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Manuscript Types

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Table 1.
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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

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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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Diagnosis, Treatment, and Management of Common Childhood Vasculitides

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Abstract

Childhood vasculitides, including immunoglobulin A vasculitis, Kawasaki disease, Behçet disease, and polyarteritis nodosa, are inflammatory disorders affecting varying-sized blood vessels. Their pathogenesis involves immune dysregulation, genetic predisposition, and environmental triggers. While treatment varies based on disease severity, immunosuppressive therapy is often required. Preventing complications depends mainly on early identification of the disease and initiating appropriate management. This review aims to guide clinicians in the early diagnosis and multidisciplinary management of childhood vasculitides by addressing their pathogenesis, clinical features, diagnostic approaches, and treatment strategies.

Keywords: Vasculitides, Behçet disease, Kawasaki disease, IgA vasculitis, polyarteritis nodosa, immunosuppressive agent

Introduction

Vasculitides are a rare group of disorders characterized by inflammation of blood vessel walls, affecting both arterial and venous systems of various calibers. Clinical manifestations are closely related to the size of the involved vessels, their anatomical location, and the intensity of inflammation. According to the 2012 Chapel Hill Consensus, vasculitides are primarily classified based on the predominant size of the affected vessels (**Table 1**)[1]. Although vasculitis may occur in both pediatric and adult populations, childhood-onset forms differ substantially in clinical presentation, disease course, treatment response, and long-term prognosis compared to adult-onset vasculitis[2].

For instance, immunoglobulin A vasculitis (IgAV) and Kawasaki disease (KD) predominantly occur during childhood, and key clinical features of vasculitic disorders may vary according to age group[2]. IgAV typically presents with abdominal pain in children, whereas adults more commonly exhibit purpuric rash and joint symptoms[3-6]. KD is extremely rare in adults, often leading to diagnostic delays; as a result, treatment strategies are mostly adapted from pediatric guidelines[2]. In polyarteritis nodosa (PAN), pediatric patients tend to have a better prognosis, with a more pronounced female predominance compared to adults[2]. In Behçet's disease, children often present with incomplete phenotypes, posing diagnostic challenges, and

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genital ulcers, thrombosis, and vascular involvement are less frequently observed than in adults[7].

The diagnostic process of pediatric vasculitis is more complex than that in adults. The rarity of these diseases, the overlap of symptoms with infections or malignancies, and the gradual evolution of clinical features can lead to significant diagnostic delays. Applying adult classification criteria directly to pediatric patients may be insufficient, as these criteria often fail to reflect the heterogeneity of disease in childhood. Therefore, the 2008 Ankara Consensus developed pediatric-specific classification criteria, and the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative later introduced evidence-based treatment recommendations for childhood vasculitides[8-10].

This review focuses on IgA vasculitis, KD, PAN, and Behçet's disease, with the aim of highlighting their pediatric-specific clinical features and therapeutic approaches to support improved diagnosis, treatment, and disease management strategies (**Table 2**).

Highlights

- Pediatric vasculitides represent a diverse spectrum of inflammatory conditions, with clinical manifestations influenced by the caliber and anatomical site of the involved vessels.
- Common vasculitic disorders observed in children include immunoglobulin A vasculitis, Kawasaki disease, Behçet disease, and polyarteritis nodosa; recognized as the most prevalent subtypes in the pediatric population.
- These vasculitic disorders are primarily driven by underlying genetic factors and disruptions in immune system regulation.
- To ensure the best outcomes, treatment plans should be customized and involve various specialties in the management of pediatric vasculitic conditions.

IgA Vasculitis

The most common type of pediatric vasculitis, IgAV, has historically been referred to as Henoch-Schönlein purpura. Classified as a small-vessel vasculitis, it predominantly involves capillaries, venules, and arterioles, with IgA contributing significantly to its underlying pathogenesis[1]. Clinically, IgAV may present as a skin-limited form or a systemic disease with renal, gastrointestinal, or musculoskeletal involvement[11].

The incidence of IgAV exhibits regional differences, with reported incidence rates between 3 and nearly 56 per 100,000 children[3,9,12,13]. Its distribution is also uneven across populations, with the highest prevalence observed in East Asians, a moderate frequency in Europeans, and the least common occurrence in populations with African genetic backgrounds[3,13]. Most cases are seen in children below the age of 10, especially those aged 4 to 7 years, where the disease is most prevalent[12,13]. The greater prevalence in this age group may stem from their increased tendency to contract pathogenic infections. This is further supported by the seasonal variation in IgAV, with higher occurrence during spring and winter, when infections are more prevalent, and lower incidence in summer. IgAV is slightly more frequent in boys than girls, with an estimated boy-to-girl prevalence ratio of 1.5:1[13].

Multifaceted and intricate biological processes characterize IgAV pathogenesis. These include a complex interplay of immune mechanisms, genetic predisposition, and environmental factors. One of the most distinctive outcomes of these mechanisms is the deposition of IgA1-dominant immune complexes (ICs) within small blood vessels, a defining feature of

Table 1. *Vasculitis subtypes according to the 2012 Chapel Hill consensus criteria*

1. Large vessel vasculitis • Takayasu arteritis • Giant cell arteritis	2. Medium vessel vasculitis • Polyarteritis nodosa • Kawasaki disease
3. Small vessel vasculitis	
ANCA-associated vasculitis	• Microscopic polyangiitis • Granulomatosis with polyangiitis • Eosinophilic granulomatosis with polyangiitis
Immune complex vasculitis	• IgA vasculitis (Henoch-schönlein purpura) • Cryoglobulinemic vasculitis • Anti-glomerular basement membrane disease • Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
4. Variable vessel vasculitis • Behçet's disease • Cogan's syndrome	5. Single-organ vasculitis • Cutaneous leukocytoclastic angiitis • Cutaneous arteritis • Primary CNS vasculitis • Isolated aortitis • Others
6. Vasculitis associated with systemic disease • Lupus vasculitis • Rheumatoid vasculitis • Sarcoid vasculitis • Others	7. Vasculitis with probable etiology • Hepatitis C-associated cryoglobulinemic vasculitis • Hepatitis B-associated vasculitis • Syphilis-associated aortitis • Drug-induced immune complex vasculitis • Drug-induced ANCA-associated vasculitis • Cancer-associated vasculitis • Other

Adapted from Jennette JC, Falk RJ, Bacon PA, et al. *Arthritis Rheum*. 2013;65:1-111. CNS; Central nervous system, ANCA; Anti-neutrophil cytoplasmic antibodies, IgA; Immunoglobulin A

Table 2. *Overview of vessel involvement, clinical features, and treatment strategies in common pediatric vasculitides*

Disease	Vessel involvement	Clinical features	Treatment approach
IgA vasculitis	Small vessels (capillaries, venules, arterioles); IgA1 immune complex deposition	• Palpable purpura (especially on lower limbs) • Arthritis/arthralgia • Abdominal pain • Renal involvement • Orchitis • CNS involvement • Pulmonary involvement	• Supportive care Systemic involvement • Corticosteroids • Immunosuppressants
Kawasaki disease	Medium and small arteries; coronary arteries at high risk of aneurysm	• Fever ≥5 days • Conjunctivitis • Mucosal changes • Extremity desquamation • Rash • Cervical lymphadenopathy • Complications of coronary artery	• IVIG within 10 days (2g/kg) • ASA (high then low dose) • Corticosteroids/biologics (IVIG resistance) • Anticoagulation (for aneurysms)
Behçet disease	Variable-vessel vasculitis (arterial and venous of all sizes)	• Recurrent oral/genital ulcers • Uveitis • Skin lesions • Arthritis • Thrombosis • CNS involvement • GI involvement	• Colchicine Systemic involvement • Corticosteroids • AZA • TNF inhibitors • Apremilast
Polyarteritis nodosa	Medium-sized muscular arteries; necrotizing arteritis	• Livedo reticularis • Nodules • Ulcers • Myalgia • Hypertension • Neuropathy	Induction • High-dose IV corticosteroids • CYC Maintance • AZA • MTX • MMF • bDMARDS

