of the period. Among them, Turkmenistan and Mongolia have the lowest and most stable spending trends, with only slight increases over time.

Figure 5 presents the total health spending per person in Central Asian countries for the year 2017. It shows significant variation in spending levels, with some countries allocating considerably more resources per capita than others. Kazakhstan had the highest per-person spending on HIV, reaching $2.11. Kyrgyzstan followed with a spending of $2.10 per person, which is relatively close to Kazakhstan's level. Tajikistan's per-person spending on HIV healthcare was slightly lower at $1.30, while Mongolia and Armenia allocated moderate resources, with per capita expenditures of $1.84 and $1.67, respectively. At the lower end of the spectrum, Azerbaijan and Turkmenistan had even lower spending levels, with Azerbaijan at $1.48 per person and Turkmenistan at $0.82 per person. Notably, Uzbekistan had the lowest per capita spending on HIV among all the Central Asian countries represented, at just $0.70.

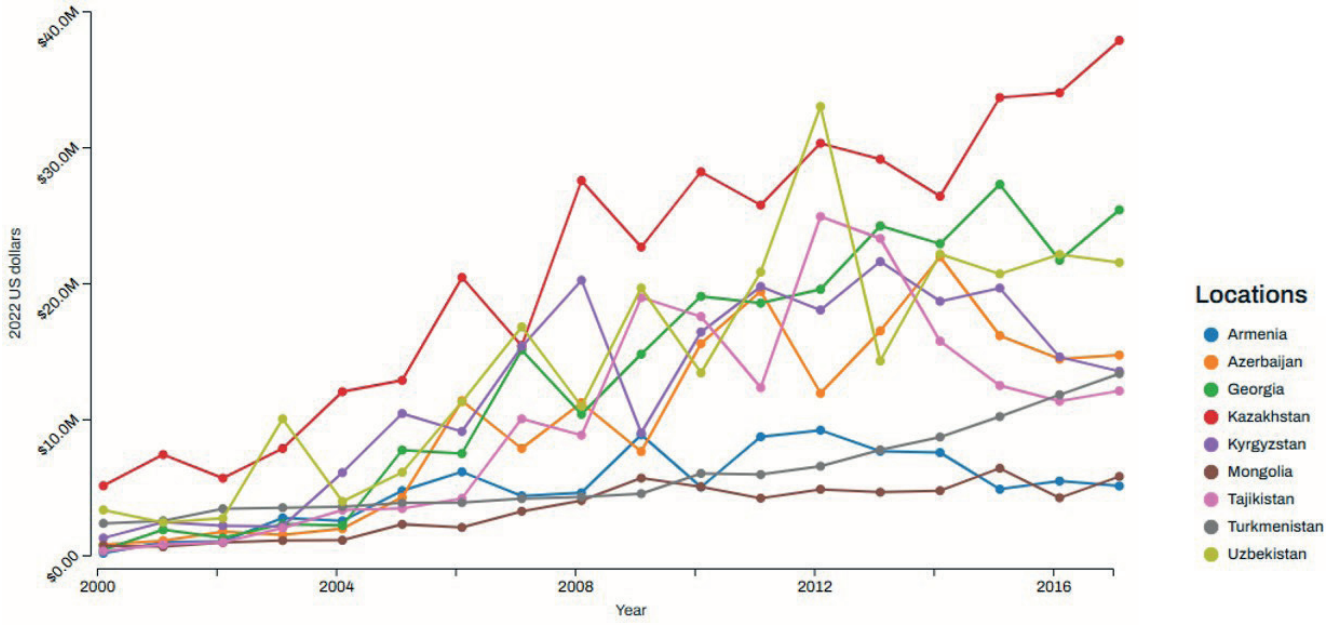

Figure 4. HIV total health spending in Central Asian countries from 2000 to 2017

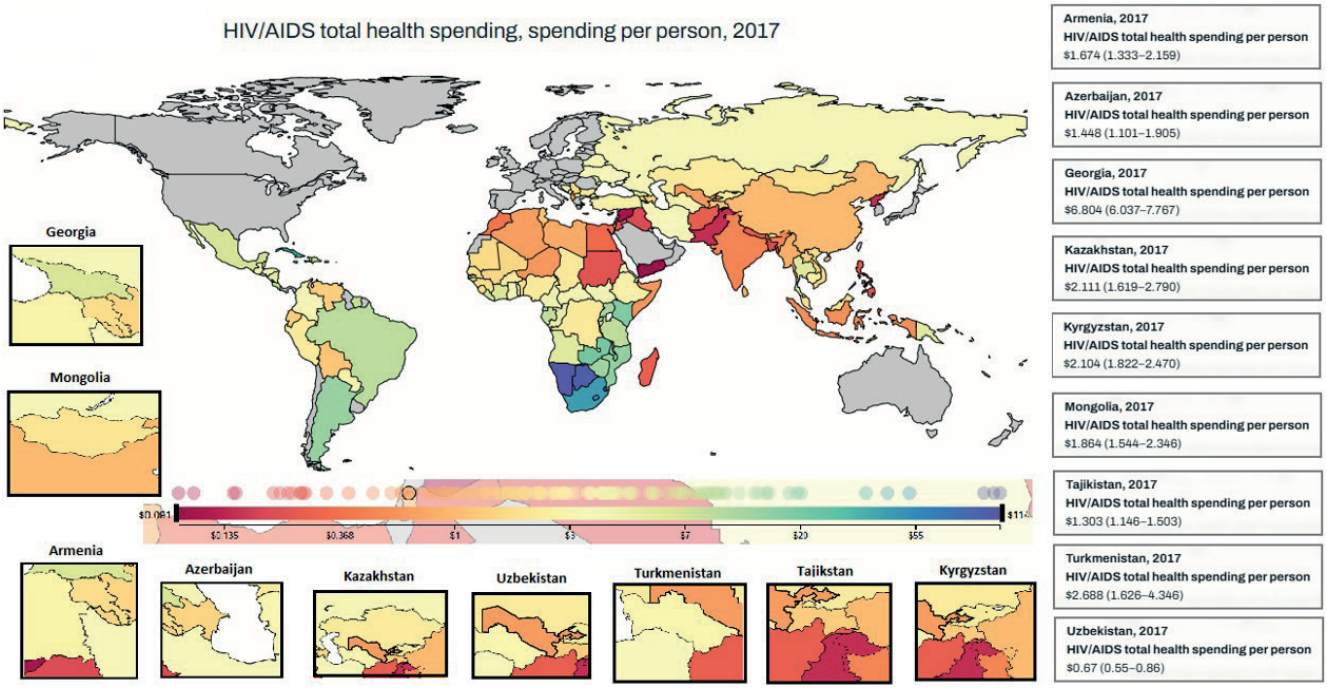

Figure 5. HIV-related total health spending per person in 2017 in all Central Asian countries

DISCUSSION

The findings of this study highlight the alarming increase in HIV-related prevalence, incidence, and mortality among children under five years of age in Central Asian countries. The global burden of HIV-related deaths and cases has seen a significant decline due to advancements in antiretroviral therapy, prevention strategies, and improved healthcare access.[15] Recent studies indicate gaps in data on HIV under-5 prevalence, incidence, and mortality in the Central Asian region.[16] Our study revealed that in Central Asia, the situation remains a significant concern as mortality rates, prevalence, and new cases continue to rise, indicating gaps in prevention and treatment programs.

Central Asia faces one of the highest rates of IDU globally, mainly due to heroin trafficking from Afghanistan.[17,18] Efforts to curb transmission were further hindered by restrictive policies—Uzbekistan, for instance, banned methadone until 2019, delaying effective opioid substitution therapy (OST) and exacerbating HIV outbreaks among PWID.[19] According to UNAIDS (2023), only 50% of people living with HIV in Eastern Europe and Central Asia were receiving antiretroviral therapy (ART), far below global targets.[20] Additionally, labor migration and unprotected sex work contributed to secondary transmission, with condom use among key populations remaining critically low.[21,22]

In contrast to Central Asia's escalating HIV crisis, Georgia achieved a significant decline in new HIV cases through a robust and systematic public health response.[23,24] A critical turning point came in 2018, when Georgia decriminalized drug use, removing legal barriers and encouraging higher uptake of HIV testing and treatment.[24]

In children under five years old, the data reveal a stark contrast between global and regional trends. While global HIV-related mortality in this age group has declined significantly, Central Asia experienced a slight increase.[25] There are several reasons affecting this, such as delayed Diagnosis and Treatment Initiation, barriers to access to care, and stigma. Low rates of HIV testing in children, often due to fear of discrimination and stigma, result in late diagnoses.[26,27] Without early detection and prompt initiation of ART, HIV rapidly progresses in young children, leading to severe opportunistic infections and higher mortality rates. In the Eastern European and Central Asian (EECA) region, which includes Central Asia, only a fraction of children living with HIV are on treatment, lagging significantly behind adult coverage. Moreover, 50% of the ART access rate affects prevention, and the new case emergency rate is at 20%. This trend underscores the need for stronger regional healthcare policies, enhanced maternal screening programs, and improved perinatal care to mitigate mother-to-child transmission of HIV.

Gender disparities in HIV-related prevalence, incidence, and mortality were also evident in the study. Across Central Asia, males exhibited higher mortality and prevalence rates than females. This is different from the global trend; following UNAIDS, women account for 49% of HIV worldwide.[28]

The data indicate substantial global advancements in mitigating HIV-associated mortality and new infections. However, Central Asia, particularly Kazakhstan and Kyrgyzstan, represents a concerning region due to the escalating incidence and prevalence of cases. These findings underscore the need for targeted interventions, improved healthcare accessibility, and strengthened prevention strategies in this region. Another key finding was the significant variation in health expenditures dedicated to HIV across Central Asian countries. Kazakhstan emerged as the highest spender on HIV healthcare, with over $40 million allocated in 2017, whereas Uzbekistan had the lowest per capita expenditure, at just $0.70 per person. UNAIDS indicated $34/person target for HIV prevention, which is not met by any of the Central Asian countries.[29] 80% of Central Asian countries' health expenditures rely on international donors; however, this is changing due to the shift of some countries to the middle-income group, contributing to unstable HIV financing. These disparities highlight the varying levels of commitment and resource allocation for HIV prevention and treatment across the region, emphasizing the need for equitable healthcare investments.

Today, in developed and industrialized countries, with timely diagnosis and treatment of HIV-infected infants and children[29], clinical manifestations of HIV in children are rare. Almost all of them reach adolescence, youth, and adulthood without clinical symptoms due to immunodeficiency. Their main problems are the continued use of antiviral drugs, drug resistance, drug side effects, psychological distress, social problems, and sexual and marital issues.[30] However, in developing countries where HIV in pregnant mothers and their infants is not diagnosed (due to lack of screening), perinatal acquisition of HIV (without antiretroviral treatment) shows one of the following three clinical scenarios.[31,32]

The first scenario, untreated HIV-positive cases have a rapidly progressive course, become symptomatic in the first

months of life, and have a median half-life of 6-9 months. These infants are most likely to have been infected in utero and have a positive HIV-related Polymerase chain reaction (PCR) within the first 48 hours of birth. Almost all children with a rapidly progressive course die before the age of 5 years.[33] The second scenario, which is predominantly HIV-positive (untreated) infants, has a gradually progressive course and becomes symptomatic in the first or second year of life. These children appear to have acquired HIV perinatally or postnatally through breastfeeding. Most of these children are PCR-positive in the first month of life and survive to the age of 5 years.[34] The third scenario includes patients with perinatal HIV whose disease (without treatment) has a very slow course and is clinically asymptomatic until after the age of 10 years, and has an increased CD4 count.[35,36]

Until recently, it was thought that few children with perinatally acquired (untreated) HIV survived the age of 5 years, but recent studies have shown that less than 18% of these children survive to the age of 15 years without treatment.[37] Children infected after birth and through breastfeeding appear to have a greater predisposition to a slow course of HIV than those who acquire the virus in utero or at birth.[38] Contrary to expectations, the percentage of HIV-positive children with a slow course is higher in Africa than in developed countries, where 1.3% of children with perinatal acquired HIV have a slow course and, without treatment, their average life expectancy is 16 years.[39] This difference seems to be because in developed countries, HIV transmission through breast milk is virtually non-existent, and all HIV-positive children are infected during delivery or before birth. In contrast, in less developed countries, up to half of HIV-positive children are infected through breast milk.[40] In a cohort study from Latin America on HIV acquired adolescents, approximately one-third of them were first diagnosed with HIV after the age of 10.[41,42]

Child mortality (under 5 years) is a phenomenon influenced by several factors and conditions, and the severity and weakness of these factors and conditions determine the occurrence and prevalence of mortality, as well as its control. Another important point that should be mentioned is that infant and child mortality is affected by a set of socioeconomic, cultural, demographic, genetic, and medical-health variables.[43,44]

Study limitations

Despite the comprehensive nature of this study, several limitations must be acknowledged. Firstly, the study relies on mortality registration systems, which may have data inconsistencies, underreporting, or misclassification of deaths related to HIV. Stigma-driven underreporting could contribute to a 30-50% reduction in statistics. For instance, the United Nations International Children's Emergency Fund (UNICEF) reported that approximately 50% of HIV-exposed infants in Uzbekistan receive PCR testing.[45] Secondly, the availability and accuracy of data for Central Asian countries vary, which may impact the reliability of country-specific estimates. Data consistency varies according to country settings. For instance, Kazakhstan and Kyrgyzstan publish annual HIV surveillance reports, mother-to-child transmission rates, and ART coverage data. In contrast, Tajikistan and Uzbekistan publish aggregated data, while Turkmenistan's data rely on WHO and UNAIDS estimates. Thirdly, the study does not account for the impact of more recent antiretroviral treatment programs or emerging healthcare policies that could influence HIV trends beyond 2019. Lastly, socioeconomic and cultural factors affecting HIV transmission and healthcare access were not deeply explored, warranting further qualitative studies.

Implications for clinical practice

The study findings have critical implications for clinical practice and public health policy. To reduce pediatric HIV-related mortality in Central Asia, a multifaceted approach is needed. Universal maternal screening and programs to prevent mother-to-child transmission (PMTCT) should be prioritized. Routine prenatal HIV testing must be integrated into maternal healthcare, following successful models from high-income countries. Ensuring that all HIV-positive pregnant women receive antiretroviral therapy (ART) is essential to minimizing perinatal transmission.

Expanding ART access and strengthening neonatal care services are critical components in improving pediatric HIV outcomes. Early ART initiation for HIV-exposed infants can significantly reduce mortality, while enhancing neonatal intensive care units (NICUs) can provide specialized support for HIV-infected newborns. Improving ART supply chains, training healthcare professionals, and addressing barriers to timely treatment initiation will also contribute to better health outcomes.

Addressing healthcare disparities across Central Asian countries is necessary to bridge the gap between high- and low-investment nations. Increased healthcare funding, particularly in low-resource settings, can ensure equitable access to prevention and treatment services. Community-based HIV programs should be expanded, especially in rural

and underserved regions, to enhance early detection and adherence to treatment.

Gender-sensitive interventions should be incorporated into HIV prevention and treatment strategies. Further research is needed to understand the underlying factors contributing to higher HIV-related mortality and prevalence among males. Developing targeted interventions that consider gender-specific vulnerabilities will help improve overall health outcomes for children under five.

Policy and funding reforms must be prioritized to strengthen national responses to pediatric acquired HIV. Governments should increase financial commitments to HIV programs and seek international aid to support prevention and treatment efforts. Strengthening collaboration with global health organizations and implementing evidence-based policies will help reduce pediatric HIV-related mortality in Central Asia and improve healthcare accessibility for affected children.

CONCLUSION

This study highlights the escalating HIV burden in Central Asia, particularly among children under five years old. While global trends show a decline in HIV-related mortality and incidence, Central Asian countries continue to struggle with rising cases and limited healthcare resources. Increasing investments in maternal screening, antiretroviral therapy, and neonatal healthcare facilities are essential to curb pediatric HIV-related mortality. Increasing the equipment and facilities of neonatal intensive care units can play an effective role in reducing child mortality. Future policies should prioritize equitable healthcare access, improve data accuracy, and address gender disparities in HIV outcomes. By implementing comprehensive prevention and treatment strategies, the region can make significant progress in reducing HIV-related mortality and improving the quality of life for affected children. Comprehensive strategies for the prevention of mother-to-child transmission (PMTCT) of HIV, diagnosis of HIV in pregnant women and perinatal acquired HIV, initiation of timely and appropriate antiretroviral therapy, as well as prevention of opportunistic infection, can help the region make significant progress in reducing HIV-related mortality and improving the quality of life of affected children.

Ethical approval

This study has been approved by the Osh State University (number OSHSU-021-5564). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: FR and KKG: ; data collection: FR, RK, and KR; analysis and interpretation of results: FR and KKG; draft manuscript preparation: FR, KR and KKG. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Obesity and self-perception in adolescents: investigating the psychological burden beyond metabolic risks

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ABSTRACT

Objective: Adolescent obesity is a significant global health issue impacting both physical and psychological health, especially body image perception. This study investigates the correlation between obesity and body image perception in adolescents with a Body Mass Index (BMI) over the 95th percentile, emphasizing gender disparities and psychosocial consequences.

Method: A cross-sectional study was conducted in pediatric clinics, which included 180 obese adolescents (95 females and 85 males). Anthropometric measurements, including weight, height, waist circumference, and neck circumference, were recorded. The Child Body Image Scale (CBIS) and the Child Body Satisfaction Scale (CBSS) are two standardized instruments that have been employed to evaluate body image. SPSS version 25.0 was employed to conduct statistical analyses.

Results: Females experienced significantly more body dissatisfaction than their male counterparts ($p < 0.05$). Girls perceived themselves as overweight and aspired to a slimmer physique, resulting in a substantial discrepancy between their perceived and ideal body images. Males exhibited a comparatively higher level of physical satisfaction. A significant negative correlation exists between age and body satisfaction ($r = -0.40$, $p < 0.01$); dissatisfaction is more prevalent among females as they age.

Discussion: These results underscore the necessity for prompt psychological therapies to address body dissatisfaction in obese teenagers. Negative body image is associated with depression, anxiety, and eating disorders. Gender disparities indicate the necessity for customized therapies, particularly for girls who are more susceptible to adverse self-image.

Conclusion: This study highlights the strong relationship between childhood obesity and negative body image. The findings show that children with obesity are more likely to feel dissatisfied with their body appearance, which may negatively affect their emotional well-being and self-esteem. The use of validated measurement tools strengthens the reliability of the results. Early identification of body image concerns can improve both mental and physical health outcomes in this vulnerable population.

Keywords: adolescent obesity, self-perception, psychological well-being, body image

INTRODUCTION

Adolescent obesity is a burgeoning global health issue that impacts not only metabolic and physiological health but also psychological well-being. Obesity is defined by the World Health Organization (WHO) as an excessive accumulation of body fat that creates health risks. In individuals under the age of 18, the 95th percentile of Body Mass Index (BMI) for age and sex is a critical threshold for obesity classification. Although the metabolic consequences of obesity, including insulin resistance, dyslipidemia, and hypertension, have been extensively investigated, its

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influence on psychological and psychosocial dimensions, particularly body image perception, is less frequently addressed in clinical practice.[1,2]

Adolescent obesity is correlated with body image dissatisfaction (BID), affecting social interactions, mental health outcomes, and self-esteem. Research has shown that body dissatisfaction is a common occurrence in childhood and tends to increase during adolescence, particularly in individuals with elevated BMI percentiles.[3,4] Obese adolescents are more prone to misperceiving their body size, leading to maladaptive behaviors such as emotional eating, unhealthy dieting, and insufficient physical activity.[5,6]

The sociocultural emphasis on slimness, amplified by media and peer influences, intensifies negative body image perceptions in adolescents. Research indicates that negative body image significantly precedes psychological distress, including anxiety, depression, and eating disorders, underscoring the need for early intervention and support systems.[7,8] Gender disparities are significant; while both sexes are susceptible to its adverse effects, adolescent females are more prone than males to experience body dissatisfaction.[9,10]

This study was conducted to examine body image in adolescents aged 18 years and younger with obesity (BMI ≥ 95th percentile), with a particular focus on gender differences and the psychosocial effects of excess weight. Childhood obesity is not merely a physical health issue but is also closely associated with psychological distress, reduced self-esteem, and body dissatisfaction. Understanding how adolescents perceive their bodies can provide important insights into the emotional burden of obesity and highlight the necessity of comprehensive intervention strategies that address both the physical and psychological aspects of care.

MATERIAL-METHOD

Study design and participants

This cross-sectional study was conducted between April 2025 and May 2025 at Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye. The study population consisted of adolescents aged 9–18 years who applied to the pediatric outpatient clinic during this period. Participants with a BMI at or above the 95th percentile for age and sex, according to national reference standards, were included in the obesity group.

Inclusion criteria

- Age between 8 and 17 years
- BMI ≥ 95th percentile for age and sex
- Voluntary participation with parental/guardian consent

Exclusion criteria

- Diagnosed psychiatric disorders
- Use of medications affecting weight or appetite
- History of bariatric surgery or weight management intervention within the last 6 months
- Incomplete questionnaire data or missing anthropometric records

Data collection and measurement

Anthropometric measurements were taken for all participants who agreed to participate in the study. Height was measured using a Harpenden stadiometer and recorded to the nearest 0.1 cm. Weight was recorded using a calibrated digital scale and again rounded to the nearest 0.1 kg. BMI was calculated by dividing weight in kilograms by height in meters squared (kg/m²). BMI percentiles were determined according to national reference standards specific to age and gender, and participants were classified.[11]

All participants completed two validated self-report questionnaires: the CBIS (Children's Body Image Scale) and the CBSS (Children's Body Satisfaction Scale), which were used to assess body image perception and satisfaction, respectively. Using the Child Body Image Scale (CBIS) developed by Truby and Paxton (2002), which comprises figure drawings that are gender- and age-specific for children between the ages of seven and twelve, body image perception was evaluated.[12] The CBIS has been reported to have an internal consistency of Cronbach's alpha = 0.84, which suggests that it is highly reliable. The scale assists in the identification of the discrepancy between the ideal and perceived body shape. The Child Body Satisfaction Scale (CBSS), which was developed by Keven-Akliman and Özabacı was employed to measure body satisfaction by evaluating satisfaction with specific body areas. The scale has exhibited exceptional psychometric properties, as evidenced by a Cronbach's alpha of 0.87.[12]

The tools were administered in a quiet clinical environment under the supervision of the participants' parents to ensure comprehension and comfort. The reliability and validity of

the scales have been previously established in pediatric populations.

The study was started after ethics committee approval was obtained (Approval Number: 2025/010.99/14/20). After informed consent was obtained from the participants and their families, the questionnaire form was given to the participants, and they were asked to complete it.

Statistical analysis

All statistical analyses were performed using SPSS Statistics version 25.0. The normality of data distribution was determined by evaluating skewness and kurtosis values, with values between ±2 indicating a normal distribution. For variables showing a parametric (normal) distribution, the Student t-test was applied, while the Mann-Whitney U test was used for non-parametric (non-normal) data. Pearson correlation analysis was performed to evaluate the relationships between continuous variables. A statistical significance threshold of 0.05 was accepted as the type I error level.[13]

RESULTS

A total of 95 girls and 85 boys participated in the study. The mean values of age, height, weight, and height circumference of the participants are shown in Table 1.

