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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr
yayin@galenos.com.tr
Web: www.galenos.com.tr
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The Journal of Pediatric Academy is the official publication of the Kayseri Child Health Association.

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Kayseri Chamber of Medicine,
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Phone: +90.352.2076666 (int) 25373

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Journal of Pediatric Academy (JPA) reports on major advances in the diagnosis and treatment of diseases in children. Each issue presents informative original research articles, review articles, case reports, image corners, and letters to the editor from leading clinicians and investigators worldwide.

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JPA is publishing 4 issues per year in March, June, September and December.

Each issue will include at least 4 original research articles, and other types such as editorial comments, invited reviews, clinical guidance, case reports, image corners, and letters to the editor.

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Manuscript Types

JPA publishes the types of articles briefly described below.

Editorial Comment:

Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with a high reputation on the topic of the research article published in the journal. The authors are selected and invited by the journal to provide such comments. The text should contain 1500 words or fewer. it includes 5 figures and/or tables or fewer and 15 references or fewer.

Research Articles:

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Statistical analysis is usually necessary to support conclusions. Statistical analyses must be conducted by international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified. Units should be prepared by the International System of Units (SI). Limitations, drawbacks, and shortcomings of the original articles should be mentioned in the Discussion section before the conclusion paragraph.

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Letters to the editor should pertain to articles published within the Journal of Pediatric Academy or highlight important new clinical or laboratory insights. The text should contain 1000 words or fewer.

Table 1.
Limitations for each manuscript type

Manuscript Type	Word Limit	Abstract Word	Limit Reference	Limit Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	100	No abstract	5	1	1

References:

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Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/tsd/serials/lji.html. Sample references are given below:

Journal Article:

1. Ang KK, Price RE, Stephens LC, et al. The tolerance of primate spinal cord to re-irradiation. *Int J Radiat Oncol Biol Phys*. 1993;25:459–464.

Journal Article published in non-English Languages:

2. Altuntaş N, Çelebi DT, Koçak M, Andıran N. Yenidoğan bebeklerde direkt coombs testi taraması ve pozitifliğinin morbidite üzerine, etkisi; tek merkezd eneyimi. *Pam Tıp Derg* 2015;8:39-44. (in Turkish)

Book Chapter:

3. Dimery IW. Chemotherapy in head and neck cancer. In: Myerhoff WI, Rice DH, eds. Otolaryngology: head and neck surgery, 2nd ed. Philadelphia: WB Saunders, 1992:1027–1045.

Entire Book:

4. Virchow R. Cellular Pathology. Philadelphia: JB Lippincott, 1863.

Software:

5. Epi Info [computer program]. Version 6. Atlanta, GA: Centers for Disease Control and Prevention; 1994.

Online Journals:

6. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database:

7. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

World Wide Web:

8. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS Web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

URL (Uniform Resource Locator)

9. (J. M. Kramer, K. Kramer [jmkramer@umich.edu], e-mail, March 6, 1996).

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Autoinflammatory Disease: Molecular Insights, Clinical Spectrum, and Emerging Therapies

Author(s)

Selen Duygu Arık, Bengisu Menentoğlu, Özlem Akgün

Affiliation(s)

İstanbul University, İstanbul Faculty of Medicine, Department of Pediatrics, Division of Pediatric Rheumatology, İstanbul, Türkiye

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Abstract

Autoinflammatory disease (AID) represents a heterogeneous group of disorders resulting from dysregulation of the innate immune system, independent of autoantibodies or antigen-specific T-cells. Clinically, AIDs are marked by recurrent or persistent systemic inflammation manifested by organ-specific involvement such as fever, rash, arthritis, serositis, mucocutaneous lesions, cytopenias, and neurological or gastrointestinal complications. This review provides a comprehensive overview of the major autoinflammatory syndromes categorized according to their underlying molecular mechanisms. It discusses the current understanding of the pathogenesis, clinical manifestations, diagnostic approaches, and treatment strategies of AID's, with particular-emphasis on genetically defined syndromes and their molecular classification. Understanding the genetic and molecular basis of these syndromes has led to significant advances in their diagnosis and management. However, variability in clinical presentation, incomplete genotype-phenotype correlations, and the rarity of many conditions continue to pose diagnostic and therapeutic challenges. Continued research into novel disease mechanisms, therapeutic targets, and long-term outcomes is essential to improve the care of individuals with these complex disorders.

Keywords: Autoinflammation, autoinflammatory disease, hereditary AIDs, periodic disease, recurrent fever

Introduction

Familial Mediterranean fever (FMF) represents the most prevalent autoinflammatory disorder worldwide; however, this review aims to provide a comprehensive overview of other autoinflammatory diseases (AIDs) beyond FMF. AIDs comprise a spectrum of disorders marked by inflammatory attacks that emerge in the absence of infections, autoantibodies, or autoreactive T-cells. These diseases arise from innate immune system abnormalities, leading to the uncontrolled activation of inflammatory pathways[1]. Clinically, AIDs often present as fever, rashes, joint pain,

Correspondence: Özlem Akgün MD, İstanbul University, İstanbul Faculty of Medicine, Department of Pediatrics, Division of Pediatric Rheumatology, İstanbul, Türkiye
E-mail: drozlemakgun@hotmail.com **ORCID:** 0000-0001-7216-0562

abdominal discomfort, and organ-specific involvement. Inflammatory episodes can occur spontaneously or be triggered by minor external factors. Diagnosing AIDS involves assessing clinical features, conducting genetic analyses, and evaluating inflammatory biomarkers[2]. Epigenetic modifications can regulate the expression of inflammatory genes and impact disease severity, while triggers such as infections, psychological stress, and environmental exposures can provoke inflammatory responses[3]. Treatment strategies focus on controlling inflammation and preventing long-term complications. Targeted biologics such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α inhibitors, along with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (CS), effectively manage many autoimmune diseases and acute inflammation.

Highlights

- Autoinflammatory diseases primarily occur due to dysregulation of the innate immune system, characterized by the absence of autoantibodies or autoreactive T-cells.
- Autoinflammatory diseases often present with overlapping features such as recurrent fever, mucocutaneous lesions, arthritis, and systemic inflammation.
- Early recognition and molecular diagnosis of these conditions enable the use of targeted treatments.

I. Diseases of Inflammasomes and Related IL-1-family Cytokines

These pathological conditions are a category of AIDs resulting from the aberrant activation of the cytoplasmic protein inflammasome complex. Activation of these mechanisms produces inflammatory cytokines like IL-1β and IL-18, and triggers pyroptosis[4]. Diseases of inflammasomes and related IL-1-family cytokines are summarized in **Table 1**.

1. Pyrin Inflammasome

Pyrin is usually kept inactive through phosphorylation by RhoA kinase, which regulates cell migration. However, when RhoA is inactivated, the pyrin inflammasome is triggered[5,6]. Microtubules play a key role in its assembly, which may explain the therapeutic effectiveness of colchicine, a microtubule inhibitor.

i. Hyperimmunoglobulin D Syndrome

Variants in the *MVK* gene, responsible for producing mevalonate kinase, an enzyme crucial for cholesterol and isoprenoid biosynthesis, cause hyperimmunoglobulin D syndrome (HIDS), a rare autosomal recessive (AR) AID[7]. Complete loss of enzyme activity results in mevalonic aciduria, while partial activity (2-30%) leads to HIDS. MVK deficiency depletes geranylgeranyl phosphate, a molecule essential for the membrane targeting of RhoA. Without RhoA's inhibitory effect, the pyrin inflammasome becomes overactive, leading to excessive IL-1β production and recurrent inflammatory episodes[8]. In more than 90% of cases, symptoms begin during the first year of life.

Clinical Features

Inflammatory episodes characterize HIDS, though persistent disease has been reported in 14% of patients. Attacks generally recur every 4 to 8 weeks, with a duration of 3 to 6 days, and may be triggered by vaccinations, physical trauma, psychological stress, or infections[9]. During attacks, patients often have symptoms including high fever, swollen lymph nodes, abdominal pain, diarrhea, vomiting, mucocutaneous involvement, aphthous ulcers, maculopapular or urticarial rashes, morbilliform rashes, pharyngitis, myalgia, arthritis, and arthralgia[9]. Some may also develop neurological issues such as headaches and, in severe cases, cognitive impairment. Although rare, Amyloid A amyloidosis remains a serious but potential complication[10].

Diagnosis

Serum IgD levels increased during and between attacks. Still, this measurement is not used in diagnosis because it has low sensitivity and specificity and 20% of patients do not show an increase. In contrast, urinary mevalonic acid levels are typically elevated during episodes and can serve as a diagnostic biomarker for these conditions. According to the Eurofever/Paediatric Rheumatology International Trials Organisation (PRINTO) HIDS classification criteria, the diagnosis requires the presence of pathogenic or likely pathogenic MVK variants (homozygous or compound heterozygous) and at least one of the following symptoms: gastrointestinal involvement, cervical lymphadenitis, or aphthous stomatitis[11].

Treatment and Management

HIDS does not respond well to colchicine, and statins are also ineffective. Patients can benefit from NSAIDs for symptomatic relief, but these generally do not provide a complete response. While patients usually show a strong response to steroids during flare-ups, anti-IL-1 treatments remain the most effective option for managing HIDS[11]. IL-6 blockers or anti-TNF agents may be used as maintenance therapy in patients who present frequent attacks and/or subclinical inflammation if anti-IL-1 treatments are insufficient. In cases of severe and refractory disease, hematopoietic stem cell transplantation (HSCT) represents a possible therapeutic approach[12].

ii. Pyrin-associated Autoinflammation with Neutrophilic Dermatosis

A single heterozygous mutation leads to pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND), a chronic neutrophilic dermatosis marked by recurrent and prolonged inflammatory episodes[13]. Genetic alterations in the *MEFV* gene underlie the disease and contribute to heightened IL-1β secretion during episodes of fever. All reported cases have been linked to the dominant p.S242R mutation in the *MEFV* gene, and recently, the E244K mutation has been identified. Both mutations in exon 2 disrupt the phosphorylation

site of the pyrin protein or its +2 position, impairing its interaction with the 14-3-3 protein and ultimately leading to dysregulation of the inflammatory response[14].

The disease differs with prolonged fever episodes, severe neutrophilic skin inflammation (e.g., cystic acne, hidradenitis suppurativa, pyoderma gangrenosum), and musculoskeletal symptoms. Serositis and amyloidosis are unexpected features[15]. Laboratory findings mostly included anemia and elevated acute-phase reactants. Individuals with PAAND respond to colchicine, and IL-1β-targeting therapies have also been effective in keeping the remission state[16].

iii. Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne (PAPA)

This AD disorder, known as pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, is associated with alterations in the *PSTPIP1* gene, resulting in dysfunction of a protein involved in inflammatory signaling pathways[17]. These mutations are thought to disrupt PSTPIP1 binding to tyrosine phosphatase, leading to hyperphosphorylation of the mutant protein, decreased affinity for pyrin in the cytosol, and unregulated IL-1β production[18]. Typically beginning in early childhood, PAPA is marked by repeated episodes of destructive oligoarticular arthritis, most often involving the knees, ankles, or elbows[19].

Table 1.
Diseases of inflammasomes and related IL-1-family cytokines

Mechanism	Disease	Gene	Heredity	Clinical findings	Target/treatment	Age of onset	Attack duration
1. Pyrin inflammasome	FMF	*MEFV*	OR/OD	Fever, pain (abdomen, chest, joint), rash	IL-1/colchicine	<20	1-3 days
	PAAND	*MEFV*	OD	Fever, myalgia, myositis, rash, abscess	IL-1/colchicine		
	HIDS	*MVK*	OR	Fever, abdominal and extremity pain, vomiting, rash	IL-1	<1	3-7 days
	PAPA	*PSTPIP1*	OD	Pyoderma gangrenosum, arthritis	IL-1, TNF		
	Hz/Hc	*PSTPIP1*	OD	Rash, hepatosplenomegaly, neutropenia	IL-1, TNF		
	PFIT	*WDR1*	OR	Fever, infection, perianal ulceration, oral inflammation	IL-18		
2. Cryopyrin inflammasome	FCAS	*NLRP3*	OD	Cold urticaria, extremity pain, conjunctivitis, fever	IL-1		<24 hours
	MWS	*NLRP3*	OD	Extremity pain, conjunctivitis, fever, hair loss, urticarial rash	IL-1		2-3 days
	NOMID	*NLRP3*	OD	CNS inflammation, urticaria, knee arthropathy, fever	IL-1	Neonatal	Continuous with occasional flare-ups
	Majeed	*LPIN2*	OR	Osteomyelitis, fever, rash, dyserythropoietic anemia	IL-1	<2	
3. NLRC4 inflammasome	AIFEC	*NLRC4*	OD	Fever, arthritis, rash, enterocolitis	IL-1, IL-18		
	FCAS/NOMID	*NLRC4*	OD	Cold urticaria, extremity pain, fever, CNS disease	IL-1		
4. NLRP12 inflammasome	FCAS	*NLRP12*	OD	Cold urticaria, extremity pain, fever	TNF, IL-1		
5. NLRP1 inflammasome	NAIAD	*NLRP1*	OD	Eye-larynx-skin dyskeratosis, fever, arthritis	IL-1, TNF		
6. Receptor antagonist deficiencies	DIRA	*IL1RA*	OR	Pustular rash, osteomyelitis, periostitis, fever	IL-1		
	DITRA	*IL36RA*	OR	Pustular psoriasis, fever, malaise	TNF, IL-17/23		

IL: Interleukin, FMF: Familial mediterranean fever, PAAND: Pyrin-associated autoinflammation with neutrophilic dermatosis, PAPA: Pyogenic sterile arthritis, pyoderma gangrenosum, and acne, HIDS: Hyperimmunoglobulin D syndrome, PFIT: Periodic fever, immunodeficiency, and thrombocytopenia, FCAS: Familial cold autoinflammatory syndrome, MWS: Muckle-Wells syndrome, NOMID: Neonatal-onset multisystem inflammatory disease, AIFEC: Autoinflammation with infantile enterocolitis, NAIAD: NLRP1-associated autoinflammation with arthritis and dyskeratosis, DIRA: Deficiency of the IL-1 receptor antagonist, DITRA: Deficiency of the IL-36 receptor antagonist, TNF: Tumor necrosis factor, CNS: Central nervous system

Attacks usually occur spontaneously or after minor trauma. By early adolescence, most patients develop severe cystic acne, pyoderma gangrenosum, and sterile, pathergia-like abscesses at injection sites; hidradenitis suppurativa, particularly in the axilla and groin. In such cases, bone marrow suppression has been observed with exposure to sulfonamide drugs. Laboratory findings are often nonspecific; therefore, genetic testing is crucial for confirming a diagnosis. Glucocorticoids may be used for short-term disease control. Anti-TNF treatments are known to be more effective in skin manifestations, while anti-IL-1 treatments are better in joint involvement[20].

iv. Periodic Fever, Immunodeficiency, and Thrombocytopenia

In recent years, this rare AR disorder has been associated with homozygous loss-of-function mutations in the *WDR1* gene, which encodes a protein essential for actin cytoskeleton regulation and turnover[21]. These mutations lead to the accumulation of actin molecules, activation of pyrin, and excessive secretion of IL-18[22]. Patients with periodic fever, immunodeficiency, and thrombocytopenia present from birth with small platelets and thrombocytopenia, neutropenia with neutrophil dysfunction, recurrent fever, oral and perianal aphthous ulcers, and opportunistic infections. Disruption of the cytoskeleton affects the function of T-cells, antigen-presenting cells, and megakaryocytes, resembling the pathophysiology seen in Wiskott-Aldrich syndrome.

Treatment options are limited; CS and biologics offer partial benefits but also increase the risk of infection. To date, the only effective treatment reported has been allogeneic bone marrow transplantation[21].

v. Neonatal Onset of Pancytopenia, Autoinflammation, Rash, and Episodes of Hemophagocytic Lymphohistiocytosis Syndrome

CDC42 is a Ras-related GTPase that fundamentally plays a role in various biological activities, including cellular attachment, directional movement, polarization, growth, and malignant progression[23]. Mutations in this protein lead to mislocalization, causing peripheral blood mononuclear cells to produce excessive amounts of IL-1β and IL-18. Furthermore, increased activation of nuclear factor kappa B (NF-κB) has been observed in related studies. Episodes of neonatal pancytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocystosis (HLH) characterize the disease[24]. IL-1 antagonists and interferon (IFN)-gamma blockade may provide partial clinical improvement; allogeneic bone marrow transplantation remains the sole option with curative potential[25].

2. NALP3/Cryopyrin Inflammasome

i. Cryopyrin-associated Periodic Syndrome

Gain-of-function AD mutations in the *NLRP3 (CIAS1)* gene cause cryopyrin-associated periodic syndrome (CAPS), a spectrum of AIDs. These pathogenic variants cause excessive IL-1β production, with most identified mutations clustered in exon 3[26]. The CAPS spectrum includes several distinct clinical entities, namely Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurological cutaneous and articular syndrome (CINCA), also known as neonatal-onset multisystem inflammatory disease (NOMID)[27,28]. Within the spectrum of NLRP3-related diseases, FCAS represents the mildest form, while CINCA/NOMID is the most severe[29]. As CINCA syndrome is a chronic AID that begins in the neonatal period and is associated with a significant risk of long-term sequelae, early recognition and intervention are essential to mitigate permanent damage.

Clinical Features

FCAS is characterized by attacks lasting 1 to 2 days, cold-induced inflammation, and presents with fever, urticaria, arthralgia/arthritis, and transient conjunctivitis[30]. In most cases, avoiding cold exposure is sufficient to manage symptoms and prevent exacerbations. MWS is the most severe form, presenting with rash, arthralgia/arthritis, hearing loss, and ocular involvement; and approximately 25% of patients develop amyloidosis[28]. NOMID follows a chronic and persistent course, with patients experiencing persistent fever and rash, abnormal bone growth, and central nervous system (CNS) symptoms such as aseptic meningitis and increased intracranial pressure[31]. Joint involvement in CINCA/NOMID can be erosive, potentially leading to permanent sequelae. Ocular involvement, such as uveitis, papilledema, and optic atrophy, is more commonly reported in CINCA/NOMID, although it can also be seen, albeit less frequently, in MWS. Progressive hearing loss is primarily associated with CINCA/NOMID, but it can also occur, though less frequently, in MWS[32].

Diagnosis

Genetic analysis should be performed for diagnosis. It is recommended to test exon 3 with clearly pathogenic variants, such as R260W, D303N, L305P, E311K, T348M, L353P, A439V; and variants of unknown significance (VUS), such as V198M, for genetic testing of NLRP3[33]. According to the Eurofever/PRINTO classification criteria, the diagnosis of CAPS requires the presence of a pathogenic or likely pathogenic heterozygous variant in the *NLRP3* gene together with at least one of the following clinical features: Urticarial rash, red eyes, or neurosensory hearing loss. However, if a VUS is detected in the *NLRP3* gene, the CAPS classification requires the presence of at least two of three clinical criteria[10].

Treatment and Management

The primary pathogenic mechanisms underlying CAPS involve NLRP3 inflammasome engagement and IL-1 overproduction; therefore, treatment typically involves anti-IL-1 therapies[34,35]. Routine monitoring of patients should include auditory and ophthalmologic examinations[11]. Cognitive testing, lumbar puncture, skeletal imaging, and brain magnetic resonance imaging (MRI) may be necessary for comprehensive assessment and management.

ii. Majeed Syndrome/Lipin 2 (LPIN2)

Majeed syndrome is a rare AR disorder caused by inactivating mutations in the *LPIN2* gene, which plays a

key role in lipid metabolism. These mutations impair the regulation of the NLRP3 inflammasome, resulting in the overproduction of IL-1β and excessive inflammation[36,37]. Majeed syndrome is primarily characterized by fever, sterile osteolytic lesions, congenital dyserythropoietic anemia, and sometimes transient neutrophilic dermatosis. Persistent inflammation in affected individuals may result in recurrent fevers, growth delays, hepatosplenomegaly, and increased levels of acute-phase reactants[37]. IL-1 inhibitors have been effective in managing fever episodes and reducing inflammation in bone tissue[38].