ASA; Acetylsalicylic acid, AZA;Azathioprine, bDMARDS;Biologic disease-modifying anti-rheumatic drugs, CNS; Central nervous system, CYC; Cyclophosphamide, GI; Gastrointestinal involvement, IgA; Immunoglobulin A, IVIG; Intravenous immunoglobulin, MMF; Mycophenolate mofetil, MTX; Methotrexate, TNF;Tumor necrosis factor

IgAV. Among the several mechanisms implicated in IgAV, altered glycosylation of IgA1 plays a prominent role. In most patients with IgAV, IgA1 lacks galactose residues, a condition known as galactose-deficient IgA1 (Gd-IgA1)[14]. IgA1 is typically glycosylated at the hinge region through a process called O-glycosylation. It is proposed that genetic susceptibility and/or mucosal infection, in conjunction with interleukin (IL)-6 production, disrupts the glycosylation process, leading to aberrant glycosylation[15]. In IgAV, abnormal glycosylation leads to the generation of Gd-IgA1, contributing to the formation and accumulation of pathogenic ICs. A key process in IgAV pathogenesis is the development of ICs containing Gd-IgA1. Following the interaction of Gd-IgA1 with specific autoantibodies (IgA1 or IgG), circulating ICs are formed and subsequently deposited in small vessels, particularly in organs such as the skin, kidneys, and gastrointestinal tract, where they trigger localized inflammation[16,17]. Gd-IgA1-rich ICs initiate activation of both the alternative and lectin complement cascades, significantly contributing to the disease process[18]. Higher levels of complement split products, including C3a, C5a, C4, and the terminal complement complex (C5b-9), have been reported in individuals with IgAV, with renal involvement showing a robust correlation with complement-mediated disease severity[19]. Activation of the complement cascade promotes cytokine secretion and attracts inflammatory cells to the injury site, thereby intensifying tissue damage. Gd-IgA1 and its corresponding autoantibodies have emerged as potential biomarkers for disease severity, particularly in cases with renal involvement. Their quantification may aid in risk stratification and personalized treatment approaches. Similarly, complement activation products such as C5a and C5b-9 have been associated with disease activity and therapeutic response. While these biomarkers offer clinical promise, their routine use remains limited, and further validation through large-scale, prospective studies is required before they can be integrated into standard clinical practice.

The genetic background in the pathogenesis of this disorder is indisputable. Genome-wide association studies (GWAS) have identified susceptibility loci within the human leukocyte antigen (HLA) class II region, particularly between HLA-DQ Alpha and DQB1, as well as at the DRB1-11 and DRB1-13 alleles[20]. The DQA1*01:01/DQB1*05:01/DRB1*01:01 haplotype is linked to IgAV pathogenesis; however, this association does not seem to apply to other autoimmune diseases[21]. Additionally, increased frequencies of HLA-A2, A11, and B35 alleles have been reported in affected individuals, suggesting a broader HLA-related predisposition[22].

As an essential finding, the diagnostic criteria emphasize the presence of palpable purpura or petechiae in the absence of thrombocytopenia[9]. In addition, at least one other clinical or histopathological feature is required, such as abdominal pain, joint involvement (arthritis or arthralgia), renal manifestations, or biopsy findings demonstrating leukocytoclastic vasculitis or glomerulonephritis with dominant IgA deposition. Palpable purpura and petechiae most commonly affect the lower extremities; however, atypical manifestations in the head, neck, and upper extremities may also occur. In more critical cases, patients may present with hemorrhagic bullae, ulcerations, or necrotic lesions[23]. Subcutaneous edema is common in the

extremities, scalp, and periorbital region. Involvement of the gastrointestinal tract often presents with sudden abdominal pain, which may coincide with symptoms like hematemesis, melena, and occasionally, bowel intussusception[24]. Kidney-related symptoms may manifest as microscopic or gross hematuria, proteinuria (including nephrotic range), hypertension and, if progressive, renal insufficiency. In pediatric IgAV, kidney involvement is a critical predictor of disease outcome, significantly influencing both morbidity and long-term prognosis[23]. For pediatric patients suspected of having IgAV, comprehensive kidney monitoring-comprising regular blood pressure tracking, urinalysis performed on morning samples, and an assessment of glomerular filtration rate (GFR)-is essential throughout both the acute phase and follow-up period[8]. Persistent, significant proteinuria exceeding 250 mg/mmol for at least four weeks typically necessitates renal biopsy in IgAV, although shorter durations might serve as relative indications depending on the clinical context. Persisting moderate proteinuria (100-250 mg/mmol) and reduced GFR are also considered among the indications for biopsy[8]. In addition, although less common, orchitis[25], penile involvement[26], cerebral vasculitis[27], and pulmonary hemorrhage[28] may also occur. Criteria for hospital admission include testicular pain and tenderness, significant crampy abdominal pain, polyarthritis (involving three or more joints), proteinuria, impaired independent mobility, and macroscopic gastrointestinal bleeding[29].

Based on the SHARE recommendation, IgAV cases limited to skin and joint manifestations are expected to resolve without complications when supported by bed rest, sufficient fluid intake, and analgesic management. Corticosteroids and immunosuppressive drugs are recommended for cases involving the gastrointestinal system, kidneys, or other organs[8]. Patients who develop nephritis, severe gastrointestinal involvement, orchitis, cerebral vasculitis, or pulmonary hemorrhage require treatment with corticosteroids. Oral prednisolone 1 to 2 mg/kg daily is recommended. In more severe presentations, pulse IV methylprednisolone (10-30 mg/kg) may be three days administered over. Persistent proteinuria may warrant treatment with angiotensin-converting enzyme inhibitors to prevent secondary injury to the glomeruli. In cases of mild IgAV nephritis, initial therapy typically consists of oral prednisolone. After histopathological confirmation via renal biopsy, immunosuppressive treatment may be intensified using second-line options like azathioprine (AZA), mycophenolate mofetil (MMF), or pulse steroid therapy. In moderate nephritis cases, oral prednisolone and/or intravenous pulse methylprednisolone are usually initiated. Depending on disease progression and clinical risk, immunosuppressive agents such as AZA, MMF, or intravenous cyclophosphamide (CYC) may be introduced. Patients presenting with severe manifestations are typically treated with corticosteroids (oral or pulse theraphy) alongside CYC, following protocols established for similar vasculitic conditions. For chronic management, the use of corticosteroids together with immunosuppressive agents such as AZA or MMF is advised, targeting both renal preservation and reduction of disease recurrence. While plasmapheresis is not part of standard treatment guidelines, it is applied in high-risk cases when deemed necessary[30].

Kawasaki Disease

First reported by T. Kawasaki in 1967[31], this febrile vascular illness primarily affects early childhood. It is considered the second most common childhood vasculitis after IgAV 31, primarily involving medium- and small-sized blood vessels[32]. Despite various clinical observations and population-based studies implying an infectious contribution, the precise etiology of the disease is still unclear[33].