The study included 180 children, with 95 girls (52.8%) and 85 boys (47.2%). The mean age of participants was 12.19 ± 3.11 years. Boys had a significantly higher mean weight (84.80 ± 33.05 kg) than girls (70.30 ± 17.39 kg) ($p < 0.05$). Similarly, boys had a greater height (160.80 ± 18.84 cm) compared to girls (153.53 ± 12.00 cm) ($p < 0.05$). BMI was also significantly different between the two groups, with boys exhibiting a higher mean BMI (31.45 ± 7.48 kg/m²) compared to girls (29.42 ± 4.60 kg/m²) ($p < 0.05$).

Waist circumference and neck circumference measurements followed similar trends, with boys showing significantly higher values than girls ($p < 0.05$). However, no statistically significant difference was found in BMI percentiles between boys (98.98 ± 1.20) and girls (97.40 ± 4.79) ($p > 0.05$), indicating that both groups were classified within the obese category.

There was no significant difference between the ages and percentiles of anthropometric measurements of boys and girls ($p>0.05$). There was a significant difference between weight (kg), height (cm), height (p), waist circumference (cm), body mass index ($^{kg/m2}$), neck circumference (cm) values ($p<0.05$); weight (kg), height (cm), height (p), waist circumference (cm), body mass index ($^{kg/m2}$), neck circumference (cm) values of boys were found to be higher than girls.

100.0% of girls (average age: 11.98 years) perceived themselves as heavier than they actually were. In terms of the body image they think most resembles themselves, 48.4% perceived themselves as thinner than they actually are, while 51.6% assessed themselves accurately. When it comes to ideal body image preferences, all girls preferred a slimmer body type than their current appearance (Table 2).

Among boys, 4.7% (average age: 8.00 years) perceived their body size accurately, while 95.3% (average age: 12.64

Table 1. Age and Anthropometric measurements

	Girls, N=95				Boys, N=85				T/Z	p
	Ort.	Std Deviation	Min	Max	Ort.	Std Deviation	Min	Max		
Age	11.98	3.03	8.00	17.00	12.42	3.19	8.00	17.00	T: -0.958	0.34
Weight (kg)	70.30	17.39	38.00	108.50	84.80	33.05	30.80	147.00	T: -3.738	0.00*
Weight(p)	98.79	2.04	93.00	99.98	99.11	1.31	95.35	99.98	Z: -0.257	0.80
Height (cm)	153.53	12.00	129.00	176.00	160.80	18.84	123.00	187.00	T: -3.121	0.00*
Height (p)	66.98	33.11	7.21	99.96	77.92	20.28	38.21	99.93	T: -2.637	0.01*
Waist Circumference (cm)	55.83	2.04	51.00	61.00	57.19	3.09	50.00	62.00	T: -3.540	0.00*
Waist Circumference (p)	76.65	26.88	20.05	99.98	80.69	28.02	0.78	99.98	T: -0.986	0.33
Body Mass Index (cm)	29.42	4.60	22.84	40.84	31.45	7.48	20.03	48.10	T: -2.215	0.03*
Body Mass Index (p)	97.40	4.79	72.57	99.98	98.98	1.20	94.41	99.98	Z: -1.138	0.26
Neck Circumference	32.49	3.08	27.50	41.00	35.55	5.09	27.00	44.00	T: -4.934	0.00*

Z: Mann-Whitney U Test, T: Independent Sample T Test, *p<0.05: Significant at the level

years) perceived themselves as heavier than they actually were. When asked which body image they most closely resembled, 34.1% perceived themselves as thinner than they actually were, 55.3% made the correct choice, and 10.6% perceived themselves as overweight. Regarding the ideal body image they aspired to, 100.0% selected an image that was thinner than their actual body measurements (Figure 1).

Table 2. Evaluation of body image and reality perception according to gender and age

		n	%	Age			
				Mean.	Sd	min	max
Girls N=95	Body Image Perception						
	Perceiving oneself as smaller than one's size	0	0,0	0,00	0,00	-	-
	Right choice	0	0,0	0,00	0,00	-	-
	Perceiving oneself to be more overweight than one is	95	100,0	11,98	3,03	8,00	17,00
	Image Perception Most Similar to Self						
	Perceiving oneself as smaller than one's size	46	48,4	11,46	2,51	8,00	16,00
	Right choice	49	51,6	12,47	3,40	8,00	17,00
	Perceiving oneself to be more overweight than one is	0	0,0	0,00	0,00	-	-
	Perception of the Image He Wants to Be Like						
	Perceiving oneself as smaller than one's size	95	100,0	11,98	3,03	8,00	17,00
	Right choice	0	0,0	0,00	0,00	-	-
	Perceiving oneself to be more overweight than one is	0	0,0	0,00	0,00	-	-
Boys N=85	Body Image Perception						
	Perceiving oneself as smaller than one's size	0	0,0	0,00	0,00	-	-
	Right choice	4	4,7	8,00	0,00	8,00	8,00
	Perceiving oneself to be more overweight than one is	81	95,3	12,64	3,11	8,00	17,00
	Image Perception Most Similar to Self						
	Perceiving oneself as smaller than one's size	29	34,1	11,17	3,13	8,00	17,00
	Right choice	47	55,3	14,04	2,27	8,00	17,00
	Perceiving oneself to be more overweight than one is	9	10,6	8,00	0,00	8,00	8,00
	Perception of the Image He Wants to Be Like						
	Perceiving oneself as smaller than one's size	85	100,0	12,42	3,19	8,00	17,00
	Right choice	0	0,0	0,00	0,00	-	-
	Perceiving oneself to be more overweight than one is	0	0,0	0,00	0,00	-	-
Total N=180	Body Image Perception						
	Perceiving oneself as smaller than one's size	0	0,0	0,00	0,00	-	-
	Right choice	4	2,2	8,00	0,00	8,00	8,00
	Perceiving oneself to be more overweight than one is	176	97,8	12,28	3,08	8,00	17,00
	Image Perception Most Similar to Self						
	Perceiving oneself as smaller than one's size	75	41,7	11,35	2,75	8,00	17,00
	Right choice	96	53,3	13,24	3,00	8,00	17,00
	Perceiving oneself to be more overweight than one is	9	5,0	8,00	0,00	8,00	8,00
	Perception of the Image He Wants to Be Like						
	Perceiving oneself as smaller than one's size	180	100,0	12,19	3,11	8,00	17,00
	Right choice	0	0,0	0,00	0,00	-	-
	Perceiving oneself to be more overweight than one is	0	0,0	0,00	0,00	-	-

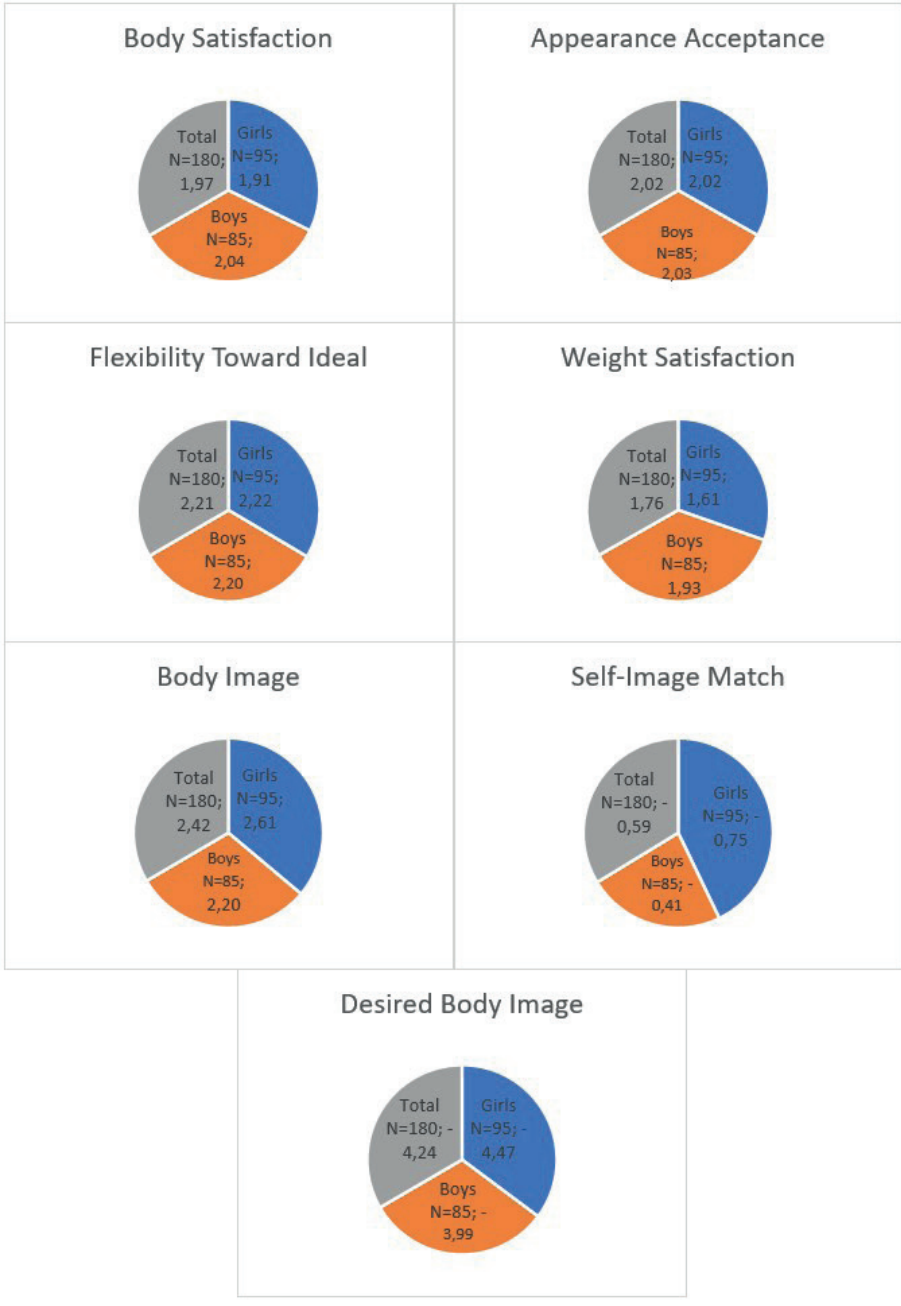

Figure 1. Physical appearance, body perception, and weight satisfaction scale

DISCUSION

This study examined how body image perception changes with age in obese children and how body image dissatisfaction increases, especially in girls. The findings of our study show that girls' satisfaction with their bodies decreases as they get older, and their body image perceptions are negatively affected. This is consistent with many studies in the literature.[14,15]

The findings of our study are consistent with international research showing that body image perception is a widespread problem among adolescents. A study examining adolescents from six different countries found that body dissatisfaction is widespread and significantly associated with sociodemographic factors and social media use.[16] These international findings emphasize the universality of body image concerns among adolescents and highlight the need for culturally adapted interventions. In this context,

our study provides valuable data on Turkish adolescents, a population that is underrepresented in global research. By providing insights into Turkish adolescents' perceptions of body image and levels of dissatisfaction, our study contributes to understanding how cultural and regional factors influence adolescents' body image.

It is known that, especially during adolescence, body image concerns increase, and this has serious effects on psychological health.[17] The increase in body dissatisfaction in girls with age has been associated with problems such as eating disorders, depression, and low self-esteem.[18] In this context, in our study, it was determined that 100% of the girls perceived themselves as overweight, and the image they wanted to resemble represented a thinner body structure. The discrepancy between the perceived body image and the ideal body image was greater in girls, suggesting a higher tendency toward negative body perception. In contrast, boys were more likely to accept their body image as it is, despite their high BMI values. These differences may reflect sociocultural influences on body ideals and should be considered when designing gender-sensitive interventions for obesity in adolescents.

Disturbances in body image perception are an important risk factor, especially for eating disorders. Studies show that individuals with body image dissatisfaction are more likely to develop eating disorders.[19] In addition, negative body image perception is strongly associated with depression and may increase suicidal thoughts.[20] In our study, a negative correlation was found between body image perception and satisfaction level, and it was shown that body satisfaction decreased with increasing age.

Comparisons between genders showed that girls had lower body satisfaction scores compared to boys. This is a finding frequently emphasized in the literature. The fact that girls are more affected by media, peer pressure, and social perceptions of beauty may cause deterioration in body image perception to become more pronounced.[21] In boys, although there is some decrease in body image satisfaction with age, this is less pronounced compared to girls. Age was negatively correlated with body satisfaction in both genders ($r = -0.40$, $p < 0.01$), suggesting that as age increased, body dissatisfaction became more prominent. This effect was stronger among girls, indicating that adolescent girls with obesity experienced higher psychological distress related to their body image compared to boys.

Four Turkish studies utilize survey data to investigate the relationship between adolescent obesity and body image perception. Ozmen et al. indicate that adolescents' self-reported overweight status correlates more significantly with body dissatisfaction, diminished self-esteem, and depression than with objective BMI metrics, particularly among female students who exhibit heightened dissatisfaction.[22] Selen and Koç point out that overweight and obese students exhibit decreased body image perception scores, and that higher internet addiction is associated with a decrease in body aesthetics.[23] Yayan and Çelebioğlu report that an obesogenic environment correlates with elevated BMI and decreased body image, whereas social support is associated with increased body satisfaction.[24] Doğan et al. observe a significant correlation between body image and sociocultural factors, especially media exposure.[25]

The results of this study should be interpreted with consideration of several limitations. The study relied solely on self-reported survey data, lacking an impartial evaluation of participants' psychological well-being, cognitive capacity, or overall health status. No clinical assessment or psychiatric evaluation was conducted, leaving it impossible to elucidate potential underlying mental health issues impacting body perception.

Furthermore, the study lacked a control group or a comparison with a larger population, thereby limiting the generalizability of the findings. The evaluation is cross-sectional, documenting an individual moment rather than assessing changes in self-perception over time. Longitudinal studies may enhance understanding of the interactions between BMI and changes in body image.

Another restriction is that just BMI and body image were compared without considering possible sociocultural influences, peer pressure, or family-related elements that might affect teenagers' self-image. Future research could combine qualitative techniques, including focus groups or interviews, to obtain a more thorough understanding of the psychological elements of body image perspective.

Moreover, the study focused on a specific age group, and findings may not be applicable to other developmental stages. Expanding the research to different age ranges and socio-economic backgrounds could provide a more comprehensive view of the topic.

CONCLUSION

This study highlights the important relationship between obesity and body image and body satisfaction in school-

aged children. Our findings indicate that children with obesity are more likely to experience dissatisfaction with their body image, which may affect their psychological well-being and self-esteem. Conducted using validated tools such as the Children's Body Image Scale (CBIS) and the Children's Body Satisfaction Scale (CBSS), this study underscores the importance of incorporating psychosocial dimensions into obesity assessments. Early diagnosis of body image disorders in overweight children can facilitate timely psychological and nutritional interventions. Future long-term studies are needed to investigate the long-term effects of body dissatisfaction on health behaviors and mental health outcomes in this vulnerable population group.

Ethical approval

This study has been approved by the Kartal Dr. Lütfi Kırdar Ethics Committee (approval date 26.03.2025, number 2025/010.99/14/20). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: EÖE; Data collection: EÖE, BY ; Analysis and interpretation of results: EÖE, BY, YA; Draft manuscript preparation: EÖE, BY, YA. 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

Does precocious puberty and its treatment cause the emotional and behavioral problems in children?

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ABSTRACT

Background: Central precocious puberty (CPP) results from the premature activation of the hypothalamic-pituitary-gonadal axis. Recent studies have indicated that children with CPP are more likely to experience social and psychiatric difficulties compared to their age- and gender-matched peers. The objective of our study was to assess the psychiatric symptoms and quality of life in children newly diagnosed with CPP and those receiving treatment for over a year, and to compare these outcomes with healthy, age- and gender-matched children.

Methods: This research was designed as a cross-sectional study, enrolling 50 CPP cases (25 at diagnosis and 25 on follow-up) and 25 healthy controls. The participants and their families completed a sociodemographic form, the Pediatric Quality of Life Inventory, the Revised Child Anxiety and Depression Scale-Child Version (RCADS-CV), the Strengths and Difficulties Questionnaire (SDQ), and the TURGAY DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S).

Results: No significant differences were found among the three groups regarding quality of life (both child and parent forms), anxiety and depression scores, or strengths and difficulties scores. Similarly, no significant differences were observed between the groups in terms of inattention, hyperactivity, oppositional defiant, and conduct disorder scores.

Conclusions: Central precocious puberty may bring about concerns regarding the potential psychosocial impact of early pubertal timing and the need for ongoing medical follow-up. In this study, however, children with CPP, both at diagnosis and during treatment, did not exhibit increased psychiatric symptoms or reduced quality of life compared to their typically developing peers. These findings are reassuring but underscore the importance of adopting a multidisciplinary approach to monitor and support the psychological well-being of children with CPP.

Keywords: precocious puberty, quality of life, inattention and hyperactivity

INTRODUCTION

The onset of puberty symptoms at an early age has been frequently observed in recent years.[1] The number of presentations with precocious puberty features and patients requiring treatment has increased in our country and all over the world.[2,3] Precocious puberty (PP) is defined as the onset of physical signs of puberty before the age of 8 years in girls and 9 years in boys, or the onset of menstruation before the age of 10 years.[4] Patients may present with early progression of secondary sexual characteristics, inappropriate body appearance, and psychological behavioural abnormalities.[5] Gonadotropin-Releasing Hormone (GnRH) analogs are used for the treatment of central precocious puberty (CPP) to preserve

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adult height potential and to alleviate psychological distress associated with early pubertal development.[6]

Adolescence and puberty are periods of major mental and psychological changes as well as biological changes.[7] While the structure of the body changes, region-specific changes in brain structure, brain function, and neurochemical transmission processes are also seen.[8] It is a challenge for adolescents trying to adapt to their changing body and brain to complete their identity development and maintain their social adaptive skills at a positive level during the process of individualization, in order to adapt to these changes.[9] While even a normal course of adolescence can cause difficulties for the adolescents and their families, it has been found that children who experience precocious puberty are more likely to have social and psychiatric problems than their peers of the same age and gender.[10]

Hormonal changes during puberty are known to increase the risk of developing emotional and behavioral problems.[9] In children who experience precocious puberty, the delay between physical and psychological maturity may also make them more vulnerable to psychopathologies.[11] Epidemiological studies have shown that early onset of puberty in girls is associated with earlier onset of sexuality, earlier age of pregnancy, and lower educational attainment, regardless of cognitive ability and socioeconomic status.[12] Previous studies of children with CPP have reported irritability, aggression, depressive symptoms, and anxiety-related symptoms.[13] In another study conducted in our country, while the depressive scores of the children were similar, a significant difference was found only in terms of anxiety disorder.[14] In children, the impact of precocious puberty on quality of life has also been reported. While some studies found low quality of life, others found no difference in quality of life between the CPP group and healthy controls.[1,14,15]

The aim of our study was to investigate psychiatric symptoms such as anxiety, depression, and irritability, and quality of life in children diagnosed with central precocious puberty and to compare these data with age- and sex-matched children without central precocious puberty.

METHODS

The research was designed as a cross-sectional study. Written informed consent was obtained from the children and their parents or guardians before the study. The study protocol was approved by the Ethics Committee of Tekirdağ Namık Kemal University, Faculty of Medicine (2022.119.06.09), in accordance with the Helsinki Declaration. Detailed information about the study was provided to the children and their parents who volunteered to participate.

Children diagnosed with CPP at the Pediatric Endocrinology Department of Tekirdag IFC City Hospital between December 2020 and June 2022 were included in the current study. A formal power analysis was not conducted prior to data collection. The sample size was determined based on the number of eligible patients and control subjects available during the study period.

The study group included 47 female and three male patients (n = 50) who were followed up for CPP at the Pediatric Endocrinology Department of Tekirdag IFC City Hospital. The diagnosis of CPP was based on a combination of signs and symptoms of CPP, such as the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys, hormonal evidence of hypothalamic-pituitary-gonadal axis activation (random LH above 0.3 mIU/mL or GnRHa stimulation test with peak LH above 5 mIU/mL) and advanced bone age. The pubertal stage was assessed with the Tanner stage. Brain magnetic resonance imaging (MRI) was performed for all patients diagnosed with CPP to exclude any organic causes of precocious puberty. Patients with abnormalities on MRI, including organic brain lesions or other structural anomalies, were excluded from the study cohort. The clinical data of the children (physical examination and laboratory findings) were evaluated from the medical records. Scales were applied to the subjects. Children with CPP were divided into two groups as at diagnosis (Group PP1) and at follow-up and after more than one year of treatment (Group PP2). The entire Group PP2 was included in the study after the one-year treatment period, and no psychological assessments were conducted at baseline.

The control group consisted of age- and gender-matched healthy children without any clinical signs of pubertal development who were admitted to the pediatric outpatient clinics of Tekirdag IFC City Hospital, had no chronic diseases, and volunteered to participate in the study. A total of 25 children and their families agreed to take part in the study. The Control Group (CG) included 21 females and four males (n=25).

The exclusion criteria for both groups included the presence of intellectual disabilities, neurological disorders, psychotic disorders, and autism spectrum disorder, as these conditions could interfere with the ability to complete

the study procedures. Exclusion criteria included chronic systemic diseases (e.g., diabetes mellitus, congenital heart disease), neurological disorders (e.g., epilepsy, cerebral palsy), and genetic syndromes (e.g., Turner syndrome, Noonan syndrome). Additionally, individuals with any chronic and/or severe medical conditions or precocious puberty with peripheral or organic causes were excluded to avoid potential confounding factors.

Clinical measures

The sociodemographic data of the children were collected using a sociodemographic form developed by the researchers. In the clinical information form, the following data were evaluated: auxological findings, physical examination, Tanner stage, and the laboratory and radiological findings of the participants.

The Strengths and Difficulties Questionnaire for Children (SDQ-C) and Parents (SDQ-P) were utilized to evaluate the behavioral traits of the participants.[16,17] The Turkish validity and reliability study was conducted by Guvenir et al.[18] This questionnaire is a brief tool for behavioral screening designed to assess mental well-being. The SDQ measures 25 traits, which are categorized into five scales: emotional difficulties, conduct problems, hyperactivity and inattention, problems with peer relationships, and prosocial behaviors.

Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S) was developed by Turgay[19]; and then adapted and translated into Turkish by Ercan et al.[20] The T-DSM-IV-S (parent and teacher forms) is based on the DSM-IV criteria and assesses hyperactivity-impulsivity (nine items), inattention (nine items), opposition–defiance disorder (eight items), and conduct disorder (15 items). The severity of each symptom is evaluated on a four-point Likert-type scale (0: not at all, 1: just a little, 2: quite a bit, and 3: very much). Subscale scores on the T-DSM-IV-S are calculated by summing the item scores for each subscale.

The Revised Child Anxiety and Depression Scale-Child Version (RCADS-CV) is a self-report questionnaire that assesses the clinical symptoms of anxiety and depression based on DSM-IV criteria. The RCADS-CV has been shown to be a reliable and valid instrument in different cultures and languages, as well as in Turkish.[21] It consists of 47 items with six subscales corresponding to generalized anxiety disorder (GAD), major depressive disorder (MDD), separation anxiety disorder (SAD), social phobia (SP), panic disorder (PD), and obsessive-compulsive disorder (OCD). It is a four-point Likert-type scale (0: never, 1: sometimes, 2: often, and 3: always). The general anxiety score is calculated by summing the scores from the first five sub-scales, while the internalization score is calculated by summing the scores from all sub-scales. The scale has no cut-off score. In our study, RCADS-CV-children (RCADS-CV-C) and RCADS-CV-parent (RCADS-C-P) forms were used.