3. NLRC4 Inflammasome

The *NLRC4* gene, composed of nine exons, is situated on the short arm of chromosome 2 at position p22.3. Gain-of-function mutations in the *NLRC4* gene create a wide range of autoinflammatory phenotypes, representing an expanding group of AIDs with an extensive clinical spectrum ranging from FCAS to NOMID[39]. In contrast to NLRP3, NLRC4 encompasses a caspase activation and recruitment domain, thereby facilitating its interaction with pro-caspase-1 independent of ASC for its activation.

Autoinflammation with Infantile Enterocolitis

Autoinflammation with Infantile Enterocolitis (AIFEC) is caused by pathogenic variants in NLRC4 and presents with systemic autoinflammation, including symptoms such as recurrent fever, fatigue, splenomegaly, vomiting, intermittent rash, and enterocolitis[40,41]. Extremely high serum IL-18 concentrations are present in AIFEC. The triggers of attacks, physical and emotional stressors, activation of the aberrant NLRC4 inflammasome, and the type three secretion system have been identified as possible facilitators. AIFEC flares share similarities with HLH, as both conditions exhibit IL-1β-associated symptoms (e.g., fever, tachycardia) and IFN-γ-associated histopathology (e.g., hemophagocytosis)[42]. A severe AIFEC attack can be misinterpreted as primary HLH due to the shared laboratory characteristics of hypertriglyceridemia, coagulopathy, cytopenia, increased soluble IL-2 receptor concentrations, and compromised *in vitro* cytotoxic activity. Unlike HLH, cytotoxic function in AIFEC returns to normal between attacks, suggesting that granule-related cytotoxicity remains intact. A key difference between HLH and AIFEC is gastrointestinal involvement: AIFEC, which commonly causes severe secretory neonatal diarrhea and enterocolitis, sometimes starts antenatally and often resolves after the first year, whereas diarrhea is rare in HLH. Notably, serum IL-18 levels remain elevated in AIFEC. In the context of therapeutic interventions, prophylactic administration of anakinra has demonstrated superior efficacy compared to low-dose CS and colchicine regarding the reduction of both the severity and occurrence of HLH-like attacks in AIFEC patients exhibiting mild gastrointestinal manifestations[40]. Recombinant IL-18 binding protein has shown dramatic efficacy in patients with neonatal AIFEC.

4. NLRP12 Inflammasome

Nucleotide-binding leucine-rich repeat-containing receptor 12 (NLRP12) is an intracellular protein with dual roles: it functions as an inflammasome and a negative regulator of inflammation[43]. It plays a crucial role in innate immunity, responding to pathogen- and damage-associated molecular patterns to modulate inflammatory processes[44]. Beyond its inflammasome activity, NLRP12 also inhibits the non-canonical pathway responsible for activating the proinflammatory transcription factor complex NF-κB[45]. This highlights how AIDs can involve overlapping proinflammatory pathways, further complicating immune regulation.

Familial Cold Autoinflammatory Syndrome 2

NLRP12-associated (NLRP12) AID arises from AD variants affecting the *NLRP12* gene. To date, no formal classification or diagnostic criteria have been established. It was named familial cold autoinflammatory syndrome 2 (FCAS2) because of its clinical similarities to FCAS. The disease typically presents with fever, elevated inflammatory markers, urticaria, arthralgia, and myalgia and is usually triggered by cold exposure[46]. Symptoms usually last one to seven days. Some patients may develop features resembling amyloidosis, sensorineural hearing loss, optic neuritis, and cryopyrinopathies. Approximately half of the patients present with cutaneous manifestations during attacks[47].

5. NLRP1 Inflammasome

The first scaffold protein discovered to facilitate inflammasome assembly was NLRP1 (nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1). In contrast to other proteins that form inflammasomes, NLRP1 activation occurs through proteolytic cleavage[48]. Predominantly expressed in keratinocytes, NLRP1 mutations are linked to skin disorders such as multiple self-healing palmoplantar carcinoma and familial keratosis lichenoides chronica[49].

NLRP1-associated Autoinflammation with Arthritis and Dyskeratosis

The disease typically manifests within the first six months of life, presenting with a broad range of polymorphic mucosal and skin lesions. These may include papillary or filiform hyperkeratosis, pseudophrynoderma, human papillomavirus-negative condylomata, and candidiasis. In addition to recurrent fever episodes and polyarthritis, patients may exhibit abnormal bone growth[49]. NLRP1 inflammasome-activating mutations lead to an overproduction of IL-1, which subsequently contributes to the depletion of $CD27^+$ memory B-cells. Therapeutic interventions that consist of anti-TNF or anti-IL-1 inhibitors have been used to control the disease.

6. Receptor Antagonist Deficiencies

i. Deficiency of the IL-1 Receptor Antagonist

Pathogenic alterations in the IL1RN gene, responsible for producing IL-1 receptor antagonist (IL-1RA), underlie this AR disorder[50]. The inability to properly secrete this aberrant protein, leads to unregulated activation of the IL-1 receptor, which subsequently induces elevated responses of IL-1α and IL-1β. Typically presenting in early neonates, the disease is characterized by sterile multifocal osteomyelitis, periostitis, neutrophilic

pustulosis, and includes the possibility of heterotopic bone formation, nail dystrophy, oral lesions, vasculitis, lung disease, and atlantoaxial subluxation[50,51]. High fever is not typically observed, but patients exhibit markedly elevated acute-phase reactants. Notably, joint involvement in deficiency of the IL-1 receptor antagonist shows a strong therapeutic response to anti-IL-1 therapy[52].

ii. Deficiency of the IL-36 Receptor Antagonist (DITRA)

Deficiency of the IL-36 receptor antagonist (DITRA) is a potentially life-threatening AID originating from loss-of-function mutations in the IL-36 receptor. It typically presents with generalized pustular psoriasis (GPP), high fever, malaise, asthenia, and episodes of systemic inflammation[53]. Reports have also noted issues with the oral mucosa, nail dystrophy, and oligoarthritis, although oligoarthritis is reported rarely. Gastrointestinal symptoms are caused by the increased secretion of proinflammatory cytokines by the intestinal epithelium. The disease predominantly occurs in early childhood or adolescence and can be life-threatening, with severe skin rashes leading to sepsis-related complications. The estimated mortality rate is 4-7%[54]. Both familial and sporadic cases of GPP have been associated with the L27P mutation in the *IL36RN* gene, which leads to diminished activity of IL-36Ra. Due to its rarity, there are no established treatment guidelines for DITRA, however, case reports and small series demonstrate good clinical responses to methotrexate (MTX), oral retinoids, anti-TNF agents, and inhibitors of IL-17 and IL-12/23[54].

II. Diseases of Interferon Production and Signaling

1. Impaired Degradation or Processing of Endogenous Nucleic Acids

Aicardi-Goutières Syndrome

Aicardi-Goutières syndrome (AGS) is an uncommon genetic disease linked to gene defects responsible for nucleic acid metabolism and intracellular signaling pathways[55]. Gene products of TREX1, RNASEH2A/B/C, SAMHD1, ADAR, and IFIH1 are critically involved in regulating these biological processes[56]. Most disease-causing mutations follow an AR inheritance pattern, with *TREX1* and *RNASEH2B* mutations being the most frequently detected. Type 1 Interferonopathy is summarized in **Table 2**. AGS presents in two distinct clinical forms. In the early-onset form (22.8%), symptoms are present from birth and closely resemble congenital infections. Affected infants exhibit severe neurological impairment, psychomotor developmental delay, and liver abnormalities[57]. The late-onset form, emerging after initial normal development, is marked by slowed cranial growth, increasing spasticity, and significant cognitive and developmental impairments[58]. Neurological symptoms such as abnormal eye movements, nystagmus, deficient visual tracking are prevalent. A unique feature is an exaggerated startle response to minor sensory stimuli. Neuroimaging typically reveals

Table 2.
Type 1 interferanopathy

Mechanism	Disease	Gene	Heredity	Clinical findings	Target/treatment
1. Nucleic acid processing and degradation	Aicardi-Goutières syndrome	*TREX1, ADAR1, RNASEH2A/B/C, SAMHD1, IFIH1*	OR (OD: IFIH1)	Fever, encephalopathy, cerebral calcification, chilblains, autoantibody positivity, neurological retardation	JAK
	Monogenic syndrome	*DNASE1/2/1L3*	OR (OD: DNASE1)	Cytopenia, glomerulonephritis, rash, oral ulcer, arthritis, autoantibodies	JAK?
2. Nucleic acid sensing	SMS	*IFIH1, DDX58a*	OD	Calcification of the heart valve or aorta, osteopenia, acro-osteolysis, dental anomalies	JAK?
	SAVI	*TMEM137*	OD	Small vessel vasculitis, arthritis, chilblain rash	JAK
3. Proteasome	CANDLE/ PRAAS, PRAID	*PSMB4,8,9,10 PSMA3, PSMG2 POMP*	OR (POMP: OD)	Fever, joint contractures, HSM, lipodystrophy, growth retardation	JAK
4. IFN signaling	AGS-like	*USP18, ISG15, STAT2*	OR	Skin ulcers, convulsions, hydrocephalus, cerebral calcification, respiratory failure	JAK
5. Other	SPENCD	*ACP5*	OR	Skeletal dysplasia, cerebral calcification, cytopenia, autoantibody	?

IFN: Interferon, SAVI: Infancy-onset STING-associated vasculopathy, STING: Stimulator of interferon genes, CANDLE: Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature, AGS: Aicardi-Goutières syndrome, JAK: Janus kinase, HSM: Hepatosplenomegaly

intracranial calcifications, white matter destruction, and cerebral atrophy, analogous to the findings observed in congenital infections. Over time, symptoms tend to stabilize without further progression of the disease. Glaucoma, which occurs in the first six months of life, affects 6% of patients but is more common in those with SAMHD1 mutations (20%) and is notably absent from cases associated with ADAR or IFIH1 mutations.

Diagnostic evaluation of AGS includes measurement of IFN-stimulated gene expression scores to assess serum IFN activity; however, this may be normal in 30% of patients with isolated RNASEH2B mutations. Also, cerebrospinal fluid pterin levels indicate CNS IFN activity[59]. Prognosis varies depending on the genetic mutation involved, with the most significant mortality rates observed within the initial five years of life, particularly in cases associated with TREX1 mutations, which have the poorest outcome[60].

2. Enhanced Nucleic Acid Sensing

Stimulator of Interferon Genes Associated Vasculopathy with Onset in Infancy

Stimulator of interferon genes (STING) associated vasculopathy with onset in infancy (SAVI) constitutes a rare AID arising from heterozygous activating mutations within the *TMEM173* gene. This gene produces STING, essential for mediating type I IFN signaling[61]. These mutations lead to overactivation of the IFN pathway, resulting in chronic inflammation and severe damage to the skin and lungs. Dermatologic features include telangiectasia on the nose and cheeks, nodular formations, and atrophic plaques on the hands[62,63]. It presents with painful ulcerative lesions, loss of capillary loops, and distal capillary loss, particularly on the fingers, toes, ears, and nose. Lung involvement contributes significantly to morbidity and mortality in SAVI and leads to fibrotic interstitial lung disease accompanied by hilar or paratracheal lymphadenopathy. Neurological findings such as basal ganglia calcifications have been observed, but are less common than in other interferonopathies. Intermittent fever, polyarthritis, myositis, and developmental delay may be present. Autoantibody positivity, such as antinuclear antibodies (ANA), rheumatoid factor (RF), and anti-neutrophil cytoplasmic antibodies (ANCA), has also been reported in some cases[63]. Due to the pivotal involvement of IFN pathway abnormalities in SAVI, Janus kinase (JAK) inhibitors have been introduced as potential therapeutic agents[63].

3. Proteasome Dysfunction

Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated Temperature

This rare autoinflammatory condition, chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature (CANDLE), is associated with pathogenic variants in several proteasome-related genes, including PSMB8, PSMA3, PSMB4, and PSMB9, which are involved in protein degradation and immune regulation[64]. Deleterious mutations in the *POMP* gene, which produces a protein essential for the maturation of the proteasome, can lead to a CANDLE-like immune dysregulation syndrome. CANDLE is characterized by high fever, arthritis, and a rash similar to pernio affecting the extremities. Common systemic features include progressive lipomuscular dystrophy, joint contractures, myositis with muscle atrophy, and hepatosplenomegaly[65]. Neurologic involvement, including basal ganglia calcifications, may occur. Inflammatory indicators are typically elevated. Increased triglyceride levels and elevated thyroid-stimulating hormone levels are also observed in association with various autoantibodies. Unlike many other AIDs, CANDLE does not respond well to traditional immunosuppressive therapies, including CS, MTX, or IL-1 inhibitors. However, JAK inhibitors are used in treatment[66].

III. Diseases of Nuclear Factor Kappa B and/or TNF Activity

1. Dysregulation of NF-κB Signaling

i. Haploinsufficiency of A20/TNF-alpha-induced Protein 3 (TNFAIP3)

A20, encoded by the *TNF-alpha-induced protein 3 (TNFAIP3)* gene, is an enzyme that regulates protein function and degradation by adding and removing ubiquitin. Loss-of-function TNFAIP3 variants inherited in an AD pattern lead to A20 haploinsufficiency (HA20) by increasing NF-κB translocation to the nucleus[67]. Even a 50% reduction in A20 activity drives systemic inflammation by increasing NF-κB signaling.

HA20 is a rare AID defined by the manifestation of systemic inflammation that arises early in life with recurrent oral, genital, and gastrointestinal ulcers[68]. Clinical features include musculoskeletal and gastrointestinal symptoms, skin lesions, neurologic and cardiac involvement, and ocular symptoms. Laboratory findings show elevated acute-phase reactants and autoantibody positivity. HA20 shares many clinical features with Behçet disease but has distinct characteristics. These include autosomal dominant (AD) inheritance, and early childhood onset, scarring oral ulcers, recurrent fever, elevated acute-phase reactants, variable presence of autoantibodies, and a disease course that is often resistant to standard treatments. Treatment strategies include colchicine for ulcer management and anti-cytokine therapies such as anti-TNF, IL-1, and JAK inhibitors to control systemic inflammation. In severe and refractory cases, HSCT may be an option[68,69].

ii. Nuclear Factor Kappa B Essential Modulator

Ablation of the C-terminal domain of NF-κB essential modulator prevents its association with the inhibitory protein A20, thereby promoting uncontrolled activation of NF-κB[70]. As a result, affected individuals exhibit marked erythroderma and colitis early in life, and malabsorption typically occurs with systemic inflammatory responses. In some cases, individuals may also suffer from recurrent bacterial infections, likely due to intrinsic immune dysregulation. Therapeutic modalities vary: CS, infliximab, and HSCT have shown efficacy in selected individuals[71].

2. Aberrant TNF Activity

i. TNF Receptor-associated Periodic Syndrome

AD missense mutations in the *TNFRSF1A* gene, encoding the TNF receptor on chromosome 12, primarily within exons 2 to 4, have been identified as the underlying cause[72,73]. These mutations cause the accumulation of TNF receptor type 1 in the endoplasmic reticulum, leading to disruption in receptor clearance, an increase in reactive oxygen radicals, and the induction of TNF receptor-associated periodic syndrome (TRAPS)-related NF-κB, thus triggering innate immunity and IL-1β overproduction, leading to chronic inflammation. TNFRSF1A gene mutations are categorized into two main groups: structural and non-structural[74-76].

Clinical Features

The age of onset varies from early childhood to adulthood, with an average of 3-10 years. Attacks tend to last longer than other AIDs, typically persisting for 3-4 weeks, while attack intervals remain variable[77]. Symptoms begin with muscle cramps and pain that migrate from the trunk to the extremities, followed by fever and systemic symptoms. Patients commonly experience recurrent fever, myalgia, abdominal pain, urticarial rash, periorbital edema, conjunctivitis, oral ulcers, and lymphadenopathy[73]. The rash is migratory, pseudocellulitic in appearance, and typically affects the extremities or trunk in areas with muscle pain. It is tender, warm, and blanches with pressure. Renal amyloidosis, a serious complication, occurs in 25% of patients, often presenting with proteinuria.

Diagnosis

According to the TRAPS classification criteria proposed by Eurofever/PRINTO, the patient must have a pathogenic (or likely pathogenic) heterozygous *TNFRSF1A* gene variant, disease attacks lasting longer than 7 days and at least one of the following: myalgia, migratory rash, periorbital edema, or family history of TRAPS. If a TNFRSF1A (VUS) is detected, at least two of five clinical criteria for classification must be met[10].

Treatment and Management

For acute attacks, CS and NSAIDs help control symptoms, but steroids do not reduce the risk of amyloidosis[78]. Anti-TNF agents (except etanercept) are generally not used, and tolerance to etanercept develops over time[79]. In contrast, anti-IL-1 therapy has shown promising results in disease management.

ii. Deficiency of adenosine deaminase 2 (DADA2)

Adenosine deaminase 2 (DADA2) deficiency is a rare monogenic AID resulting from biallelic mutations in the *ADA2* gene[80]. The disease manifests with vasculitis, immune dysregulation, and hematologic abnormalities[81]. Researchers have identified over 100 ADA2 gene mutations that cause diverse clinical presentations, with severity and symptoms varying even among individuals with the same mutations.

Clinical Features

Vasculitic manifestations include fever, arthritis, myositis, and various genitourinary, dermatologic, neurologic, cardiac, pulmonary, gastrointestinal, and ocular complications. Patients may develop renal involvement (such as renal artery aneurysms, glomerulonephritis, or nephrocalcinosis), skin manifestations (leukocytoclastic vasculitis, livedo racemosa, or necrotic ulcers), neurologic complications (ischemic or hemorrhagic strokes, seizures, or peripheral neuropathy), cardiac abnormalities (cardiomyopathy, myocardial infarction, or pericarditis), pulmonary manifestations (such as pleuritis, ARDS), gastrointestinal involvement (pancreatitis, mesenteric ischemia, or bowel perforation), Raynaud phenomenon, and ocular involvement (uveitis, optic neuritis, or retinal vasculitis)[82]. Initial clinical signs typically emerge during early childhood, with an average onset between 5 and 7 years.

Immunodeficiency is a hallmark of DADA2 and predisposes patients to recurrent bacterial and viral infections. Patients often exhibit autoimmune neutropenia, eczema, and increased susceptibility to herpesvirus and other double-stranded DNA viruses. Hematologic abnormalities include pure red cell aplasia, pancytopenia, myelofibrosis and HLH. Less commonly, they include portal hypertension, hepatosplenomegaly, hepatic fibrosis, autoimmune lymphoproliferative syndrome-like features, Hodgkin lymphoma, or atypical cutaneous acute myeloid leukemia.

Unlike classic childhood polyarteritis nodosa (PAN), in which CNS involvement is rare, pediatric cases with PAN-like symptoms often present with arterial infarctions in the CNS. In addition, DADA2 can present with a combination of livedo reticularis and neurologic manifestations and may resemble Sneddon syndrome. Vascular abnormalities, including mesenteric and renal aneurysms, share striking similarities to those seen in PAN on both imaging and histologic examination, making diagnosis difficult.

Diagnosis

Elevated inflammatory markers are present. Plasma ADA2 enzyme activity below 5% of the standard value, along with the detection of a homozygous mutation in the *ADA2* gene, is critical for diagnosis. Brain MRI is used to assess stroke status.