KD primarily occurs in boys and typically manifests before the age of five[34]. Japan reports the most significant number of KD cases globally, with an incidence nearing 239 per 100,000 children, whereas South Korea and Taiwan follow with rates of approximately 113 and 69 per 100,000, respectively[35]. A family history, especially in parents or siblings, increases susceptibility[36]. The incidence of KD fluctuates with the seasons, reaching its highest levels during winter in Japan. In contrast, in the U.S., a rise is commonly observed throughout winter and into the spring months[37].

There is growing evidence that infections might activate the immune system in genetically susceptible individuals, even though the exact etiology of KD is not determined[38]. Early genetic studies identified HLA-DRB1, HLA-B5, Bw51, and Bw44 as susceptibility factors[39]. KD exhibits autoimmune-like features, with immune dysregulation playing a central role[40]. Inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) influences T-cell function and contributes significantly to the immunopathology of the disease. ITPKC dysfunction impairs immune regulation, enhancing T-cell responses and elevating cytokine secretion[41]. Following intravenous immunoglobulin (IVIG) treatment, levels of key proinflammatory cytokines such as IL-6, IL-20, interferon-gamma, and tumor necrosis factor-α (TNF-α) show a marked reduction[42]. A shift toward T helper 17 (Th17) over regulatory T-cells (Treg) promotes cytokine-driven inflammation[43]. Initially secreted by T-cells and later by innate immune cells, TNF-α facilitates endothelial activation and leukocyte attachment[36]. TNF-α enhances endothelial cell activation by upregulating adhesion molecule levels and stimulating chemokine secretion, facilitating leukocyte-endothelial interactions[36]. It also stimulates matrix metalloproteinase-9, leading to elastin degradation and aneurysm formation, making TNF-α inhibitors potential therapeutic agents[41]. Additionally, nitric oxide levels are elevated in KD but decrease rapidly after IVIG therapy[44].

The clinical course of KD is typically divided into acute, subacute, and convalescent phases[45]. KD is diagnosed when a persistent fever of at least five days is accompanied by four or more characteristic signs, including diverse skin eruptions, non-purulent redness in both eyes, mucosal changes in the mouth, alterations in the hands or feet, and swelling of the cervical lymph nodes. A four-day fever may suffice if all criteria are met[46], and experienced clinicians may diagnose cases with a three-day fever based on clinical presentation[46,47].

KD represents one of the leading causes of acquired cardiovascular conditions in the pediatric population, and in the absence of treatment, it may lead to coronary artery aneurysm formation. The American Heart Association (AHA) recommends evaluating for incomplete KD in

infants who exhibit persistent unexplained fever for seven days, or fever lasting five days accompanied by two to three of the characteristic clinical signs. The diagnostic approach includes evaluation of inflammatory markers, relevant laboratory investigations, echocardiographic assessment, and ongoing clinical monitoring. Elevated erythrocyte sedimentation rate and C-reactive protein levels, along with at least three additional lab criteria-including hypoalbuminemia (<3.0 g/dL), anemia, thrombocytosis (≥450,000/mm³), leukocytosis (≥15,000/mm³), elevated alanine aminotransferase, or sterile pyuria (≥10 white blood cell/hpf), support incomplete KD diagnosis (**Figure 1**)[48].

KD presents with a sudden high fever (39-40 °C) that can persist for 1-3 weeks if untreated, though spontaneous resolution within a week may occur. Fever generally resolves within 36 hours following the administration of IVIG treatment. In the early stage of KD, a non-itchy macular skin eruption frequently develops on the torso and limbs and may be associated with peeling in the perineal region[49]. Other findings in the acute phase may involve widespread redness on the palms and soles, along with tender edema affecting the hands and feet[50]. In the subacute phase, periungual desquamation becomes evident, particularly around the fingers, usually within 2-3 weeks of disease onset. Beau's lines may also emerge later in the clinical course.

Ophthalmologic manifestations include bilateral, painless, and non-exudative conjunctivitis, a common finding in KD[50]. Oropharyngeal involvement may present with cracked, desiccated lips, a distinct erythematous 'strawberry tongue,' and non-purulent inflammation of the tongue surface. Cervical lymphadenopathy, typically unilateral and affecting the anterior cervical chain, is frequently observed. Among the less common manifestations are gastrointestinal complaints like vomiting and diarrhea, alongside findings such as sterile pyuria, painful urination, joint inflammation, and non-infectious meningeal irritation[41]. In individuals who have received the Bacillus Calmette-Guérin vaccine, localized redness or scabbing at the inoculation site is recognized as a distinctive clinical indicator[50]. Cardiac complications

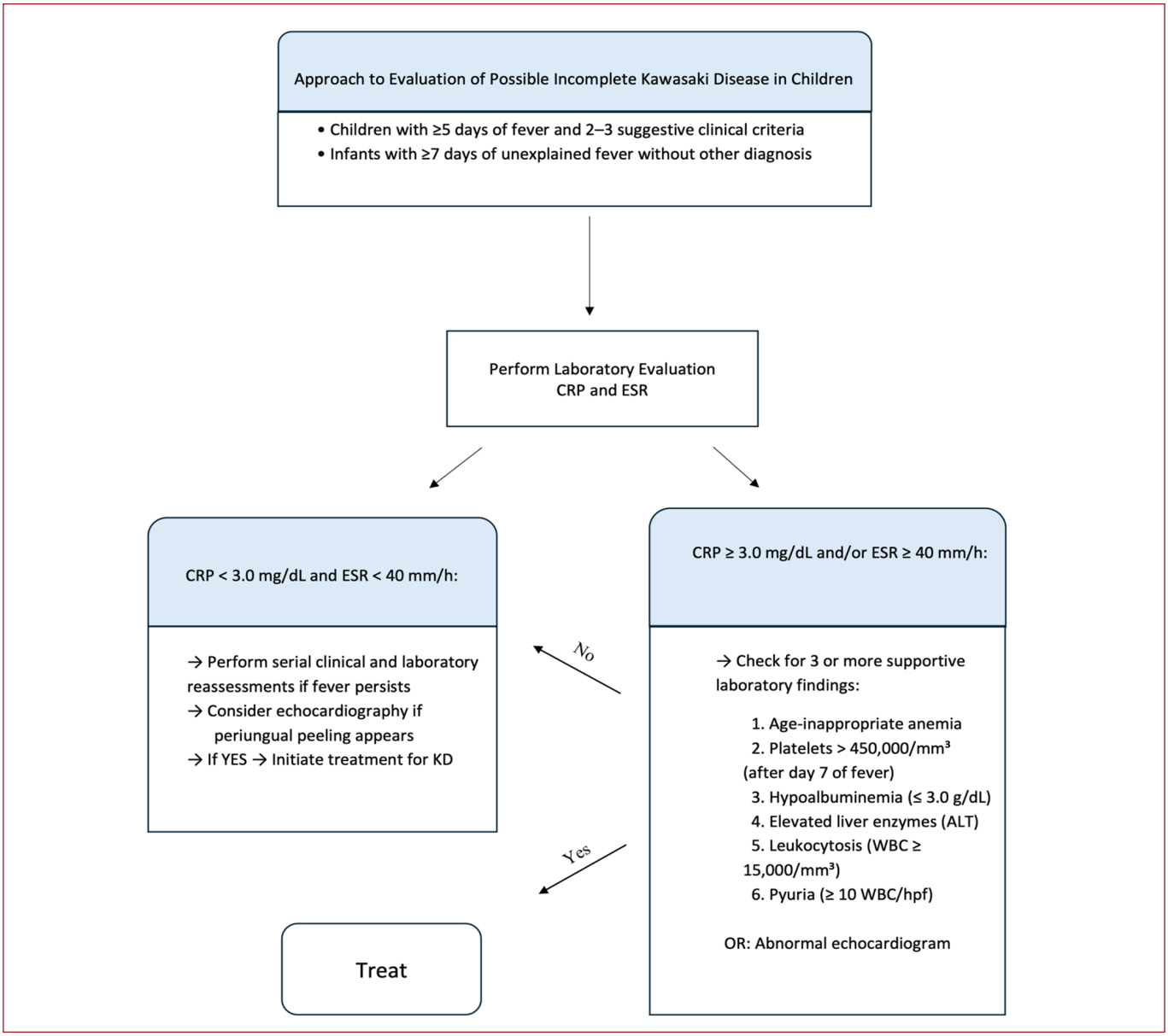

Figure 1. Diagnostic algorithm for incomplete Kawasaki disease

Adapted from Jone P-N, Tremoulet A, Choueiter N, et al. *Circulation*. 2024;150:e481-e500[48]

CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate, WBC; White blood cell, ALT; Alanine aminotransferase, KD: Kawasaki disease

often emerge in the early stage of KD and can include inflammation of the valves, myocardium, or pericardium, as well as the development of Kawasaki shock syndrome[45]. Kawasaki shock syndrome represents a more severe clinical presentation characterized by vasodilatory shock, hypotension, and impaired tissue perfusion, which may occur with or without underlying myocardial dysfunction[51]. Coronary artery dilatation and aneurysm formation typically develop in the later stages of KD, particularly during the subacute and recovery periods. In the absence of timely intervention, nearly 20% of pediatric patients may progress to coronary artery aneurysm formation[45].

Both the AHA and American Academy of Pediatrics endorse IVIG in combination with acetylsalicylic acid (ASA) as the primary approach to managing acute KD[52]. Administering IVIG at a dose of 2 g/kg over a 12-hour period, preferably during the initial 10 days of illness, is associated with the best clinical response[53]. IVIG is also indicated beyond 10 days if fever persists or inflammatory markers remain elevated[54]. Possible complications-such as sterile meningeal inflammation, red blood cell destruction, and infusion, associated side effects, require close clinical surveillance. In addition, live attenuated vaccines, such as those against measles, mumps, and varicella, recommended to be delayed for up to 11 months after IVIG administration due to potential interference with vaccine efficacy[46].

ASA is typically administered in moderate to high dosages during the early stages of the illness. After the patient remains afebrile for 48-72 hours, ASA is reduced to a maintenance dose of 3-5 mg/kg/day and generally sustained throughout a 6- to 8-week course[46]. In the presence of varicella or influenza, ASA should be temporarily substituted with agents like clopidogrel due to Reye syndrome risk[46]. Refractory KD refers to fever persisting beyond 36 hours after IVIG treatment[52]. In IVIG-resistant cases, the most frequently used second-line treatments include a repeat IVIG infusion (2 g/kg), systemic corticosteroids in combination with IVIG, and infliximab (5 mg/kg)[46]. Retrospective data suggest that infliximab may reduce the duration of fever and hospitalization, although it appears similar to a second IVIG dose in terms of coronary artery outcomes. No clear superiority has been demonstrated between pulse and prolonged oral corticosteroid regimens. However, some studies suggest that longer steroid courses may improve both clinical outcomes and coronary artery status. For patients unresponsive to these options, additional therapies may include cyclosporine, the IL-1 receptor antagonist anakinra, therapeutic plasma exchange, and the cytotoxic agent CYC in rare cases. Owing to the limited evidence base, treatment strategies should be tailored to the individual, considering prior response and disease severity. For individuals presenting with sizable coronary artery aneurysms, the use of anticoagulants such as low-molecular-weight heparin or warfarin is advised to minimize the risk of thrombosis[53]. Low-dose ASA is continued for six weeks in those without coronary involvement, whereas long-term antiplatelet or anticoagulation therapy is needed for those with aneurysms[46].

Early recognition and prompt intervention in KD are critical for minimizing death rates, reducing disease-related complications, and preventing long-term sequelae.

Behçet Disease

Behçet disease was initially identified in 1937 by Behçet[55], who described it as a syndrome involving recurrent oral and genital ulcers in addition to uveitis. In 1946, the inclusion of superficial thrombophlebitis expanded its clinical spectrum[56].

Behçet disease is a form of variable vessel vasculitis that affects both arterial and venous structures across a wide range of calibers[1]. The disease manifests as a chronic inflammatory condition affecting multiple organ systems, characterized by repeated episodes of oral and genital ulceration. It may also involve the skin, eyes, joints, gastrointestinal tract, and central nervous system. Its heterogeneous presentation poses challenges for definitive diagnosis and classification.

Behçet disease is most frequently reported in populations residing along the ancient Silk Road, notably in East Asia, the Middle East, and the Mediterranean area. Prevalence rates differ widely, reaching 370 per 10,000 in Türkiye, while being significantly lower in regions such as Japan (13.5), Israel (11.9), the U.S. (5.2), the UK (0.64), and Italy (3.8-15.9)[57]. Epidemiological data on pediatric cases remain limited[58]. Data on pediatric Behçet's disease are limited; however, a recent international report indicated childhood onset in 26% of cases, typically between ages 4 and 15[59].

While its precise cause is uncertain, BD is thought to result from immune dysregulation driven by genetic and environmental factors[60]. Infections and alterations in the microbiota are considered important triggers[61,62]. BD has been significantly correlated with the HLA-B5 antigen, particularly the B51 subtype of the HLA-B5 antigen, which is linked to genital, ocular, and cutaneous manifestations, whereas gastrointestinal involvement is less commonly observed[63,64]. GWAS has also implicated variants in major histocompatibility complex class I, IL-10, and IL-23R-IL12RB2 regions in disease susceptibility[65]. A20 protein (HA20) deficiency, which regulates nuclear factor kappa B activation, has been linked to BD-like phenotypes[66,67]. In children, Th17 overactivity appears to coincide with impaired Treg[68]. Genomic studies implicate IL-23 receptor gene variants in the genetic predisposition to BD.

In 1990, the International Study Group (ISG) introduced diagnostic guidelines for adult Behçet's disease, which require recurrent oral ulceration that occur three or more times annually, along with at least two additional findings such as genital ulcers, eye involvement, skin lesions, or a positive pathergy reaction[69]. Cases with only one additional feature are considered incomplete Behçet's disease. Mason and Barnes later introduced broader criteria to capture more diverse clinical presentations[70]. Established in 2014, the International Criteria for Behçet's Disease (ICBD) have shown greater diagnostic sensitivity compared to the earlier ISG guidelines[71]. The ICBD awards 2 points for mucosal

and ocular signs, and 1 point for pathergy, neurological, or vascular features. Diagnosis is confirmed with a score of 4 or above. Developed in 2016, the pediatric-Behçet's disease criteria award 1 point for each major feature: Oral or genital ulcers, skin lesions, eye inflammation, neurological findings, and vascular signs; a minimum score of 3 confirms the diagnosis[72].