The Pediatric Quality of Life Inventory (PedsQL), developed by Varni et al.[22] in 1999, is designed to assess the overall quality of life in children aged 2 to 18 years. The scale includes four subscales that evaluate physical, emotional, social, and school-related functioning. A validity and reliability study for the Turkish version of the inventory was carried out for the 2–18 age group. The PedsQL measures four functional domains, with four subcategories: 8 items related to physical functioning, five items related to emotional functioning, five items related to social functioning, and five items related to school functioning, totaling 23 items. Scoring is conducted in three areas: total physical health score, total psychosocial health score (assessing emotional, social, and school functioning), and the overall total score. A higher total score indicates a better quality of life. The Turkish validity and reliability study was conducted by Cakin Memik et al.[23] In our study, both the child (PedsQL-C) and parent forms (PedsQL-P) of the PedsQL were used.

Statistical analyses

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) was used for the analysis of the variables. First, the Kolmogorov–Smirnov test was used to check the normal distribution of the variables. When the assumption of normality was met, parametric statistical tests were used. When the assumption of normality was not met, non-parametric statistical tests were used. The student's t-test or Mann–Whitney U–test was used to assess differences between two groups according to the normal distribution of the measured parameters. Chi-square test was used to compare the categorical variables. Quantitative variables were expressed as mean (standard deviation), median (25^{th} percentile / 75^{th} percentile), while categorical variables were shown as number (n) and frequency (%). The variables were analyzed at a 95% confidence level, and a p-value less than 0.05 was considered significant.

RESULTS

The group PP1 (mean age: 7.55 ± 0.71 years), PP2 (mean age: 9.68 ± 0.66 years), and CG (mean age: 8.79 ± 1.02 years) were not similar in age (p:0), due to the difference between PP1 and PP2. All cases of the PP1 group (n:25), 88% of the PP2 group (n:22), and 84% of the CG (n:21) were female. The clinic characteristics of group PP1 and PP2 are summarized in Table 1. The pubertal stages were as follows: Tanner 2 in four patients, Tanner 3 in 13 patients, Tanner 4 in 20 patients, and Tanner 5 in 13 patients. The 12% (n:3) and 13.6% (n:3) of the children had early menarche in groups PP1 and PP2, respectively. The duration of GnRHa treatment in group PP2 ranged from 13 to 36 months. The mean duration of treatment was 14.42±5.65 months. All of the patients in group PP2 demonstrated either stabilization or regression of pubertal signs and achieved adequate hormonal suppression, following GnRH agonist therapy. Growth velocity remained appropriate for age, further supporting effective hormonal control.

The SDQ-C, SDQ-P, PedsQL-C, and PedsQL-P scores are shown in Table 2. The three groups had similar scores in the SDQ-behavior, SDQ-emotional, and total scores in the child and parent questionnaires (p:0.812, p:0.79, p:0.959, respectively in the child questionnaires and p:0.824, p:0.852, p:0.599, respectively in the parent questionnaires). No significant differences were found between the groups in terms of PedsQL-total scores in the child and parent forms (p:0.505, p:0.992; respectively).

The RCADS-CV-C and RCADS-CV-P scores of PP1, PP2, and CG are shown in Table 3. No significant difference was found between groups in terms of RCADS-CV scores. Internalizing and anxiety scores were similar between groups for children (p:0.987, p:0.929 respectively) and parents (p:0.942, p:0.824 respectively).

The ARI-C and ARI-P scores of the groups are given in Table 4. The ARI scores were found to be similar between the three groups in children and parent forms (p:0.581, 0.730, respectively).

Table 1. Sociodemographic and clinical features of the PP group

	PP1	PP2
Chronological age (years)	7.55 ± 0.71 (5.73 - 8.40)	9.68 ± 0.66 (7.7 – 10.68)
Chronological age at presentation (years)	7.55 ± 0.71 (5.73 - 8.40)	7.97 ± 0.60 (6.7 – 8.87)
Female/Male	25/0	22/3
Menarche at diagnosis	12% (n:3)	13.6% (n:3)
Weight (kg)	36.75 ± 10.23 (21.7 - 64)	36.42 ± 7.31 (24.7 – 49.7)
Weight SDS	1.4 ± 1.1 (-0.8 – 3.7)	1.31 ± 0.85 (-0.3 – 2.85)
Height (cm)	139.34 ± 7.98 (123-160)	136.82 ± 8.55 (116-156)
Height SDS	1.85 ± 1.11 (-0.3 – 4.4)	1.18 ± 1.15 (-0.95 – 3.5)
BMI	18.58 ± 3.32 (13.4 – 26.6)	19.27 ± 2.45 (15.36 – 25.32)
BMI SDS	0.75 ± 1.03 (-1.6 – 2.6)	1.06 ± 0.69 (-0.49 – 2.58)
Bone age	10.86 ± 1.18 (7.88- 12.5)	10.78 ± 1.51 (8 – 13.5)
Basal LH (mIU/mL)	2.61 ± 2.32 (0.1 - 8.3)	2.31 ± 1.9 (0.1-7.5)
Basal FSH (mIU/mL)	4.33 ± 1.70 (0.9 – 7.1)	4.76 ± 2.12 (1.3 – 9.9)
GnRH stimulated peak LH (mIU/mL)	10.55 ± 5.52 (6 – 18.1)	18.56 ± 21.92 (5.3 - 62)
Pubertal stage at presentation	T1: 0 T2: 2 T3: 3 T4: 11 T5: 9	T1: 0 T2: 2 T3: 10 T4: 9 T5: 4

Data were presented as mean±SD
T: Tanner stage, BMI: Body Mass Index, SDS: Standard Deviation Score
FSH: follicule-stimulating hormone (N; 1.1–14.5), LH: luteinizing hormone (N; 0.02–7.0)
GnRH stimulated peak LH (prepubertal; <5)

Table 2. SDQ-A, SDQ-P, and PedsQL-A, PedsQL-P Scores

	PP1 n:25	PP2 n:25	CG n:25	p value
SDQ-A emotional	2 (0.5-2.5)	1 (0-3)	1 (0-2)	0.790
SDQ-A behavior	1 (0-2)	1 (0-2)	1 (0.5-2)	0.812
SDQ-A ADHD	4 (2-5)	4 (2-5)	4 (3-5)	0.585
SDQ-A peer	2 (0-2.5)	2 (0-3)	1 (0-2.5)	0.710
SDQ-A prosocial	9 (7.5-10)	8 (6-10)	9 (8-10)	0.917
SDQ-A total	10 (4-11)	8 (5-11)	8 (5.5-10)	0.959
SDQ-P- emotional	1 (0-3.5)	2 (1-2)	1 (0-2.5)	0.852
SDQ-P behavioral	1 (0.5-2)	1 (0-2)	1 (0-1.5)	0.824
SDQ-P ADHD	3 (2-5)	4 (2-5)	3 (2-5)	0.804
SDQ-P peer	2 (1-3)	1 (1-4)	1 (0-2.5)	0.406
SDQ-P total	9 (5.5-11.5)	8 (6-12)	7 (4-10.5)	0.599
PedsQL-C psychical	84.375 (71.875-89.062)	78.125 (71.875-89.062)	81,25 (68.75-90.625)	0.928
PedsQL-C psychosocial	83.333 (75-92.5)	83.333 (77.5-93.333)	90 (83.33-95)	0.289
PedsQL-C total	83.437 (73.359-90.468)	82.968 (74.531-91.875)	87.812 (81.25-91.718)	0.505
PedsQL-P psychical	79.687 (61.718-91.406)	81.25 (71.875-90.625)	87.5 (64.843-100)	0.751
PedsQL-P psychosocial	84.166 (65.416-93.333)	85 (66.666-93.333)	82.5 (71.25-92.083)	0.987
PedsQL-P total	84.296 (63.710-91.445)	82.968 (67.812-91.406)	81.796 (69.804-90.976)	0.992

Data were presented as median (25-75th percentiles)
(SDQ-A): The Strengths and Difficulties Questionnaire-Adolescent; (SDQ-P): The Strengths and Difficulties Questionnaire-Parent; PedsQL-A: Pediatric Quality of Life Inventory -Adolescent Form; PedsQL-P: Pediatric Quality of Life Inventory-Parent Form

Table 3. RCADS-CV-A and RCADS-CV-P scores

	PP1 n:25	PP2 n:25	CG n:25	p
RCADS-CV-C anx.dep. score	38 (33-45)	39 (30-47)	37 (32.5-46)	0.987
RCADS-CV-A anxiety score	39 (32-44)	40 (31-49)	38 (31.5-46.5)	0.929
RCADS-CV-P anx.dep. score	45.5 (42.75-55)	49 (41-55)	46 (42.5-55)	0.942
RCADS-CV-P anxiety score	45.5 (42-54.75)	48.5 (41.25-57)	46 (41.5-55.5)	0.824

Data were presented as median (25-75th percentiles)
RCADS-CV-A: Revised Child Anxiety and Depression Scale-Child Version-Adolescent Form
RCADS-CV-P: Revised Child Anxiety and Depression Scale-Child Version-Parent Form

Table 4. ARI-A, ARI-P, and T-DSM-IV-S scores

	PP1 n: 25	PP2 n: 25	CG n: 25	p
ARI-C-total	5 (0-7)	2 (1-4.25)	1 (1-2)	0.581
ARI-P total	2 (0-6)	2 (0.5-3.5)	1 (0-2)	0.730
T-DSM-IV-S-IA	4.5 (3.25-9.5)	6 (0-10)	4 (1-6)	0.439
T-DSM-IV-S-HA	4 (1.25-6.5)	5 (1-11)	4 (2-7)	0.913
T-DSM-IV-S-ODD	4.5 (1-9.25)	3 (2-8)	3 (1-5)	0.892
T-DSM-IV-S-CD	0 (0-0)	0 (0-2)	0 (0-0)	0.359
T-DSM-IV-S-Total	14.5 (6-21)	15 (3-30)	17.5 (6.75-28.25)	0.903

Data were presented as median (25-75th percentiles)
ARI-C: Affective Reactivity Index- Children Form; ARI-P: Affective Reactivity Index- Parent Form;
T-DSM-IV-S-IA: Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale-Inattention Score
T-DSM-IV-S-HA Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale- Hyperactivity
T-DSM-IV-S-ODD Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale-Oppositional Defiant Score
T-DSM-IV-S-CD Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale- Conduct Disorder Score

DISCUSSION

In the current study, we analyzed behavioral and emotional problems, quality of life, anxiety, and depressive status of children with CPP (at diagnosis and at follow-up). We compared the results with age- and sex-matched healthy controls. In terms of behavioral and emotional problems, quality of life, anxiety, and depressive status, the CPP groups did not differ from age-matched controls.

In our study, no significant difference was found between the PP1 and PP2 groups regarding the age of pubertal onset. However, when examining bone age advancement, basal and stimulated hormonal levels, we observed differences between the groups, as one group was evaluated at the beginning of treatment, while the other had been receiving treatment for at least one year. Despite these clinical differences, no significant differences in emotional and behavioral outcomes were found between the two groups. These findings suggest that the duration of treatment or pubertal timing, at least within the context of our study, did not significantly affect psychological outcomes.

In contrast to previous reports indicating elevated behavioral and emotional problems in children with CPP, we found no significant differences in SDQ-A and SDQ-P scores among the three groups (PP1, PP2, CG) (Table 3). Specifically, emotional symptoms; including worries, fears, and frequent unhappiness, were reported at similar levels across groups. Similarly, behavioral problems, such as temper outbursts, disobedience, and aggressive behaviors, did not differ significantly between groups. Both child- and parent-reported SDQ scores indicated that children with CPP did not exhibit increased emotional or behavioral difficulties compared to their typically developing peers. During puberty, psychological changes are known to follow physiological changes due to the activation of the hypothalamic-pituitary-gonadal axis.[24] As the children in the CPP group were younger, and the potential effects of hormonal changes were addressed early with GnRH agonist therapy, it is suggested that children diagnosed with CPP did not experience any significant emotional or behavioral differences compared to the control group. This conclusion is further supported by the consistent reports from both children and parents, who reported no changes in emotional or behavioral status. While GnRH agonists primarily serve to suppress puberty, their impact on emotional and behavioral outcomes remains an area of interest. Some studies suggest that GnRH agonists may alleviate the psychological distress associated with early puberty, particularly in girls, by delaying pubertal onset and reducing the social challenges that accompany early maturation.[25] Furthermore, it may impact cognitive development both indirectly, through suppression of sex hormone activity on the maturing brain, and directly, via GnRH receptors located in non-reproductive neural regions.[6,26] Further longitudinal studies are needed to clarify the direct effects of GnRH therapy on psychological well-being in children with CPP.

In the TURGAY scale, which evaluates the symptoms of attention deficit hyperactivity, oppositional defiant disorder, and conduct disorder, similar scores were found between the three groups. During adolescence, children experience some behavioral and emotional difficulties, increased risk-taking behavior and impulsivity, as well as difficulties in controlling anger.[27] In a cross-sectional study conducted in 2023, externalizing behaviors were found to be more prevalent in female adolescents with CPP compared to the control group.[28] In another study, although the score assessing externalizing behaviors was not considered clinically significant, it was found to be higher in adolescent girls compared to the control group. It was also suggested that the effect on behavior emerged at a later age.[29] The findings of our study indicate that, although biological markers of adolescence have been observed in children, it is believed that their behavioral manifestations are more closely associated with their psychosocial developmental stage and chronological age than with this biological process. Furthermore, the data suggest that children do not exhibit behavioral patterns that are unique to the adolescent period.

The majority of studies conducted thus far on precocious puberty in children have focused on girls. In some of these studies, elevated rates of depression and anxiety have been observed in children experiencing precocious puberty.[13,30] The onset of menarche has been shown as a reason for depressive symptoms.[30] Among anxiety disorders, social anxiety, which is associated with a lower self-image, has been reported to be more prevalent.[14] Conversely, similar to our study, some studies have reported that the groups diagnosed and treated with CPP did not exhibit any differences in terms of depressive and anxiety symptoms.[31] It is known that there should be a serious psychosocial stressor for the emergence of depression in childhood in association with the development of children's cognitive and emotional abilities.[32] Since the children in our study were relatively younger, it is thought that they did not differ from healthy children in terms of depressive and anxiety symptoms, even if they exhibited symptoms of adolescence.

It is established that children with a chronic disease experience a negative impact on their quality of life.[33,34] There are limited studies that have analyzed the quality of life of children with precocious puberty. In one of these studies, the CPP group included both treated and newly diagnosed children, and no significant differences were found in the quality of life of this group compared to healthy children.[14] In another study, a total of 193 children were examined, including 59 children with CPP, 53 children with premature thelarche, and 81 healthy children and their parents. No significant differences were found between the CPP, PT, and control groups.[1] In our study, the quality of life of the group of children newly diagnosed with CPP and the group of children who had been receiving treatment for at least one year was found to be similar to that of healthy children, according to both self-report and parental report. The favorable response to treatment and the absence of significant adverse effects during the treatment indicate that psychological well-being in children is associated with a high level of quality of life.

It should be noted that our study has certain limitations. First, the limited sample size makes it difficult to generalize our results. The study included all eligible subjects who met the inclusion criteria within the study period. Additionally, the imbalance between the patient and control groups may have affected the study's statistical power. One limitation is the inability to conduct a subgroup analysis by sex due to small sample sizes. As a result, the potential impact of sex differences on psychological outcomes remains unclear and should be interpreted with caution. Future research with larger, sex-specific samples is needed to more comprehensively assess these differences. Although children's psychiatric symptoms were assessed through scales, it is possible that structured psychiatric interviews for children might yield more accurate diagnoses of potential psychiatric disorders. A more detailed evaluation of children's physical characteristics, such as height and weight, which change with the puberty process, could have provided a more accurate interpretation of the results. Furthermore, psychological problems that may arise in the longer term can be evaluated by longitudinal follow-up of the study groups.

CONCLUSION

In the present study, psychiatric symptoms and quality of life were compared between the three groups, and no significant difference was detected. Although central precocious puberty is not considered a chronic condition, its requirement for sustained medical management and long-term surveillance may predispose affected individuals to psychosocial challenges. While it is a favorable finding that there is no difference in terms of these symptoms in children with early adolescence, it is crucial to consider children with CPP in a multidisciplinary approach and to assess the cases for the potential negative impacts on their quality of life.

Ethical approval

This study has been approved by the Tekirdağ Namık Kemal University (approval date 28.6.2022, number 2022.119.06.09). Patients and/or parents provided written informed consent, and all studies were conducted in accordance with the principles of the Declaration of Helsinki.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: ÖK, GYA; data collection: ÖK; analysis and interpretation of results: ÖK, GYA; draft manuscript preparation: ÖK, GYA. All authors reviewed the results and approved the final version of the article.

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Original Article

Micronutrient status in adolescents with autoimmune thyroiditis: a case-control study

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ABSTRACT

Objective: Autoimmune thyroiditis (AIT) is the most common thyroid disorder in adolescents, with genetic and environmental factors contributing to its pathogenesis. The role of micronutrients in AIT remains a topic of controversy. This study aims to evaluate the levels of iodine, selenium, vitamin A, vitamin E, magnesium, and vitamin B12 in adolescents diagnosed with AIT compared to healthy controls.

Methods: A case-control study was conducted from September 2022 to September 2023, including 37 adolescents with newly diagnosed AIT and 36 age- and sex-matched healthy controls. Serum levels of thyroid hormones, thyroid autoantibodies (anti-thyroid peroxidase [TPO] and anti-thyroglobulin [Tg]), and micronutrient levels were assessed. Statistical analyses were performed to compare the groups and to evaluate correlations between thyroid autoantibody levels and micronutrients.

Results: All patients had elevated thyroid autoantibody levels, with a median of 135.5 IU/mL for anti-Tg and 535 IU/mL for anti-TPO. No significant differences were observed in urinary iodine, selenium, magnesium, vitamin A, vitamin E, or vitamin B12 levels between the groups. Correlation analysis revealed no significant associations between thyroid autoantibodies and micronutrient levels ($p>0.05$).

Conclusion: This study suggests that iodine, selenium, magnesium, vitamin A, vitamin E, and vitamin B12 levels are not significantly altered in adolescents with AIT. These micronutrients alone may not serve as reliable biomarkers for the diagnosis or progression of AIT. Further research is needed to elucidate the potential role of micronutrient supplementation in the management of AIT.

Keywords: autoimmune thyroiditis, adolescents, micronutrients, selenium, iodine, vitamin B12, thyroid autoimmunity

INTRODUCTION

Autoimmune thyroiditis (AIT) is the most common thyroid disorder in the pediatric population in iodine-sufficient regions. Although AIT can manifest at any age, it is most frequently diagnosed during adolescence and exhibits a higher prevalence in females. The etiology of AIT is attributed to the presence of circulating autoantibodies against thyroid antigens, initiating a chronic autoimmune destructive process. This process involves the formation of immune complexes and complement activation in the basement membrane of follicular cells, leading to lymphocytic infiltration, fibrosis, and a subsequent decline in the number of functional thyroid follicles necessary for hormone synthesis.[1]

The diagnosis of AIT primarily relies on elevated serum titers of thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab), along with diffuse hypoechogenicity on thyroid ultrasonography. AIT can present with a euthyroid state, hypothyroidism, or transient hyperthyroidism.[2] The exact pathogenesis of AIT

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remains incompletely understood; however, both genetic predisposition and environmental factors play crucial roles.[3] Approximately 70% of disease susceptibility is attributed to the genetic background, with environmental triggers contributing significantly to disease onset. Family and twin studies further support the substantial genetic influence on AIT, yet the 55% concordance rate for overt hypothyroidism in monozygotic twins highlights the equally pivotal role of environmental factors.[4,5] Potential environmental triggers for AIT include infections, medications, hormonal influences (such as estrogen), dietary factors, stress, and smoking.[3] Among dietary factors, iodine excess or deficiency, selenium deficiency, and vitamin D deficiency have been associated with an increased risk of AIT.[6]

There is also limited evidence suggesting that vitamin A, zinc, and vitamin B12 may influence thyroid metabolism, although data on their direct relationship with AIT remain scarce.[6] The objective of this study is to evaluate iodine, selenium, vitamins A, E, and B12, and magnesium levels in adolescents diagnosed with AIT compared to healthy adolescents, to further understand their potential role in thyroid autoimmunity.

MATERIALS AND METHODS

This case-control study was conducted over one year, from September 2022 to September 2023. During this timeframe, newly diagnosed adolescents aged 10–18 years with AIT were enrolled. Participants were included if they had been investigated for goiter and/or thyroid function abnormalities and subsequently diagnosed with AIT. The diagnosis of AIT was confirmed by elevated serum anti-thyroid peroxidase (anti-TPO) and/or anti-thyroglobulin (anti-Tg) antibodies, with positivity defined as levels exceeding 35 IU/mL for anti-TPO and 45 IU/mL for anti-Tg. Additionally, diffuse heterogeneity observed on thyroid ultrasonography was considered a supportive diagnostic criterion. Age- and sex-matched healthy adolescents were included as the control group. Pubertal status was assessed based on physical examination and the Tanner staging system. All participants were in Tanner stage II or higher, and pubertal status was similar between the two groups.

Exclusion criteria comprised individuals with a prior diagnosis of any chronic disease and those receiving multivitamin supplements or other medications that could influence thyroid function or metabolic parameters.

Thyroid function tests were performed using a chemiluminescent immunometric assay (Architect i4000, Abbott Laboratories, Diagnostics Division, IL, USA). The reference ranges were as follows: thyroid-stimulating hormone (TSH), 0.35–4.94 mIU/L; free triiodothyronine (fT3), 2.43–4.47 pg/mL; and free thyroxine (fT4), 0.78–1.31 ng/dL. Anti-Tg antibodies (TG-Ab) were measured using the same assay, with values below 5.6 IU/mL considered normal. Similarly, anti-TPO antibodies (TPO-Ab) were quantified using the chemiluminescence immunometric method, with normal values defined as 0–4.1 IU/mL.

Serum glucose levels were measured using Abbott kits on an Abbott i-STAT 8000 analyzer. The hexokinase/glucose-6-phosphate dehydrogenase (G-6-PDH) method was used for measurement. Insulin levels were determined using the chemiluminescent microparticle immunoassay (CMIA) method with an Abbott i16000 analyzer and Abbott diagnostic kits. Vitamin A, vitamin E, and selenium levels were measured using inductively coupled plasma mass spectrometry (ICP-MS). Urinary iodine concentration was assessed using ammonium persulfate digestion followed by the Sandell-Kolthoff reaction, with a reference range of 100– 199 µg/L. Vitamin B12 levels were determined using a chemiluminescent microparticle immunoassay (CMIA) method on an Abbott i2000 analyzer, with normal values ranging from 200 to 900 pg/mL.