Treatment and Management

Unlike high-dose glucocorticoids, conventional immunosuppressive therapies have generally been ineffective in managing the disease. The vasculitic manifestations, however, show a strong response to TNF-α inhibition[83]. HSCT has demonstrated potential in normalizing enzyme activity and resolving the vasculitic, hematologic, and immunologic symptoms associated with the disease. Diseases related to dysregulation of NF-κB signaling and/or TNF activity are summarized in **Table 3**.

Table 3.
Diseases of NF-κB and/or TNF activity

Mechanism	Disease	Gene	Heredity	Clinical findings	Target/treatment
1. Dysregulation of NF-κB signaling	Haplo A 20	*TNFAIP3*	OD	Oral, gastrointestinal and genital ulcers, fever, arthritis, recurrent infection	TNF, IL-1, JAK?
	RELAhaploinsuf	*RELA*	OD	Cytopenia, lymphoproliferative disease, oral and gastrointestinal ulcers	TNF
2. Aberrant TNF activity	Blau	*NOD2*	OD	Granulomatous dermatitis, uveitis, arthritis	TNF
	TRAPS	*TNFRSF1A*	OD	Episodic fever, abdominal pain, headache, conjunctivitis, painful rash	IL-1, TNF
	DADA2	*ADA2*	OR	Systemic vasculitis, fever, rash, stroke, cytopenia	TNF, HSCT
3. Disorders of linear ubiquitination	ORAS	*OTULIN*	OR	Fever, panniculitis, diarrhea, arthritis	TNF
	LUBAC	*HOIL1, HOIP*	OR	Fever, recurrent infection, HSM, amylopectin-like deposits in muscles	TNF?

NF-κB: Nuclear factor kappa B, TNF: Tumor necrosis factor, IL: Interleukin, JAK: Janus kinase, HSCT: Hematopoietic stem cell transplantation, TRAPS: TNF receptor-associated periodic syndrome, DADA2: Deficiency of adenosine deaminase 2, ORAS: OTULIN-related autoinflammatory syndrome, LUBAC: Linear ubiquitin chain assembly complex, HSM: Hepatosplenomegaly

iii. Nucleotide-binding Oligomerization Domain Protein 2 - Blau Syndrome

The nucleotide-binding oligomerization domain 2 (NOD2) protein, encoded by the *NOD2* gene, belongs to the NOD-like receptor family and serves as a critical mediator of innate immune activation and inflammatory signaling[84]. Pathogenic variants that enhance the function of this gene result in heightened NF-κB activity, leading to dysregulated synthesis of proinflammatory mediators. The clinical picture typically includes rash, arthritis, and uveitis, with skin involvement appearing first between 1 and 2 years of age as a spreading maculopapular rash and possible erythema nodosum. Arthritis is polyarticular and symmetric, often causing severe arthritis with joint swelling. Ocular involvement, affecting 75-90% of patients within two years of onset, presents as granulomatous iridocyclitis and posterior uveitis that may progress to destructive panuveitis[85].

Since the primary affected organs are the skin, joints, and eyes, diagnostic evaluation includes tissue biopsy, ophthalmologic assessment, and imaging studies of the joints. Serum angiotensin-converting enzyme levels are usually normal. Genetic testing for NOD2 mutations can help confirm the diagnosis, but mutations may not be detected in all cases.

Treatment typically begins with CS; prednisolone is started at 1-2 mg/kg/day, tapered over 8-12 weeks, and maintained at the lowest effective dose for at least six months. MTX can be used at a dose of 10-15 mg/m² per week[86]. Patients with refractory disease may require additional immunosuppressive therapy, such as azathioprine, cyclophosphamide, cyclosporine, adalimumab, or infliximab, to control disease progression and prevent complications.

3. Disorders of Linear Ubiquitination

Ubiquitination, an essential post-translational modification, plays a key role in directing proteins for proteasomal degradation. Linear ubiquitin chains, in particular, are vital for regulating intracellular signaling pathways such as the TNF receptor and NF-κB. This specific form of ubiquitination is mediated by the linear ubiquitin chain assembly complex (LUBAC), which is crucial for maintaining effective signal transmission[87]. To maintain balanced LUBAC activity, the OTU deubiquitinase (OTULIN) selectively removes linear ubiquitin chains, preventing excessive LUBAC autoubiquitination and preserving cellular homeostasis.

i. OTULIN-related Autoinflammatory Syndrome

Homozygous OTULIN deficiency leads to excessive NF-κB signaling, resulting in a severe inflammatory condition that appears from the neonatal period onwards. Affected individuals present with persistent fever, systemic inflammation, diarrhea, sterile neutrophilic dermatitis, arthritis, and growth failure[88]. Treatment options include TNF inhibitors, which can help control inflammation, or bone marrow transplantation in severe cases[89].

ii. Deficiency of Linear Ubiquitin Chain Assembly Complex

A deficiency of LUBAC, resulting from homozygous deletions in either (heme-oxidized IRP2 ubiquitin ligase 1 or its interacting partner HOIP, leads to recurrent episodes of autoinflammation in affected individuals. Attacks typically present with prolonged fever lasting up to 2 weeks, invasive bacterial infections, hepatosplenomegaly, and amyloidosis. LUBAC deficiency, unlike other NF-κB-related disorders, impairs NF-κB signaling but paradoxically increases IL-1β sensitivity, indicating a complex and unclear pathogenesis[90].

IV. Autoinflammation Mediated by Miscellaneous Mechanisms

i. Coatomer Protein Complex Subunit Alpha Syndrome

The *coatomer protein complex subunit alpha (COPA)* gene encodes the α subunit of the COPI protein, which is essential for mediating vesicle transport from the Golgi apparatus to the endoplasmic reticulum (ER). This retrograde vesicular movement prevents the excessive accumulation of STING within the ER[91]. Pathogenic COPA variants disrupt this process, leading to overactive STING signaling and excessive production of type I IFNs. This mechanistic link explains the clinical similarities between COPA syndrome and SAVI. Interstitial lung disease, pulmonary hemorrhage, and inflammatory arthritis predominantly distinguish COPA syndrome. Affected children typically present with chronic cough and tachypnea within the first five years of life[92].

Many individuals with COPA syndrome exhibit autoantibody positivity, such as RF, anti-cyclic citrullinated peptide, ANA, and ANCA[92]. Treatment options include systemic CS, MTX, azathioprine, hydroxychloroquine, etanercept, and intravenous immunoglobulin.

ii. Autoinflammation and PLCG2-associated Antibody Deficiency and Immune Dysregulation

This AD autoinflammatory condition, called autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation, results from mutations in the *PLCG2* gene and involves features such as immune dysregulation and impaired antibody production[93]. It is characterized by widespread inflammatory skin lesions, not triggered by cold. Patients may develop interstitial lung disease, ocular involvement, gastrointestinal inflammation, and mild immune deficiency[93]. Additionally, lymphoproliferative disorders and autoimmune manifestations may coexist. Glucocorticoids can be effective in managing symptoms.

iii. Cleavage-resistant Receptor-interacting Serine/Threonine Kinase 1 Induced Autoinflammatory Syndrome

Receptor-interacting protein kinase 1 (RIPK1) is a pivotal modulator of innate immune signaling, significantly activating NF-κB and other proinflammatory pathways[94]. Individuals presenting with biallelic loss-of-function mutations in RIPK1 demonstrate increased susceptibility to infections, progressive polyarthritis, and early-onset inflammatory bowel disease[94]. Most affected individuals experience recurrent febrile episodes with lymphadenopathy, occurring at one- to seven-day intervals every two to four weeks, typically within the first six months of life. Elevated acute-phase reactants mark these episodes, and skin rashes are absent. CS effectively controls disease flares, while IL-6 blockade has shown promising results in many patients[95].

Ethics

Informed Consent: The consent form was not needed due to the study design.

Footnotes

Author Contributions: Arık SD: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Menentoğlu B: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Akgün Ö: Surgical and Medical Practies, Concept, Design, Analysis or Interpretation, Writing.

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Thyroid Autoantibody Positivity Based on Individual Compliance with a Gluten-free Diet in Pediatric Patients with Celiac Disease

Author(s)

Elif Eviz[1], Demet Teker Düztaş[2]

Affiliation(s)

[1]Şanlıurfa Eyyubiye Training and Research Hospital, Clinic of Pediatric Endocrinology and Diabetes, Şanlıurfa, Türkiye

[2]Şanlıurfa Eyyubiye Training and Research Hospital, Clinic of Pediatric Gastroenterology, Şanlıurfa, Türkiye

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Abstract

The prevalence of concurrent celiac disease (CD) and autoimmune thyroid disorders is elevated relative to the general population, and it has been proposed that non-adherence to a gluten-free diet (GFD) exacerbates this risk. This study aimed to assess individual adherence to a GFD in children with CD and to examine the correlation between celiac antibody positivity and thyroid autoantibody positivity. Three hundred and thirty-four cases with CD, were retrospectively evaluated in terms of their age at diagnosis, duration of CD, individual compliance with GFD, and celiac [tissue transglutaminase antibody, tissue thyroglobulin (tTG)- immunoglobulin A (IgA)] and thyroid autoantibody (anti-thyroid peroxidase, anti-TG) positivity. The cases were divided into two groups: Group 1, with positive thyroid autoantibodies, and group 2, with negative thyroid autoantibodies. They were compared in terms of the same parameters. Additionally, the relationship between compliance with a GFD, duration of CD, and thyroid autoantibody positivity was examined. The average age of the cases was 10.8±4.1 years, with 63.5% being female. The median age at diagnosis of CD was 6.5 years, and the average time from onset to diagnosis was 2.7 years. In 47% of patients, individual compliance with the diet was poor; 69% tested positive for tTG-IgA, and 7.2% were positive for thyroid autoantibodies. The age at diagnosis of CD in group 1 was greater than that in group 2 (7.4 vs. 6.5 years, p=0.454), and the duration of CD was significantly longer in group 1 compared to group 2 (4.9 vs. 2.5 years, p=0.002). The prevalence of tTG-IgA positivity and inadequate individual adherence to the GFD were greater in group 1 compared to group 2 (79% vs. 68%, p1=0.258, 58% vs. 46%, p2=0.236, respectively). Our research shows that the rising prevalence of thyroid autoantibody positivity correlates with both older age at diagnosis and extended duration of celiac disease, implying that prolonged gluten exposure may play a role in thyroid autoimmunity.

Keywords: Gluten exposure, thyroid autoantibody, celiac autoantibody

Correspondence: Elif Eviz MD, Şanlıurfa Eyyubiye Training and Research Hospital, Clinic of Pediatric Endocrinology and Diabetes, Şanlıurfa, Türkiye
E-mail: evzelf@gmail.com **ORCID:** 0000-0002-8889-6811

Introduction

Autoimmune thyroid diseases (ATD) rank among the most prevalent autoimmune disorders in pediatric populations, with an incidence of roughly 3%[1]. Hashimoto's thyroiditis (HT) is the most prevalent of these disorders, marked by the infiltration of autoreactive B and T-cells into the thyroid parenchyma, leading to irreversible destruction of thyroid tissue. The primary autoantigens targeted in HT are thyroid peroxidase (TPO) and thyroglobulin (TG)[2-4]. HT occurs most commonly during adolescence[1,5].

Highlights

- Celiac disease (CD) have an increased risk of autoimmune thyroid disease.
- It is thought that shared common genes and/or gluten exposure may cause this.
- In this study, the prevalence of thyroid autoantibody positivity was found to be 7.2% among individuals with CD.
- The age at diagnosis of CD was higher in those with thyroid autoantibody positivity.
- The duration of CD was longer in those with thyroid autoantibody positivity.

Genetically susceptible individuals are at a higher risk of developing celiac disease (CD), a chronic autoimmune disorder triggered by the consumption of gluten, a protein found in cereals such as wheat, barley, and rye. The prevalence is 1% in Western societies. It typically causes gastrointestinal symptoms and findings such as marked malabsorption, weight loss, and/or developmental delay 2. The principal serologic diagnostic is serum tissue transglutaminase (tTG) immunoglobulin A (IgA), and its positivity necessitates further screening for CD[5].

Numerous studies indicate that the prevalence of co-occurrence of CD and ATD is greater in childhood than in adulthood. The reported rate in children varies between 2% and 7.8%, which is around three times higher than that of the general population[1]. A study of children with CD in Italy showed a prevalence of ATD at 10.5%, around four times greater than that of the normal population[6]. In research by Elfström et al.[7] in 2008, this rate was also determined to be between 2 and 4 times 7. The prevalence of CD among patients with ATD varies considerably, with reported percentages between 0% and 9.9%[3].

The correlation between CD and HT has been elucidated through two distinct hypotheses. CD and HT possess one or more shared genes. Although human leukocyte antigen-DQ2 and DQ8 haplotypes are present in 69% of persons with CD, the weak correlation between HT and these haplotypes indicates a shared genetic susceptibility 2. The second hypothesis posits that the degradation of intestinal barrier integrity, resulting from the persistent consumption of gluten by children with CD who are not adhering to a gluten-free diet (GFD), induces a systemic immune response and facilitates the onset of additional autoimmune disorders[1].

This study aims to determine the prevalence of HT among children with CD who are monitored at our center, as well as to evaluate the degree of individual compliance with a GFD and to investigate the correlation between tTG-IgA and thyroid autoantibody positivity.

Materials and Methods

A retrospective analysis was done on the outpatient clinic records of 396 patients diagnosed with CD monitored at the Pediatric Gastroenterology Clinic of Şanlıurfa Training and Research Hospital, from March 2023 to June 2024, and subsequently referred to the pediatric endocrinology clinic for potential thyroid dysfunction. Patients aged 1 to 18 years who tested positive for tTG-IgA, received a histopathological diagnosis of CD, and had thyroid autoantibodies assessed during follow-up were included in the study. Patients with other chronic conditions who declined to participate in the trial and whose data were not accessible were excluded. A total of 334 instances were incorporated into the final analyses. Data regarding age; date of diagnosis of CD; duration of CD; presence of CD symptoms; individual compliance assessments to a GFD; height; height standard deviation score (SDS); body mass index (BMI); BMI SDS; tTG-IgA; thyroid-stimulating hormone (TSH); free T4 (fT4); anti-TPO; and anti-TG values were extracted from outpatient clinic records.

tTG-IgA levels in serum were measured by enzyme-linked immunosorbent assay using commercially available Orgentec (Mainz, Germany) kits. The measurement range of the kit was 20-200 U/mL, and results outside these values were reported as upper or lower limit values. Considering the manufacturer's instructions, a threshold value of 20 U/mL was used as the cut-off for seropositivity. Anti-TPO and anti-TG levels were measured by electrochemiluminescence immunoassay using commercially available Elecsys (Mannheim, Germany) kits. Threshold values of ≥35 IU/mL for anti-TPO and ≥115 IU/mL for anti-TG were considered as thyroid autoantibody positivity[6,7].

Celiac symptoms were deemed present when intestinal symptoms (such as stomach pain, constipation, bloating, weight loss) and/or extraintestinal symptoms (including short stature, delayed menstruation, oral aphthae, exhaustion) were reported in patient histories. Participants were categorized into two groups, "excellent adherence" and "poor adherence", based on their dietary compliance level as reported by the patients themselves in the evaluation of individual adherence to the GFD[8]. The connection between age, presence of celiac symptoms, individual adherence to a GFD, tTG-IgA positivity, duration of CD, and thyroid autoantibody positivity was assessed.

The patients were categorized into two groups based on the presence of thyroid autoantibodies (anti-TPO and anti-TG): Group 1 comprised individuals with positive autoantibodies, whereas group 2 included those with negative autoantibodies. The evaluation assessed differences between the groups regarding age, duration of CD, presence of CD symptoms, individual compliance with a GFD, height, height SDS, BMI, BMI SDS, tTG-IgA positivity, TSH, sT4 should be change as fT4, anti-TPO, and anti-TG.

Statistical Analysis

Analyses were conducted using SPSS version 26 (IBM SPSS Statistics for Windows, Version 26.0, IBM Corp, Armonk, NY, USA). The Kolmogorov-Smirnov test was employed to assess the normality of the variable distributions. Mean ± standard deviation values were employed to characterize normally distributed continuous variables, whereas median and interquartile ranges were utilized for non-normally distributed continuous variables. Categorical variables were described using frequency and percentages. In paired group comparisons, Student's t-test was employed for normally distributed independent continuous variables, while Mann-Whitney U test was utilized for non-normally distributed independent continuous variables. The chi-square test was employed to analyze categorical variables. Spearman correlation analysis assessed the relationships between continuous variables, while point-biserial correlation analysis examined the associations between categorical and continuous variables. A value of p less than 0.05 was accepted as statistically significant.

Statistical Analysis

The protocols adhered to the principles of the Declaration of Helsinki and received approval from the Harran University Clinical Research Ethics Committee (approval number: HRÜ/25.07.26, date: 14.04.2025).

Results

The average age of the patients in the study was 10.8±4.1 years, with 63.5% (212) female; and the median age at diagnosis of CD was 6.5 years. At the time of the visit, when they were evaluated for thyroid autoantibody positivity, the median duration of CD was 2.7 years, 52% (151) reported the presence of celiac symptoms, and 47% (156) had poor individual dietary compliance assessments. The median height-SDS was -1.3, BMI was 16.4 kg/m^2, and BMI-SDS was -0.3 in the patients whose demographic parameters are given in **Table 1**. Celiac antibody (tTG-IgA) positivity was present in 69% (230) of the patients; thyroid autoantibody positivity (anti-TPO and/or anti-TG) was present in 7.2% (24).

The evaluation of patients based on thyroid autoantibody positivity revealed that the mean age of patients in group 1 (n=24) was 12.9±3.7 years, while the mean age in group 2 (n=310) was 10.6±4.1 years. A statistically significant difference was observed between the two groups (p=0.008). The median duration of CD was 4.9 years in group 1 and 2.5 years in group 2, demonstrating a statistically significant difference (p=0.002). No statistically significant differences were observed between the groups in terms of gender, height-SDS, BMI, and BMI-SDS (p1=0.918, p2=0.941, p3=0.135, p4=0.712). While no statistically significant difference was observed, the rate of tTG-IgA positivity was greater in group 1 compared to group 2 (79% vs. 68%, p=0.258). Conversely, the prevalence of celiac symptoms was significantly lower in group 1 than in group 2 (25% vs. 46.8%, p=0.042). The rate of poor individual adherence to the GFD was higher in group 1 compared to group 2, with no statistically significant difference observed (58% vs. 46%, p=0.236) (**Table 2**).

The median duration of CD was 3.5 years for patients exhibiting poor individual dietary adherence (n=156) and 2.1 years for those with good individual dietary adherence (n=178), demonstrating a statistically significant difference (p=0.004). A weak positive correlation was observed between the duration of CD and poor individual dietary adherence, as well as anti-TPO levels (r1=0.141, p1=0.010; r2=0.116, p2=0.034). No significant correlation was observed between individual dietary adherence and anti-TPO and anti-TG levels (r1=0.052, p1=0.346; r2=0.028, p2=0.605). The tTG-IgA antibody showed no correlation with anti-TPO and anti-TG (r1=0.007, p1=0.906; r2=0.008, p2=0.888).