Behçet disease primarily affects the skin and eyes[73]. Recurrent aphthous ulcers occur in 95-97% of patients and are generally considered the first symptom[74]. Genital ulcers, observed in 50-85% of cases, may heal with scarring[75]. Papulopustular lesions commonly affect the face, chest, and back, but can also appear more diffusely[76]. Erythema nodosum-like nodules are painful and non-ulcerative, usually located on the lower limbs. Musculoskeletal involvement affects around 50% of patients, commonly as non-erosive oligoarthritis in the knees, ankles, hands, and wrists[77]. Ocular involvement, a key contributor to morbidity, is often bilateral and presents as panuveitis or retinitis, though anterior uveitis can occur in isolation[78]. Vascular involvement in Behçet's disease may present as thrombotic events in veins, arterial blockages, or aneurysms, with deep vein thrombosis of the lower limbs being the most observed presentation[79]. Neurological involvement affects around 5% of patients and is categorized into parenchymal and vascular types. Parenchymal involvement impacts the brainstem and corticospinal tracts, while the vascular form presents as cerebral sinus venous thrombosis. Gastrointestinal manifestations frequently include ulcerative lesions localized to the terminal ileum and cecal region, typically manifesting as abdominal pain, episodes of vomiting, and diarrhea[80]. The pathergy reaction assesses cutaneous hypersensitivity following minimal skin injury; a positive test is characterized by the emergence of a papule or pustule at the puncture site within 24 to 48 hours.

Therapeutic approaches in Behçet's disease vary according to clinical severity and the systems affected. Topical corticosteroids are commonly prescribed to manage mucosal lesions, while systemic formulations are reserved for more serious complications, such as ocular inflammation, vascular pathology, or gastrointestinal involvement[81]. The primary treatment approach includes colchicine for managing mucocutaneous lesions and arthritis, with AZA used in more severe cases affecting the eyes, blood vessels, or gastrointestinal system[82-85]. Methotrexate and MMF are alternative options for neuro-Behçet and mucocutaneous disease. Cyclosporine A is beneficial in managing severe ocular manifestations, whereas CYC is typically employed in critical cases involving the pulmonary arteries or central nervous system[81,86,87].

Treatment of aneurysmal involvement in the pulmonary vasculature or heart typically involves intensive glucocorticoid therapy combined with CYC, while TNF inhibitors may be considered in refractory cases[86]. Anti-TNF therapies-including agents like etanercept, infliximab, and adalimumab-have shown efficacy in managing complex Behçet's disease presentations, such as ocular, neurological, gastrointestinal, vascular, joint, and mucocutaneous involvement[86,88]. Infliximab and adalimumab show particular efficacy in uveitis and severe gastrointestinal disease[88].

For gastrointestinal Behçet's disease, 5-ASA and sulfasalazine are effective in mild cases, while refractory cases require AZA, anti-TNF agents, or immunosuppressants such as thalidomide[89]. Apremilast, a phosphodiesterase-4 inhibitor, has shown efficacy in treating mucocutaneous lesions, arthritis, and overall disease activity, both as monotherapy and in combination with immunosuppressants or TNF inhibitors[90].

Behçet disease is a relapsing-remitting systemic inflammatory condition, with approximately 25% of cases beginning in childhood. While its clinical features resemble those in adults, the entire disease spectrum may take years to develop, often delaying diagnosis

Oral and genital ulcerations frequently emerge during the initial stages of Behçet's disease and can significantly affect patients' quality of life. However, ocular, neurological, and arterial involvement are the primary determinants of morbidity and mortality[91]. Given its heterogeneous course and multi-organ involvement, Behçet's disease requires an individualized and multidisciplinary treatment approach based on disease severity and affected systems.

Polyarteritis Nodosa

PAN involves inflammation of medium-sized arteries, with necrotizing changes being the hallmark histopathological feature[1]. This condition is infrequently encountered in the pediatric population, affecting roughly one child per million. Additionally, the current epidemiological data are limited and require further investigation. No sex-related differences have been identified, and the peak age at presentation is between 7 and 11 years[13]. The pathogenesis is not fully understood. Necrotizing vascular inflammation is driven by the coordinated actions of innate and adaptive immune systems[92].

Diagnostic confirmation of PAN is based on defined clinical and pathological criteria. These criteria include either a histological confirmation of necrotizing arteritis or the detection of vascular abnormalities through angiography. To establish a diagnosis, at least one clinical manifestation must be present, such as skin lesions, muscle pain, elevated blood pressure, peripheral nerve dysfunction, or renal involvement,alongside histopathological or angiographic findings[9]. This condition is characterized histopathologically by fibrinoid necrosis in affected vessel walls, with neutrophilic infiltration at the vessel's periphery, and erythrocyte extravasation into the lower dermis subcutaneous adipose tissue. Notably, giant cells and granulomas are absent, and no immune deposition detected[92]. Imaging typically reveals vascular changes such as fusiform or saccular aneurysms and arterial narrowing. Despite the increasing use of non-invasive imaging methods-namely magnetic resonance and computed tomography angiography-conventional angiography remains the preferred standard in radiologic assessment[93]. Skin findings may present as livedo reticularis or racemosa,

Table 3. *Key distinctions between polyarteritis nodosa and deficiency of adenosine deaminase 2*

	Polyarteritis nodosa	Deficiency of adenosine deaminase 2
Age on onset	Childhood or adulthood	Typically early childhood
Genetic	None/unknown	*ADA2* gene (formerly known as CECR1)
Inheritance pattern	Sporadic, usually autoimmune	Autosomal recessive
Clinical features	Systemic inflammation Vasculitis Myalgia Peripheral neuropathy	Systemic inflammation Vasculitis Early-onset stroke Immunodeficiency
Laboratory findings	Elevated inflammatory markers (CRP, ESR) Reactive thrombocytosis Autoantibodies absent or low	Elevated inflammatory markers (CRP, ESR) Cytopenias Reduced ADA2 activity
Treatment	Steroids Immunosuppressants	Anti-TNF therapy

ADA; Adenosine deaminase, CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate, TNF; Tumor necrosis factor

subcutaneous nodules, or ulcerations. Less commonly, digital ischemia and Raynaud's phenomenon may occur. Renal manifestations vary widely, from isolated hematuria to impaired kidney function. Involves the kidneys, as the disease mainly affects medium and small renal vessels rather than capillaries.

Fever, general weakness, fatigue, weight loss, loss of appetite, muscle pain, muscle tenderness, and high blood pressure are common clinical manifestations of the disease. Fever, mucocutaneous symptoms, and musculoskeletal involvement have been reported as the most frequent clinical features in pediatric PAN cases, as shown in a cohort of 56 patients[94]. Similarly, Eleftheriou et al.[95] reported a higher prevalence of fever, weight loss, fatigue, and musculoskeletal involvement. Additionally, Kasap Cuceoglu et al.[96] found skin and musculoskeletal system involvement to be more frequent in their study. Although less common, studies have also shown cardiac, respiratory, and neurological involvement. In pediatric patients presenting with PAN-like features, differential diagnosis is broad, with monogenic vasculitides, particularly adenosine deaminase 2 deficiency (DADA2),requiring careful exclusion[10]. DADA2 should be strongly considered in cases with early onset, consanguinity, neurological manifestations such as stroke, lymphopenia, and lack of thrombocytosis (**Table 3**)[96].

Treatment recommendations for rare vasculitis have been established by the SHARE consortium, which includes pediatric rheumatologists and nephrologists from across Europe[10]. The treatment plan usually consists of an initial induction period, followed by extended maintenance therapy, which ranges from 12 to 36 months, adjusted based on the course of the disease. Treatment typically begins with intravenous administration of high-dose corticosteroids (ranging from 10-30 mg/kg/day, provided it does not exceed 1 g/day) for three consecutive days, followed by oral steroids at 1-2 mg/kg/day for maintenance. The dosage is subsequently reduced stepwise and typically discontinued by the end of 12 months. CYC is utilized in induction regimens as periodic infusions (500-1000 mg/m², not exceeding 2 g per dose), administered every few weeks for up to six months, together with steroid therapy. Additionally, therapeutic plasma exchange may be utilized. For maintenance purposes, agents such as AZA, methotrexate, and MMF can be used as first-line therapeutic strategies. For individuals who do not respond to standard induction therapy or present with refractory disease, biologic agents offer an alternative therapeutic option. Although no clear preference is established for the initial biological agent, TNF blockade, B-cell depletion, or IL-6 inhibition are considered potential options[97].