Thisstudy has been approved by the Umraniye Training and Research Hospital Ethics Committee (approval date 25.08.2022, number 19661). Written informed consent was obtained from the parents of all enrolled participants.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA). The normality of distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as median and interquartile range (IQR) for non-normally distributed data and as mean ± standard deviation (SD) for normally distributed data. Categorical variables were presented as frequencies and percentages. The differences between the two groups were analyzed using the Mann-Whitney U test for non-normally distributed continuous variables and the independent samples t-test for normally distributed continuous variables. Categorical variables were compared using the Chi-square test or Fisher's exact test when appropriate. Correlation analyses were performed using Spearman's rank correlation coefficient. To determine whether micronutrient levels could serve as diagnostic markers for distinguishing patients with HT from controls,

we conducted an ROC analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 73 adolescents (37 patients with autoimmune thyroiditis and 36 healthy controls) were included in the study. The median age was 14.5 years [IQR: 12-16] in the patient group and 14 years [IQR: 13-16] in the control group (p=0.775). The proportion of male participants was 27.0% (10 males, 27 females) in the patient group and 30.6% (11 males, 25 females) in the control group (p=0.941). All adolescents in both the patient and control groups were in the pubertal stage, as assessed by clinical evaluation.

The biochemical characteristics of the study groups are summarized in Table 1, which shows significant differences in Anti-TG, Anti-TPO, Glucose, LDL, Sex Hormone-Binding Globulin (SHBG), fT3, and TSH levels, but no differences in terms of micronutrient levels.

To further explore the clinical relevance of micronutrient levels in Hashimoto's thyroiditis (HT), we assessed their correlation with thyroid autoantibodies (Anti-TG and Anti-TPO). No significant correlations were observed between thyroid autoantibodies and micronutrient levels (Table 2). Although not statistically significant, magnesium exhibited a weak negative correlation with Anti-TG (r=-0.308, p=0.081), and selenium demonstrated a weak negative correlation with Anti-TPO (r=-0.296, p=0.094).

Furthermore, the ROC analysis, conducted to ascertain whether micronutrient levels could serve as diagnostic markers for HT, demonstrated that none of the assessed micronutrients had adequate discriminative power, as their Area Under the Curve (AUC) values were close to 0.5 (Table 3).

Table 1. The biochemical parameters in patients with newly diagnosed Hashimoto thyroiditis and in the control group

Parameter	Patient Group (n=37)	Control Group (n=36)	p-value
Anti-TG (IU/ml)	135.5 [34-363]	0.885 [0.63-2.24]	**<0.001***
Anti-TPO (IU/ml)	535 [181-1000]	0.5 [0.5-0.51]	**<0.001***
fT3 (pg/mL)	3.11±1.06	3.54±0.51	**0.001***
fT4 (ng/dL)	0.93±0.16	0.96±0.10	0.300
TSH (uIU/L)	3.19 [2.31-8.1]	2.06 [1.57-2.695]	**0.001***
Urinary Iodine (ug/L)	112 [95-146]	107 [71-151]	0.321
Magnesium (mg/dL)	1.97 [1.65-2.10]	1.93 [1.71-1.51]	0.632
Selenium (ug/L)	67.9 [57.3-85.7]	69.25 [58.3-89.5]	0.556
Vitamin A (ug/dL)	37.9 [32.75-41.5]	39.2 [34.5-42.9]	0.846
Vitamin E (mg/dL)	0.85 [0.565-0.85]	0.84 [0.65-0.98]	0.960
Vitamin B12 (ng/L)	263.5 [207-337]	239 [194-400]	0.768

*p < 0.05. TSH: Thyroid-stimulating hormone, fT3: Free triiodothyronine, fT4: Free thyroxine,
Anti-TPO: Anti-thyroid peroxidase antibody, Anti-TG: Anti-thyroglobulin antibody.

Table 2. Correlations between autoantibody and micronutrient levels

Parameter	Anti-TG (r)	Anti-TG (p)	Anti-TPO (r)	Anti-TPO (p)
Urinary Iodine	0.041	0.828	0.078	0.678
Magnesium	-0.308	0.081	0.194	0.278
Selenium	0.055	0.759	-0.296	0.094
Vitamin A	-0.23	0.222	0.027	0.889
Vitamin E	0.125	0.519	-0.194	0.313
Vitamin B12	0.092	0.618	-0.03	0.87

Statistical significance was defined as p < 0.05. Anti-TG: Anti-thyroglobulin antibody, Anti-TPO: Anti-thyroid peroxidase antibody.

Table 3. The results of the ROC Curve analysis for the micronutrient level

Test Variable	AUC	SE	p-value	95% CI
Urinary Iodine	0.569	0.079	0.384	0.415-0.724
Selenium	0.590	0.083	0.258	0.428-0.753
Magnesium	0.445	0.079	0.492	0.290-0.600
Vitamin A	0.493	0.08	0.931	0.335-0.651
Vitamin E	0.483	0.08	0.835	0.326-0.640
Vitamin B12	0.515	0.079	0.848	0.360-0.671

Statistical significance was defined as $p < 0.05$. AUC: Area under the curve, SE: Standard error, CI: Confidence interval.

DISCUSSION

In this study, we investigated the relationship between autoimmune thyroiditis (AIT) and micronutrient levels, including iodine, selenium, magnesium, vitamin A, vitamin E, and vitamin B12, in adolescents. Our findings indicated that while the thyroid autoantibody levels are significantly elevated in patients with AIT, no strong correlations were observed between these autoantibodies and micronutrient levels.

These results suggest that micronutrient status alone may not be a reliable distinguishing factor in adolescents with AIT.

Several studies have highlighted the role of micronutrients in thyroid function and autoimmunity. Iodine is an essential element for thyroid hormone synthesis, but both deficiency and excess have been implicated in the development of autoimmune thyroid disease.[7] In our study, urinary iodine levels did not differ significantly between the AIT and control groups, suggesting that iodine status was not a major determinant of AIT in our population. However, considering regional variations in iodine intake, further studies with larger populations are needed to confirm this finding.

Selenium, an essential trace element with antioxidant properties, has been suggested to play a role in thyroid autoimmunity by modulating immune responses and reducing oxidative stress.[8] Although previous research has demonstrated a potential protective effect of selenium supplementation in patients with AIT,[9] our study did not find a significant difference in serum selenium levels between AIT patients and controls. Additionally, no strong correlation was observed between selenium levels and thyroid autoantibodies. These findings suggest that selenium's effects on AIT development and progression may be more complex and potentially influenced by both genetic and environmental factors.

Further systematic reviews and meta-analyses have provided additional insights into the role of selenium supplementation in AIT. A comprehensive meta-analysis by Huwiler et al. evaluated randomized controlled trials and found that selenium supplementation effectively reduced thyroid peroxidase antibodies (TPOAb) levels and thyrotropin (TSH) concentrations in patients with Hashimoto's thyroiditis.[10] Wang et al. reported that selenium supplementation may reduce TPOAb and thyroglobulin antibody (TgAb) levels after 3 and 6 months, particularly in patients not receiving levothyroxine therapy.[11] These findings suggest that while selenium supplementation may have a beneficial effect on reducing thyroid autoantibody levels in AIT patients, the overall evidence remains inconclusive. Our results align with this uncertainty, reinforcing the need for further research on selenium's role in AIT management.

Magnesium plays a key role in enzymatic reactions, including those related to thyroid function. Emerging evidence suggests that its deficiency may heighten inflammatory responses in autoimmune diseases.[6] While we observed a weak negative correlation between magnesium and anti-TG levels, this association was not statistically significant. Further research with larger sample sizes is needed to explore whether magnesium status influences thyroid autoimmunity.

The role of vitamins in thyroid health has been an area of growing interest. Vitamin A, through its effects on immune regulation, has been hypothesized to influence thyroid autoimmunity.[6] Similarly, vitamin E has been investigated for its potential role in reducing oxidative stress in thyroid disorders.[9] However, our study did not find significant differences in vitamin A or vitamin E levels between AIT patients and controls, nor were there any significant correlations with thyroid autoantibodies. These findings align with previous studies that have reported inconsistent results regarding the impact of these vitamins on AIT.[12]

Vitamin B12 deficiency has been frequently reported in patients with AIT and other autoimmune disorders.[6] However, our study found no significant difference in vitamin B12 levels between AIT patients and controls. The lack of a significant association may be attributed to differences in dietary intake, absorption efficiency, or genetic predisposition in our study population.

There are several limitations to consider. First, the relatively small sample size may have limited our ability to detect weak associations. Second, we did not assess dietary intake, which could have provided additional insights into the role of nutritional factors in AIT.

In conclusion, our study suggests that while thyroid autoantibodies are significantly elevated in adolescents with AIT, their levels do not strongly correlate with iodine, selenium, magnesium, vitamin A, vitamin E, or vitamin B12 levels.

These findings suggest that micronutrient status alone may not be a distinguishing factor for AIT in adolescents. Further research involving larger and more diverse populations is warranted to better understand the relationship between micronutrients and thyroid autoimmunity.

Ethical approval

This study has been approved by the Umraniye Training and Research Hospital Ethics Committee (approval date 25.08.2022, number 19661). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: GS; data collection: GS; analysis and interpretation of results: GS, HK; draft manuscript preparation: GS, HK. All authors reviewed the results and approved the final version of the article.

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Original Article

Low bone mineral density in rare metabolic disorders: data from a Turkish cohort of patients with glycogen storage disorders and organic acidemias

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ABSTRACT

Objective: To evaluate bone mineral density (BMD) and the nutritional and biochemical factors affecting it in children with glycogen storage diseases (GSD) and organic acidemias (OA), which are rare metabolic disorders.

Methods: This retrospective study included 31 pediatric patients with genetically confirmed diagnoses—15 with GSD (types I and III) and 16 with OA (methylmalonic and propionic acidemia). BMD was assessed using dual-energy X-ray absorptiometry (DXA) and reported as age-adjusted Z-scores. Anthropometric data, three-day dietary records (analyzed with BeBIS 8.2), and serum markers, including vitamin D, Parathyroid Hormone (PTH), calcium, phosphorus, and others, were analyzed. Malnutrition and stunting were defined using World Health Organization (WHO) growth standards. Pearson correlation analysis was used, with a significance level set at $p<0.05$.

Results: In the GSD group, the mean DXA Z-score was −2.59±1.45, and low BMD (Z≤−2.0) was identified in 53.3% of patients. In the OA group, the mean Z-score was −1.91±1.19, with low BMD observed in 50%. Among GSD patients, DXA Z-scores correlated positively with dietary calcium intake ($r=0.53$, $p=0.04$), height-for-age Z-score ($r=0.52$, $p=0.04$), and serum vitamin D ($r=0.58$, $p=0.02$), while negative correlations were found with age ($r=-0.87$, $p=0.00$), disease duration ($r=-0.87$, $p=0.002$), and PTH ($r=-0.67$, $p=0.006$). In the OA group, DXA Z-scores showed a significant positive correlation only with dietary calcium intake ($r=0.67$, $p=0.004$). Vitamin D deficiency was common, with sufficiency (defined as>30 ng/mL) achieved in only 20% of GSD and 31.2% of OA patients.

Conclusion: Low bone mineral density is prevalent in both GSD and OA populations and appears to be influenced by modifiable factors such as calcium intake and vitamin D status. These findings highlight the importance of routine monitoring of bone health and nutrition in these patients. Multidisciplinary management is crucial for reducing long-term skeletal risks and optimizing clinical outcomes.

Keywords: bone mineral density, glycogen storage disease, organic acidemia, vitamin D

INTRODUCTION

Organic acidemias (OAs) and glycogen storage diseases (GSDs) are rare inherited metabolic disorders and may lead to long-term complications because of their multisystemic effects.[1,2] Methylmalonic acidemia (MMA) and propionic acidemia (PA) are subtypes of OA caused by enzymatic defects in organic acid metabolism.[3] MMA and PA result from the accumulation of metabolites due to impaired catabolism of valine, isoleucine, methionine, threonine, odd-chain fatty acids, and cholesterol.[4] GSDs result from deficiencies in enzymes involved in glycogen metabolism,

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with type I and type III being the most prevalent subtypes.[5,6] GSD type I results from glucose-6-phosphatase deficiency, while type III is due to a deficiency in the glycogen debranching enzyme.[7]

In hepatic forms of GSD, the primary therapeutic goal is the maintenance of normoglycemia. To achieve this, uncooked cornstarch is frequently used, alongside a diet restricted in simple sugars.[8] Beyond normoglycemia, dietary management also aims to prevent complications, including hepatocellular adenomas/carcinomas, renal failure, myopathy, and osteoporosis.[9] Dietary recommendations differ between subtypes: in GSDI, sucrose, fructose, galactose, and lactose are typically restricted, whereas in GSDIII, a diet rich in protein and/or fat with limited sucrose is often advised.[5,6]

In MMA and PA, dietary therapy focuses on minimizing the production of toxic organic acids while supporting normal growth and development. This is accomplished by restricting natural protein intake—particularly the precursor amino acids isoleucine, valine, threonine, and methionine—and supplementing with amino acid mixtures that exclude these compounds. Adequate energy intake is also essential to prevent catabolism.[3,10]

Monitoring and preserving bone health in these patient groups is critical not only for growth and development but also for maintaining quality of life and preventing fractures.[11] Several studies have reported reduced bone mineral density (BMD) and increased fracture risk in patients with OA and GSD.[12-15] Multiple factors influencing bone mineralization in these populations have been identified, including restrictive dietary regimens, insufficient calcium intake, chronic metabolic acidosis, persistent inflammation, vitamin D deficiency, mitochondrial dysfunction, and metabolic imbalances related to hypoglycemia in GSD.[16,17]

We hypothesized that low bone mineral density is common in patients with GSD and OA, and that it is associated with nutritional and biochemical parameters. This study was conducted to evaluate bone mineral density and investigate associated factors in patients with organic acidemias and glycogen storage disorders. The ultimate goal is to raise awareness of bone health monitoring in these patients and to contribute to the development of appropriate follow-up guidelines. There is a limited number of studies in the literature that have examined bone health and identified risk factors influencing BMD in these rare disorders. In particular, the scarcity of studies focusing on BMD in OA patients highlights the importance of this research in addressing a significant gap in the literature.

MATERIAL METHOD

Study design and subjects

A total of 31 patients were included in this study, comprising 15 individuals with GSD and 16 with OA. This study was conducted retrospectively at a single-center metabolic center. All participants had genetically confirmed diagnoses and were regularly followed at Gaziantep Cengiz Gökçek Maternity and Children's Hospital . A retrospective design was chosen because these diseases are rare, and prospective records would be time-consuming to achieve a sufficient sample size. At our center, patients are regularly followed, and necessary disease-related assessments are recorded. This allowed us to obtain a sufficient dataset without creating additional patient burden on the hospital. The study protocol was approved by the Ethics Committee of Gaziantep University (Date: 24.07.2020, Approval Number: 2020/259), and written informed consent was obtained from all patients and/or their parents.

Inclusion criteria: Patients were eligible if they met the following: (i) a genetically confirmed diagnosis of GSD type I/III, or MMA/PA; (ii) age between 2 and 18 years at the time of the index DXA; (iii) at least one valid pediatric DXA scan with Z-scores reported according to the 2019 International Society for Clinical Densitometry (ISCD) recommendations; (iv) availability of a three-day dietary record analyzed with BeBIS 8.2, together with routine biochemical measurements (including vitamin D, PTH, calcium, phosphorus, and other relevant markers); and (v) ≥12 months of regular follow-up at our clinic (≥3 visits/year); (vi) Patients who had been attack-free within the past 12 months. Exclusion criteria: (i) Secondary bone disease unrelated to the underlying inborn metabolic disorder; (ii) chronic medications known to significantly affect bone metabolism in the 6 months prior to index DXA; (iii) chronic kidney disease ≥ stage 3; (iv) lack of contemporaneous dietary or laboratory data; (v) poor-quality or invalid DXA; (vi) Patients who experienced one or more metabolic decompensation episodes within the past 12 months. The process of patient selection, including inclusion and exclusion criteria, is summarized in a STROBE-compliant flow diagram (Figure 1).

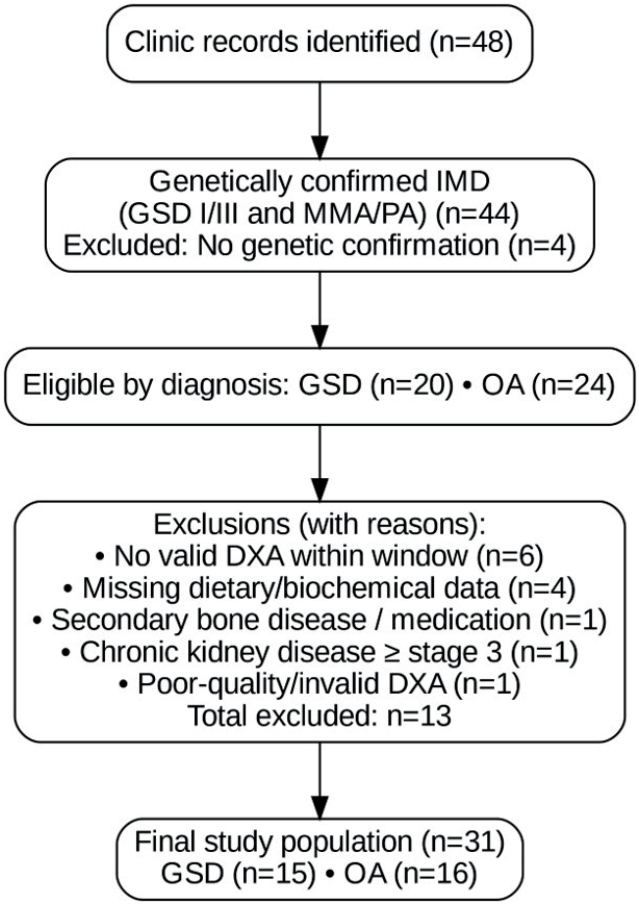

Figure 1. Flow diagram of patient selection (STROBE-compliant)

IMD: Inborn metabolic disease; GSD: glycogen storage disease, OA: organic acidemia; DXA: dual-energy X-ray absorptiometry

Bone mineral density assessment

BMD measurements were performed using dual-energy X-ray absorptiometry (DXA) with a Hologic Explorer densitometer (USA). The device was calibrated daily using a standard phantom. Patients were positioned supine according to the 2019 pediatric guidelines of the ISCD. All scans were performed by the same experienced technician, thereby eliminating inter-observer variability. Device-reported quality control parameters remained within accepted standards. The precision error was evaluated in accordance with the recommendations of the ISCD, considering the minimum acceptable precision threshold for an individual technician.[18] As per the 2019 ISCD official position, BMD results were reported as age-related Z-scores. A Z-score of ≤ −2.0 standard deviations (SD) was classified as "below the expected range for age".[18]

Biochemical and anthropometric assessments

Medical records were reviewed to collect information on clinical status, dietary treatments, and relevant biochemical data. All patients had been monitored at least three times annually as part of their routine follow-up. No episodes of metabolic acidosis requiring hospitalization have been reported in the last year. All participants adhered to individualized dietary regimens tailored to their specific metabolic conditions. Normoglycemia for GSD patients was maintained with individualized dietary plans. Dietary compliance was assessed based on parent and patient reports at each visit, and patients were found to be compliant with the diet. Dietary intake was recorded over a three-day period and analyzed using the Nutrition Information System software (BeBIS 8.2) by a dietitian experienced in the nutritional management of metabolic disorders. BeBIS has been adapted for the Turkish population, and it is widely used in national nutrition research. Anthropometric measurements, including body weight and height, were assessed and converted into age- and sex-specific Z-scores using WHO Anthro and AnthroPlus software. Malnutrition was defined as a weight-for-age Z-score below −2 SD, while stunting was defined as a height-for-age Z-score below −2 SD. Biochemical analyses included measurements of serum calcium, phosphorus, alkaline phosphatase (ALP), parathyroid hormone (PTH), vitamin D, lactate, uric acid, creatine kinase (CK), triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bicarbonate, and pH. Vitamin D status with >30 ng/mL is considered sufficient.[19] Information on physical activity, pubertal development, and menstrual status in female patients was not assessed.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 28.0. Descriptive statistics for continuous variables were presented as mean, minimum, maximum, and standard deviation (SD) values. The distribution of continuous variables was assessed using the Shapiro–Wilk test, histograms, and skewness–kurtosis values. As all variables showed normal distribution, parametric tests were applied. Associations between variables were examined using Pearson's correlation coefficient. All correlations were performed with a single primary outcome (BMD Z-score). Therefore, multiple testing adjustment was not applied, as the analyses were designed to explore potential correlates of bone health rather than to test multiple independent hypotheses. Statistical significance was defined as a p-value <0.05.

RESULTS

Among the 15 patients diagnosed with GSD, 9 had GSDI (5 females, 4 males) and 6 had GSDIII (4 females, 2 males). The mean age of the GSD group was 7.15±3.54 years, ranging from 3.0 to 13.8 years. Of the 16 patients with OA, 12 had MMA (7 females, 5 males) and 4 had PA (2 females, 2 males), with a mean age of 7.53±4.17 years (range: 3.0–16.3 years). The mean duration of treatment was 6.77±3.34 years in the GSD group and 7.25±4.18 years in the OA group. The mean age and treatment duration of GSD and OA patients were similar. Table 1 provides detailed patient characteristics and DXA measurements.

Based on weight-for-age Z-scores, malnutrition was identified in 9.1% of GSD patients and 16.6% of OA patients. According to height-for-age Z-scores, 57.1% of GSD patients and 50% of OA patients were classified as stunted. The mean DXA Z-score was −2.59±1.45 in GSD patients, with 53.3% exhibiting reduced BMD. By subtype, 44.4% of GSDI and 66.6% of GSDIII patients had low BMD. In the OA group, the mean DXA Z-score was −1.91±1.19, and 50% of the patients had low BMD.