Table 1.
Demographic data in the whole group

n=334	Median (IQR)
Age, years*	10.8±4.1
Gender, F:M, %	63.5:36.5
Duration of CD, years	2.7 (1.2-5.6)
Height, cm	135 (119-150)
Height-SDS	-1.3 (-2 - -0.4)
BMI, kg/m^2	16.4 (14.9-19)
BMI-SDS	-3 (-1.1-0.4)
TSH, uIU/mL	2.1 (1.6-2.8)
fT4, pmol/L*	16.5±2.2
Anti-TPO, IU/mL	11.3 (8.7-14.6)
Anti-TG, IU/mL	14.8 (13.3-16.3)
Thyroid autoantibody positivity rate, %	7.2
tTG-IgA, U/mL	67.4 (14.2-200)
tTG-IgA positivity rate, %	69
Presence of celiac symptoms, %	52
Poor individual adherence to GFD, %	47

*: Mean
± SD, BMI: Body mass index, CD: Celiac disease, GFD: Gluten-free diet, IQR: Interquartile range, SDS: Standard deviation score, F: Female, M: Male, tTG: Tissue thyroglobulin, IgA: Immunoglobulin A, TSH: Thyroid-stimulating hormone, SD: Standard deviation, TPO: Thyroid peroxidase

Table 2.
Demographic data, compliance rates to GFD and laboratory parameters according to thyroid antibody positivity (anti-TPO and anti-TG positivity)

	Group 1 (thyroid antibody +) median (IQR) (n=24)	Group 2 (thyroid antibody -) median (IQR) (n=310)	p
Age, years*	12.9±3.7	10.6±4.1	0.008
Gender, F:M, %	62.5:37.5	63.5:36.5	0.918
Age at diagnosis of CD, years	7.4 (5.3-9.4)	6.5 (4.5-9.8)	0.454
Duration of CD, years	4.9 (3-8.4)	2.5 (1.2-5.4)	0.002
Height, cm	143 (134-159.7)	132 (118-150)	0.005
Height-SDS	-1.5 (-2 - -0.06)	-1.3 (-2 - -0.4)	0.941
BMI, kg/m^2	17.8 (15-19.8)	16.3 (14.8-18.7)	0.135
BMI-SDS	-0.27 (-1.3-0.05)	-0.36 (-1.1-0.4)	0.712
TSH, uIU/mL	3.1 (1.9-6.6)	2.1 (1.6-2.7)	<0.001
fT4, pmol/L*	15.8±2.9	16.5±2.2	0.114
Anti- TPO, IU/mL	104 (38.3-226)	11 (8.6-13.9)	<0.001
Anti-TG, IU/mL	166 (76-462.6)	14.6 (13.2-16)	<0.001
tTG-IgA, U/mL	40.6 (21.4-200)	68.1 (14.1-200)	0.960
tTG-IgA positivity rate, %	79	68	0.258
Presence of celiac symptoms, %	25	46.8	0.042
Poor individual adherence to GFD, %	58	46	0.236

*: Mean ± SD, BMI: Body mass index, CD: Celiac disease, GFD: Gluten-free diet, IQR: Interquartile range, SDS: Standard deviation score, F: Female, M: Male, tTG: Tissue thyroglobulin, IgA: Immunoglobulin A, TSH: Thyroid-stimulating hormone, SD: Standard deviation, TPO: Thyroid peroxidase

Discussion

In our study, group 1 showed an older age at the time of CD diagnosis and a poorer individual dietary adherence assessment compared to group 2; nevertheless, the differences were not statistically significant. However, as the duration of CD increased, the rate of poor individual adherence with he GFD increased, and the duration of CD was detected to be longer in group 1.

As age increases during childhood, a gradual decrease in intestinal-related symptoms and malabsorption findings, and an increase in extra-intestinal findings are observed[9]. The change in these clinical findings, especially during adolescence, causes a decrease in compliance with the GFD, along with the decrease in social pressures and the alleviation of symptoms[10]. In our study, the fact that patients with positive thyroid autoantibodies were older, had fewer celiac symptoms and still had higher tTG-IgA levels suggests that compliance with GFD was inadequate in this patient group. This supports the hypothesis that continuous gluten exposure in children with CD who do not follow a GFD may initiate a systemic immune response by compromising intestinal barrier integrity, potentially leading to the onset of additional autoimmune diseases.

Individuals with CD who do not adhere to a GFD are at an elevated risk for developing additional autoimmune diseases. The age at which CD is diagnosed and the presumed duration of gluten exposure are regarded as predictive factors for the onset of additional autoimmune diseases[11]. Various studies have reported differing outcomes concerning the effects of a GFD in individuals with CD and concurrent ATD. The observed effects involve clinical outcomes, including regression of subclinical hypothyroidism, alterations in thyroid autoantibody levels, normalization of thyroid volume, and modifications in thyroxine requirements among patients diagnosed with hypothyroidism[12].

In a study evaluating the age at diagnosis of CD, it was reported that children diagnosed with CD after the age of 10 years had four times higher rates of concomitant autoimmune diseases than those diagnosed after the age of 2 years[13]. In another study, it was found that the age at diagnosis of children with CD with concomitant ATD was higher than that of those children without ATD[14]. In a study by Meloni et al.[15], ATD developed in 34 of 324 children with CD, and the age at diagnosis was 6.6 years in children with CD alone, whereas the age at diagnosis for CD was 10.5 years in patients with CD and autoimmune thyroiditis. In our study, there was no statistically significant difference between group 1 and group 2 in the age at diagnosis of CD; however, similar to the literature, the age at diagnosis was older in group 1.

A study on the age at diagnosis of CD indicated that children diagnosed after the age of 10 showed four times the rates of concurrent autoimmune diseases compared to those diagnosed after the age of 213. A separate study indicated that the age at diagnosis for children with CD and concomitant ATD was greater than for those without ATD[14]. Meloni et al.[15] conducted a study revealing that ATD occurred in 34 out of 324 children with CD. The average age at diagnosis for children with CD alone was 6.6 years, while those with both CD and autoimmune thyroiditis had a diagnosis age of 10.5 years. Our study found no statistically significant difference in the age at CD diagnosis between group 1 and group 2; however, consistent with existing literature, group 1 demonstrated a trend toward an older age at diagnosis.

Gluten exposure is considered a significant predictor of autoimmune disease onset, and the literature examines its impact on the formation of thyroid autoantibodies in patients with CD, with varied conclusions. A study conducted by Metso et al.[16] monitored 27 individuals with CD and 27 healthy controls over the course of one year. While no significant difference in anti-TPO positivity was detected at diagnosis or during follow-up between the two groups, a not statistically significant elevation in anti-TPO titers was noted in the group with CD, despite adherence to a GFD. In another study by Oderda et al.[17], anti-TPO positivity was detected in 6 of 41 children diagnosed with CD. It has been reported that these children were older at the time of diagnosis (mean age 7.5 years; comparison group: 2 years), and thyroid antibody positivity was observed more frequently in children older than 6 years. After 1-5 years of follow-up, antibodies became negative in two of the 6 patients with anti-TPO positivity, and antibody titers increased in the other four patients. The younger age of the children with antibody negativity suggests that delayed diagnosis and longer gluten exposure may be related to the development of thyroid autoantibodies. In line with these findings, it is emphasized that starting a GFD may be insufficient to suppress already developed thyroid autoimmunity, but rapid identification and the early removal of gluten may safeguard against the onset of thyroiditis[17]. In another study with long-term follow-up data, 324 children with CD were followed up for approximately 11 years, during which 34 patients developed thyroid autoantibody positivity. Antibody positivity was observed at diagnosis in 11 cases, while it showed up during GFD treatment in 23 cases. In a follow-up period of 2-9 years, it was observed that anti-TPO and/or anti-TG levels remained elevated in 9 out of 11 patients who were antibody positive at diagnosis, despite adherence to a GFD15.

In a multicenter study by Sategna-Guidetti et al.[18], 241 adult patients with CD were evaluated for thyroid autoantibodies and thyroid functions before and one year after starting a GFD. Initially, euthyroid ATD was detected in 16% of the cases, and subclinical hypothyroidism or hyperthyroidism was reported to develop in 25% of these individuals during the follow-up period. It was emphasized that individual adherence to GFD was poor in these patients. It has been reported that 5.5% of individuals with normal thyroid function tests at the time of diagnosis developed thyroid dysfunction during follow-up despite good compliance with a GFD. In a longitudinal study including 90 university students with CD, high anti-TPO titers were detected in 13 (14.4%) of these cases at the time of diagnosis. Following the GFD, anti-TPO positivity was observed at 11.1%, 6.6% and 2.2% at 6, 12 and 24 months, respectively, and in the two cases where antibody positivity continued at 24 months, anti-TPO titers were found to be quite low. These findings suggest that a GFD may reduce anti-TPO titers over time[19]. Abu Hanna et al.[20] found a significant negative correlation between tTG-IgA levels below three times the upper limit of normal and the accelerated normalization of these levels. Additionally, they noted a correlation with the onset of autoimmune illness. Researchers suggest that a GFD may reduce thyroid autoantibodies by decreasing tTG-IgA levels, hence offering a protective effect against the onset of autoimmune disorders. Likewise, another investigation indicated that sustained tTG-IgA positivity correlated with an elevated risk of irreversible hypothyroidism[21]. Our study's findings indicate that gluten exposure may contribute to thyroid autoimmunity. In group 1, the duration of CD was markedly prolonged, and the incidence of individual non-adherence to the diet and individuals were tTG-IgA positive were elevated but not considerable. The findings, consistent with existing literature, indicate that the length of gluten exposure and adherence to a GFD may significantly influence the development of thyroid autoantibodies.

Our study group found no significant association between tTG-IgA levels and anti-TPO and anti-TG antibodies. However, research by Légeret et al.[22] revealed a small but statistically significant negative connection between anti-TG and tTG-IgA levels. Although this finding points to a possible relationship between serological activity and thyroid autoimmunity, data on this subject in the literature are inconsistent[19,23,24]. Although a possible association between CD and thyroid dysfunction or ATD is thought to exist, the strength and direction of this association remain inconsistent in the literature due to factors such as methodological differences between existing studies, sample sizes and follow-up periods. A certain period of time is required for thyroid autoantibodies to be detected. However, the lack of a clear consensus on this period is the main reason for the inconsistent results in the studies. There is no consensus in the guidelines regarding when patients with CD should undergo screening for autoimmune thyroiditis in children, and the decision regarding the timing of the examination is left to the clinician.

Study Limitations

This study is limited by its retrospective and cross-sectional design. Another important limitation is that neither tTG-IgA levels nor individual dietary adherence assessment are gold standard methods for assessing gluten exposure in the evaluation of GFD compliance[25]. This makes it difficult to draw a definitive conclusion about gluten exposure.

Conclusion

Our study observed that the frequency of thyroid autoantibody positivity increased with age at diagnosis of CD, consistent with existing literature. This finding suggests that prolonged gluten exposure with delayed diagnosis may contribute to thyroid autoimmunity. Therefore, the development of screening strategies to prevent delayed age at diagnosis in CD and early initiation of a GFD may have a potential role in the prevention of comorbidities such as thyroid autoimmunity.

Ethics

Ethics Committee Approval: The protocols adhered to the principles of the Declaration of Helsinki and received approval from the Harran University Clinical Research Ethics Committee (approval number: HRÜ/25.07.26, date: 14.04.2025).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Author Contributions: Eviz E: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Teker Düztaş D: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

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Integrating Clinical and Laboratory Markers to Predict Transfusion in Pediatric Trauma Patients

Author(s)

Mehmet Akif Dündar[1], Emin Ceran[1], Sedanur Tekin Can[2], Başak Nur Akyıldız[1]

Affiliation(s)

[1]Erciyes University Faculty of Medicine, Department of Pediatrics, Pediatric Intensive Care Unit, Kayseri, Türkiye

[2]Erciyes University Faculty of Medicine, Department of Pediatrics, Kayseri, Türkiye

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Abstract

Trauma-related hemorrhage represents a leading contributor to avoidable deaths in pediatric patients and often necessitates prompt transfusion decisions. Unlike adults, children may maintain hemodynamic stability until significant blood loss occurs, making early recognition of transfusion needs particularly challenging. This investigation sought to determine dependable clinical and laboratory predictors of blood transfusion during the initial 24-hour period of pediatric trauma and to establish a practical risk stratification tool to aid emergency decision-making. This retrospective study included pediatric trauma patients under 18 years of age who were admitted to a Pediatric Intensive Care Unit. Clinical and laboratory data at admission were recorded, and patients were grouped based on whether they received blood transfusions during the initial 24-hour period. Univariate and multivariate logistic regression analyses were conducted to determine independent predictors. Receiver operating characteristic curve analysis was employed to establish optimal threshold values and develop a combined risk score for transfusion prediction. Among 95 pediatric trauma patients, 34.7% required blood transfusion within 24 hours. Transfused patients had significantly lower pediatric trauma scores, higher glucose levels, lower platelet counts, and were more frequently intubated. Multivariate analysis identified intubation, glucose, and platelet count as independent predictors of transfusion. A combined risk score incorporating these variables demonstrated high discriminative ability (area under the curve=0.831). Risk stratification revealed transfusion rates of 3.8% in low-risk patients, 30.2% in moderate-risk patients, and 100% in high-risk patients. The combination of intubation, glucose, and platelet count provided a simple yet effective tool for predicting transfusion needs in pediatric trauma. The resulting risk score outperformed individual parameters and allowed for early identification of high-risk patients. This model may help guide timely transfusion decisions and optimize care in emergency settings. Prospective validation is warranted to confirm its clinical utility and broader applicability.

Keywords: Pediatric trauma, blood transfusion, predictive biomarkers, intensive care

Correspondence: Mehmet Akif Dündar MD, Erciyes University Faculty of Medicine, Department of Pediatrics, Pediatric Intensive Care Unit, Kayseri, Türkiye
E-mail: mehmetakifdundar@erciyes.edu.tr **ORCID:** 0000-0003-3042-7999

Introduction

Trauma-related hemorrhage remains among the primary contributors to avoidable deaths in pediatric patients worldwide. In trauma settings, reduction in circulating blood volume secondary to bleeding is the most common cause of shock. Hemorrhagic shock stands as the second leading cause of trauma-related deaths after traumatic brain injury and represents a frequently treatable condition when identified promptly. This makes early identification and management of hemorrhage crucial for improving outcomes in pediatric trauma cases[1,2].

This topic was chosen due to the critical importance of timely blood transfusion decisions in pediatric trauma care. Unlike adult patients, children possess unique physiological responses to blood loss that can mask significant hemorrhage until critical decompensation occurs. The ability to predict which pediatric trauma patients will require blood transfusion during the initial 24-hour period could significantly impact patient outcomes and resource allocation in emergency settings[3-5].

The primary problem addressed in this study is the difficulty in accurately predicting blood transfusion needs in pediatric trauma patients. Blood loss exceeding 30% reduces oxygen delivery and increases anaerobic glycolysis, resulting in tissue hypoperfusion manifested as lactic acidosis. Based on this pathophysiology, lactic acidosis has been strongly associated with trauma mortality. Base deficit has also been utilized as a prominent marker of metabolic acidosis and tissue hypoperfusion. Additionally, vital signs including heart rate and systolic blood pressure serve as readily obtainable clinical indicators for assessing shock. The shock index, computed as the ratio of heart rate to systolic blood pressure, has emerged as a useful tool for monitoring acute circulatory failure[6,7].

Metabolic stress markers have gained recognition as important indicators in trauma patients. Glucose elevation during trauma reflects the body's stress response and has been associated with injury severity. Furthermore, pediatric-specialized scoring systems, including the pediatric trauma score, have been developed to provide comprehensive assessment of injury severity in children. Coagulation abnormalities, reflected by the elevated international normalized ratio (INR), frequently accompany severe trauma and significantly impact transfusion decisions[8,9].

To address this clinical challenge, a retrospective analysis was conducted examining multiple clinical and laboratory parameters in pediatric trauma patients. The investigation was structured to assess the predictive performance of various biomarkers and clinical indicators for blood transfusion needs. Patients, were systematically compared by examining differences between those who received transfusions and those who did not, with comprehensive analysis of their clinical characteristics and outcomes[1,10].

In our clinical experience, we observed that traditional vital signs alone may be insufficient for accurately predicting transfusion needs in pediatric trauma patients, as children can maintain hemodynamic stability until significant blood loss occurs. We hypothesized that combining clinical and laboratory parameters beyond hemoglobin levels would enhance the prediction of blood transfusion needs in pediatric trauma patients. This study aimed to identify reliable predictors of blood transfusion needs within 24 hours, determine optimal cut-off values for clinical application, and evaluate the independent contribution of various parameters. Through this research, we sought to develop a practical approach that could improve early recognition of children requiring blood transfusion in emergency settings.

Highlights

- A novel risk score predicts transfusion needs in pediatric trauma patients.
- Intubation, glucose, and platelet count are independent predictors.
- The combined score shows strong discriminative ability (area under the curve=0.831).
- Risk stratification accurately identifies high-risk patients.
- Early prediction may guide transfusion decisions and improve outcomes.

Materials and Methods

This retrospective investigation was performed at the Pediatric Intensive Care Unit (PICU) of Erciyes University Medical Faculty Hospital between June 2017 and September 2021. The study was approved by the Ethics Committee of Erciyes University Medical Faculty (approval number: 2021/734, date: 03.11.2021). All pediatric trauma patients younger than 18 years who were admitted to the PICU were retrospectively reviewed. Patients with complete medical records who survived at least one hour after admission were incorporated into the study. Exclusion criteria included incomplete medical records, death within the first hour of admission, patients who were transferred after receiving blood products at other centers, and those with known hematological disorders or bleeding diathesis.

Patient data were extracted from electronic medical records and comprised demographic characteristics (age, gender, weight), trauma etiology, affected organ systems, type of head trauma, presence of pneumothorax, indication for intubation, mechanical ventilation duration, surgical interventions, oxygen support requirements, pediatric trauma score, PRISM score, duration of stay in the intensive care unit, total hospital stay duration, and inotropic support needs. Vital signs encompassing heart rate, respiratory rate, systolic and diastolic blood pressure, and oxygen saturation were recorded at admission. Shock index was computed by dividing heart rate by systolic blood pressure at admission. Laboratory values were collected from blood samples obtained at the time of admission to the PICU before any interventions. The following tests were documented: complete blood count, blood glucose, liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT), kidney function tests (blood urea nitrogen), creatinine], inflammatory markers (C-reactive protein, procalcitonin), coagulation parameters (INR), and blood gas analysis including lactate, pH, and base excess.

Patients were categorized into two groups based on blood transfusion requirement within the first 24 hours of admission: the transfusion group, (patients who received blood transfusion) and the non-transfusion group (patients who did not receive blood transfusion). The primary outcome was the need for blood transfusion within 24 hours of admission to the PICU, determined by attending physician assessment of clinical and laboratory parameters.

Transfusion decisions during the study period were based on clinical judgment considering hemoglobin levels, hemodynamic status, ongoing bleeding, and anticipated surgical blood loss. General institutional guidelines suggested transfusion consideration for hemoglobin levels between 7-8 g/dL in stable patients, or 8-10 g/dL with active bleeding or instability, though final decisions were left to the discretion of the attending physician.

Statistical Analysis

All statistical computations were performed using TURCOSA statistical software (Turcosa Analytics Ltd. Co., Türkiye). Post-hoc power analysis using G*Power 3.1 revealed that with 33 transfused and 62 non-transfused patients, the study had 85% power to detect a medium effect size (Cohen's d=0.65), with α=0.05. Data normality was evaluated through the Shapiro-Wilk test. Parametric data were expressed as mean ± standard deviation, while non-parametric data were presented as median and interquartile range. Categorical data were summarized as frequencies and percentages. Group comparisons utilized appropriate statistical methods. Non-parametric continuous variables were analyzed using the Mann-Whitney U test, while categorical variables were examined using chi-square or Fisher's exact tests. Univariate logistic regression identified factors associated with transfusion needs. Variables achieving p<0.10 in univariate analysis were entered into multivariate logistic regression using backward elimination.