Conclusion

Pediatric vasculitides are complex and heterogeneous disorders that demand timely recognition and individualized, multidisciplinary management.

IgAV, although often self-limiting, requires close follow-up when renal involvement is present, as it significantly influences long-term prognosis. Corticosteroids and immunosuppressive agents play a key role in preventing chronic renal damage in these cases. KD, a leading cause of acquired heart disease in children, necessitates prompt IVIG treatment to reduce the risk of coronary aneurysms. Patients with IVIG resistance or cardiovascular involvement may benefit from adjunctive corticosteroids or biologics. Behçet's disease typically follows a relapsing-remitting course with multisystem involvement. Early identification of mucocutaneous symptoms and monitoring for ocular, neurologic, or vascular manifestations guide escalation to systemic immunosuppressive or biologic therapy. PAN, though rare, can be life-threatening. Early systemic involvement warrants aggressive induction therapy with corticosteroids and CYC, followed by maintenance with steroid-sparing agents. In suspected monogenic mimics such as DADA2, genetic testing and targeted biologics (e.g., anti-TNF) should be considered.

Future research should prioritize the development of non-invasive biomarkers for early diagnosis and disease monitoring, the establishment of multicenter pediatric cohorts to better understand disease variability, and the evaluation of steroid-sparing treatment strategies to improve outcomes and minimize long-term toxicity.

Ethics

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

Footnotes

Author Contributions: Başer Taşkın B: Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Doğru A: Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Aktay Ayaz N: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

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The Antibiotic Usage Patterns in Pediatric Patients with Lower Respiratory Tract Infections at Quang Tri General Hospital, Central Vietnam

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Abstract

Lower respiratory tract infections (LRTI) are a significant cause of morbidity and mortality in children, especially in developing countries such as Vietnam. This study analyzed antibiotic use patterns in pediatric patients with LRTI at Quang Tri General Hospital in 2023. A cross-sectional design was used, examining 381 medical records of children aged 2 months to 5 years who received antibiotics for at least 3 days. Pneumonia was the most common diagnosis (82.4%), with severe illness observed in one-third of cases. The most commonly used antibiotic was cefotaxime (42.1%), mainly administered intravenously (62.3%). Antibiotic regimens varied, with an average of 1.55 drugs per patient. Most patients improved (99.0%) after treatment. The findings are consistent with existing literature on LRTI in children and provide insights into antimicrobial stewardship practices. This study highlights the importance of standardized protocols to optimize treatment and minimize inappropriate antibiotic use.

Keywords: Lower respiratory tract infections, pediatrics, antibiotics

Introduction

Lower respiratory tract infections (LRTIs) are among the most severe and prevalent respiratory illnesses, often leading to emergency hospital admissions and, in some cases, fatalities, especially in children and the elderly. The burden of these conditions significantly impacts patients, families, and society. In Vietnam, statistics show that a child may experience respiratory illnesses 5-7 times annually, with pneumonia accounting for 21-75% of emergency hospitalizations[1]; the majority of cases occur in children aged 1-5 years[2]. Identifying the causes of LRTIs in children is crucial for effective treatment. However, this remains

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challenging due to such factors as sampling techniques, prior antibiotic use, low pathogen detection rates, and patient cooperation. Treatment methods vary depending on disease progression, patient condition, and causative agents. Antibiotic therapy is frequently employed with good outcomes in managing LRTIs. To support clinicians, the Vietnamese Ministry of Health has issued specialized guidelines, such as "Guidelines for Diagnosis and Treatment of Respiratory Diseases"[3] and "Guidelines for Antibiotic Use"[4].

Highlights

- The study analyzed antibiotic usage patterns for pediatric lower respiratory tract infections, focusing on prescribing practices, bacterial testing, and administration routes.
- Findings highlighted cefotaxime as the most prescribed antibiotic, with intravenous administration predominating, reflecting guideline adherence.
- Despite limited bacterial testing, the 99.0% improvement rate underscores effective regimens and the need for better diagnostics.

Quang Tri Provincial General Hospital, a first-class facility with over 1,178 beds, treats over 1,000 pediatric LRTI cases annually[5]. Given the high patient load and diverse cases, ensuring appropriate antibiotic management is critical. This study was conducted to analyze the antibiotic usage patterns in pediatric patients with LRTIs at the hospital in 2023, providing insights into clinical practices and potential areas for optimization.

Materials and Methods

Study Subjects

This study focused on medical records of pediatric patients aged 2 months to 5 years diagnosed with LRTIs at the Pediatrics Department of Quang Tri Provincial General Hospital from January 1, 2023 to October 1, 2023, with ICD-10 codes for pneumonia (J12-J18) or acute bronchitis (J20) and had received antibiotic treatment for a minimum of 3 days.

Methods

Study Design

A cross-sectional descriptive study was conducted using data from inpatient medical records that met inclusion criteria.

Sample Size

The sample size was calculated using the formula for estimating a single proportion:

$$n = c \times Z^2_{\alpha/2} \times \frac{p(1-p)}{d^2}$$

In which: $z^2_{\alpha/2}$: confidence level (95%); p: estimated proportion (64.4% based on a 2021 study at Nghe An Obstetrics and Pediatrics Hospital[6]); d: margin of error (0.05).

With c=1 and n=353, a total of 381 patients meeting the criteria were included using a convenience sampling method. Data collection spanned from January 1, 2023, to October 1, 2023.

Data Collection

The study assessed the following aspects:

Demographics: Patient ID, age, gender, ethnicity, and residence (urban/rural).

Characteristics of LRTIs: Diagnoses based on ICD-10 codes (J12-J18 for pneumonia, J20 for bronchitis), disease severity (classified per 2015 Ministry of Health guidelines), treatment duration, comorbidities, and medical history.

Antibiotic use: Types of antibiotics used, initial treatment regimens, and duration of therapy.

Treatment outcomes: Categorized as cured, improved, unchanged, or worsened.

Statistical Analysis

Data were extracted from medical records using a structured data collection form. Information was entered and managed using Epidata and Excel software, with statistical analysis performed in SPSS version 20.0.

This streamlined approach ensured comprehensive and reliable insights into antibiotic usage and treatment outcomes for LRTIs in pediatric patients at Quang Tri Provincial General Hospital.

Ethics Statement

This study was approved by the Ethics Committee in Biomedical Research of Hue University of Medicine and Pharmacy (approval number: H2023/355, date: 02/06/2023). Informed consent was obtained from the parents of all patients participating in the study, after they were fully informed about the purpose, procedures, and potential risks associated with the research.

Results

There were 381 participants, with average age of 18.69±13.97 months, ranging from 2 to 59 months. Most subjects were male (61.9%), nearly 1.5 times the number of females. The majority (91.3%) were of Kinh ethnicity, and most lived-in rural areas (73.5%) (**Table 1**).

Pneumonia accounted for 82.4% of cases, and severe conditions comprised one-third of diagnoses. The average treatment duration was 7.64±3.72 days. Comorbidities were observed in 64.3% of patients, nearly twice as common as in patients with isolated LRTIs (**Table 2**).

Only 43.3% of patients underwent bacterial testing, leaving the majority (56.7%) without this diagnostic evaluation (**Table 3**).