Biochemical parameters of the patients are presented in Table 2. Serum levels of calcium, phosphorus, ALP, and PTH were within normal ranges in both groups. However, the mean serum vitamin D levels were below the sufficiency threshold in both patient groups. Only 20% of GSD patients (3 out of 15) and 31.2% of OA patients (5 out of 16) had sufficient vitamin D levels (>30 ng/mL). Elevated mean serum lactate levels were observed in GSDI and OA

Table 1. Demographic characteristics and DXA Z-scores of patients with GSD and OA

	GSD (n=15)	OA (n=16)
Age (years)	7.15±3.54 (3.00 – 13.80)	7.53±4.17 (3.00 – 16.30)
Treatment duration (years)	6.77±3.34	7.25±4.18
Weight-for-age Z-score	-0.39±1.55 (-2.05 – 3.34)	-0.7±1.49 (-3.73 – 1.76)
Height-for-age Z-score	-2.25±1.58 (-4.3 – 1.57)	-2.06 ± 1.74 (-6.02 - 0.32)
DXA Z-score	-2.59±1.45 (-6.00 – 0.50)	-1.91 ± 1.19 (-3.80 - -0.20)

Values are presented as mean ± standard deviation (min–max). GSD: Glycogen storage disease; OA: Organic acidemia; DXA: Dual-energy X-ray absorptiometry

Table 2. Biochemical parameters and calcium intake levels of patients with GSD and OA

Parameters	Normal range	GSD (n=15)	OA (n=16)
Calcium, mg/dL	8.7-10.4	9.9±0.61 (8.69 – 11.20)	9.61±0.45 (9.09 – 11.09)
Phosphorus, mg/dL	4.5-5.5	4.97±0.87 (3.60 – 7.60)	4.98±0.84 (3.30 – 6.20)
ALP, U/L	40-500	274.4±82,7 (150.0 – 447.0)	264.9±95,7 (118.0 – 463.0)
PTH, pg/mL	14-72	46.2±21.2 (18.2 – 85.0)	46.4±19.8 (20.0 – 84.6)
Vitamin D, ng/mL	30-100	20.7±10.25 (7.5 – 39.2)	21.4 ± 9.48 (7.10 – 34.3)
Lactate, mmol/L (GSDI)	<2	4.37±1.33 (3.30 – 6.60)	2.62 ± 0.99 (1.2 – 4.4)
Uric acid, mg/dL (GSDI)	2.0-5.5	5.39±1.98 (2.90 – 9.10)	-
CK, U/L (GSDIII)	33-211	8680±625.0 (281.0 – 2128.0)	-
Triglyceride, mg/dL	<150	443.0±345.3 (133.0 – 1390.0)	-
AST, U/L	1-40	168.3±163.5 (35.0 – 600.0)	-
ALT, U/L	10-49	149.0±116.4 (38.0 – 389.0)	-
Bicarbonate, mEq/L	22-26	-	23.2±2.25 (18.1 – 26.2)
Ph (GSDI)		7.39±0.30 (7.36 – 7.44)	7.40±0.02 (7.33 – 7.45)
Calcium intake (% of requirement met)		81.26±6.47 (70.0 – 90.0) GSDI → 83.1±6.1 (75.0-90.0) GSDIII → 78.5±6.4 (70.0-88.0)	161.8±53,34 (69.0 – 252.0)

Values are presented as mean ± standard deviation (min–max). Reference ranges represent clinical normal values. ALP: Alkaline phosphatase; PTH: Parathyroid hormone; CK: Creatine kinase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

patients, while GSDIII patients exhibited elevated CK levels. Additionally, GSD patients had elevated mean triglyceride, AST, and ALT levels. In OA patients, bicarbonate levels were within normal limits. Dietary calcium intake, expressed as a percentage of the recommended daily allowance, was notably higher in OA patients compared to those with GSD. Dietary calcium intake as a percentage of the recommended daily intake was significantly higher in OA patients compared to patients with GSD.

Variables showing significant correlations with patients' DXA scores are presented in Figure 2. A significant positive correlation was found between dietary calcium intake and DXA Z-scores in both GSD and OA patients ($p<0.05$). In the GSD group, DXA Z-scores also showed a significant positive correlation with height-for-age Z-scores and serum vitamin D levels, and a significant negative correlation with age, treatment duration, and serum PTH levels ($p<0.05$). In addition, no significant association was found between lactate levels and DXA measurements in patients with GSDI and OA ($p>0.05$).

DISCUSSION

This study aimed to evaluate bone health and the factors influencing BMD in patients with OA and GSD. The findings demonstrated a high prevalence of reduced BMD in both patient groups. In particular, among GSD patients, BMD was significantly associated with dietary calcium intake, age, duration of treatment, height-for-age Z-score, serum PTH levels, and serum vitamin D status. There are studies in the literature with limited samples evaluating bone health in GSD and OA patients.[12,15,20]

In our study, malnutrition was identified in 9.1% of GSD patients and 16.6% of OA patients. Stunting was identified in 57.1% of GSD patients and 50% of OA patients. One study found a 66% rate of stunting and a 5.5% rate of underweight in GSD patients.[21] In a similar study in the literature, the stunting rate in GSD patients was reported as 50%.[22] Consistent with our findings, previous studies have also reported a high prevalence of stunting and malnutrition among OA patients.[10] Consistent with these findings, we observed a high rate of stunting, particularly

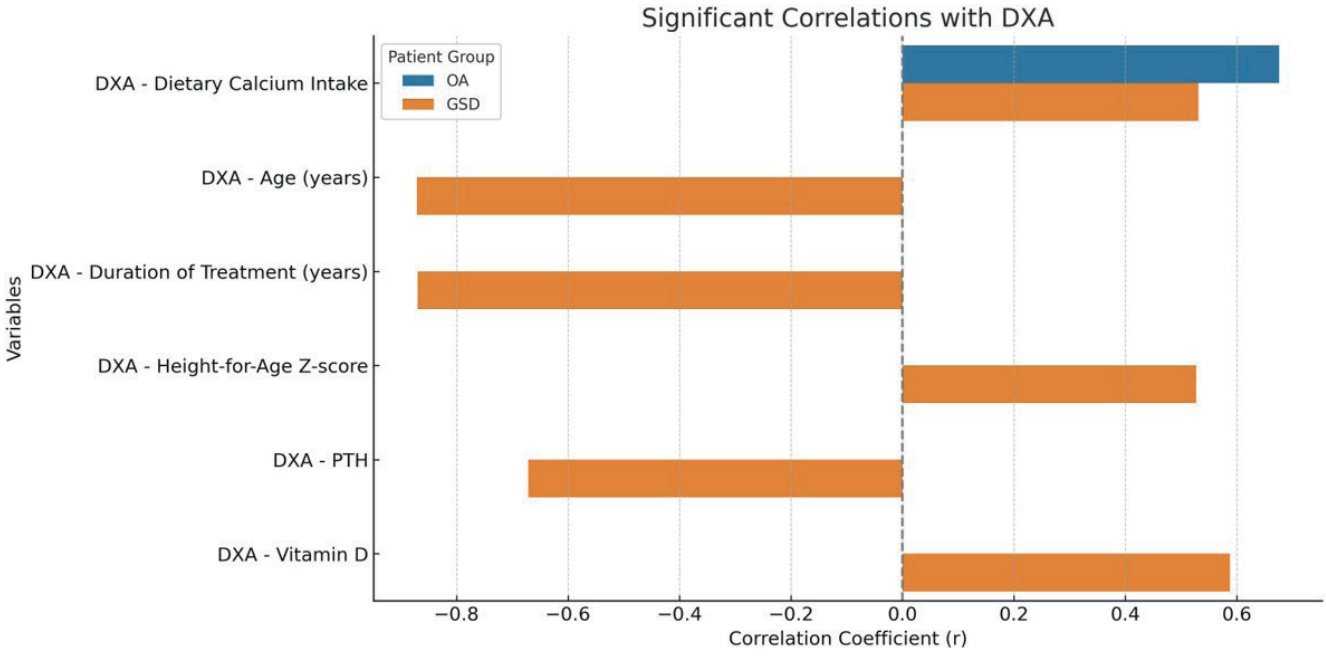

Figure 2. Variables showing significant correlations with DXA Z-scores in patients with GSD and OA

OA patients: DXA Z-scores were positively correlated with dietary calcium intake ($p=0.004$, $r=0.676$). GSD patients: DXA Z-scores were negatively correlated with age ($p<0.001$, $r=-0.871$), treatment duration ($p<0.001$, $r=-0.870$ and serum PTH levels ($p=0.006$, $r=-0.671$). DXA Z-scores were positively correlated with height-for-age Z-score ($p=0.043$, $r=0.527$), serum vitamin D ($p=0.021$, $r=0.588$), and dietary calcium intake ($p=0.042$, $r=0.531$). Correlation analyses were performed using Pearson method. GSD: Glycogen storage disease; OA: Organic acidemia; DXA: Dual-energy X-ray absorptiometry; PTH: Parathyroid hormone

among GSD patients. Given the observed associations between anthropometric parameters and DXA scores, routine monitoring of growth status in these patients is essential.

When the DXA results of the patients were evaluated, decreased BMD was observed in 53.3% of GSD patients. This high prevalence is consistent with previous studies and supports the notion that GSD patients are at significant risk for compromised bone health. Contributing factors include recurrent hypoglycemia, vitamin D deficiency, and suboptimal metabolic control. In GSDIII patients, the pathophysiology of low BMD is likely multifactorial, involving altered muscle physiology, metabolic dysregulation, and nutritional inadequacies. Additionally, physical inactivity and associated muscle weakness may further exacerbate bone loss.[5,23,24] Several studies have reported an increased risk of osteoporosis and fragility fractures in patients with GSD[5,6,12-14,22,24-27] particularly in those with GSDIII.[26] A recent Polish cohort likewise demonstrated predominantly negative BMD Z-scores, emphasizing the need for careful dietary and metabolic monitoring[21]. Although treatment guidelines for GSD emphasize the need for DXA assessments[5,6], they provide no detailed recommendations regarding the timing or frequency. Our results indicate that bone health evaluation should be initiated at an earlier stage in these patients. Also, these findings underscore the importance of early detection and continuous follow-up to prevent skeletal complications. Identifying factors that influence BMD may enhance patient management and guide clinical decisions.

In the OA group, reduced BMD was observed in 50% of patients, consistent with previous reports suggesting a high prevalence of impaired bone health in this population. Potential contributing factors include protein-restricted diets, chronic metabolic acidosis, and vitamin D deficiency.[15] A case series involving OA patients similarly reported decreased BMD in the majority of participants.[28] In a study involving MMA patients, 54.5% of patients were found to have decreased bone mineral density.[15] Although current treatment guideline for OA recommend performing DXA assessments in older children[2], our findings demonstrate that low bone mineral density can already be present at younger ages. These results suggest that bone health evaluation should be initiated earlier in this patient group. The literature on bone health in OA is extremely limited, with only a few small studies and case series available. This scarcity of data makes our findings particularly valuable, as they expand the limited evidence base and provide new insights into skeletal outcomes in MMA and PA. Given the chronic nature of protein restriction and cumulative metabolic derangements in these disorders, our results emphasize the need for systematic bone health monitoring and support multicenter longitudinal studies to better define risk factors and long-term outcomes in this neglected group. The results of our study are in line with these limited reports and support the need for routine bone health assessments and individualized monitoring strategies in patients with OA.

In our study, it was observed that the majority of GSD and OA patients had insufficient serum vitamin D levels. A study reported that 78.8% of GSD patients had low serum vitamin D levels.[21] Another study reported vitamin D insufficiency in 84% of GSD patients.[27] Moreover, one study showed a significant positive correlation between serum vitamin D levels and DXA Z-scores, which was also observed in our cohort.[14] Both GSD and OA patients require regular monitoring of serum parameters and careful monitoring with the use of supplements such as vitamin D when necessary. Similar to the literature, serum calcium, phosphorus, ALP, and PTH levels in our GSD patients are within normal values.[21,27,29] Similar to the studies conducted, serum triglyceride, AST, ALT, and CK levels for GSDIII patients were found to be higher than normal in the patients included in the study.[12,13,20] In our GSDI patients, uric acid levels were found to be higher than normal. High uric acid levels are among the complications of the disease in GSDI patients[6] and uric acid levels were higher than normal in the GSDI patients included in our study. One study has reported that serum lactate levels tend to be low in most patients with GSDI.[21] In GSDI, impaired urate clearance is a known complication; however, no significant correlation between uric acid and BMD was observed in our cohort. This likely reflects the multifactorial nature of bone involvement in GSD, where chronic acidosis, hypoglycemia, vitamin D deficiency, and dietary restrictions may outweigh the effect of uric acid. The paradoxical role of uric acid—protective at moderate levels but detrimental when chronically elevated—further complicates interpretation.[30] This difference may be due to various factors, including the clinical stability of the patients included in the study, their adherence to treatment, and the diversity of dietary treatments.

Regarding calcium intake, the percentage of recommended daily intake met was 81.2% overall in the GSD group (83.1% in GSDI and 78.5% in GSDIII). Regarding calcium intake, the percentage of recommended daily intake met was 161.8% in the OA group. In a similar study in the literature, it was stated that the vast majority of GSD patients (94%

of patients) had inadequate calcium intake.[21] In line with our results, Jacoby et al.[16] also highlighted the impact of nutritional factors on bone health in hepatic GSD patients. GSDI patients are advised to follow a diet limited to dairy products containing nutrients such as calcium, phosphorus, and protein that will support bone health.[6] However, lactose-free enteral formulas added to the diet may compensate for this deficiency. Similarly, OA patients, who receive amino acid mixtures free of precursor amino acids, often consume high levels of calcium from these formulas. In both patient groups, a positive and significant correlation was observed between dietary calcium intake and DXA scores ($p<0.05$). The bioavailability of calcium from foods is higher than that of calcium from amino acid mixtures.[31] Therefore, even if OA patients consume high amounts of calcium in their diets, their bodily absorption may be limited. These results suggest that the amount of calcium patients consume may have an impact on bone mineralization. Therefore, even if OA patients consume large amounts of calcium through amino acid mixtures, their absorption may remain limited. Our findings indicate that calcium intake is a critical determinant of bone mineralization. In GSD patients, dietary calcium intake should be actively supported, whereas in OA patients, where the bioavailability of calcium from amino acid mixtures is relatively low, increasing natural protein intake—when clinically tolerated—may provide more effective support for skeletal health.

This study has several limitations. Due to the rarity of the disease, this study was conducted on a small and heterogeneous patient group. Furthermore, there is no information on the patients' physical activity levels, pubertal status, or menstrual status in female patients. A further limitation is the limited availability of published data on OA-related bone health, which constrains meaningful comparisons with existing studies. This underscores both the novelty and the importance of our findings. Further longitudinal studies with larger sample sizes are needed to better understand the determinants of bone health in these populations.

CONCLUSIONS

This study demonstrates that low bone mineral density is common among patients with GSD and OA. In these individuals, impaired bone mineralization may increase the long-term risk of osteoporosis. Existing guidelines for GSD and OA highlight the importance of DXA assessments but lack specific recommendations on their timing and frequency. The present study demonstrates that low BMD can be detected even in younger patients, underscoring the importance of initiating bone health monitoring at earlier stages. Our findings emphasize the need for early and comprehensive monitoring, particularly during childhood and adolescence. Clinical follow-up should include DXA scans, biochemical evaluations, nutritional assessments, and growth monitoring. A multidisciplinary follow-up approach involving metabolic specialists, dietitians, and physiotherapists is essential for optimal patient care. Early and regular individualized follow-up strategies may help to prevent future skeletal complications and improve overall quality of life.

Ethical approval

This study has been approved by the Ethics Committee of Gaziantep University (approval date 24.07.2020, number 2020/259). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: BKA, EG; data collection: BKA; analysis and interpretation of results: BKA, EG; draft manuscript preparation: BKA, EG. 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

Is the patch repair of partial anomalous pulmonary venous drainage equivalent to the Warden procedure?

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ABSTRACT

Introduction: Partial anomalous pulmonary venous return (PAPVR) is a congenital heart defect frequently associated with a sinus venosus atrial septal defect (ASD). Surgical repair varies depending on the anatomical position of the anomalous pulmonary veins. This study aims to compare the outcomes of three surgical techniques - single patch, two-patch technique, and Warden procedure- used in the repair of PAPVR with sinus venosus ASD.

Methods: A retrospective study was conducted, analyzing the outcomes of 87 patients who underwent surgical repair for PAPVR between January 2011 and August 2024. Patients were divided into three groups based on the surgical technique used: 44 underwent the Warden procedure, 33 were treated with the single-patch technique, and 10 received the two-patch technique.

Results: No mortality was observed across all techniques. The median age at operation was 5.4 years (1.4–10.4 years), and the median hospital stay was 3.0 days (IQR 3.0–4.0). Logistic regression analysis revealed a higher likelihood of immediate postoperative complications with the Warden technique (OR: 5.00, 95% CI [1.30–19.25], p = 0.0193). No patients required a pacemaker implantation. Four patients who had a single (2) and double patch (2) technique needed a reintervention on the systemic or pulmonary venous pathway, while no patient who had a Warden procedure needed a reintervention of the venous pathways.

Conclusion: Despite a higher risk of early complications, the Warden procedure seems to preserve patients from reinterventions on the systemic or pulmonary venous pathway.

Keywords: partial anomalous pulmonary venous return, warden procedure, congenital heart surgery, sinus venosus ASD, pediatric cardiac surgery, reintervention

INTRODUCTION

Partial anomalous pulmonary venous return (PAPVR) is a rare congenital heart defect, occurring in 0.4–0.7% of the population.[1] It involves one or more pulmonary veins draining abnormally into the right atrium (RA), either directly or via systemic veins.[2] PAPVR often coexists with sinus venosus atrial septal defects (ASDs), most commonly involving the right upper pulmonary vein draining into the superior vena cava (SVC).[3]

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This study evaluates the outcomes and postoperative complications of three surgical techniques—single-patch, two-patch, and Warden procedures—for right-sided PAPVR repair in pediatric patients at our institution over the past 15 years.

PATIENTS AND METHODS

This study was approved by the Institutional Ethics Committee (Approval no: Pro00014533). A total of 87 PAPVR repairs performed between 2011 and 2024 were reviewed, comparing outcomes of single-patch, two-patch, and Warden techniques. Among the 87 patients, 44 underwent the Warden procedure, 33 underwent the single-patch technique, and 10 underwent the two-patch technique.

Patient characteristics such as age, weight, sex, and the presence of comorbidities, including chromosomal anomalies, prematurity, and non-cardiac risk factors (e.g., renal dysfunction, pulmonary disease) were collected. Associated cardiac anomalies and additional interventions were also documented, including secundum ASDs, patent ductus arteriosus (PDA), and the need for concurrent pulmonary artery patching or secondary ASD closure. These data are summarized in Table 1.

Definitions and variables

Reintervention was defined as any surgical or catheter-based procedure required after hospital discharge following the initial repair. In-hospital reinterventions (e.g., for pneumothorax, pericardial effusion, or temporary pacing) were excluded, as they reflect immediate postoperative care rather than long-term surgical durability. The SVC gradient was categorized by Doppler flow evaluation as mild (<3 mmHg), moderate (3–5 mmHg), or severe (>5 mmHg), determined by institutional cardiologists. Pulmonary vein velocity was categorized as normal or elevated. Preoperative and postoperative conduction blocks were assessed using ECG recordings, with any complete or incomplete conduction block classified as a conduction abnormality.

Surgical Approaches: All cases were approached via median full sternotomy under cardiopulmonary bypass.

Single-Patch Technique: An intra-caval baffle redirects anomalous pulmonary veins to the LA through the sinus venosus ASD.

Two-Patch Technique: One patch redirects the veins, while another enlarges the SVC.

Warden Procedure: The SVC is transected above the anomalous connection and reattached to the right atrial appendage, while a patch redirects the pulmonary veins to the LA.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as medians and interquartile ranges (IQR). Chi-square, Fisher's exact tests, T-tests, or Mann-Whitney U-tests were used as appropriate. Logistic regression analysis was conducted to estimate odds ratios (OR) and 95% confidence intervals (CI). All p-values <0.05 were considered statistically significant. Analysis was performed using RStudio version 4.3.1.[4]

RESULTS

1. Demographic and clinical characteristics:

Table 1 summarizes the demographics and baseline characteristics of the 87 patients included in the study. Among them, 51 (59%) were female, and 36 (41%) were male. The median age at the time of operation was approximately 65 months (95% CI [31, 127]). The median weight was 18 kilograms (95% CI [12, 41]). Eight patients (9%) had a known chromosomal abnormality, and 26% (n = 23) had a preoperative risk factor associated with a non-cardiac diagnosis such as renal dysfunction, pulmonary disease, prematurity, hypothyroidism, or significant developmental delay.

2. Surgical techniques and operative metrics

Among the techniques, 44 patients underwent the Warden procedure, 33 underwent the single-patch technique, and 10 underwent the two-patch technique. Cardiopulmonary bypass and cross-clamp times differed significantly across groups ($p < 0.01$). Median CPB times were 88, 71, and 91 minutes; cross-clamp times were 47, 38, and 43 minutes for Warden, single-patch, and two-patch groups, respectively. Core temperatures also varied ($p = 0.03$); values are shown in Table 1. Extubation in the operating room was achieved for 63% (n = 55) of patients, and only one patient (1%) required postoperative mechanical circulatory support. This Warden patient required venoarterial ECMO for right ventricular failure immediately postoperatively; support was weaned after 3 days. The average length of hospital stay following surgical repair was 3 days (95% CI [3, 4]).

Table 1. Descriptive analysis of surgical techniques in PAPVR repair

Perioperative Variable	Overall Median (IQR); n (%) N = 87	Two-Patch Median (IQR); n (%) N = 10	Single-patch Median (IQR); n (%) N = 33	Warden Median (IQR); n (%) N = 44	p-value
Gender					
Male	36 (41%)	8 (80%)	13 (39%)	15 (34%)	**0.03**
Female	51 (59%)	2 (20%)	20 (61%)	29 (66%)	
Age at operation (months)	64.5 (931.1–125.1)	49.2 (30.9, 99.1)	49.0 (27.5, 85.7)	99.3 (45.7, 173.2)	0.06
Weight at operation (kg)	18 (12, 41)	17 (13, 18)	16 (11, 30)	24 (15, 50)	0.13
Prematurity	12 (14%)	1 (10%)	4 (12%)	7 (16%)	0.91
Chromosomal Abnormalities	8 (9%)	1 (10%)	0 (0%)	7 (16%)	NA
Pre-Op non-cardiac risk factors	23 (26%)	2 (20%)	5 (15%)	16 (36%)	0.11
ASD Type					
Superior Sinus Venosus	67 (77%)	9 (90%)	26 (79%)	32 (73%)	not applicable
Inferior Sinus Venosus	5 (6%)	1 (10%)	4 (12%)	0 (0%)	
Secundum	5 (6%)	0 (0%)	2 (6%)	3 (7%)	
Intact	10 (11%)	0 (0%)	1 (3%)	9 (20%)	
Preoperative Moderate/Severe Dilation RV Dilation	57 (66%)	10 (100%)	21 (64%)	26 (59%)	not applicable
Preoperative Qp/Qs (ratio)	2.50 (2.00, 2.98)	2.55 (2.13, 3.00)	2.45 (1.95, 2.95)	2.45 (2.00, 2.80)	0.66
Anomalous Pulmonary Vein Drainage Site					not applicable
SVC	46 (53%)	7 (70%)	7 (21%)	32 (73%)	
SVC-RA Junction	25 (29%)	3 (30%)	12 (36%)	10 (23%)	
RA (including IVC-RA junction)	12 (14%)	0 (0%)	12 (36%)	0 (0%)	
Others (IVC, Coronary Sinus, Innominate Vein)	4 (5%)	0 (0%)	2 (6%)	2 (4%)	
Additional Operational Procedure					**0.01**
None	47 (54%)	1 (10%)	16 (48%)	30 (68%)	
Additional secundum ASD/ PFO Closure	35 (40%)	8 (80%)	16 (48%)	11 (25%)	
Others	5 (6%)	1 (10%)	1 (4%)	3 (7%)	
CPB Time (min)	84 (71, 102)	88 (83, 99)	71 (62, 84)	91 (75, 123)	**<0.01**
Cross Clamp Time (min)	41 (33, 49)	47 (44, 52)	38 (32, 43)	43 (34, 55)	**<0.01**
Lowest Core Temp -Rectal (°C)	32 (30, 33)	33 (32, 34)	32 (31, 32)	31 (30, 32)	**0.03**
Length of Hospital Stay (days)	3.00 (3.00, 4.00)	3.00 (3.00, 3.00)	3.00 (2.73, 4.00)	4.00 (2.93, 4.18)	0.41
Length of Follow-Up (days)	417 (14, 1,453)	854 (478, 999)	399 (13, 1,656)	260 (20, 1,112)	0.84

ASD = atrial septal defect; PFO = patent foramen ovale; RA = right atrium; SVC = superior vena cava; IVC = inferior vena cava; RV = right ventricle; Qp/Qs = pulmonary-to-systemic flow ratio, CPB = cardiopulmonary bypass

3. PAPVR pathoanatomic characteristics

The most common PAPVR pattern involved the right upper and middle pulmonary veins draining into the SVC, seen in 55% (n = 48) of patients. Among these, the choice between Warden (53%) and patch techniques (58%) was balanced. However, when drainage was exclusively to the SVC (n = 32), the Warden procedure was used significantly more often (73%, $p < 0.001$).