Receiver operating characteristic (ROC) curve analysis determined optimal thresholds for continuous variables in predicting transfusion requirements. Area under the curve (AUC) values were calculated with 95% confidence intervals (CIs). DeLong's method facilitated pairwise AUC comparisons. The diagnostic performance for categorical variables was evaluated using contingency tables. A composite risk score incorporated independent predictors from multivariate analysis. Point allocation reflected odds ratios (ORs) and clinical relevance. Chi-square trend analysis evaluated risk stratification performance, while ROC analysis assessed the composite score's discriminative capacity. Statistical significance was defined as p<0.05.

Results

Patient Characteristics and Group Comparisons

Ninety-five pediatric trauma patients were included in this investigation. Thirty-three patients (34.7%) received blood transfusion within 24 hours, while 62 patients (65.3%) did not require transfusion. The median age was 4 years (2-11) in the transfusion group versus 7 years (4-13.25) in the non-transfusion group (p=0.119). Male patients represented 51.5% of the transfusion group compared to 77.4% of the non-transfusion group (p=0.010). Body weight showed no significant difference between groups (p=0.386). Traffic accidents were the predominant trauma mechanism in the transfusion group (67.7% vs. 48.3%), though the overall distribution of mechanisms did not reach statistical significance (p=0.097). No penetrating trauma cases were observed. Patients requiring transfusion exhibited significantly lower pediatric trauma scores (3.5 vs. 7, p<0.001), lower Glasgow Coma Scale scores (5 vs. 12, p<0.001), and higher PRISM scores (13 vs. 0, p<0.001). Heart rate (126 vs. 114 bpm, p=0.042) and shock index (1.2 vs. 1.0, p=0.028) were elevated in transfused patients. Systolic and diastolic blood pressure demonstrated no significant differences between groups. Laboratory values at PICU admission demonstrated several significant differences. Hemoglobin levels were reduced in transfused patients (10.6 vs. 12.3 g/dL, p<0.001), and platelet counts were also reduced in transfused patients (307 vs. 350.5 ×10³/μL, p=0.023). Glucose levels were increased (212 vs. 132.5 mg/dL, p<0.001), lactate was higher (2.81 vs. 2.3 mmol/L, and p=0.013), pH was lower (7.32 vs. 7.4, p<0.001), and base excess was more negative (-4.9 vs. -3 mEq/L, p=0.033). Liver enzymes were significantly elevated in the transfusion group: AST (259 vs. 55.3 U/L, p<0.001) and ALT (123 vs. 29.15 U/L, p<0.001). INR (1.27 vs. 1.115, p<0.001) and creatinine levels (0.55 vs. 0.45 mg/dL, p=0.009) were higher in transfused patients.

Transfused patients required more intensive interventions. Intubation (84.8% vs. 24.2%, p<0.001), surgical procedures (57.6% vs. 16.1%, p<0.001), and inotropic support (42.4% vs. 6.5%, p<0.001). Multiple organ involvement was more common in transfused patients (87.9% vs. 54.8%, p=0.025). PICU length of stay was longer in the transfusion group (6.5 vs. 3 days, p=0.002), as was the total hospital stay (14 vs. 8 days, p=0.002). **Table 1** presents group comparisons.

Predictors of Blood Transfusion Requirement

Univariate analysis identified significant associations between transfusion requirement and pediatric trauma score (OR=1.61, 95% CI: 1.31-1.97, p<0.001), glucose (OR=1.02, 95% CI: 1.01-1.03, p<0.001), platelet count (OR=1.00, 95% CI: 1.00-1.00, p=0.018), shock index (OR=0.18, 95% CI: 0.05-0.70, p=0.013), and intubation (OR=17.54, 95% CI: 5.75-53.51, p<0.001).

Multivariate backward Wald analysis revealed three independent predictors: intubation, identified as the strongest predictor (OR=7.69, 95% CI: 2.25-26.32, p=0.001), glucose levels (OR=1.02, 95% CI: 1.01-1.03, p=0.017), and platelet count, which trended toward significance (OR=1.00, 95% CI: 1.00-1.00, p=0.092). **Table 2** displays the complete results.

ROC Analysis and Diagnostic Performance

Five continuous variables were evaluated for transfusion prediction within 24 hours. pediatric trauma score achieved the highest discriminative ability (AUC=0.832, 95% CI: 0.741-0.901, p<0.001) with an optimal cut-off of ≤5 (sensitivity 78.1%, specificity 80.6%). Glucose demonstrated strong performance (AUC=0.795, 95%

CI: 0.699-0.871, p<0.001) with cut-off ≥187 mg/dL (sensitivity 78.8%, specificity 82.3%).

Platelet count showed moderate ability (AUC=0.642), lactate levels demonstrated an AUC=0.655, and shock index showed an AUC=0.637. Intubation status revealed a significant association (χ^2=31.98, p<0.001) with the highest sensitivity (84.8%) and negative predictive value (90.4%). Pairwise comparisons showed that the pediatric trauma score outperformed both lactate and the shock index, while glucose exceeded the performance of the shock index. **Table 3** contains diagnostic metrics.

Combined Risk Score Development and Validation

A three-component risk score was constructed using multivariate predictors: intubation (2 points), glucose >187 mg/dL (2 points), and platelet count <321,000/μL (1 point), thus creating a range of 0 to 5 points.

Risk stratification created three distinct groups with progressively increasing transfusion rates: low risk (0 points, n=26, 27.4%) with 3.8% transfusion rate; moderate risk (1-2 points, n=53, 55.8%) with 30.2% transfusion rate; and high risk (3-5 points, n=16, 16.8%), where all patients required transfusion. While the high-risk group demonstrated a 100% transfusion requirement, the interpretation of this finding should be tempered by the limited sample size (n=16) in this stratum.

The combined score achieved an AUC=0.831 (95% CI: 0.744-0.918, p<0.001), exceeding individual parameters. An optimal cut-off of ≥1.5 points yielded 97.0% sensitivity and 40.3% specificity. High-risk patients demonstrated a 100% transfusion requirement. In contrast, low-risk patients exhibited a 96.2% negative predictive value. **Table 4** outlines the complete results.

Table 1.
Comparison of demographic data, clinical scores, vital signs and laboratory values between transfusion and non-transfusion groups

Variables	Transfusion group (n=33)	Non-transfusion group (n=62)	p-value
Demographics			
Sex (male), n (%)	17 (51.5)	48 (77.4)	0.010*
Age (years)	4 (2-11)	7 (4-13.25)	0.119
Weight (kg)	25 (15-35)	25 (15-42.5)	0.386
Trauma mechanisms			0.097
Traffic accidents, n (%)	21 (67.7)	28 (48.3)	
Falls from height, n (%)	8 (25.8)	20 (34.5)	
Other mechanisms, n (%)	2 (6.5)	10 (17.2)	
Clinical scores			
Pediatric trauma score	3.5 (1-5)	7 (6-9)	<0.001*
Glasgow coma scale	5 (3-10)	12 (10-13)	<0.001*
PRISM score	13 (4-17.75)	0 (0-4.5)	<0.001*
Vital signs			
Heart rate (bpm)	126 (106.5-156)	114 (95.75-132.25)	0.042*
Shock index	1.2 (0.90-1.57)	1.0 (0.85-1.21)	0.028*
Laboratory values			
Hemoglobin (g/dL)	10.6 (9.4-11.4)	12.3 (11.2-13.1)	<0.001*
Platelet count (×10³/μL)	307 (242.5-418.5)	350.5 (288.25-430.75)	0.023*
Glucose (mg/dL)	212 (189-294)	132.5 (112.75-161.75)	<0.001*
AST (U/L)	259 (111.85-640.5)	55.3 (36.675-149.75)	<0.001*
ALT (U/L)	123 (55.5-400.5)	29.15 (18.175-99.225)	<0.001*
Creatinine (mg/dL)	0.55 (0.425-0.765)	0.45 (0.36-0.5925)	0.009*
INR	1.27 (1.17-1.485)	1.115 (1.04-1.18)	<0.001*
pH	7.32 (7.225-7.4)	7.4 (7.36-7.47)	<0.001*
Base excess (mEq/L)	-4.9 (-9.35 to -1.8)	-3 (-5.5 to -1.75)	0.033*
Lactate (mmol/L)	2.81 (2.2-4.835)	2.3 (1.4925-3.0275)	0.013*
Clinical interventions			
Intubation, n (%)	28 (84.8)	15 (24.2)	<0.001*
Surgery, n (%)	19 (57.6)	10 (16.1)	<0.001*
Inotropic support, n (%)	14 (42.4)	4 (6.5)	<0.001*
Outcomes			
Multiple organ involvement, n (%)	29 (87.9)	34 (54.8)	0.025*
ICU length of stay (days)	6.5 (3-11.75)	3 (2-6.5)	0.002*
Hospital length of stay (days)	14 (8.25-28.75)	8 (5-13.5)	0.002*

Data are presented as median (Q1-Q3) for continuous variables and n (%) for categorical variables. *Mann-Whitney U test for continuous variables, Chi-square test for categorical variables, ICU: Intensive care unit, PRISM: Pediatric risk of mortality, INR: International normalized ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, CRP: C-reactive protein

Discussion

This study aimed to identify reliable predictors of blood transfusion needs within the initial 24 hours of admission in pediatric trauma patients and to develop a practical risk assessment tool for use in emergency settings. The results supported our hypothesis that integrating clinical and laboratory parameters beyond hemoglobin levels would enhance the prediction of transfusion needs. Specifically, intubation status, elevated glucose levels, and reduced platelet count emerged as independent predictors of transfusion, and their integration into a combined risk score demonstrated excellent discriminative performance (AUC=0.831), accurately identifying patients at elevated risk for transfusion.

To the best of our knowledge, this is the first study to propose a validated composite risk score for predicting blood transfusion needs in pediatric trauma using widely available admission parameters. The predictive performance of the combined score surpassed that of any single variable. Notably, all patients classified as high-risk required transfusion, while those in the low-risk category had a high likelihood of avoiding it. This three-tiered stratification provides clinicians with a simple yet powerful framework for early identification and prioritization of children who may benefit from prompt transfusion in acute care settings.

Among the independent predictors, intubation proved to be the most significant. This association likely reflects the close link between respiratory compromise and the

Table 2.
Univariate and multivariate logistic regression analysis for factors associated with blood transfusion in pediatric trauma patients

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Pediatric trauma score	1.61	1.31-1.97	**<0.001**	0.87	0.66-1.13	0.288
Lactate (mmol/L)	0.82	0.66-1.01	0.063	1.05	0.78-1.42	0.733
Glucose (mg/dL)	1.02	1.01-1.03	**<0.001**	1.02	1.01-1.03	**0.017**
Platelet count (×10³/μL)	1.00	1.00-1.00	**0.018**	1.00	1.00-1.00	0.092
Shock index	0.18	0.05-0.70	**0.013**	3.05	0.48-19.39	0.237
Intubation (yes vs. no)	17.54	5.75-53.51	**<0.001**	7.69	2.25-26.32	**0.001**

Bold values indicate statistically significant associations (p<0.05).
OR: Odds ratio, CI: Confidence interval, INR: International normalized ratio, NS: Not significant (removed by backward Wald method). Multivariate analysis was performed using backward Wald method. Variables with p>0.10 were sequentially removed from the model. Final model included intubation, glucose, and platelet count as predictors of transfusion requirement

Table 3.
ROC analysis and diagnostic performance of parameters predicting blood transfusion

Parameter	AUC	95% CI	p-value	Optimal cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Pediatric trauma score	0.832	0.741-0.901	<0.001	≤5	78.1	80.6	67.6	87.7
Glucose (mg/dL)	0.795	0.699-0.871	<0.001	≥187	78.8	82.3	70.3	87.9
Platelet count (×10³/μL)	0.642	0.537-0.738	0.021	≤321,000	60.6	64.5	47.6	75.5
Lactate (mmol/L)	0.655	0.550-0.750	0.009	≥2.38	72.7	56.5	47.1	79.5
Shock index	0.637	0.532-0.733	0.037	≥1.26	45.5	83.9	60.0	74.3
Intubation*	-	-	<0.001	Present	84.8	75.8	65.1	90.4

AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value, ROC: Receiver operating characteristic, CI: Confidence interval, *Intubation analyzed using chi-square test (χ^2=31.98, p<0.001)

Table 4.
Combined risk score for predicting blood transfusion requirement

Risk factor/category	Criteria/range	Points	n (%)	Transfusion rate	Performance metrics
Risk score components					
Intubation	Present	2	-	-	OR: 7.69 (2.25-26.32)
Glucose	>187 mg/dL	2	-	-	OR: 1.01 (1.00-1.02)
Platelet count	<321,000/μL	1	-	-	OR: 1.00 (1.00-1.00)
Risk categories					
Low risk	0 points	-	26 (27.4%)	3.8% (1/26)	NPV: 96.2%
Moderate risk	1-2 points	-	53 (55.8%)	30.2% (16/53)	-
High risk	3-5 points	-	16 (16.8%)	100.0% (16/16)	PPV: 100%
Overall performance					
Combined score	0-5 points	-	95 (100%)	34.7% (33/95)	AUC: 0.831 (0.744-0.918)
Optimal cut-off	≥1.5 points	-	-	-	Sensitivity: 97.0%
Statistical significance	-	-	-	-	χ^2=41.49, p<0.001

Risk score developed from multivariate logistic regression coefficients. Points assigned based on odds ratios and clinical significance. AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value, OR: Odds ratio

severity of traumatic injury. A markedly higher proportion of transfused patients required intubation, underscoring the role of airway management as both a marker and a consequence of physiological decompensation in severely injured children. These findings are in line with reports from adult trauma cohorts, where airway intervention has also been associated with increased transfusion needs, reinforcing the relevance of this marker across age groups.

Glucose elevation also showed strong predictive value for transfusion. Hyperglycemia, as part of the systemic stress response to trauma, reflects the activation of neuroendocrine and inflammatory pathways associated with injury severity. Our findings align with previous pediatric studies reporting that elevated glucose levels are associated with more severe trauma and poorer clinical outcomes. Tsai et al.[11] demonstrated, using propensity score-matched analysis, that stress-induced hyperglycemia significantly impacted outcomes in children with trauma, while Tuggle et al.[12] showed that hyperglycemia was associated with increased infection rates in pediatric trauma patients. Thus, glucose at admission may serve not only as a metabolic marker but also as a practical indicator for transfusion triage.

The association between lower platelet counts and increased transfusion requirement underscores the role of early coagulopathy in trauma-related hemorrhage. Although platelet count alone had moderate discriminative ability, its inclusion in the risk score enhanced overall performance. This finding highlights the possibility that early coagulation disturbances may precede overt bleeding and transfusion need in pediatric trauma patients[13].

The pediatric trauma score demonstrated the highest individual discriminative ability among all evaluated parameters (AUC=0.832), underscoring its value as a comprehensive indicator of injury severity in children. However, pediatric trauma score was not retained in the final multivariate model due to collinearity with the included variables. Since pediatric trauma score components include airway status, systolic blood pressure, and neurological status, which overlap with our model variables (intubation, hemodynamic parameters, and altered consciousness), including pediatric trauma score would have introduced multicollinearity and potentially biased the regression analysis.

We therefore retained only the most clinically straightforward and independently significant predictors. Several recent pediatric trauma studies have similarly emphasized the prognostic value of trauma scores and physiological markers in children. For instance, Wendling-Keim et al.[14] highlighted the utility of trauma scores for outcome prediction in pediatric polytrauma, while Lammers et al.[15] and Choi et al.[16] reported the predictive accuracy of pediatric shock indices and their age-adjusted modifications. In addition, coagulopathy and lactate dynamics have been identified as important predictors of adverse outcomes in pediatric trauma[17-19]. These findings support our results and indicate that integrating routinely available clinical and laboratory parameters into structured tools can improve risk stratification specifically in children.

An unexpected finding in our cohort was the higher proportion of female patients in the transfusion group (48.5% vs. 22.6%, p=0.010). While this contrasts with typical pediatric trauma demographics where males predominate, the interpretation of this finding requires caution given our sample size. Previous studies have shown conflicting results regarding sex-based differences in pediatric transfusion requirements. Some reports suggest that anatomical differences in pelvic vasculature and blood volume relative to body size may influence bleeding patterns, though these mechanisms remain unproven in pediatric populations[20,21]. The observed difference in our study may also reflect chance variation or unmeasured confounders such as injury patterns specific to each sex. This finding requires validation in larger, multicenter studies before drawing definitive conclusions about sex-based transfusion risk.

The need for transfusion was associated with increased morbidity. Patients who received transfusions had longer intensive care and hospital stays and required more frequent surgical interventions and inotropic support, reflecting greater injury severity and clinical complexity[22]. These outcomes highlight the importance of early and accurate identification of patients at risk for transfusion, as timely intervention may reduce complications and resource burden.

The strong predictive performance of our combined risk score addresses a critical unmet need in pediatric trauma care. Traditional vital signs often fail to detect early blood loss in children due to their robust compensatory mechanisms. By integrating intubation status, glucose, and platelet levels into a practical tool, our study provides a structured approach to guide early transfusion decisions, potentially improving triage accuracy and clinical outcomes.

Important methodological constraints require acknowledgment. The retrospective nature of this study restricts causal inference capabilities and introduces potential selection bias. These findings, from a single-institution investigation conducted at a tertiary care center, have inherent limitations in generalizability. Our patient population, referral patterns, and institutional protocols may differ substantially from other healthcare facilities, particularly community hospitals or centers in different geographic regions. The risk score's performance may vary in settings with different case-mix severity, resource availability, or transfusion thresholds. Furthermore, the limited sample size within the high-risk stratum (n=16) significantly constrains the robustness of conclusions for this subgroup. While all 16 high-risk patients required transfusion (100%), this small sample raises concerns and limits CI precision due to potential overfitting. External validation in larger, multicenter cohorts is essential before clinical implementation of this scoring system.

Conclusion

In summary, we established and validated a practical, three-component risk assessment tool for predicting blood transfusion requirements in pediatric trauma patients during the first 24 hours of admission. The integration of intubation status, glucose levels, and platelet count

demonstrated strong discriminative ability and offered a valuable framework for early risk stratification. Future multicenter, prospective investigations are required to validate this scoring system and evaluate its impact on clinical workflows. Incorporating this tool into automated systems could further streamline emergency care in pediatric trauma.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Erciyes University Medical Faculty (approval number: 2021/734, date: 03.11.2021).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Author Contributions: Dündar MA: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Ceran E: Surgical and Medical Practies, Concept, Analysis or Interpretation; Tekin Can S: Surgical and Medical Practies, Design, Data Collection or Processing, Akyıldız BN: Surgical and Medical Practies, Concept.

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Evaluation of Hypernatremic Dehydration in Newborns After Discharge-in a Newborn Clinic

Author(s)

Öznur Yılmaz Gondal

Affiliation(s)

Beykent University Faculty of Medicine, Department of Pediatrics, İstanbul, Türkiye

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Abstract

Neonatal hypernatremic dehydration (NHD), a consequence of inadequate fluid intake in newborns, can cause morbidity and mortality. This study aims to evaluate the signs, symptoms, and laboratory findings of newborns with NHD and define the approaches that may help to prevent its occurrence. Eighty-five newborns (gestational age ≥37 weeks) with ≥10% weight loss and diagnosed with NHD at their first post-discharge visit were retrospectively evaluated over a five-year period. The control group consisted of 85 healthy newborns with <10% weight loss. Among the NHD group, 54.1% were female, with a mean gestational age 38.1±1.1 weeks, mean birth weight 3359±369 g, mean weight loss of 11.83±1.28%, and a mean age of 3.91±0.9 days at presentation. All mothers exclusively breastfed their infants; however, formula supplementation was significantly more common in the control group (p=0.001). The most common presenting complaints were jaundice (54.1%) and pink-orange discoloration on diapers (25.8%). The presence of black or dark green stool, urination <5 times perday, and pink or orange-stained diapers was significantly higher in the NHD group (p<0.05). Hyperbilirubinemia was also more prevalent in the NHD group (p<0.05). Only 16.5% of the mothers in the NHD group suspected insufficient milk intake. None of the newborns developed severe hypernatremia or complications. Despite breastfeeding education prior to discharge, mothers lacked sufficient knowledge about monitoring feeding adequacy. Educating mothers about signs of insufficient fluid intake, such as jaundice, infrequent urination, pink/orange-stained diapers and dark stools, and closer post-discharge monitoring of at-risk newborns, can help prevent NHD.