The antibiotics used for initial treatment were relatively diverse, with each patient receiving an average of 1.55 types of drugs (ranging from 1 to 9 types). The range varied from single-antibiotic regimens to combinations involving up to nine antibiotics. The most commonly

Table 1.
Characteristics of study subjects

Attribute		Frequency (n)	Percentage (%)
Age (mean ± SD)/mo		18.69±13.97	
Gender	Male	236	61.9
	Female	145	38.1
Ethnicity	Kinh	348	91.3
	Other	33	8.7
Residential area	Rural	280	73.5
	Urban	101	26.5
Total		381	100.0

SD: Standard deviation

Table 2.
Diagnosis, severity, and comorbidities (n=381)

Attribute		Frequency (n)	Percentage (%)
Diagnosis	Pneumonia	314	82.4
	Acute bronchitis	67	17.6
Severity	Non-severe	254	66.7
	Severe	127	33.3
Treatment duration (mean ± SD/d)		7.64±3.72 days	
Comorbidities	Present	245	64.3
	Absent	136	35.7

SD: Standard deviation

Table 3.
Bacterial testing

Bacterial testing	Frequency (n)	Percentage (%)
Performed	165	43.3
Not performed	216	56.7
Total	381	100.0

prescribed drug was cefotaxime (42.1%), followed by amoxicillin 250 mg + clavulanic acid 31.25 mg (20.8%) and gentamicin (17.9%). The least frequently used antibiotics were trimethoprim-sulfamethoxazole and levofloxacin, each accounting for 0.2% (**Figure 1**).

The most common route of administration was intravenous injection, accounting for 62.3%, followed by oral administration at 35.8%. Only 1.9% of patients were prescribed intravenous antibiotic infusion for treatment (**Figure 2**).

64.0% of the patients were prescribed medication twice daily. A total of 10 patients in the study were prescribed medication three times daily, representing 1.7% (**Figure 3**).

Overall evaluation of the treatment's effectiveness showed that most patients experienced positive outcomes, with 99.0% of pediatric cases reporting improvement in LRTIs during hospitalization. Only 2 cases (0.5%) showed no changes, and another 2 cases (0.5%) experienced worsened conditions (**Table 4**).

Discussion

The study was conducted on 381 pediatric cases treated at the Pediatric Department of Quang Tri General Hospital, with confirmed ICD-10 diagnoses of pneumonia (J12-J18) and bronchitis (J20). The average age of the study participants was recorded as 18.69±13.97 months, with the youngest being 2 months old and the oldest 59 months old. This age distribution is consistent with other studies, both domestic and international. For example, a 2021 study on 1,423,509 children hospitalized for LRTIs in Thailand found that most patients were aged 1-5 years, accounting for 58.26% of cases[7]. Similarly, a study at Thanh Hoa Children's Hospital, Vietnam, on 820 children under 5 years old treated for acute lower respiratory infections reported an average age of 22.1±2.6 months, with 90.6% of cases occurring in the 1-5 age group[2].

In this study, male children accounted for a higher proportion (61.9%), 1.5 times the number of female cases. This finding aligns with observations in Thailand, where over four years of observation until 2021, 58.67% of hospitalizations for LRTIs were male, compared to 41.33% female[7]. Similarly, a 2021 study in Nghe An, Vietnam reported a male-to-female ratio of 1.8:1[1]. Despite differences in location and time of research, most studies consistently note that male children are more frequently hospitalized for LRTIs than females.

Regarding clinical diagnoses, the majority of pediatric patients in our study, were diagnosed with pneumonia (82.4%), while severe pneumonia or severe bronchitis accounted for one-third of the cases. A 2021 study in Thailand similarly identified pneumonia as the most common condition among children with LRTIs, representing 61.58% of all hospitalizations[7]. In Vietnam, pneumonia has been one of the leading causes of both morbidity and mortality among children under five in recent years. It accounts for approximately 33% of all deaths in young children due to various causes[8].

The average length of hospital stay for patients in this study was 7.64±3.72 days, with the shortest being 3 days and the longest being 39 days. A 2022 study by Ha[9] reported average hospitalization durations ranging from 7.4±1.6 days to 9.4±3.6 days, depending on the severity of the diagnosed infection. Longer treatment durations were found to correlate with more severe cases. The relatively short treatment period observed in our study indicates that LRTIs remain acute conditions, with most pediatric patients responding well to the current treatment protocols applied at the hospital. These findings are consistent with the Vietnam Ministry of Health (VMoH) 2015 guidelines on the diagnosis and treatment of common pediatric illnesses[8].

In this study, 64.3% of patients had comorbid conditions, nearly double the number of patients diagnosed with LRTIs alone. Common comorbidities included gastrointestinal inflammation, dermatological conditions, and other respiratory diseases. Similarly, the 2022 study by Ha[9] reported that among 148 pediatric pneumonia cases, 59 children had comorbidities. The most prevalent was rhinitis-pharyngitis (14.19%), followed by digestive disorders (10.81%), and other conditions