The second most frequent pattern was drainage at the SVC–right atrial (RA) junction (29%, n = 25), with 23% receiving Warden and 35% patch repairs; no significant preference was observed.

In patients with drainage directly into the RA or (inferior vena cava–right atrial) IVC-RA junction (14%, n = 12), all underwent patch repair. Less common drainage sites (5%, n = 4) included the IVC, coronary sinus, or innominate vein.

The Warden procedure was associated with longer cardiopulmonary bypass (median 91 vs. 71 minutes, $p < 0.01$) and cross-clamp times (43 vs. 38 minutes, $p < 0.01$), and slightly lower core body temperatures ($p = 0.03$).

The most common accompanying ASD type in PAPVR patients was superior sinus venosus, identified in 77% (n = 67) of cases. Additional procedures were performed in 46% of patients, primarily secundum ASD or PFO closures. Rare procedures included Maze, tricuspid repair, (Right Pulmonary Artery) RPA plasty, PDA ligation, and (Right Coronary Artery) RCA button transfer with PA reconstruction (1 case each; see Table 1).

At the most recent follow-up, 86% of patients had no measurable SVC gradient (<3 mmHg), while 7% had mild (3–5 mmHg) and 7% moderate (>5 mmHg) gradients. All patients demonstrated normal pulmonary vein velocities.

4. Postoperative outcomes

Immediate Complications: Postoperative complications occurred in 15 patients (17%), with the Warden technique showing a significantly higher rate (27%, OR: 5.00, p < 0.05) compared to the single-patch and two-patch techniques (7%). Despite this, reintervention rates did not differ significantly between surgical techniques (OR: 0.23).

Conduction Blocks: Preoperative conduction blocks were present in 24 patients (28%). Among these, resolution was achieved in 42% of patients in the Warden group compared to 66% in the single-patch or two-patch groups. Postoperative conduction blocks developed in 19 patients (30%) who did not have preexisting blocks, with a higher incidence in the Warden group (37%) compared to the single-patch or two-patch groups (23%). No patients required a pacemaker implantation.

For patients without preoperative conduction blocks, 37% (n = 12) of those undergoing the Warden procedure developed postoperative conduction blocks compared to 23% (n = 12) in the single-patch or two-patch groups. In contrast, among patients with preoperative conduction blocks, resolution was achieved in 42% (n = 5) of the Warden group and 66% (n = 8) of the single-patch or two-patch group.

Reinterventions: No reoperations were required in the cohort. However, five patients (6%) underwent catheter-based reinterventions. Four of these occurred in patients repaired with the single-patch or two-patch techniques and included balloon angioplasty of the SVC, right pulmonary venous baffle, SVC stent placement, and balloon valvuloplasty of the right upper pulmonary vein. Logistic regression analysis did not identify a difference in reintervention rates between surgical techniques (OR: 0.23, 95% CI [0.02–2.12], p = 0.19) (Table 2). Notably, no patient in the Warden group required reintervention on the venous pathways.

DISCUSSION

Challenges and considerations in PAPVR surgical management

The surgical management of PAPVR poses unique challenges due to variability in anatomy. While it may not be considered one of the most technically demanding cardiac surgeries, the complexity lies in achieving a repair that is not only effective but also free of long-term complications.

Table 2. Logistic regression analysis for immediate complication and reintervention

	PAPVR Repair Method			
	Overall	**Warden**	**Single Patch and Two Patch**	**p-value**
Reintervention	5 (6%)	1 (2%)	4 (9%)	0.20
Immediate Complications	15 (17%)	12 (27%)	3 (7%)	0.02
		OR	**(95% CI) 2.5 % 97.5 %**	**p-value**
Immediate Complication		5.00	1.30, 19.25	0.0193
Reintervention		0.23	0.02, 2.12	0.19

OR = odds ratio; CI = confidence interval

The choice of surgical technique—single-patch, two-patch, or Warden—depends on the location of the anomalous veins and the flow dynamics. For example, the Warden procedure is preferred for veins farther from the sinus venosus defect, as it minimizes the risk of obstruction. However, it requires significant technical expertise, especially in cases with a short right atrial appendage, where stretch anastomosis or patch augmentation may be necessary.[5] Ultimately, surgical decisions rely on the surgeon's expertise and judgment.

The Warden technique is also frequently used in anatomically complex cases of PAPRV, particularly in younger, smaller patients with additional defects.[6] However, this increased complexity can lead to longer cardiopulmonary bypass and cross-clamp times, as well as a higher risk of anastomotic stenosis at the cavo-atrial junction. Some claimed that prophylactic measures, such as augmentation of the anastomosis, are essential to reduce these risks and ensure optimal outcomes.[7] We do not share this point of view and do not add patches to these anastomoses. In a broader context, our approach aligns with multiple published reports that emphasize individualized surgical strategies based on pulmonary venous anatomy and drainage site. Studies by Mathis et al. and Binsalamah et al. highlight how the choice of repair should be anatomically guided, particularly when balancing technical feasibility and long-term flow characteristics.[6-8] Furthermore, Alsoufi et al. observed that outcomes are optimized when repair techniques are adapted to the drainage location and associated cardiac anatomy.[9] These studies reinforce that no single technique is universally superior, but that tailored approaches lead to comparable results in terms of mortality and reintervention.

Postoperative outcomes and complications

Rhythm abnormalities, such as junctional rhythms, were observed in 9% (n = 8) of our patients, with 5 requiring temporary pacing. However, no patients required permanent pacemaker implantation, consistent with prior studies.[7,8] These findings suggest that transient rhythm disturbances are common but rarely lead to long-term complications, irrespective of the repair technique. While the observed rhythm abnormalities were self-limited, caution is still warranted near the atrioventricular node and His bundle region — particularly around the triangle of Koch — during suture placement, as inadvertent injury to conduction tissue remains a theoretical risk.

Reintervention rates were low in our cohort, with four cases primarily related to obstruction in the single-patch or two-patch group. No reintervention occurred in the Warden group. Literature reports similarly low reoperation rates across techniques (related to SVC or pulmonary vein obstructions, anastomotic strictures, and arrhythmias caused by damage to the SA node or its blood supply), with no clear superiority in terms of reintervention-free survival.[5-7]Although the Warden procedure is traditionally described in pediatric populations, its application in older children and adults has also been reported in the literature. In our cohort, the decision to perform a Warden repair in selected older patients was based on anatomic considerations—such as high insertion of the anomalous pulmonary veins into the superior vena cava and concerns for sinus node preservation. This approach has been supported by prior reports, including institutional series demonstrating favorable outcomes in adolescent and adult patients undergoing the Warden procedure.[7,9,10]

The Warden technique in our study showed a significantly higher likelihood of immediate postoperative complications (OR: 5.00, p = 0.0193), most of them benign, such as arrhythmias, sinus node dysfunction, and respiratory complications. Interestingly, studies such as Zubritskiy's reported fewer sinus node dysfunction cases with the Warden technique compared to two-patch repairs, highlighting variability in complication rates and the need for individualized surgical strategies.[10,11]

Our findings underline the complexity of PAPVR repair and the need for meticulous surgical planning to minimize complications and optimize outcomes. This study is limited by its retrospective nature and sample size, underscoring the need for prospective, multicenter trials to further refine technique selection and long-term management strategies.

CONCLUSION

Despite a higher rate of early postoperative complications, the Warden procedure showed favorable long-term outcomes, with no reinterventions on systemic or pulmonary venous pathways. This suggests that in selected patients, it provides reliable and durable reconstruction. As all three techniques had low morbidity, surgical choice should be individualized based on anatomy and institutional experience.

At our institution, we shifted to a preference for the Warden procedure, reflecting a lower threshold for its selection. Ultimately, all techniques yield comparably low morbidity and mortality rates, highlighting the critical importance of individualized surgical planning.

Ethical approval

This study has been approved by the Children's National Medical Center Institutional Review Board (approval date 25.11.2020, number Pro00014533). The institution provides departmental allowance for retrospective research, under which this study was conducted.

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Author contribution

The authors declare contribution to the paper as follows: Study conception and design: AT, CY; data collection: ZBE, MO, MD; analysis and interpretation of results: AT, YdU, CY; draft manuscript preparation: AT, ZBE, MO. 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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Case Report

Moyamoya disease and cerebral arteriovenous malformation combination presenting with cutaneous findings

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ABSTRACT

Moyamoya disease (MMD) is a rare, chronic, progressive intracranial arteriopathy primarily affecting children. It is characterized by stenosis or occlusion of the internal carotid and cerebral arteries, often presenting with ischemia or hemorrhagic strokes. The co-occurrence of MMD and cerebral arteriovenous malformation (AVM) is exceedingly rare. We report the case of a seven-year-old male who presented with persistent intraoral bleeding. Physical examination revealed a cavernous hemangioma in the palatal mucosa and a hyperpigmented epidermal nevus. Magnetic resonance imaging identified an intracerebral AVM, subsequently diagnosed as MMD. The patient underwent anterior interhemispheric AVM resection and received prophylactic antiplatelet therapy. He remains under clinical follow-up with no complications or neurological sequelae. Recognizing dermatological manifestations associated with MMD is essential, particularly when concurrent vascular anomalies are present. A multidisciplinary approach, incorporating both endovascular and surgical strategies, is critical in managing such complex cases.

Keywords: arteriovenous malformation, child, hemangioma, Moyamoya disease, nevus

INTRODUCTION

Moyamoya disease (MMD) is a progressive steno-occlusive disorder involving the supraclinoid segments of the internal carotid arteries and the proximal portions of the middle and anterior cerebral arteries. This condition leads to early-onset ischemic or hemorrhagic strokes. The term [ITALIC]"Moyamoya"[/ITALIC], derived from Japanese, describes the hazy, smoke-like appearance of the collateral vascular network seen on angiographic imaging. Although initially identified in East Asian populations, MMD is now recognized globally as a notable cause of pediatric stroke.[1,2]

MMD, a rare condition that can be idiopathic or associated with various underlying disorders, including neurofibromatosis-1, sickle cell anemia, Down's syndrome, antiphospholipid syndrome, renal artery stenosis, congenital heart defects, and autoimmune thyroiditis. Based on the presence or absence of associated conditions, MMD is classified into two categories: idiopathic Moyamoya disease and Moyamoya syndrome (MMS). The former is diagnosed in patients without any identifiable underlying pathology, while the latter is defined by its association with systemic diseases.[3-5] Although MMD primarily affects the cerebral vasculature, it may also involve other organs such as the kidneys, eyes, musculoskeletal system, and skin. Comprehensive systemic evaluation is therefore essential to identify possible syndromic associations and prevent delayed or missed diagnoses.[3-5]

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In this report, we present the case of a seven-year-old boy who was admitted with persistent intraoral bleeding caused by a cavernous hemangioma located on the palatal mucosa. Cranial magnetic resonance imaging (MRI) revealed cerebral arteriovenous malformations (AVM) consistent with a diagnosis of Moyamoya disease.

CASE REPORT

A seven-year-old male patient was admitted with persistent oral bleeding, which originated from a hemorrhagic cavernous hemangioma located on the right side of the palatal mucosa. The bleeding was continuous and unresponsive to conservative measures.

The patient had been born via spontaneous vaginal delivery and had undergone surgery for strabismus at the age of two. There was a history of consanguinity between the parents (first-degree cousins).

On physical examination, his height was 117 cm (-1.7 SDS), and his weight was 20 kg (-1.2 SDS). He had facial asymmetry and a hemorrhagic cavernous hemangioma on the right palatal mucosa. Additionally, a hyperpigmented, helical epidermal nevus was observed on the left side of the trunk, extending from the left shoulder to the lower abdomen and right gluteal region, following the 'Blaschko's lines' along the left arm (Figure 1).

The patient's initial work-up, including hematological, biochemical, thyroid functions, and coagulation parameters, was all within normal limits. Abdominal ultrasonography, cardiac echocardiography, skeletal survey, and ophthalmologic evaluation were also unremarkable. A pediatric genetics consultation was requested. Whole-exome sequencing (WES) revealed no pathogenic variants. Given the rarity and complexity of MMD, identifying a causative gene remains challenging. Since no specific genetic test is currently available for MMD, additional system evaluations such as ophthalmologic, cardiac, dermatologic, and skeletal assessments were recommended only in the presence of clinical suspicion. No associated genetic syndrome was identified upon re-evaluation by the genetics team.

Cranial MRI demonstrated a dilated tortuous arteriovenous malformation in the right frontal lobe, fed by the distal branches of the anterior cerebral artery (ACA), draining into the cortical veins and central nervous system. A second AVM was detected in the corona radiata, with dilated parietotemporal draining veins fed by perisylvian branches

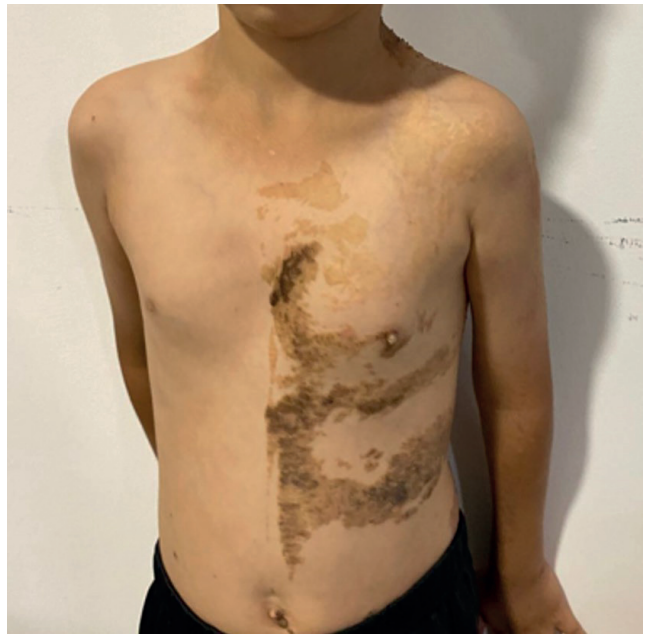

Figure 1. Helical hyperpigmented epidermal nevus on the left half of the trunk extending from the left shoulder to the lower umbilicus and right gluteus and following the Blasko lines on the left arm

of the middle cerebral artery (MCA), draining into the internal cerebral veins and the straight sinus via pericallosal dilated venous structures (Figure 2, Figure 3, Figure 4). At the level of the basal ganglia and mesencephalon, arterial angiomatosis resembling the classic "moyamoya" appearance was observed (Figure 5).

Digital subtraction angiography (DSA) confirmed the presence of two AVMs: one fed by distal branches of the right ACA and draining into the superior sagittal sinus, and another fed by MCA branches, draining into the internal cerebral vein. Capillary anastomoses were noted between the two AVMs. Selective bilateral internal carotid artery (ICA) injections revealed globally abnormal, tortuous arteriolar networks with delayed capillary filling, more pronounced on the right side (Figures 5, Figure 6, Figure 7). Based on these findings and the revised 2021 diagnostic criteria, the patient was diagnosed with MMD—characterized by stenosis of the intracranial ICA, narrowing at the terminal portion, and the development of abnormal collateral networks in the basal ganglia and periventricular white matter.[4]

The patient underwent surgical excision of the right parietal interhemispheric AVM. Postoperative follow-up showed no

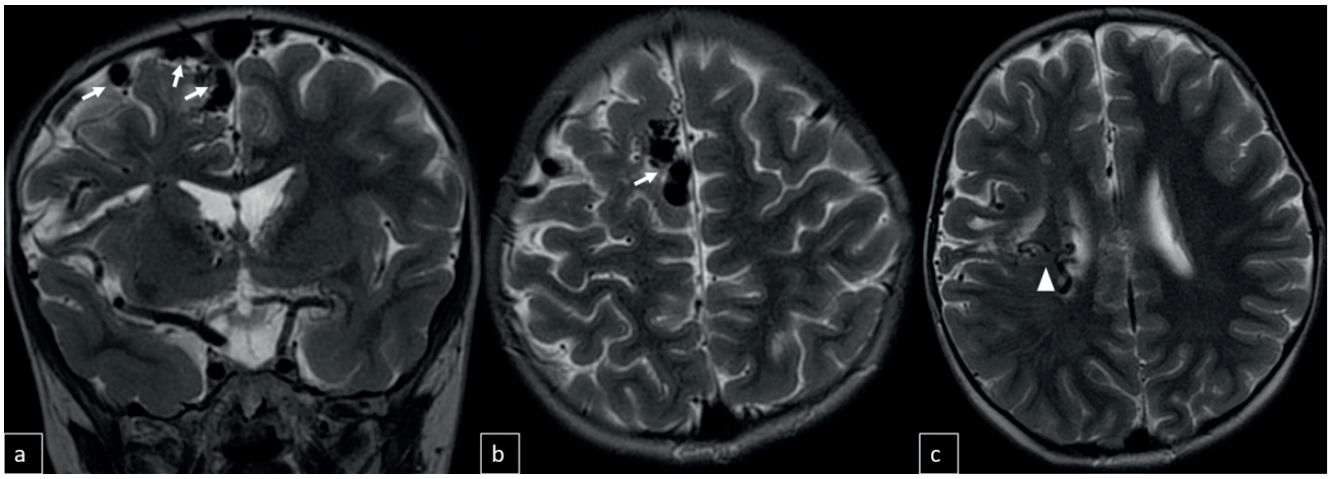

Figure 2. Coronal (a) and axial (b, c) T2A brain MRI sequences show the enlarged venous structures of the frontal AVM draining into the superior sagittal sinus (white arrows), tortuous, wide veins (arrowheads) draining into the internal cerebral veins of the second AVM observed in the temporoparietal region, and enlargement of the feeding middle cerebral artery (black arrow)

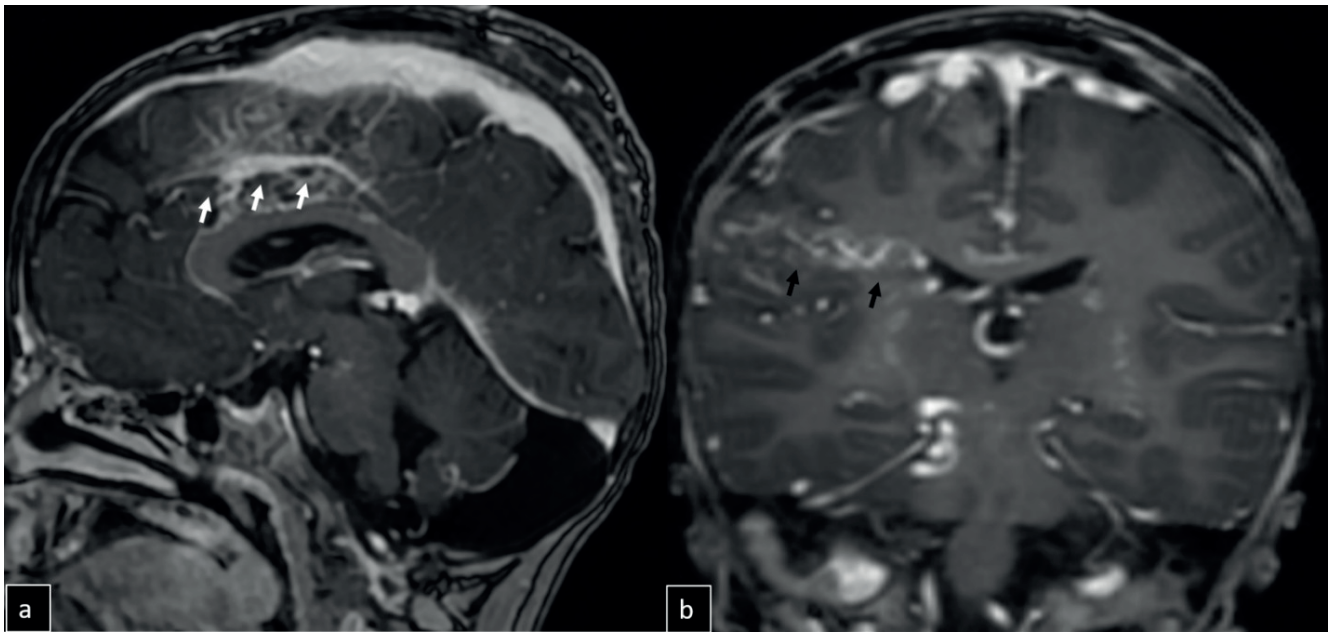

Figure 3. Sagittal (a) and coronal (b) post-contrast T1A brain MRI images show the nidus structure of the temporoparietal AVM (white arrows) and the collecting veins draining into the internal cerebral veins (black arrows).

complications or neurological deficits, and no residual AVM was observed. Due to the proximity of the corona radiata AVM to the corticospinal tract, gamma knife radiosurgery was preferred and planned for a later age. Prophylactic low-dose aspirin was initiated to prevent ischemic events. Encephaloduroarteriosynangiosis (EDAS), an indirect cerebral revascularization technique, was considered for MMD, but was postponed due to potential bleeding risks in the presence of untreated AVMs. The patient continues to be followed up regularly without further complications.

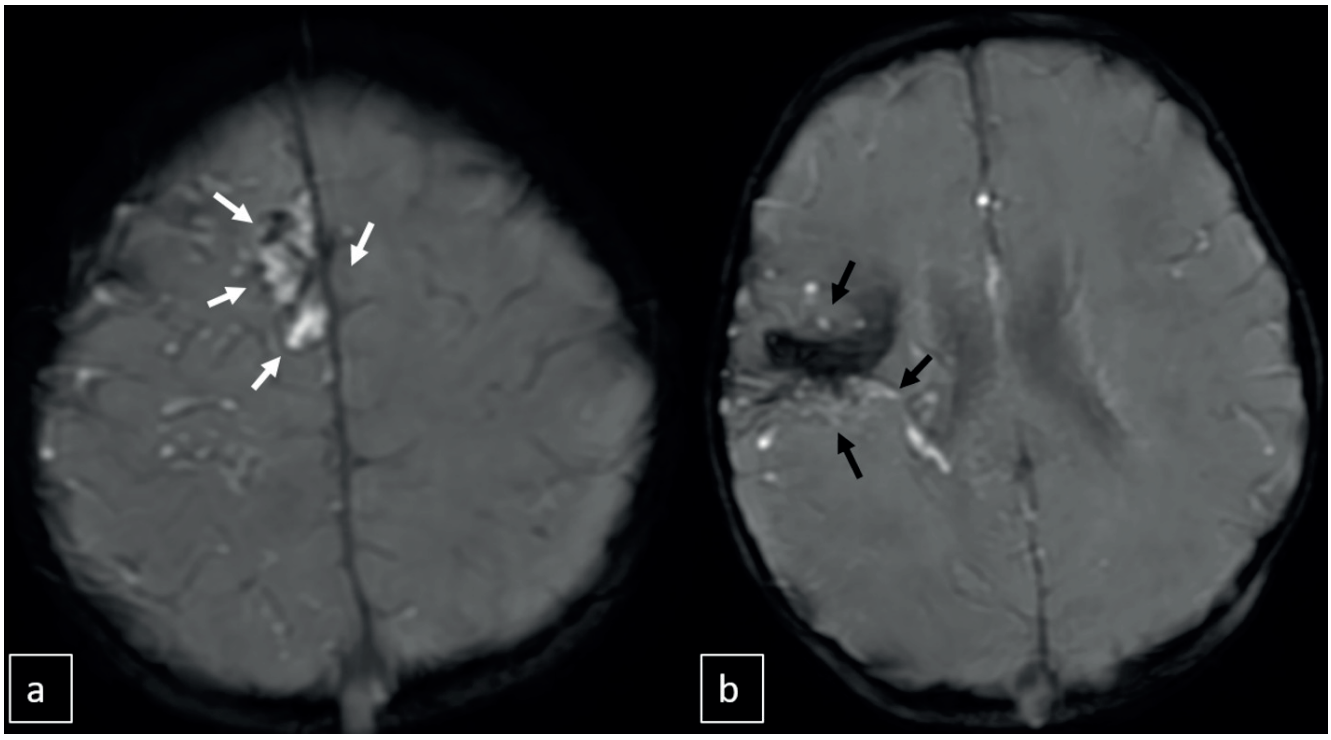

Figure 4. In the blood-sensitive SWI sequence, nidus structures showing intense vascularity of AVMs are seen in (a) the frontal paracentral area (white arrows) and (b) the parietotemporal area (black arrows).