Keywords: Dehydration, hypernatremia, newborn

Introduction

The newborn period is a critical time for establishing coordinated care between mother and infant, as mothers learn breastfeeding techniques and how to monitor their newborn's vital signs. Breastfeeding plays a vital role in newborns' health, growth, and development, decreases the risk of infections and sudden infant death syndrome, and reduces the risk of chronic diseases such as obesity and diabetes, in the long term[1-3]. However, breastfeeding difficulties during this period may lead to complications, including hypoglycaemia, dehydration, hyperbilirubinemia, and even acute renal failure due to insufficient milk intake[4].

Newborns may lose up to 7-10% of their birth weight in the first 4-5 days; complications are more likely when weight

Correspondence: Öznur Yılmaz Gondal Assist. Prof., Beykent University Faculty of Medicine, Department of Pediatrics, İstanbul, Türkiye
E-mail: oznuryilmaz@yahoo.com **ORCID:** 0000-0003-3983-0557

loss exceeds 10%[5-7]. Hypernatremia, defined as serum sodium >145 mEq/L, is common among term newborns with feeding difficulties[8]. Hypernatremia and weight loss are closely correlated[9,10]. Insufficient milk intake, poor feeding, inadequate dilution of formula, or gastrointestinal losses can lead to neonatal hypernatremic dehydration (NHD). In the first week of life, insufficient milk intake is the most frequent cause of NHD. If untreated, it may cause cerebral oedema, intracranial haemorrhage, seizures, acute kidney injury, disseminated intravascular coagulation, and death[11-14]. Moderate to severe neurodevelopmental delay is also a possible long-term outcome[15].

Highlights

- Hypernatremic dehydration in newborns with feeding problems can lead to severe complications.
- Mothers lack sufficient knowledge about monitoring the adequacy of breastfeeding.
- This study aims to define the approaches that can help to prevent this complication.

Baby-Friendly Hospital Initiative (BFHI), launched by the World Health Organization in 1991, successfully promoted exclusive breastfeeding for the first 6 months through caregiver and maternal education[16]. However, simultaneously increasing caesarean section (C/S) rates may have inadvertently contributed to higher NHD incidence[17,18]. Despite pre-discharge instructions on breastfeeding techniques, mothers may not know how to monitor the adequacy of breastfeeding and may face life-threatening complications. This study aims to evaluate the clinical and laboratory presentation of NHD in newborns and identify preventive strategies.

Materials and Methods

We retrospectively reviewed 85 term newborns (≥37 weeks of gestation) born at Central Hospital, İstanbul, from 2018-2023, who were diagnosed with NHD at their post-discharge visit. Inclusion criteria were ≥10% weight loss and serum sodium >145 mEq/L.

Data collected included delivery mode, sex, gestational age, birth weight, weight at presentation, maternal-reported feeding history, nursing behaviour, urine and stool output, stool colour, presence of pink or orange stain in diapers, jaundice, and laboratory results (including serum electrolytes, urea, creatinine, glucose and total bilirubin levels). Stool colour was categorized as black, dark green, green, yellow-green, and yellow based on maternal description.

Routine hospital protocol includes daily weight monitoring before discharge; newborns with ≥7% weight loss receive close follow-up and supplementation as needed. The first outpatient visit occurs 48-72 hours post-discharge. At that visit, the total bilirubin levels are measured in cases of visible jaundice. In newborns with ≥10% weight loss, serum glucose levels, renal function tests, and electrolytes are also evaluated. Hypernatremia severity was categorized as mild (146-149 mEq/L), moderate (150-169 mEq/L), or severe (>170 mEq/L)[8,19].

The control group comprised 85 healthy newborns (≥37 weeks), with weight loss <10%, randomly selected from newborns admitted to the pediatrics outpatient clinic for their first routine control after discharge in the same period as the study group.

Exclusion criteria (applied to both groups) included prematurity (<37 weeks), asphyxia, sepsis, congenital anomalies, metabolic and endocrinologic disorders, congenital heart disease, diarrhoea, respiratory distress, or neonatal intensive care unit admission.

Laboratory assays were performed using the Beckman Coulter AU480 Chemistry Analyzer. UniCel DxC SYNCHRON systems Glucose reagent (GLUH), when used in conjunction with UniCel DxC 600/800 SYNCHRON system(s) and SYNCHRON systems AQUA CAL 1 and 3, is intended for the quantitative determination of serum glucose concentration. Urea reagent was used for the quantitative kinetic ultraviolet measurement of urea. Creatinine reagent is used for the quantitative measurement of serum creatinine. Total bilirubin reagent was used in conjunction with UniCel DxC 600/800 systems and SYNCHRON systems bilirubin Calibrator for the quantitative determination of serum total bilirubin concentration. ISE Electrolyte Buffer reagent and ISE Electrolyte Reference reagent, when used in conjunction with UniCel DxC 600/800 system(s) and SYNCHRON systems AQUA CAL 1, 2 and 3, are intended for the quantitative determination of serum sodium, potassium, and chloride concentration.

Approval of the conduct of the study was granted by the Beykent University Non-Interventional Clinical Research Ethics Board (approval number: E-45778635-050.99-96905, date: 15.03.2023).

Statistical Analysis

Descriptive analyses were performed, mean, standard deviation and percentages were calculated. The Kolmogorov-Smirnov test was used to determine the normal distribution of the variables. The Independent Student's t-tests and Mann-Whitney U tests were used in the analysis of independent quantitative data. The chi-square tests and Fisher's tests were used in the analysis of independent qualitative data. A Spearman's correlation test was used in defining the strength and direction of the relationship between the ranks of data. Significance was taken at the level $p<0.05$. Analyses were performed using the Statistical Package for Social Sciences version 28 (IBM SPSS Statistics).

Results

Among 85 newborns, the female to male ratio was 1.17 in the NHD group and 0.93 in the control group, ($p=0.443$). The mean weight loss was 11.83±1.28% in the NHD group, and 4.08±2.73% in the control group ($p<0.001$). The mean age on admission was 3.91±0.9 days in the NHD group, and 4.17±0.5 days in the control group ($p<0.001$) (**Table 1**).

All of the newborns in both groups were exclusively breastfed; formula supplementation was significantly higher in the control group ($p=0.001$) (**Table 2**).

Urination <5 times a day and the presence of pink-orange discoloration on diapers were more frequent in the NHD group (p<0.001) (**Table 2**).

In the NHD group, defecation pattern was recorded in 47 patients, and in the control group, 69 patients. Dark stool (black/dark green) was significantly higher in the NHD group, while yellow/yellow-green stool predominated in controls (p<0.001) (**Table 2**).

Serum total bilirubin levels were measured in 78 subjects from the NHD group and 72 subjects from the control group (**Table 2**). The mean serum total bilirubin level was significantly higher in the NHD group (p<0.001). In the NHD group, the ratio of newborns with serum total bilirubin levels above 10 mg/dL and 15 mg/dL was significantly higher than the control group (p<0.001) (**Table 2**).

Symptoms on admission were recorded in 60 of the patients in the NHD group (**Table 3**). Only 16.5% (n=14) of the mothers had suspected milk insufficiency in their babies (seven of the newborns had poor feeding, five had inconsolable crying, one had rare urination, and one had unsatisfied prolonged nursing).

The mean serum sodium was 149.9±2.9 mEq/L; serum potassium 4.4±0.6 mEq/L; serum chloride 113.9±3.5 mEq/L; serum urea 31.9 mg/dL (12-103), serum creatinine 0.48 mg/dL (0.2-0.78) in the NHD group. In the NHD group, there was mild hypernatremia in 42 (49.4%) and moderate hypernatremia in 43 (50.5%) of the infants. No patients had severe hypernatremia.

The comparison of laboratory parameters in newborns with mild and moderate hypernatremia groups is listed in **Table 4**. Serum urea and serum chloride levels were significantly higher in the NHD group with moderate hypernatremia (p=0.001). In the NHD group, there was a positive correlation between serum sodium and serum urea levels (p=0.001). No correlation was found between serum sodium and serum glucose levels. Although the mean serum total bilirubin level was significantly higher in the NHD group, no correlation was found between serum sodium and serum total bilirubin levels. Weight loss percentage was significantly higher in newborns with moderate hypernatremia (p=0.005).

Thirty-seven (43.5%) of the patients in the NHD group were admitted to the neonatal intensive care unit. The indication for hospitalization was moderate hypernatremia in 23 of the patients, hyperbilirubinemia in 6, and moderate hypernatremia + hyperbilirubinemia in 8 of the patients. However, eight of them refused hospitalization. Among the patients who refused

Table 1.
Demographic characteristics of newborns with NHD and control group

	NHD group (n=85)	Control group (n=85)	p-value
Gender (female/male) ratio	46 (54.1%)/39(45.9%)	41 (48.2%)/44 (51.7%)	0.443[1]
Gestational age (weeks)	38.1-39.6	38.3-39.3	0.581[2]
Maternal age (years)	29.0-34.0	30.0-36.0	0.224[2]
Mode of delivery (C/S/NSVD)	71 (83.5%)/14(16.5%)	69 (81.2%)/16 (18.8%)	0.687[1]
Birth weight (g)	3359±369	3346±374	0.814[3]
Admission weight (g)	2962±331	3207±347	<0.001[3]
Weight loss (%)	10.7-13.0	2.4-6.4	<0.001[2]

[1]: Chi-square test (Fisher's test) [2]: Mann-Whitney U test, [3]: Independent Student's t-test, C/S: Cesarean section, NVSD: Normal spontaneous vaginal delivery, NHD: Neonatal hypernatremic dehydration

Table 2.
Comparison of formula feeding, urination frequency, stool color, presence of urate crystals in urine, and serum total bilirubin levels in newborns with NHD and control group

		Control group		NHD group		p
		Mean ± SD/n-%		Mean ± SD/n-%		
Formula feeding	(-)	64	75.3%	80	94.1%	**0.001**[1]
	(+)	21	24.7%	5	5.9%	
Urination frequency (/day)	<4	12	14.1%	46	100.0%	<0.001[1]
	≥5	73	85.9%	0	0.0%	
Dark green		4	5.8%	24	51.0%	
Green		4	5.8%	6	12.8%	
Yellow-green		20	28.9%	1	2.1%	<0.001[1]
Yellow		39	56.5%	1	2.1%	
Black		2	2.9%	9	19.1%	
No stool		0	0%	6	12.7%	**0.001**[1]
Urate crystals	(-)	80	94.1%	40	48.7%	<0.001[1]
	(+)	5	5.9%	45	51.3%	
Serum total bilirubin (mg/dL)		9.6±3.7		12.6±3.6		<0.001[2]
Serum total bilirubin ≤10 mg/dL		35	48.6%	16	20.5%	<0.001[1]
Serum total bilirubin >15 mg/dL		4	5.6%	20	25.6%	**0.001**[1]

[1]: Chi-square test (Fisher's test) [2]: Mann-Whitney U test, SD: Standard deviation, NHD: Neonatal hypernatremic dehydration

hospitalization, 6 were followed up in the clinic and were given feeding advice, and 2 of them did not come for control. Twenty-nine patients were hospitalized and received intravenous fluids. Fourteen patients also received phototherapy. The average hospital stay was 1.2 days, and no complications were recorded. Mean serum sodium levels were 144.3±3.26 mEq/L at the end of the first day of treatment. Six patients with moderate hypernatremia (serum sodium: 150-156 mEq/L) who refused hospitalization, were followed up with feeding recommendations and did not have any complications.

Discussion

NHD is a frequent complication in newborns with inadequate fluid intake, and can be life-threatening if untreated[20,21]. The incidence was reported ranging from 0.2% to 8% in different studies[15,22-26]. These rates may change due to many factors, such as newborn follow-up policies of the country, screening facilities, and access to follow-up data after discharge. In a 2019 study, the incidence was reported as 30.9% in the first 72 hours in healthy newborns[8]. Our observed incidence of 1.1% aligns with the data of Ergenekon et al.[15] from Türkiye (1%).

Rising NHD has been attributed to increased rates of exclusive breastfeeding following the introduction of the BFHI, higher rates of C/S, as well as heightened awareness[10,17,18,27]. Butler and Trotman[24] noted increased detection of NHD post-BFHI and also stated that, as the awareness increased, one-third of the cases of NHD were recognized during the postnatal ward predischarge and therefore were less severe[18]. Pelleboer et al.[25], also, emphasized closer supervision of breastfeeding techniques in the postnatal ward, and stated that the longer mothers spend time in the postnatal ward, the more they are educated on the adequacy of breastfeeding. However, the increased costs of hospital stay and quicker recoveries after C/S have decreased the duration of stay to 24-48 hours, making closer evaluation of breastfeeding techniques more difficult[28].

In our clinic, since all newborns were discharged between 24-48 hours after birth —regardless of the mode of delivery— were diagnosed at their first visit after discharge. However, before discharge, all newborns are weighed daily, and if they lose nearly or more than 7% of their weight, they are closely monitored and provided with milk supplements as needed. Closer evaluation is emphasized for babies who experience over 7% weight loss is also emphasized in other studies[29,30]. In a study by Uras et al.[31], it is reported that 95% of the hypernatremia cases occurred above 7% weight loss. Lavagno et al.[13] reported that 96% of hypernatremia occurred above 10% weight loss, and severity increased with increasing weight loss.

Some studies have indicated that NHD can be attributed to inadequate breastfeeding, which is associated with delayed maturation of breast milk and insufficient supply, resulting in elevated serum sodium levels in breast milk[32]. It is reported that C/S delivery, primiparity, breast anomalies, delayed first breastfeeding, and advanced maternal age above 30 are risk factors in delayed lactogenesis[33]. In a cohort study in 2018, it was stated that 74.5% of the NHD cases were exclusively breastfed, 21.65% were mix-fed, and 3.9% of the formula-fed infants[8]. A study on weight loss in neonates has revealed that 10% of infants delivered vaginally and 25% of infants delivered via C/S experience a weight

Table 3.
Clinical presentation of newborns with hypernatremia

Symptoms	n	%
Jaundice	46	54.1
Pink or orange discoloration on diaper (urate crystals)	22	25.8
Inconsolable crying	8	9.4
Poor feeding	7	8.2
Increased body temperature	4	4.7
Rare urination	3	3.5
Difficulty in waking up	2	2.3
Unsatisfied prolonged nursing	2	2.3
No stool	1	1.2

Table 4.
Comparison of mild and moderate hypernatremia in terms of demographic features and laboratory tests

	Mild hypernatremia (n=42)	Moderate hypernatremia (n=43)	p-value*
Gender (female/male)	24/18	22/21	0.580
Gestational age (weeks)	38.54±1.00	38.94±1.16	0.151
Mode of delivery (C/S/NSVD)	34/8	37/6	0.527
Birth weight (g)	3369.35±397.1	3349.76±344.8	0.829
Admission weight (g)	2984.04±364.08	2941.04±303.51	0.530
Age at presentation (d)	3.80±1	4.02±0.8	0.147
Weight loss (%)	11.45±1.23	12.19±1.23	**0.005**
Serum glucose (mg/dL)	58.86±17.8	64.09±14.1	0.024
Serum urea (mg/dL)	24±11.2	40.22±21.7	**0.001**
Serum creatinine (mg/dL)	0.43±0.14	0.52±0.15	0.103
Serum potassium (mEq/L)	4.43±0.64	4.38±0.56	0.754
Serum chloride (mEq/L)	111.3±1.8	115.84±3.2	**<0.001**
Serum total bilirubin (mg/dL)	12.6±3.59	12.59±3.57	0.900

*: Mann-Whitney U test, NSVD: Normal spontaneous vaginal delivery, C/S: Cesarean section

loss exceeding 10% within the initial 72 hours of their lives[34]. Hobbs et al.[35], and Fan et al.[36] also emphasized the negative impact of C/S on breastfeeding. In our study, 83.5% of the neonates were delivered via a C/S, and the average maternal age at birth was 32.2 years. There was no significant difference in terms of mode of delivery and maternal age between the groups. However, the rate of receiving formula was significantly higher in the control group.

Iyer et al.[37] emphasized that weighing the babies at postnatal between 72-96 hours was an effective method in the early diagnosis of NHD. In a study in 2021, the mean age at presentation was 5.6 days, and 6 patients had acute renal failure, 2 had convulsions, and 1 had bradycardia[24]. In a previous study by Trotman et al.[18], the mean age at presentation was 7.4 days, and the rate of acute renal failure, death, convulsions, and intraventricular bleeding was higher by 18%. Our hospital policy is the daily weight control and examination of the baby 48-72 hours post-discharge. The mean age at presentation was 3.91 days. Serum urea levels were elevated in 33 (38.8%) of the patients; however, serum creatinine and serum potassium levels were normal. We did not observe severe hypernatremia; all the patients were discharged without any complications. In many studies where severe complications were reported, the age at presentation was higher than expected[18,20,23,25,38]. As the age at presentation increases, the severity of hypernatremia and complications tend to increase. Therefore, examination of the newborn on the fourth day after birth seems to be a reasonable time for the first assessment. Trotman et al.[18] reported that babies visited by domiciliary services had lower mean serum sodium, urea and creatinine levels, and emphasized the early control of the newborn after discharge.

In hospitals designated as baby friendly, mothers receive instructions on breastfeeding techniques and are urged to exclusively provide breast milk to their infants. However, there may be a lack of education in recognizing early signs of inadequate feeding and dehydration. Hence, it is possible for well-educated mothers desiring to adhere to exclusive breastfeeding guidelines to inadvertently overlook inadequate feeding practices.

The first sign of NHD is weight loss, and is accompanied by a decreased urine output, reduced bowel movements, and the appearance of urate crystals in urine[39-41]. Monitoring urine output is crucial for identifying poor feeding, and is emphasized in studies about NHD[42]. In our study, the NHD group exhibited a significantly higher presence of pink-orange discoloration on diapers and a significantly lower frequency of urination.

According to a study, the assessment of wet and soiled diaper counts in breastfed infants may not be a dependable measure for determining appropriate nutrition. Additionally, it was found that even neonates with a weight loss above 10% might still exhibit up to six instances of wet and dirty diapers[43]. In contrast, we found that the number of soiled diapers was significantly lower in the NHD group and the rate of black or dark green stool was significantly higher.

In Korea, a brochure was developed to guide the monitoring of exclusively breastfed newborns. Pale, odourless urination at least 4-5 times a day, 2-3 bowel movements with stool colour turning from brown to mustard yellow, and the baby being content after breastfeeding are regarded as signs of adequacy of breastfeeding[44]. In the study conducted, a significant proportion of the maternal participants showed a lack of awareness regarding the indicators associated with inadequate feeding practices and dehydration.

Infants with insufficient milk intake may also present with inconsolable crying, prolonged unsatisfied feeding, jaundice, and fever[14]. Some may not show signs of distress or appear sleepy and satisfied after feeding; however, they have difficulty waking up and can easily be overlooked. The most common presenting symptoms that we encountered were jaundice, pink or orange discoloration in urine, inconsolable crying, and poor feeding. However, only 16.5% of the mothers had suspected milk insufficiency.