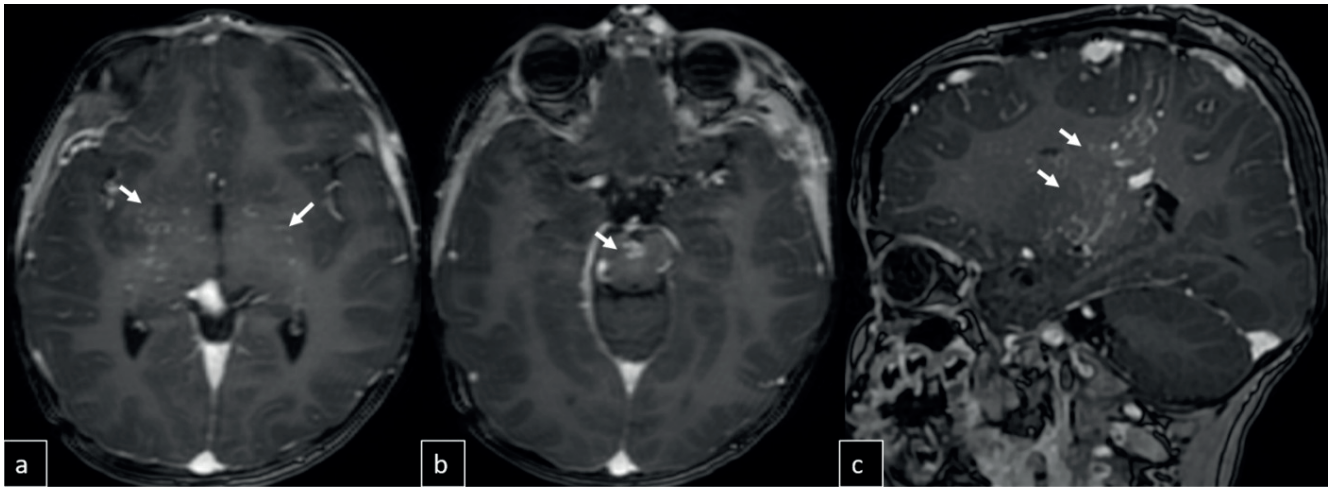

Figure 5. In brain MRI post-contrast axial (a, b) and sagittal (c) T1A images, tortuous dense arterial structures associated with Moya Moya-like arterial angiomatosis are observed in the basal ganglia and at the level of the mesencephalon (white arrows).

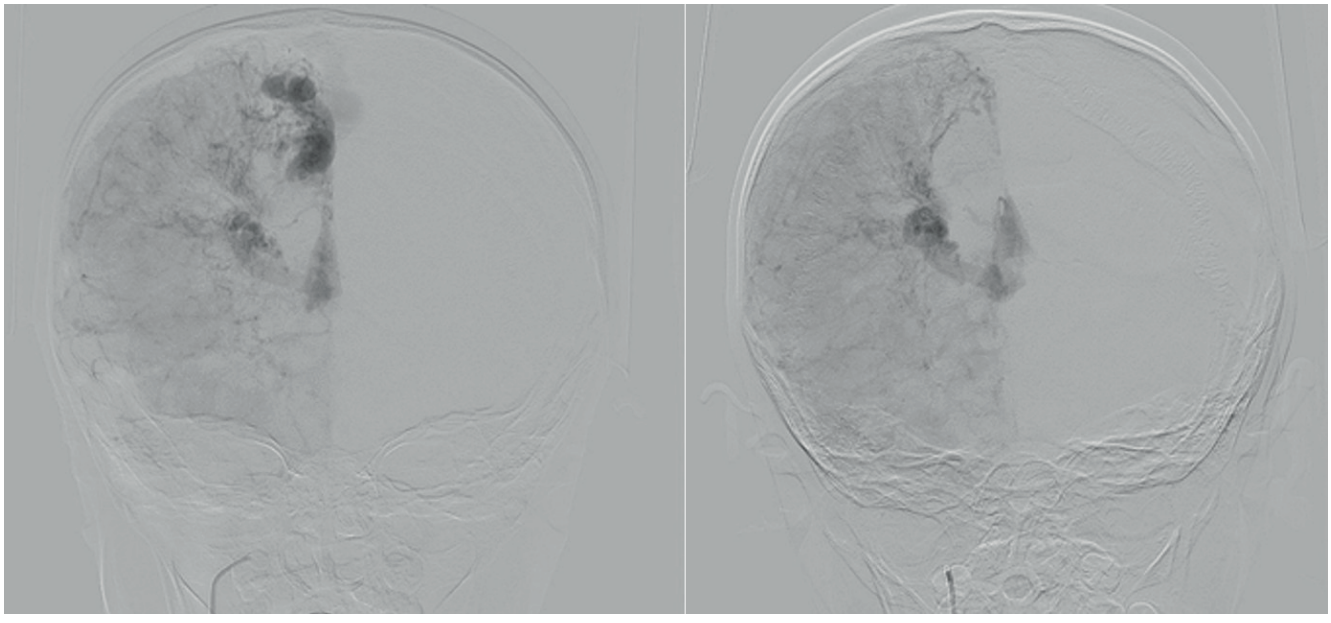

Figure 6. In preoperative diagnostic digital subtraction angiography (DSA); two AVMs are observed, which are fed by the distal branches of the anterior cerebral artery in the right internal cerebral artery injections, drain into the cortical veins in the anterior neighborhood of the right frontal lobe and the superior sagittal sinus, and start from the perisylvian branches of the middle cerebral artery at the level of the corona radiata and drain into the internal cerebral veins and sinus rectus via pericallosal dilated venous structures (a). In postoperative DSA, the AVM site is seen in the control DSA after resection of the AVM with anterior interhemispheric localization. However, the filling of the mentioned AVM is not observed. Filling of the AVM with corona radiata localization is observed (b).

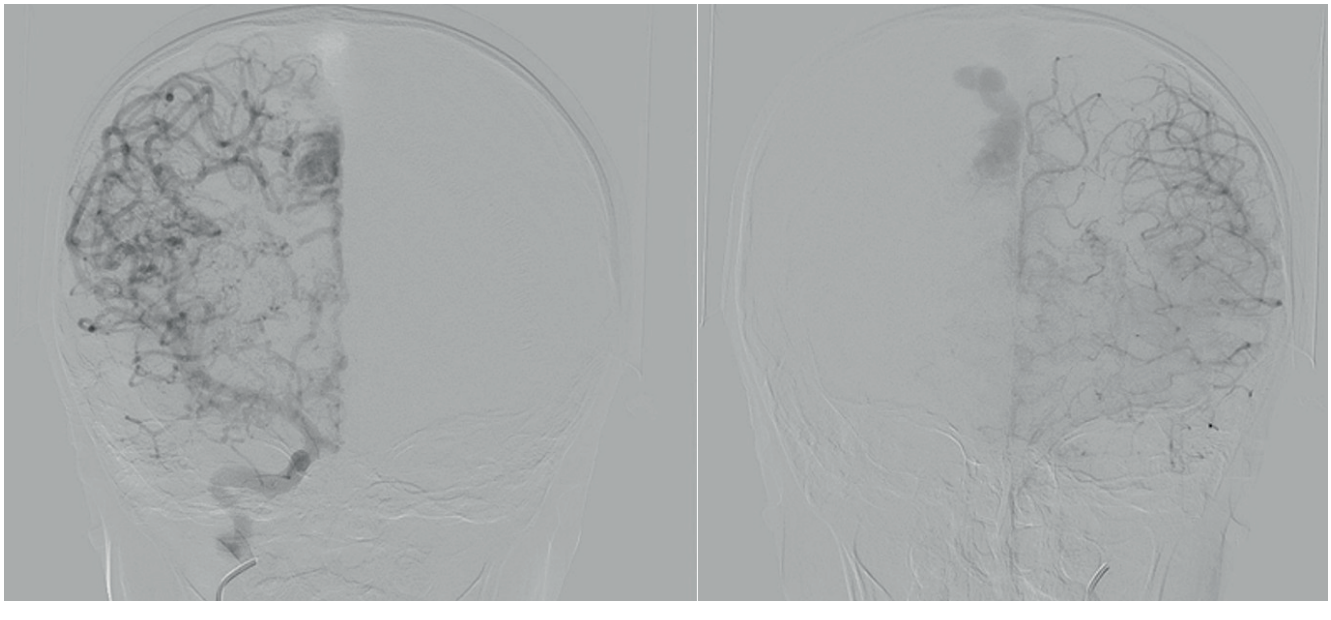

Figure 7. Preoperative diagnostic digital subtraction angiography (DSA) images of right internal cerebral artery injections on the left (a) and left ICA injections on the right(b) are shown. Globally, aberrant and tortuous arteriolar capillary fillings, prominent in the right hemisphere, and a distinct smoke sign on the right with anastomoses between them are observed. These findings indicate MMH.

DISCUSSION

MMD is a cerebrovascular disorder of unknown etiology. Although it can be associated with hereditary or systemic conditions, the underlying cause remains unidentified in more than half of pediatric patients.[4-6] A genetic predisposition is suspected, particularly in patients with a positive family history.

Associated syndromes may present with a variety of systemic manifestations, including facial dimorphisms, cardiac anomalies, developmental delay, ophthalmologic abnormalities, short stature, macrocephaly, short neck, and cutaneous findings.[3] In our patient, comprehensive clinical, radiological, laboratory, and multidisciplinary evaluations—including neurology, dermatology, and genetics—did not reveal any associated systemic disorder.

In children, MMD most frequently presents with ischemic rather than hemorrhagic strokes, with the former accounting for up to 80% of cases. Triggers such as crying, blowing, and hyperventilation can induce ischemic attacks through hypocapnia-induced vasoconstriction.[7] Clinical manifestations may include headaches, seizures, and cognitive impairment. However, due to limited verbal communication skills in early childhood, diagnosis may be delayed.[8] In our case, the diagnosis was made incidentally during the evaluation of intraoral bleeding from a cavernous hemangioma, prior to the onset of any ischemic or hemorrhagic neurological events.

Hemangiomas are benign vascular tumors resulting from vascular endothelial proliferation. Although rare, hemangiomas have been reported in association with MMD.[3] In our patient, a hemorrhagic cavernous hemangioma was observed in the right palatal mucosa. Similar co-occurrences have been documented in the context of Morning Glory Disc Anomaly (MGDA) and Sturge-Weber syndrome.[3] However, our patient did not exhibit any MGDA findings on fundoscopic examination, nor any facial port-wine stains, leptomeningeal angiomatosis, or glaucoma suggestive of Sturge-Weber syndrome.[3] Dermatological findings reported in association with MMD include congenital melanocytic nevi, Becker nevi, and hairy pigmented macules.[3] Our patient presented with a helical hyperpigmented epidermal nevus following Blaschko's lines. Although the exact pathophysiological relationship between skin lesions and MMD remains unclear, some hypotheses suggest a shared origin in primary neuroectodermal dysgenesis or mesodermal anomalies during embryogenesis.[9] Abnormal proliferation of smooth muscle cells, angiogenesis-related factors (e.g., fibroblast growth factors, hepatocyte growth factor), and adhesion molecules may contribute to both vascular malformations and cutaneous manifestations.[10,11]

The simultaneous presence of MMD and AVM is exceedingly rare, with few cases reported in the literature. It remains unclear whether this coexistence is coincidental or mechanistically linked. High-flow stress in AVMs may induce intimal hyperplasia in feeding arteries, leading to a moyamoya-like vascular response. Additionally, the abnormal angiogenic environment in MMD, characterized by increased expression of angiogenic and inflammatory mediators, may predispose to the formation of de novo AVMs or promote arteriovenous shunting through collateral pathways.[12]

DSA remains the gold standard for the diagnosis of MMD and associated vascular anomalies.[4,13,14] Diagnosis is based on stenosis or occlusion of the distal internal carotid artery and/or vessels of the circle of Willis, accompanied by the development of prominent basal collateral networks.[4,13,14] In our case, the diagnosis of MMD was confirmed through DSA following MRI findings.

Surgical revascularization is currently the most effective treatment modality in MMD.[15] Antiplatelet agents are commonly used to reduce the risk of ischemic complications.[15] However, treatment of MMD-associated AVMs remains controversial due to the delicate balance between preserving collateral circulation and preventing hemorrhage. Surgical resection of AVMs may risk disrupting collateral channels; thus, radiosurgical approaches such as gamma knife therapy are often preferred.[12,15] In our case, gamma knife radiosurgery was scheduled for a later age due to the proximity of the AVM to the corticospinal tract. EDAS was considered but postponed due to bleeding risk in the presence of untreated AVMs.

The prognosis of MMD is influenced by patient age, severity of vascular involvement, presence of neurological symptoms, and coexisting vascular malformations.[16] Our patient, who showed no neurological deficits and remains under close surveillance, exemplifies the importance of early diagnosis and individualized multidisciplinary management in rare pediatric cerebrovascular disorders.

This case illustrates a rare co-occurrence of MMD, cerebral AVM, and cutaneous lesions in a pediatric patient. The presence of atypical skin findings may provide early diagnostic clues for underlying neurovascular disorders. Timely recognition and a tailored multidisciplinary approach

are essential to prevent complications and optimize long-term outcomes.

Ethical approval

This study has been approved by the Etlik City Hospital's Ethics Committee (approval date 25.09.2024, number AEŞH-BADEK-2024-874). For case reports and for studies requiring informed consent, whether it was obtained should also be declared here.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: DG; data collection: ŞY; analysis and interpretation of results: EÖ; draft manuscript preparation: MEE, DG. 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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Case Report

Extremely rare cause of acute urinary retention: Guillain-Barré syndrome

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ABSTRACT

Guillain-Barré syndrome (GBS) is an acute immune-mediated demyelinating disease. Early recognition of this disease is crucial as it can progress to life-threatening conditions such as respiratory failure or autonomic dysfunction. Typical clinical signs of GBS include progressive weakness of the extremities, bulbar muscles, and ophthalmoplegia. In pediatric cases, acute bladder dysfunction is more suggestive of acute myelopathy. In this study, we aimed to raise awareness about this rare but serious condition by presenting one of the youngest pediatric GBS cases in the literature, who presented with acute urinary retention as the first finding and was successfully treated with intravenous immunoglobulin.

Keywords: acute urinary retention, Guillain-Barré syndrome, pediatric

INTRODUCTION

Acute urinary retention (AUR) is rarely observed in otherwise healthy children.[1] Common causes include urinary tract infections, severe constipation, and urinary stones. However, more serious conditions such as acute flaccid paralysis should also be considered due to their potentially severe consequences.[2,3]

This report aims to raise awareness about Guillain-Barré syndrome, a rare cause of AUR, and to emphasize the importance of a detailed neurological examination in a previously healthy female child presenting with AUR.

CASE PRESENTATION

A six-year-old girl was admitted to the pediatric emergency department and evaluated by a pediatric surgeon for severe abdominal pain and acute urinary retention, which had developed within 12 hours. She was admitted to the pediatric ward. The patient had a history of an upper respiratory tract infection approximately two weeks prior to the onset of symptoms. On physical examination, the patient exhibited suprapubic fullness and discomfort, consistent with bladder distention. A Foley catheter was inserted, confirming acute urinary retention by draining a large volume of urine.

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The patient was referred to the pediatric neurology department. On initial neurological examination, the absence of deep tendon reflexes in all extremities was noted. The patient's gag reflex was preserved, and there were no signs of ophthalmoplegia, ataxia, or other cranial nerve abnormalities. However, on the second day of hospitalization, she began to exhibit new-onset bilateral leg pain and decreased sensory perception in the lower extremities, and impaired ability to walk on tiptoes. Additionally, muscle strength was decreased (4/5) in all extremities. Moreover, no other signs or symptoms of autonomic dysfunction were observed during clinical follow-up. Intermittent urinary catheterization was administered four times per day throughout the duration of urinary retention.

An electromyography (EMG) study was conducted due to the emerging neurological symptoms, including weakness during tiptoe walking and complaints of constipation. The EMG revealed F-responses were absent and findings compatible with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the most common variant of Guillain-Barré Syndrome.

Spinal MRI with contrast revealed pathological enhancement of the cauda equina nerve roots in the sagittal sequence, further supporting the diagnosis (Figure 1). Cerebrospinal fluid (CSF) analysis via lumbar puncture demonstrated albuminocytologic dissociation: elevated protein level (57 mg/dL; reference range: 15–45 mg/dL) with no white blood cells. CSF glucose was within normal limits. No oligoclonal bands were detected, and polymerase chain reaction (PCR) testing was negative for herpes simplex virus, varicella zoster virus, and enterovirus. Serologic evaluations for coeliac disease, paraneoplastic syndromes, and anti-ganglioside antibodies were also negative.

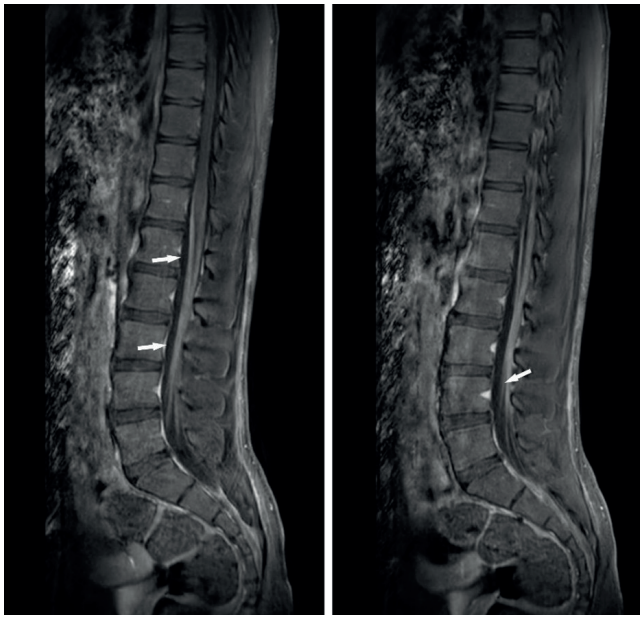

Figure 1. Lumbar spinal MRI (in sagittal sequence) showing pathological contrast enhancement of the cauda equina (white arrows).

The patient was diagnosed with Guillain-Barré Syndrome presenting as the AIDP variant and treated with intravenous immunoglobulin (IVIG) (2 gr/kg total dose, 0,4 gr/kg for five days) and supportive physical therapy. Marked clinical improvement was observed by the sixth day of treatment. At the 30-day follow-up, the patient's neurological examination was completely normal, and she reported no residual symptoms.

DISCUSSION

Guillain-Barré syndrome is a disease that typically develops after an infection, which causes acute weakness and occurs at an incidence of 1.2-2.3 per 100,000 people annually. GBS typically presents with rapidly progressing weakness (within a few days), often associated with pain, sensory disturbances, and paresthesia symmetrically affecting the extremities. Involvement of the respiratory muscles can lead to respiratory failure and mortality. Approximately 2/3 of patients develop autonomic dysfunction.[1,2,4]

Mortality, which is the most critical complication in the first month of Guillain-Barré syndrome, has a significant rate. However, this is usually the case in initially misdiagnosed cases, as the initial symptoms are often nonspecific and many clinical variants can occur. Therefore, suspicion is crucial for early diagnosis and accelerating treatment. AUR is quite rare among pediatric GBS cases.[1,4,5] Our case is one of the youngest reported patients presenting with AUR.

Involvement of non-limb muscles is rather an unusual presentation of GBS, and acute urinary retention has been reported in as low as 10% of cases.[4] This is thought to be caused by a combination of hypo- and hyperactivity in both parasympathetic and sympathetic innervation of the bladder and urethra. AUR in GBS is primarily attributed to autonomic nervous system involvement, particularly affecting the innervation of the bladder and urethral sphincters. Dysregulation of sympathetic and parasympathetic pathways may lead to detrusor underactivity or sphincter dyssynergia, resulting in

impaired bladder emptying. Several studies have shown that autonomic dysfunction, including cardiovascular and urogenital disturbances, occurs in up to two-thirds of GBS patients, even in the early stages and in mild forms of GBS.[1,2,6] The fact that our patient presented with AUR in the early stage, there was no other autonomic system involvement, and weakness developed later shows that pediatric cases can present with different clinical pictures, similar to older cases.

There are many variants of GBS. Acute Inflammatory Demyelinating Polyneuropathy (AIDP) is the most common variant of GBS cases. In the AIDP form, peripheral nerve remyelination occurs relatively faster within weeks compared to other forms, leading to a better prognosis.[5,6] Our patient suffered from the AIDP variant of GBS, which strongly supports her good recovery.

In conclusion, GBS is an acute immune-mediated demyelinating disease. Early recognition of this disease is crucial as it can progress to life-threatening conditions such as respiratory failure or autonomic dysfunction. Typical clinical manifestations of GBS include progressive weakness of the limbs, bulbar, facial muscles, and ophthalmoplegia. We report an early school-age pediatric case of GBS presenting with acute urinary retention, which was successfully treated with IVIG.

Ethical approval

Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: ZNA, SK; data collection: ZNA, TT; analysis and interpretation of results: BEA, SK; draft manuscript preparation: NPT, BEA. 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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Case Report

Pulmonary pseudosequestration in an infant: a case report

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ABSTRACT

Bronchopulmonary vascular malformations constitute a broad spectrum of developmental disorders in which a part of the lung is perfused exclusively from the systemic arterial tree with or without tracheobronchial communication. Pseudosequestration is a rare congenital pulmonary anomaly involving a lung segment with abnormal systemic arterial supply but a preserved connection to the bronchial tree. We present the case of a 5-month-old male referred for evaluation of a cardiac murmur. Initial investigations, including laboratory tests and chest X-ray, revealed ground-glass opacities in the left lung, prompting further imaging. Thoracic computed tomography (CT) and CT angiography demonstrated an aberrant systemic artery originating from the descending aorta and supplying the left lower lobe. Digital subtraction angiography (DSA) was subsequently performed to rule out vascular malformations and confirmed the diagnosis of pseudosequestration. Endovascular treatment was successfully completed with coil embolization and occlusion of the aberrant vessel using an Amplatzer Vascular Plug. The patient remained asymptomatic during a 20-month follow-up period. The case underscores the critical role of early recognition and noninvasive imaging in managing rare congenital pulmonary vascular anomalies.

Keywords: child, pseudosequestration, pulmonary

INTRODUCTION

Normal bronchial connection while receiving anomalous systemic arterial nutrition is an extremely rare pathology and may be difficult to recognize in relatively uncomplicated periods of life. Symptoms may manifest later in life as a consequence of left-sided volume overload resulting from a left-to-left shunt due to abnormal and large aberrant arterial feeding. Symptomatic patients typically present with hemoptysis, exertional dyspnea, pulmonary hypertension, and congestive cardiac failure.[1] Despite its aberrant arterial supply, the defining feature distinguishing pseudosequestration from pulmonary sequestration is its preserved connection to the bronchial tree. No abnormal venous connections or distinct nidus formations, such as those observed in arteriovenous malformations, are present.

Thoracic computed tomography (CT) and CT angiography are the most accessible, noninvasive, and essential diagnostic tools for identifying normal lung parenchyma and isolated abnormal arterial relationships associated with this condition.[2] In cases of pseudosequestration, the basal segments of the left lung are most frequently affected, with no radiographic abnormalities detected in the involved lung parenchyma.[3] We present a case of pseudosequestration involving an anomalous systemic arterial supply to a morphologically normal basal segment of the left lower lobe. This case stands out due to its incidental diagnosis in an asymptomatic infant and the successful endovascular treatment that followed

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CASE REPORT

A 5-month-old infant was referred to our hospital after a suspected cardiac murmur was detected during a routine health check-up. Born via cesarean section at 39 weeks, the patient had no history of neonatal hospitalization, respiratory distress, or episodes of infection or bronchiolitis. Routine laboratory tests, including a complete blood count and assessments of kidney and liver function, were all normal. Chest X-ray revealed ground-glass opacities in the left upper and middle lung zones and opacification in the left lower zone (Figure 1). Thoracic CT and CT angiography were performed for further evaluation, with CT angiography demonstrating an aberrant vessel originating from the supradiaphragmatic descending aorta (Figure 2). This large systemic artery had three branches supplying the left lower lobe. Venous drainage from the affected lung parenchyma occurred via a dilated, tortuous left inferior pulmonary vein into the left atrium (Figure 3). No parenchymal abnormalities were observed, and the left lower lobe bronchus and its segmental branches appeared normal. These findings supported a diagnosis of pseudosequestration, as the affected lobe maintained a connection with the bronchial tree, differentiating it from true sequestration.

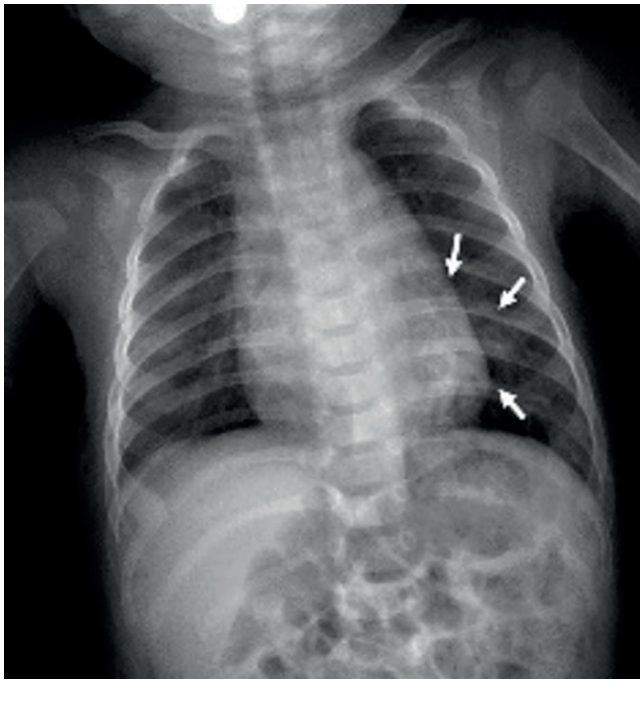

Figure 1. Frontal chest radiography shows linear opacities in the left middle and lower zones (arrows).

To confirm the diagnosis and exclude arteriovenous malformation, digital subtraction angiography (DSA) was performed (Figure 4). The DSA findings were consistent with the CT findings, and the aberrant branches were embolized with coils. The primary aberrant systemic artery, measuring 6.6 mm in its proximal segment, was occluded with an Amplatzer Vascular Plug, effectively terminating the aberrant arterial supply (Figure 5). No complications were observed during a 7-month follow-up period.

DISCUSSION

Pulmonary sequestration is a bronchopulmonary foregut malformation (BPFM) in which segmental lung tissue forms without connection to the bronchial tree or pulmonary arteries. Sequestration is classified as interlobar or extralobar based on the pleural relationship of the aberrant segment.[4] In cases of pseudosequestration, the lung maintains normal communication with the tracheobronchial tree. It is most frequently observed in the left lower lobe, with its blood supply typically originating from an artery branching off the descending thoracic aorta. There is no abnormal venous drainage in this anomaly. This rare congenital anomaly is usually detected incidentally in infants and typically involves the lower lobes, where the blood supply is from an artery branching from the descending thoracic aorta.[5,6] Yamanaka et al. reviewed 12 cases of systemic arterialization of lung segments, of which six patients were under six years of age. The predominant characteristics included male sex, left-sided involvement, and the descending thoracic aorta as the origin of the aberrant artery. In all cases, a single aberrant artery supplied the basal segments of the lower lobe of the lung. [7] In our patient, involvement of the left lower lobe and an aberrant arterial structure originating from the thoracic aorta were identified.

The development of this malformation is explained by the arrest of pulmonary artery growth during the development of the bronchial tree, resulting in an absence of pulmonary blood supply. Pseudosequestration may be congenital or may arise as a consequence of acquired conditions such as bronchiectasis, pulmonary tuberculosis, pulmonary infections, pulmonary thromboembolism, or chronic obstructive pulmonary disease. In affected patients, symptoms may also be attributable to the underlying disease.[8] Primary patients may present with symptoms such as murmur, hemoptysis, exertional dyspnea, pulmonary hypertension, and congestive cardiac failure.[1] Given the severity of these complications, early diagnosis and timely intervention are of critical importance. In this case, the

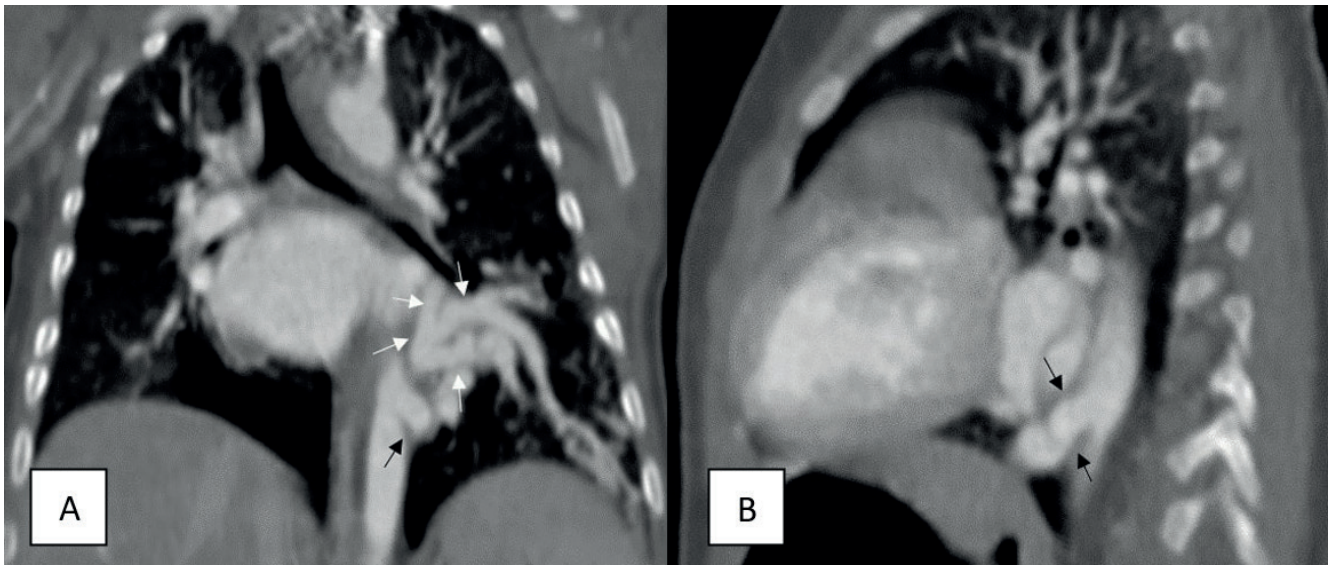

Figure 2. CT angiography, coronal (A) and sagittal (B) reformatted MIP images clearly reveal an aberrant vessel originating from the descending aorta (black arrows). Coronal image (A) also shows dilated branches of the aberrant artery (white arrows).

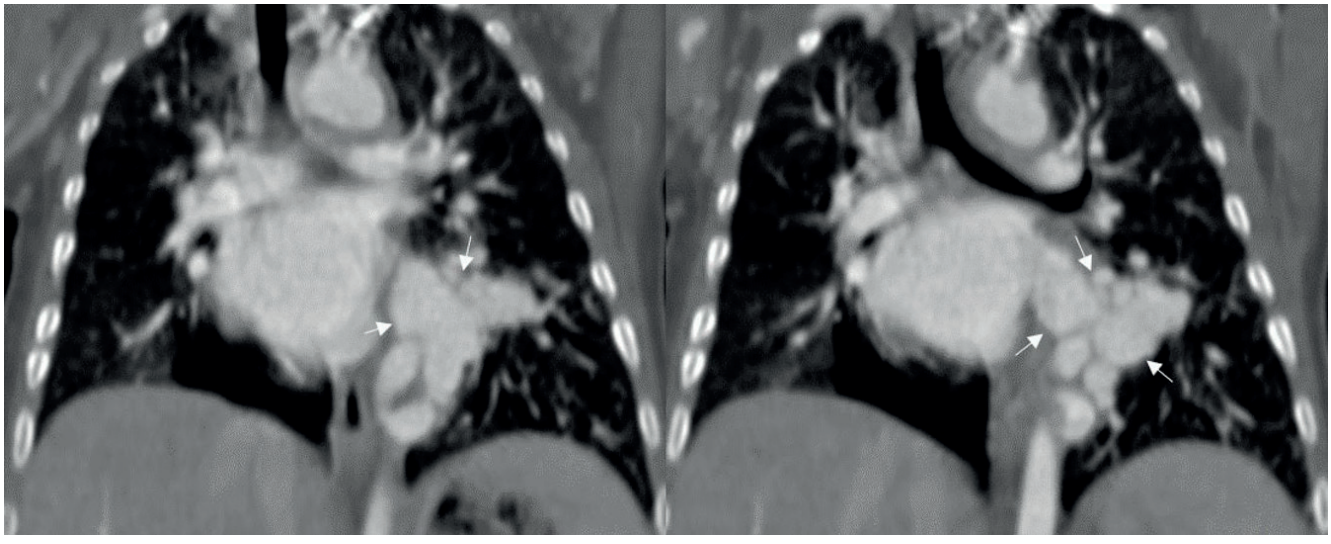

Figure 3. Coronal reformatted CT angiography images demonstrate dilated and tortuous left lower pulmonary vein draining the abnormal lung segment.

only clinical finding was an incidentally detected cardiac murmur.

CT imaging is the preferred noninvasive modality for diagnosing pseudosequestration, providing essential information on the origin of the aberrant artery, its vascular supply, and native pulmonary artery anatomy.[9] Additionally, CT enables the exclusion of other vascular malformations and confirms normal bronchial branching. Dual blood supply, originating from both the systemic and pulmonary arteries, has been reported in certain patients.[8] CT angiography with 3D volumetric imaging and multiplanar reformations is invaluable for treatment planning and determining dual pathology.

As discussed by Yamanaka et al.,[7] surgical resection, including lobectomy or segmentectomy, was often the primary approach in treating complicated cases.

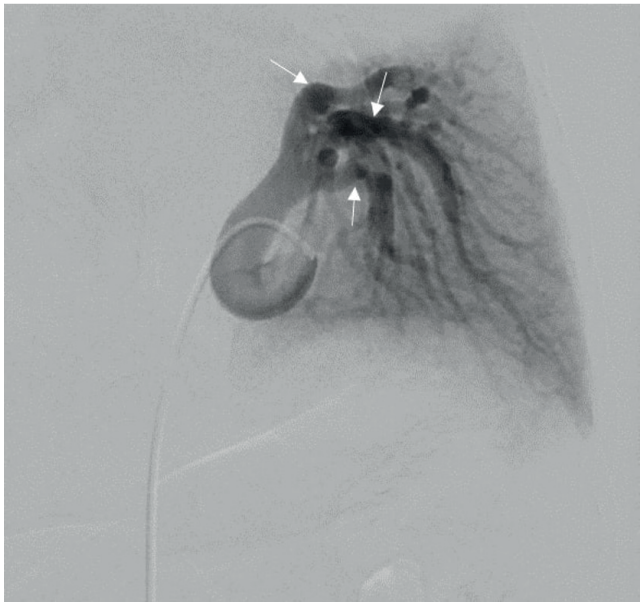

Figure 4. Selective angiography of the aberrant artery originating from the aorta shows a large vascular structure and three main branches in coronal view (arrows).

Endovascular treatments, such as coil embolization of the aberrant artery, present viable and less invasive alternatives. Singh et al.[1] successfully treated an aberrant arterial structure originating from the thoracic aorta in the left lower lobe using coil embolization.

In this case, endovascular embolization was chosen over surgery for its minimally invasive approach, lower perioperative risk, and lung preservation. It successfully occluded the aberrant artery while maintaining normal bronchial and venous drainage. At 20 months of follow-up, the treated lung segment remains viable, with no signs of ischemia, fibrosis, or recurrent shunting, supporting the efficacy of this approach.

Pseudosequestration represents a rare congenital pulmonary anomaly involving a lung segment with aberrant arterial supply but a normal bronchial structure. Thoracic CT and CT angiography serve as crucial noninvasive diagnostic tools. Early diagnosis is essential to detect vascular abnormalities in otherwise normal lung parenchyma, as delayed detection can lead to complications such as pulmonary hypertension and heart failure. This case highlights the critical need to differentiate pseudosequestration from true sequestration due to their disparate management approaches.

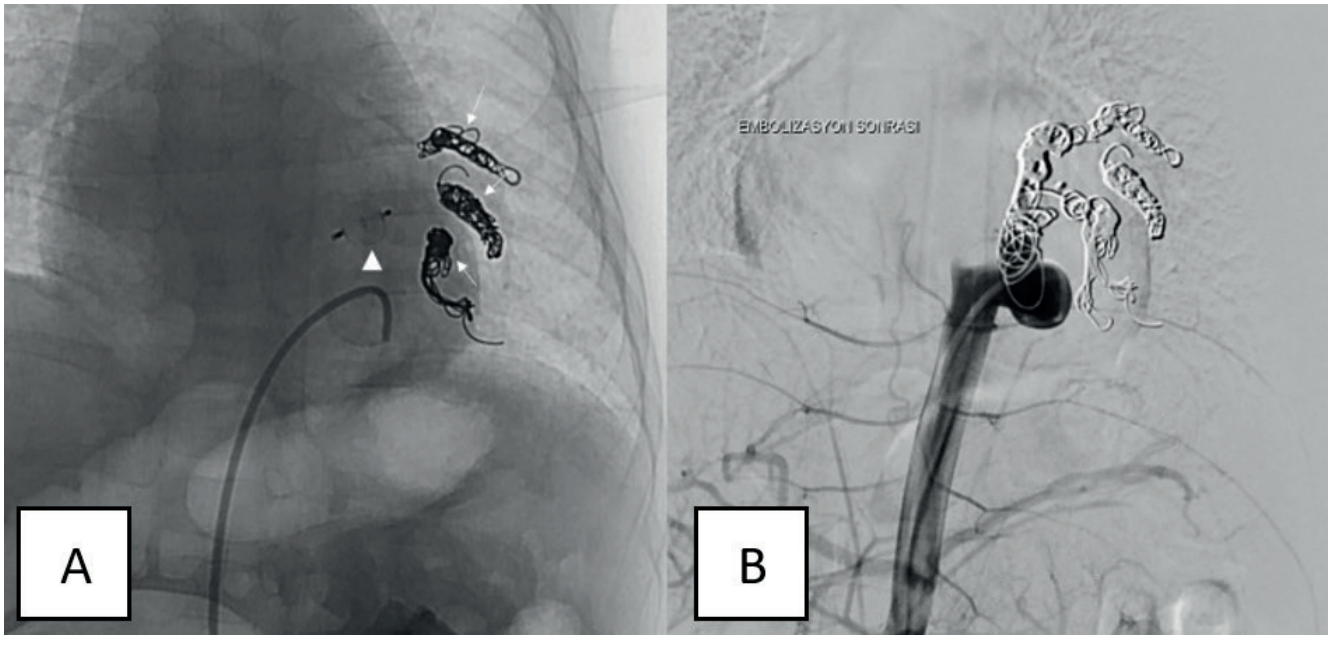

Figure 5. Coronal view DSA images show successful coil embolization of the aberrant arterial supply's branches (arrows) in (A) and Amplatzer Vascular Plug occlusion (arrowhead) in (B).

Ethical approval

Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: ŞY, ÖSF; data collection: ŞY; analysis and interpretation of results: SB, TU, ÖSF; draft manuscript preparation: ŞY, ÖSF. 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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Letter to the Editor

Long-term successful anti-CD20 therapy in infantile giant cell hepatitis with autoimmune hemolytic anemia: the second known surviving case in Turkey

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Dear Editor,

Giant cell hepatitis with autoimmune hemolytic anemia (GCH-AHA) is a rare autoimmune disorder of infancy and early childhood with a poor prognosis. Mortality is high, often due to acute liver failure, sepsis, or complications of liver transplantation. The disease is characterized by Coombs-positive hemolytic anemia and histological evidence of multinucleated giant hepatocytes, frequently following an aggressive course despite immunosuppressive therapy.[1,2] Based on the available literature and clinical records, this appears to be the second known surviving case of GCH-AHA in Turkey.

A 9-month-old male infant was diagnosed with Coombs-positive autoimmune hemolytic anemia (AHA) at 6 months of age and was receiving methylprednisolone. During steroid tapering, he developed jaundice and hepatomegaly. Laboratory evaluation revealed severe transaminase elevation (AST: 4433 U/L, ALT: 4999 U/L), hyperbilirubinemia (total: 7.43 mg/dL, direct: 4.43 mg/dL), and reticulocytosis (15.4%). *Acinetobacter baumannii* was produced in the blood culture, which was treated with intravenous antibiotics. Viral and autoimmune serologies were negative.

Liver biopsy demonstrated multinucleated giant hepatocytes, dense lymphoplasmacytic infiltrates, periportal/interface hepatitis, and focal eosinophils and neutrophils, consistent with GCH (Figure 1). Methylprednisolone (2 mg/kg/day) and intravenous immunoglobulin (IVIG, 1 g/kg) were started, with partial improvement by day 5. On day 10, due to clinical and biochemical deterioration, anti-CD20 monoclonal antibody (rituximab, 375 mg/m² weekly) was initiated. Azathioprine (2 mg/kg/day) was added after the third dose, and mycophenolate mofetil after the sixth dose.

The patient received a total of nine doses of rituximab and five infusions of IVIG. Complete biochemical remission was achieved within 500 days (Figure 2). At the time of writing, follow-up has reached 1000 days, with the patient remaining clinically stable on azathioprine and mycophenolate mofetil.

Previous studies have reported that rituximab may be effective in refractory GCH-AHA, although relapses are common.[3,4] Early administration, in combination with other immunosuppressants, may improve outcomes and reduce progression to liver failure. In the current case, prolonged and combined immunosuppressive therapy resulted in long-term survival with an uneventful follow-up of 1000

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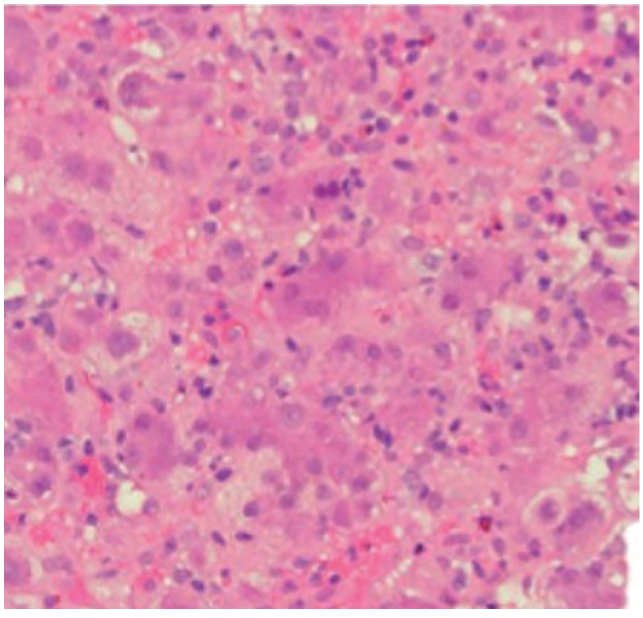

Figure 1. Liver biopsy showing multinucleated giant hepatocytes with dense lymphoplasmacytic infiltrates and interface hepatitis, consistent with giant cell hepatitis.

days. This is an exceptionally rare outcome, making this, to the best of our knowledge, the second known surviving case reported from Turkey.[5] Notably, this patient received a total of nine doses of rituximab, exceeding the commonly reported regimens of four to six doses.[3] This extended protocol was guided by persistent cholestatic liver enzyme elevations and incomplete remission.

Anti-CD20 monoclonal antibody therapy should be considered early in the management of steroid-refractory GCH-AHA to improve survival and prevent irreversible liver injury.

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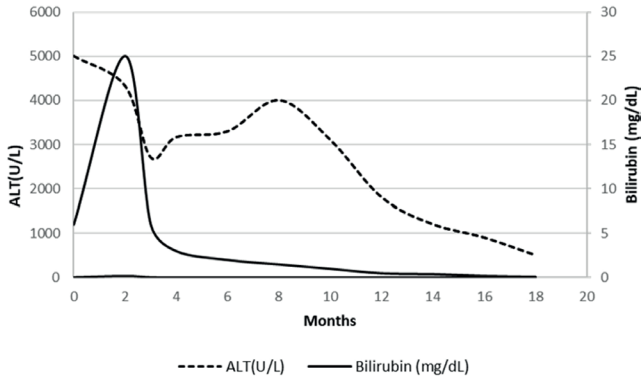

Figure 2. Longitudinal changes in serum alanine aminotransferase (ALT) and total bilirubin levels demonstrating biochemical response during follow-up of an infant with giant cell hepatitis and autoimmune hemolytic anemia.

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Conflict of interest

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