Another important clinical situation associated with NHD is hyperbilirubinemia. In a review, it was reported that 45% of the hypernatremia cases developed jaundice[14]. The incidence of hyperbilirubinemia was notably elevated within our study cohort, and a positive association was observed between serum sodium and serum total bilirubin levels. According to existing literature, hypernatremia may negatively impact the functionality of the blood-brain barrier. This impairment could potentially ease the passage of bilirubin over the blood-brain barrier, consequently increasing the susceptibility to bilirubin encephalopathy[45]. In the present study, the diagnosis was established at an earlier stage in comparison to existing scholarly literature. The maximum recorded level of serum total bilirubin was 19.5 mg/dL, and none of the neonates exhibited signs of bilirubin encephalopathy. Although hypoglycaemia may be a contributing factor to poor feeding, the average serum glucose level was 61.4 mg/dL in our cases with NHD, and no correlation was found between serum glucose and serum sodium levels.

Study Limitation

A limitation of the study was its retrospective design, which resulted in missing anamnestic data for some patients; therefore, only the available data could be evaluated.

Conclusion

NHD is a frequent consequence of inadequate fluid intake in newborns, and early diagnosis is crucial for prompt management and prevention of severe complications. Education of healthcare providers and parents not only on lactation management but also on recognizing early signs of inadequate breastfeeding, like weight loss, dark colour stool, decreased frequency of urination, pink or orange-stained diapers, and jaundice, is essential. Daily pre-discharge weights and outpatient monitoring at 48-72 hours post-discharge; with special attention to infants with ≥7% weight loss, can assist in early detection and timely intervention.

Ethics

Ethics Committee Approval: Approval of the conduct of the study was granted by the Beykent University Non-Interventional Clinical Research Ethics Board (approval number: E-45778635-050.99-96905, date: 15.03.2023).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

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Migraine, Tension-Type Headache and Magnesium in Children

Author(s)

Gökçe Gizem Barin[1], Hamit Acer[2]

Affiliation(s)

[1]Denizli State Hospital, Clinic of Child and Adolescent Mental Health and Diseases, Denizli, Türkiye
[2]Denizli State Hospital, Clinic of Pediatric Neurology, Denizli, Türkiye

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Abstract

This study aimed to evaluate the relationship between migraine, tension-type headache (TTH), and magnesium (Mg) in order to shed light on possible treatment and prophylaxis options. The file registration information of patients under the age of 18 who presented with headache complaints and were diagnosed with migraine and TTH according to the International Classification of Headache Disorders Criteria was retrospectively scanned. A total of 156 patients, 93 (60%) female and 63 (40%) male, were included in the study. No difference was detected between the Mg, vitamin D, and calcium levels of the migraine group, TTH group, and control group. We think that our study is important for investigating the relationship between migraine, tension headache, Mg, calcium, and vitamin D. It needs to be supported by more clinical and laboratory studies, to enable new treatment perspectives.

Keywords: Migraine, tension-type headache, magnesium

Introduction

Magnesium (Mg) has been used in medical treatments since the 17th century and is recognized as an essential mineral crucial for maintaining numerous physiological processes in the human body[1]. Historically, Epsom salt—primarily consisting of Mg sulfate—was commonly used to address conditions such as abdominal pain, constipation, and muscle cramps. In contemporary medicine, Mg has gained attention for its therapeutic benefits in pain management, largely due to its ability to regulate calcium influx into cells and block N-methyl-D-aspartate (NMDA) receptors[2].

Globally, migraine is one of the most prevalent causes of acute and recurrent headaches. In the United States, it affects approximately 18% of women and 6% of men, with more than half of sufferers reporting impaired productivity in their daily lives[3]. Among children, migraines not only disrupt academic performance, but also significantly diminish family quality of life due to symptoms such as nausea, vomiting, sensitivity to light (photophobia), sensitivity to sound (phonophobia), and occasional visual or sensory disturbances. Mg's role in stabilizing neuronal electrical activity is particularly relevant here[4]. Research has identified a link between migraines and reduced Mg levels in both

Correspondence: Hamit Acer MD, Denizli State Hospital, Clinic of Pediatric Neurology, Denizli, Türkiye
E-mail: dr_hamitacer@hotmail.com **ORCID:** https://orcid.org/0000-0002-0767-5751

serum and cerebrospinal fluid, suggesting that Mg deficiency could contribute to migraine development. As a result, Mg is often recommended for both prevention and treatment of migraines[5].

Tension-type headache (TTH) represents another frequent primary headache disorder in children. Despite its high occurrence, TTH is often challenging to diagnose in clinical settings due to symptom overlap with migraines. Pediatric patients may exhibit migraine-like symptoms during TTH episodes, and vice versa. While the Mg-migraine connection has been extensively studied, there is limited research on Mg levels in children diagnosed with TTH.

This study aims to explore the relationship between serum Mg levels and two major headache types—migraine and TTH—in pediatric patients, with the goal of supporting the development of improved therapeutic and preventive strategies.

Highlights

- Magnesium (Mg) levels were evaluated in pediatric patients with migraine and tension-type headache (TTH).
- No significant difference in serum Mg levels was observed between migraine, TTH, and control groups.
- The study also assessed calcium and vitamin D levels, with no notable variations among the groups.
- Intracellular Mg and ionized calcium measurements may provide more definitive insights in future studies.
- Findings suggest that serum Mg alone may not be a reliable marker for pediatric primary headaches.
- Larger, prospective studies are recommended to explore the role of Mg, calcium, and vitamin D in headache pathogenesis.

Materials and Methods

This retrospective study was conducted by reviewing the medical records of patients under the age of 18 who presented to the Pediatric Neurology Department of Denizli State Hospital with complaints of headache between March and November 2023 and who were diagnosed with migraine or TTH based on the International Classification of Headache Disorders Criteria[6].

The control group (CG) consisted of healthy children with no headache complaints who presented to our hospital for routine pediatric follow-up visits. Data on the patients' demographic characteristics, clinical findings, complete blood count, and biochemical parameters at the time of initial admission were recorded using a standardized data collection form. To minimize potential confounding factors, the CG was selected from the same sociodemographic region as the patient groups. Thus, both patients and controls were comparable in terms of general living conditions, dietary habits, and environmental factors such as sunlight exposure, which may influence vitamin D status. Furthermore, since both patients and controls were recruited during the same time period (March-November 2023), seasonal variations that might affect laboratory parameters such as vitamin D levels were avoided.

Patients with known chronic illnesses, those using dietary supplements, or those receiving any regular medication were excluded from the study.

Ethics Committee approval of the study was obtained with the Pamukkale University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee meeting dated 19.03.2024 and numbered 06. All participants and their legal guardians provided written informed consent prior to inclusion in the study.

It should be noted that only serum Mg levels were assessed, as ionized or intracellular Mg measurements could not be performed due to the unavailability of these assays in our laboratory.

Statistical Analysis

Statistical analyses were performed using the SPSS software package version 22.0 (IBM Corp., Armonk, NY, USA). The distribution of all variables was assessed using the Shapiro-Wilk test to determine whether they followed a normal or non-normal distribution. Variables with normal distribution were expressed as mean ± standard deviation, while categorical variables were presented as frequency and percentage (%).

For comparisons between two groups, the Independent Samples t-test was used for normally distributed variables, and the chi-square test was used for categorical variables. A p-value of <0.05 was considered statistically significant for all analyses.

Additionally, according to the post hoc power analysis, Cohen's d value was found to be 0.566, which indicates a medium effect size. Therefore, it is suggested that the sample size should be increased in future studies to obtain more meaningful and robust results.

Results

A total of 156 patients were included in the study, with a mean age of 13.9±1.9 years. Of these, 93 (59.5%) were female and 63 (40.5%) were male. The study population was divided into three groups: migraine group (MG), TTH group, and CG. No statistically significant differences were found between the groups in terms of age and sex. The mean number of headache days per month was 8.4±4.4 in the MG and 20.6±10.2 in the TTH group. The demographic and clinical characteristics of the study groups are presented in **Table 1**.

Patients in the MG and TTH groups were evaluated according to their clinical characteristics (**Table 2**). Among MG patients, 12 (21%) reported aura prior to headache onset; 7 (12%) described visual aura and 5 (9%) described sensory aura. Regarding headache frequency, 17 (30.4%) reported attacks every 2-3 days, 8 (14.3%) every 4-7 days, 19 (33.9%) once a week, and 12 (21.4%) once every two weeks. In terms of headache laterality, 40 (72%) of MG patients had unilateral headaches, and 11 (20%) had bilateral headaches. The most common location of pain was the temporal region (49 patients, 87%), followed by the frontal region (4 patients, 8%) and diffuse headache involving the entire head (3 patients, 5%).

Table 1.
Demographic and clinical characteristics of the study groups

Variable	MG (n=56)	TTHG (n=50)	CG (n=47)	p-value
Age (± SD)	13.6 (±2.1)	14.4 (±2.04)	13.5 (±1.71)	0.66
Gender, n (%)				0.359
Male	20	19	23	
Female	36	31	24	
Number of headache days per month	8.4 (±4.4)	20.6 (±10.2)	–	<0.001

MG: Migraine group, TTHG: Tension-type headache group, CG: Control group, SD: Standard deviation

Table 2.
Headache characteristics and associated symptoms of the study groups

Variable	Migraine (n=56)	TTHG (n=50)
Pain character (%)		
Unilateral	40 (72)	4 (8)
Bilateral	11 (20)	18 (36)
Occipital region	-	28 (56)
Temporal region	49 (87)	12 (24)
Frontal region	4 (8)	11 (22)
Holocranial	3 (5)	27 (54)
Aura (%)		
Visual	7 (12)	-
Sensory	5 (9)	-
Symptoms (%)		
Nausea	38 (67)	7 (14)
Vomiting	7 (12)	1 (2)
Photophobia-phonophobia (%)		
Both	41 (73)	4 (8)
Photophobia	1 (1.7)	1 (2)
Phonophobia	1 (1.7)	6 (12)
Headache frequency (%)		
Daily	-	26 (52)
Every 2-3 days	17 (30.4)	8 (16)
4-7 days/week	8 (14.3)	6 (12)
Once a week	19 (33.9)	9 (18)
Every 2 weeks	12 (21.4)	1 (2)
Family history (%)		
	43 (76)	11 (22)

TTHG: Tension-type headache group

During headache attacks in the MG group, 38 patients (67%) experienced nausea, 7 (12%) experienced vomiting, and 11 (20%) reported no accompanying symptoms. Both photophobia and phonophobia were reported by 41 (73%) patients; 13 (23%) reported neither, while 1 (1.7%) reported only photophobia and 1 (1.7%) only phonophobia. A family history of migraine (in at least one first-degree relative such as mother, father, or sibling) was reported in 43 patients (76%).

In the TTH group, 26 patients (52%) experienced daily headaches, 8 (16%) every 2-3 days, 6 (12%) every 4-7 days, 9 (18%) once a week, and 1 (2%) once every two weeks. Regarding headache location, 4 patients (8%) had a headache unilateral, 18 (36%) had a headache bilateral, and 28 (56%) had a headache localized in the neck region. Pain was described by 12 patients (24%) in the temporal area, by 11 patients (22%) in the frontal area, and by 30 patients (60%) in the occipital area.

During headache episodes in the TTH group, 7 patients (12%) reported nausea, 1 (2%) reported vomiting, and 42 (84%) reported no accompanying symptoms. Both photophobia and phonophobia were present in 4 (8%) patients. One (2%) had only photophobia. Six (12%) had only phonophobia, and 39 (78%) had neither symptom.

Regarding serum Mg levels, the overall mean Mg level for the entire study group was 2.03±0.14 mg/dL. When the participants were grouped into patient (MG+TTH) and CGs, the mean Mg level was 2.03±0.14 mg/dL in each group (p=0.8). When compared separately, the mean serum Mg levels were 2.02±0.11 mg/dL in the Mg group, 2.04±0.16 mg/dL in the TTH group, and 2.03±0.14 mg/dL in the CG. No statistically significant differences were found among the groups (p=0.75). Laboratory findings of the patients are summarized in **Table 3**.

Table 3.
Comparison of laboratory parameters between the groups

Variable	Migraine (n=56) Mean ± SD	TTHG (n=50) Mean ± SD	Control (n=50) Mean ± SD	p-value
Magnesium	2.02±0.114	2.04±0.168	2.035±0.141	0.750
Calcium	9.34±0.34	9.3±0.46	9.46±0.36	0.252
Vitamin D	11.5±5.2	12.61±5.38	10.7±4.49	0.248
Phosphorus	4.4±0.59	4.05±0.74	4.18±0.684	0.012

SD: Standard deviation, TTHG: Tension-type headache group

Discussion

This research provides valuable insights into the relationship between Mg and the two most prevalent types of pediatric headaches: migraine and TTH. In addition, this study highlights the clinical characteristics of pediatric patients diagnosed with these conditions.

Globally, severe headaches affect nearly 60% of children and adolescents, with migraines accounting for approximately 7.7% to 9.1% of these cases[7]. Similar to chronic illnesses such as rheumatoid arthritis or cancer, migraines in children can lead to reduced academic performance, diminished quality of life, and decreased overall productivity. As such, addressing migraines and other headache disorders through effective treatment strategies is crucial. Despite extensive research, the underlying mechanisms of migraine pathogenesis remain incompletely understood. Among various proposed triggers, hypomagnesemia has been identified as a potential contributor[8,9].

Fila et al.[10] suggested that dietary Mg supplementation and related compounds may help prevent or alleviate migraine attacks by reducing oxidative stress, which is believed to play a role in migraine development. However, the literature on serum Mg levels in migraine sufferers has yielded inconsistent findings. While some researchers have reported that patients with severe migraine attacks tend to exhibit lower Mg levels compared to those with milder symptoms, Talebi et al.[11] also noted significantly reduced serum Mg concentrations in migraine patients relative to healthy controls, and found an association between lower Mg levels and higher attack frequency. Conversely, other studies have observed no significant differences in serum Mg levels between migraine patients and healthy individuals. In this research, similarly, no statistically significant difference was found in serum Mg levels between the MG and controls. This may be partly explained by the fact that only about 1% of total body Mg is present in serum, and our analysis focused exclusively on serum measurements. Although there are studies in the literature that did not find a difference in serum Mg levels between migraine patients and healthy controls, Mg is currently used as one of the leading options in the treatment of migraine. The data from this study may contribute to the existing literature by providing insight into the reconsideration of the use of Mg in migraine therapy.

It is important to note that Mg does not provide direct pain relief but exerts its effects by inhibiting NMDA receptors and regulating calcium ion entry into neurons. This study also assessed serum Mg levels in pediatric patients with TTH. The results revealed no significant differences in Mg concentrations among the TTH, migraine, and CGs. This suggests no apparent variation in serum Mg levels across these cohorts. Nonetheless, future studies utilizing more advanced techniques, such as measuring intracellular Mg concentrations in erythrocytes, may yield more definitive findings.

Mg's role in blocking neuronal calcium influx, has also encouraged researchers to explore calcium metabolism in the context of migraine pathogenesis[12]. A large-scale retrospective study by Yin et al.[13], which analyzed over one million patient records, found an association between hypercalcemia and a 1.8-fold increased risk of migraine. In contrast, this study did not identify any significant differences in serum calcium levels among the migraine, TTH, and CGs. This outcome could be influenced by several factors, including the relatively small sample size, the timing of blood sample collection (outside of headache episodes), and the reliance on serum rather than ionized calcium measurements.

Another notable aspect of this study was the evaluation of vitamin D levels, which are known for their anti-inflammatory, antioxidant, and neuroprotective effects, as well as their role in calcium homeostasis. Existing randomized controlled trials on this topic have produced conflicting results. For example, a study of 73 migraine patients found no significant difference in vitamin D levels between patients and controls. However, Cayir et al.[15] in a study conducted in Türkiye, reported that vitamin D supplementation in combination with standard migraine therapy reduced migraine attack frequency[14]. Another local study observed higher vitamin D levels in healthy controls compared to migraine patients[16]. In our study, no significant differences were detected in vitamin D levels across the patient and CGs.

Study Limitations

This study has several limitations. First, blood samples were collected at the time of diagnosis rather than during active headache episodes. Additionally, serum calcium rather than ionized calcium was measured, and resource constraints prevented the assessment of intracellular Mg levels. Nevertheless, although intracellular Mg concentrations could not be determined, therapeutic decisions regarding Mg supplementation are typically based on serum Mg levels. Furthermore, data on lifestyle factors such as sunlight exposure and physical activity, which may affect vitamin D status, were not adequately documented.

Conclusion

In conclusion, we believe that our study is valuable in investigating the relationship between migraine TTH, and the levels of calcium, Mg, and vitamin D. Although our sample size is limited, we hope our findings will contribute to future research in this field. Further clinical and laboratory studies are needed to clarify these relationships and develop new treatment perspectives.

Ethics

Ethics Committee Approval: Ethics Comittee approval of the study was obtained with Pamukkale University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee meeting dated 19.03.2024 and numbered 06.

Informed Consent: All participants and their legal guardians provided written informed consent prior to inclusion in the study.

Footnotes

Author Contributions: Barin GG: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Acer H: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

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Case Report

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A Rare Case of Paralytic Rabies; an Uncommon Presentation of a Daunting Disease

Author(s)

Upasana Ghosh, Bela Verma

Affiliation(s)

Department of Pediatrics, Grant Government Medical College and JJ Group of Hospitals, Mumbai, India

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Abstract

Rabies is a fatal zoonotic disease. Timely and complete post-exposure prophylaxis can prevent the disease. A 10-year-old boy presented with a history of fever and altered mentation for 6 days. There was no history of hydrophobia or aerophobia. The child had features of raised intracranial tension and hypotonia of all limbs with absent deep tendon reflexes. Parents revealed the history of an unprovoked dog bite on the right arm (category III) 1 month ago, for which he received 4 intramuscular doses of anti-rabies vaccine, but did not receive anti-rabies immunoglobulin. Based on this history, he was clinically diagnosed with paralytic rabies, and the diagnosis was confirmed by the presence of rabies antibody in cerebrospinal fluid. He was started on Milwaukee protocol, however the child succumbed after 10 days of hospital stay. This case report highlights the importance of history-taking to make a clinical diagnosis of rabies. Health care workers' awareness is crucial for accurate categorization of the animal bite, and ensuring timely post-exposure prophylaxis.

Keywords: Rabies, rabies vaccine, paralytic rabies

Introduction

Rabies is caused by a bullet-shaped, negative-sense, single-strand, enveloped RNA virus from the family Rhabdoviridae, genus Lyssavirus. It is a vaccine-preventable disease which occurs in over 120 countries and 40% of the victims are children[1].

Around 30-35% of people who get bitten by the rabies-infected animal and do not receive post-exposure prophylaxis contract the disease[2]. After the bite, the virus directly enters the peripheral unmyelinated axon terminals and migrates retrogradely towards the cell body and then spreads via synaptic junctions. After reaching the central nervous system, the virus spreads within the axons centrifugally to the peripheral and autonomic nervous system, and peripheral organs[3]. There are two forms of rabies, furious and paralytic. Furious rabies is characterised by its classical signs of hydrophobia, aerophobia, etc., and constitutes about 70% of human rabies cases, making it easy to diagnose[4]. The diagnosis becomes difficult,

Correspondence: Upasana Ghosh MD,
Department of Pediatrics, Grant Government Medical College and JJ Group of Hospitals, Mumbai, India
E-mail: ghoshupasana16@gmail.com **ORCID:** 0009-0006-2060-6132

when the characteristic features like aerophobia and hydrophobia are lacking, as in the present case. Additionally, paralytic rabies may mimic Guillain-Barré syndrome, where the history of animal bite and details of post-exposure prophylaxis play an important role in making a clinical diagnosis of rabies. Herein, we present a case of paralytic rabies that presented with features of Guillain-Barré syndrome.

Clinical Description

A 10-year-old boy presented with the chief complaints of fever and altered sensorium for the last 6 days. There was a history of irrelevant talk 2 days prior to the hospitalization. There was no history of convulsions, vomiting, or headache, hydrophobia, or aerophobia. On asking leading questions, parents revealed that the child had a history of category III unprovoked stray dog bite on the right arm one month ago. The wound was cleaned thoroughly with soap and water. The child had received 4 doses of purified Vero cell rabies vaccine on day 0, 3, 7, and 14 (intramuscular); however, he did not receive any immunoglobulin. At admission, he was haemodynamically stable. There was neck rigidity; bilateral pupils were equal and reacting; cranial nerve examination was normal; Glasgow coma scale (GCS) was E4M5V2. There was hypotonia in all the limbs; power was grade 2/5 in all 4 limbs; all deep tendon reflexes were absent; plantar reflex was unresponsive. There was no facial palsy. Fundus examination was normal. Respiratory and cardiovascular system examination was unremarkable. This patient had features of Guillain-Barré syndrome and meningoencephalitis with a background history of dog bite (in the absence of aerophobia and hydrophobia); therefore, he was diagnosed clinically with paralytic rabies. The nerve conduction study could not be done due to logistic issues.

The child was kept nil by mouth and started on 3% NaCl in view of the raised intracranial pressure (ICP). Complete blood count, serum electrolytes, and blood glucose were normal. Cerebrospinal fluid (CSF) analysis showed 37 cells/mm^3 with 40% neutrophils and 60% lymphocytes, a sugar level of 71 mg/dL, and protein 4000 mg/dL. A computed tomography scan of the brain was unremarkable. The child was put on the Milwaukee protocol (as per institutional protocol), which consisted of a midazolam drip, amantadine, zinc, and vitamin C. On day 2 of hospitalization, the child developed tachycardia, and fluid refractory shock requiring inotropes. Broad spectrum antibiotics were initiated, suspecting septic shock. On day 3, the GCS deteriorated further and the child developed respiratory failure, requiring mechanical ventilation. A corneal impression smear, done on day 2 of hospitalization, was positive for Rabies virus nucleoprotein antigen. The Rabies virus neutralising antibody (RVNA) titre, as measured by the Rapid fluorescent focus inhibition test (RFFIT), was 256 in CSF and 4096 in serum, which were sent on day 2 of hospitalization. However, CSF and saliva tested negative for rabies viral RNA by real-time polymerase chain reaction (PCR). The child required a higher fraction of inspired oxygen and ventilatory pressure. Chest X-ray revealed haziness on the right upper zone, likely due to ventilator-associated pneumonia. Antibiotics were escalated to piperacillin-tazobactam. For increased ICP, a child was given 20% mannitol intermittently. The child had no improvement in the respiratory parameters or raised ICP; eventually, he succumbed on day 10 of hospitalization due to probable refractory raised ICP, sepsis, and multi-organ failure. Post mortem studies were not done.

Discussion

Rabies encephalitis is a fatal disease with a preventable cause. The present case is “dumb rabies”, which presented with features of encephalitis, without any aerophobia or hydrophobia. Our patient had received 4 doses of anti-rabies vaccine, but had not received anti-rabies immunoglobulin, resulting in an increased risk of the disease. Thus, clinical history is vital to diagnose a case of paralytic rabies. For serological diagnosis, there are tests for antigen detection (rapid Rabies enzyme immunodiagnosis, direct rapid immunohistochemical test, real-time PCR, viral isolation (rapid tissue culture infection test), mouse inoculation test and antibody detection tests like fluorescent antibody test, RFFIT and the fluorescence antibody virus neutralization test[5]. Antibody in CSF is rarely detected after vaccination and is considered diagnostic of rabies regardless of immunization status[2]. Guillain-Barré syndrome is known to be associated with old rabies vaccines, which were cultured in the neural tissues[6]. Our patient had not received neural vaccine and the diagnosis was confirmed by high titre of RVNA in CSF and positive rabies virus nucleoprotein antigen in corneal impression smear.

Human rabies is almost 100% fatal. The initial report of survival of an adolescent girl using the Milwaukee protocol received quite an interest but subsequently met with a lot of criticism[7,8]. In our patient, the Milwaukee protocol was used as it was the institutional policy at that time. It consists of the administration of ketamine, midazolam, amantadine, ribavirin, and phenobarbitone, targeting the N-methyl-D-aspartate receptors. We could not fully implement the protocol due to logistic issues. Our patient developed refractory raised ICP and fluid refractory shock, which resulted in his death on day 10 of hospitalization.

This case illustrates the need for history-taking in a case of acute meningoencephalitis so that a diagnosis of rabies is not missed even in the absence of characteristics features of aerophobia and hydrophopbia. Awareness among healthcare workers needs to be improved for correctly categorizing the wound and administering post-exposure prophylaxis. Prevention of clinical rabies with early post-exposure prophylaxis with the use of anti rabies vaccine and immunoglobulin (when indicated), remains the only proven method to prevent rabies.

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Ethics

Informed Consent: Written informed consent was obtained from the parents before writing this case report.

Footnotes

Author Contributions: Ghosh U: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Data Collection or Processing, Literature Search, Writing; Verma B: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Data Collection or Processing, Literature Search, Writing.

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Failed Conservative Management in a 6-year-old Girl with Urethral Prolapse: Is Always the Surgery the Solution?

Author(s)

Eirini Yerolemidou[1], Adelais Tzortzopoulou[1], Moschos Ververidis[1], Panagiota Antonopoulou[2], Orthodoxos Achilleos[1]

Affiliation(s)

[1]Second Departement of Pediatric Surgery, Panagiotis & Aglaia Kyriakou Children's Hospital, Athens, Greece

[2]Department of Computed Tomography and Magnetic Resonance Imaging Radiology, Agia Sofia Children's Hospital, Athens, Greece

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Abstract

Urethral prolapse (UP) is a rare condition in young female children, with an incidence of 1 in 3000. It commonly presents with vaginal bleeding or dysuria, and is characterized by a circular protrusion of the distal urethra mucosa through the external urethral meatus, forming a round, soft red-purple colored mass. A 6-year-old girl was admitted to our surgical department with symptoms of vaginal bleeding over the last 4 days. Physical examination revealed a doughnut-shaped mass prolapsing from the pudendal labia. Abdominal ultrasound, pelvic magnetic resonance imaging, and blood tests, including hormonal tests, were normal. We initially decided on conservative treatment with topical oestrogen cream and sitz baths. After 12 days, no improvement was observed, and surgical management was undertaken. The surgical approach involved the complete excision of the prolapsed tissue and mucosal to mucosal anastomosis with Vicryl 5/0 sutures. A cystoscopy was previously performed, and the results was normal. Postoperative follow-up over a 6-month period showed no recurrence or urethral stricture. UP in children should always be considered in cases of unexplained vaginal bleeding. Management remains controversial. Surgical excision is recommended for severe cases and in cases that conservative management is uneffective whithin 2-4 weeks.

Keywords: Urethral prolapse, children, urethral and vaginal problems, congenital disease

Correspondence: Adelais Tzortzopoulou, MD, PhD, Second Departement of Pediatric Surgery, Panagiotis & Aglaia Kyriakou Children's Hospital, Athens, Greece
E-mail: t.k.adelais@gmail.com **ORCID:** https://orcid.org/0000-0002-6561-1625

Introduction

Urethral prolapse (UP) is a very rare condition in children, with an incidence of 1 in 3000. It most commonly occurs in prepubertal black females and is rare in Asia, with an incidence of 1 in 73,000 in Japan. UP was first described by Solinger in 1732 as a circular protrusion of the distal urethral mucosa, which everts through the meatal opening. Edema and congestion of the prolapsed tissues are seen, with a characteristic, round, soft, red-purple mass prolapsing from the pudendal labia. It commonly presents with vaginal bleeding or dysuria, or as an asymptomatic doughnut-shaped sign at the site of the urethral opening[1,2].

The differential diagnosis includes ectopic ureterocele, condyloma, vaginal polyp, ureteric cysts, and malignancies of the abdomen, vagina, or urethra, such as rhabdomyosarcoma. It is also important to mention that in some cases, it may cause concern regarding sexual abuse among health personnel[3,4].

In this article, we present a 6-year-old white girl from Greece who was admitted to our surgical department with bleeding, and a doughnut-shaped mass of red and purple tissue surrounding the urethra, obscuring the hymenal orifice.

Case Report

The patient was admitted to the hospital with vaginal bleeding that had been ongoing for the past three days. The bleeding was accompanied by symptoms such as itching, frequent urination, and dysuria. There was no history or clinical suspicion of trauma. On examination, the child appeared well, with no signs of distress. Vital signs were within normal limits. A thorough assessment was conducted by the surgical and endocrine departments to rule out other potential causes of vaginal bleeding.

An ultrasound was conducted as part of the clinical investigation, with no major clinical findings from the kidneys, bladder, or adrenal glands. The pediatric-type uterus had dimensions slightly above the normal age range, and the ovaries showed multiple follicles. No fluid was observed in the Douglas pouch.

Hormonal evaluation revealed results consistent with prepubertal status, including normal prolactin and dehydroepiandrosterone levels. Additionally, all malignancy markers were negative. Routine laboratory tests, including complete blood count, biochemical markers, and thyroid function tests, all returned normal results. Urinalysis showed the presence of 30-35 red blood cells per high-power field, 2+ hemoglobin, and traces of leukocyte esterase; without other signs of urinary tract infection.

Following consultation with the multidisciplinary team investigating suspected cases of sexual or other forms of abuse, tests for sexually transmitted diseases were requested and returned negative. No further investigation was deemed necessary.

The patient underwent an examination under general anesthesia, during which urethral mucosal prolapse was identified. The prolapse was reduced, followed by urethral catheterization using an 8 Fr Foley catheter. The hymen was found to be intact. The urethral mucosa prolapsed again, albeit to a lesser degree (**Figure 1**). Further hormonal evaluation and local therapy with oestrogel were scheduled; with a follow-up examination under anesthesia in one week.

The surgical procedure was performed under general anesthesia in a lithotomy position. After inserting an indwelling urinary catheter, four guiding sutures (Vicryl 4/0) were placed. The protruding urethral mucosa was resected with monopolar cautery, and the intervening tissue was sutured with Vicryl 5/0 stitches (**Figure 2**).

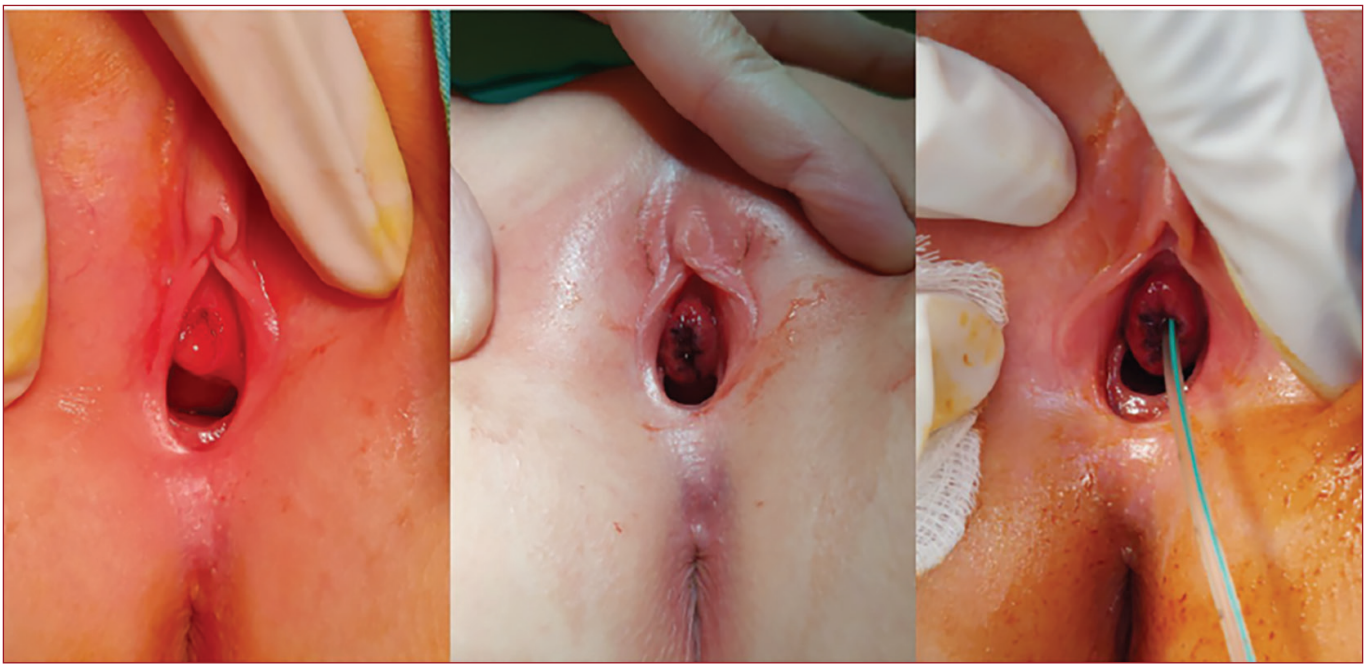

Figure 1. Examination under general anesthesia and catheterisation using an 8 Fr Folley catheter

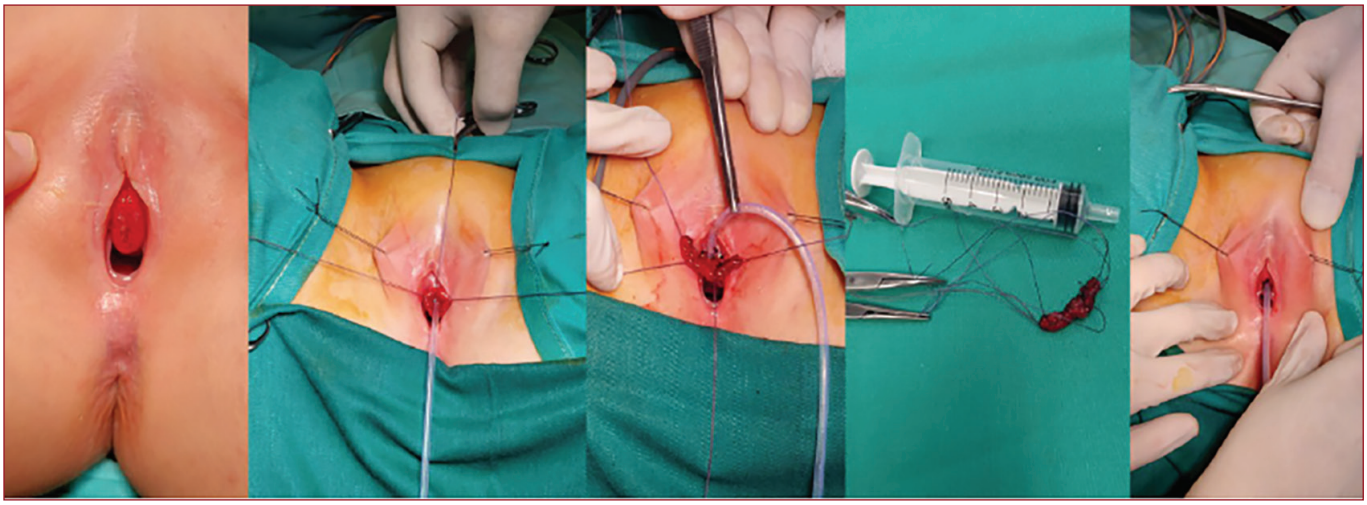

Figure 2. Surgical technique: Guiding suteres, resection of protruding urethral mucosa, suturing the remaining tissue after placement of Folley catherer

A Foley catheter (10 Fr) was placed for 72 hours and was removed postoperatively without complications. The patient voided well and was discharged. Clinical examinations at 1 week, 1 month, and 6 months postoperatively were all normal. A follow-up abdominal and pelvic magnetic resonance imaging performed after 4 months was also normal. A uroflowmetry was not performed, as our patient remained asymptomatic after the surgery. The parents, who are the patient's legal guardian, have been informed for this publication and have given their writen informed consent.

Discussion

The management of UP remains controversial. Some authors advocate for conservative treatment, which aims to reduce mucosal edema, improve local hygiene, and address estrogen deficiency by using a combination of sitz baths, topical estrogen cream, antibacterial wash/soap, and topical antibiotics. Others prefer surgical management. However, no clear treatment algorithm exists. Generally, surgical treatment is favored in children when symptoms are disturbing, such as in our patient, who was very anxious due to her bleeding for 15 days, or in cases when the prolapsed tissue appears ischemic, in which case surgery is beneficial[2].

In 2011, Holbrook and Misra[5] reviewed their 13-year experience with 23 black female children who had UP without symptoms (mild prolapse). Thirteen patients were successfully treated conservatively, while seven underwent prolapse reduction under general anesthesia. Only one patient had a recurrence after two years, which required further reduction in the operating theater. Additionally, two patients underwent partial reduction, but the prolapse resolved completely over an observation period of 3 months following the procedure[5].

A 2008 review by Hillyer et al.[6] reported on 34 female patients with UP, 30 of whom were successfully treated with surgery. Surgical excision of the prolapsed mucosa circumferentially over a Foley catheter was performed. All patients were discharged within 24 hours post-operation. No recurrence was noted during the follow-up period. A 2014 review by Ballouhey et al.[7] concluded that conservative management should be the first-line treatment for uncomplicated patients, while surgical resection is safe and effective for those with significant symptoms. In their study, 19 young girls with UP underwent surgery. The urethral mucosa was resected with cautery, and the intervening tissue was sutured with two sutures. A Foley catheter was inserted and removed two days after surgery. A medical examination performed 1 month after discharge and the flowmetry control 2 to 4 months later showed no recurrence or meatal stenosis[6,7].

Our patient was a Caucasian female with a doughnut-shaped mass prolapsing from the pudendal labia and bleeding for the past four days, initially thought to be vaginal bleeding. Blood tests, including hormonal evaluations, were normal, and an ultrasound did not reveal any abdominal mass. She had no history of constipation, asthma, or other conditions that could increase abdominal pressure. For these reasons, we initially chose conservative management with sitz baths and estrogen cream. After 12 days, there was no improvement, and the bleeding persisted, making the patient anxious. Given the lack of response to conservative treatment, we opted for surgical management. As supported by the literature, surgery is the preferred option in complicated cases and when symptoms persist. Although there is no universally accepted surgical technique, we followed the guidelines of Hillyer et al.[6] and Ballouhey et al.[7]: Resecting the urethral mucosa and leaving a Foley catheter in place for 3 days. The surgery was uneventful, with no postoperative complications.

Conclusion

UP is a rare condition in children with an unknown etiology and controversial management. Physical examination should always be the first step in establishing an accurate diagnosis. Surgical resection of the prolapsing urethral mucosa is a safe and cost-effective treatment, offering low recurrence rates, especially in children presenting with symptoms.

Ethics

Informed Consent: The parents, who are the patient's legal guardian, have been informed for this publication and have given their written informed consent.

Footnotes

Author Contributions: Yerolemidou E: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Data Collection or Processing, Literature Search, Writing; Tzortzopoulou A: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Data Collection or Processing, Literature Search, Writing; Ververidis M: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Data Collection or Processing, Literature Search, Writing; Antonopoulou P: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Data Collection or Processing, Literature Search, Writing; Achilleos O: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Data Collection or Processing, Literature Search, Writing.

Conflict of Interest: The authors have no conflicts of interest to declare.

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