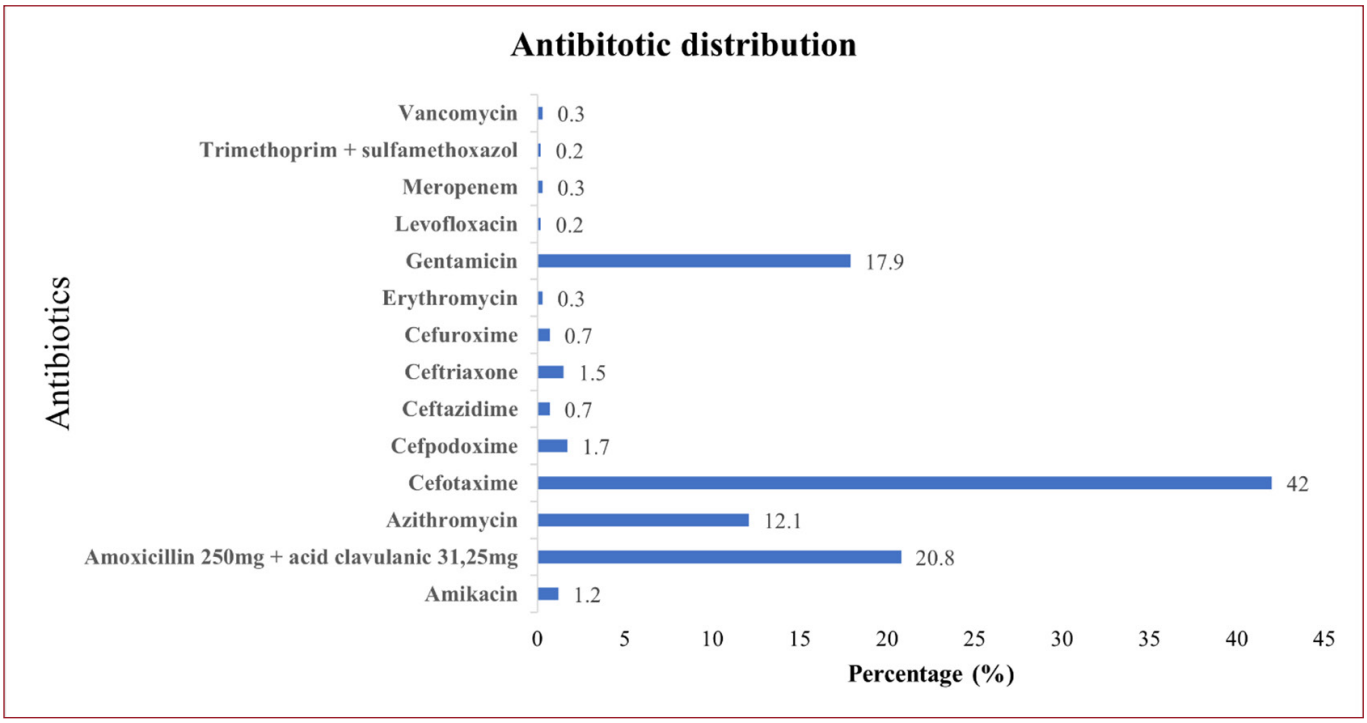

Figure 1. The use of antibiotics in initial regimens

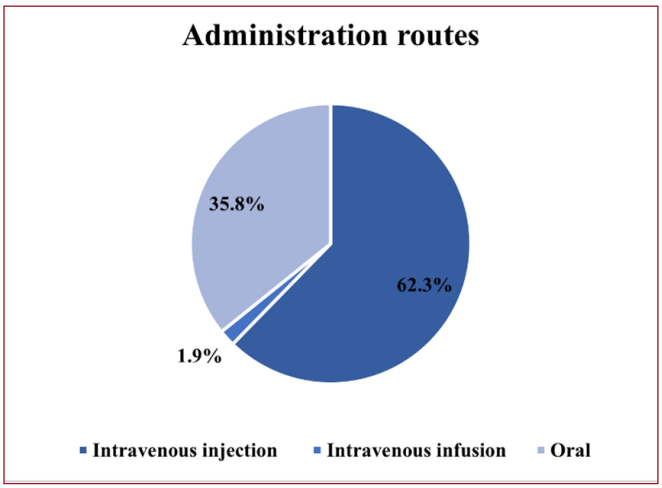

Figure 2. Administration routes

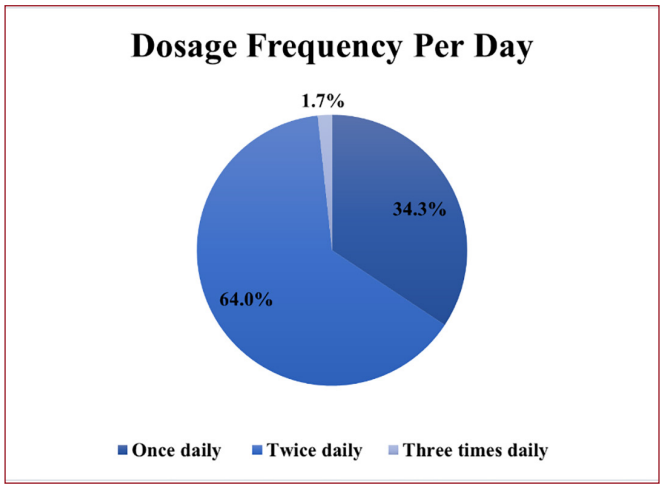

Figure 3. Frequency of medication administration

such as anemia and laryngitis (6.76%). Bacterial testing was conducted for 43.3% of patients, while most of the remaining group did not undergo this examination. However, no specific pathogens were identified.

Table 4.
Treatment outcomes

Treatment outcomes	Frequency (n)	Percentage (%)
Improved	377	99.0
Unchanged	2	0.5
Worsened	2	0.5
Total	381	100.0

Among the antibiotics prescribed in initial treatment regimens, cefotaxime was the most frequently used (42.1%), followed by amoxicillin-clavulanic acid (20.8%) and gentamicin (17.9%). Less commonly used antibiotics included trimethoprim-sulfamethoxazole and levofloxacin (both 0.2%). Subsequent adjustments in treatment showed that azithromycin was most frequently prescribed during the first modification (28.4%), while ceftriaxone and amikacin were prominent in the second. This differs slightly from previous studies, such as one by Thuy and Lien[10], conducted in Hau Giang, Southern Vietnam, (2018), where Amoxicillin was the most commonly used antibiotic (24.6%). However, the findings align with the VMoH guidelines recommending cefotaxime for severe pneumonia in children. A 2021 study conducted at Nghe An Obstetrics and Pediatrics Hospital found that ceftriaxone was the most commonly used antibiotic, prescribed for 44.4% of patients (36 out of 81)[6]. Similarly, a 2022 study in Lao Cai, Northern Vietnam by Ha[9] reported that penicillin was the most frequently used antibiotic group, accounting for 68.93% of cases. Second- and third-generation cephalosporins were used in 7.77% of cases, aminoglycosides in 13.11%, macrolides in 8.74%, and cotrimoxazole in just 1.46%. Cefotaxime, a third-generation cephalosporin, is a broad-spectrum antibiotic used for its antimicrobial properties, with cefotaxime sodium as its main component. It is formulated as injectable powders and solutions, primarily prescribed for respiratory tract infections like bronchitis, and pneumonia. The

VMoH recommends cefotaxime for treating severe pneumonia in children[11]. The second most commonly prescribed antibiotic is amoxicillin, a second-generation broad-spectrum penicillin. Amoxicillin can penetrate the outer membrane porin channels of Gram-negative bacteria, enhancing its effectiveness in treating bacterial infections[11].

The most commonly used administration route in this study was intravenous injection, accounting for 62.3% of cases in the initial prescribed regimen, 54.5% in the first replacement regimen, and 50% in the second replacement regimen. Notably, intravenous administration was prioritized more frequently in replacement regimens. According to the VMoH guidelines[11], amoxicillin is the only recommended oral antibiotic for treating LRTIs while most other antibiotics are recommended for intravenous or intramuscular use. These findings align with several studies conducted in recent years[12-15]. In addition, most patients responded well to the initial antibiotic regimen, with no need to switch treatments. On average, each patient used 1.55 types of antibiotics in the initial regimen prescribed, similar to the 1.6 average recorded in 2019 by Tam[12].

Analysis revealed that the majority of patients showed positive progress: 99.0% experienced improvement in their LRTIs upon hospitalization, while 0.5% saw no changes, and 0.5% experienced worsening conditions. These results differ slightly from previous findings, such as Ha's[9] 2022 study. In that study, pneumonia treatment at the pediatric ward showed 91.2% of patients recovering from pneumonia, 2.0% presenting with severe pneumonia, and improvement rates beyond full recovery of 5.4% for pneumonia and 1.4% for severe pneumonia, with no cases of worsening conditions reported.

Our study reveals distinctive antibiotic patterns, with cefotaxime dominance (42.1%) contrasting sharply with Northern Vietnam's penicillin preference (68.9%)[9] and Southern Vietnam's amoxicillin use (24.6%)[10], reflecting significant within-country variation. This geographic variation within Vietnam mirrors the broader diversity seen across other neighboring countries, where penicillin dominates in Guang Dong, China (29.3%)[16] and amoxicillin-clavulanate leads in Bangalore, India (58%)[17]. The contradiction of high clinical success (99%) and a 56.7% untested microbiological testing limit, raises an interesting question regarding the resource-limited settings versus reliance on empiric treatment efficacy.

These outcomes are noteworthy, especially in the context of rising global and domestic antibiotic resistance rates. The application of antibiotic treatment regimens for pediatric LRTIs at Quang Tri General Hospital, Vietnam, the demonstrates an encouraging effectiveness.

Study Limitations

Several limitations exist that should be considered in this study. First, bacteriological testing was performed in only 43.3% of cases, limiting the ability to associate specific pathogens with antibiotic efficacy. Second, the study was conducted in a single hospital, potentially reducing the ability to generalize the findings to other regions or health care settings. In addition, convenience sampling may have introduced selection bias, affecting the representativeness of the sample. Future research should incorporate multicenter designs, prospective methodologies, and comprehensive bacteriological testing to provide a better understanding of LRTI treatment practices in children.

Conclusion

This study on 381 pediatric patients revealed an average age of 18.69±13.97 months, with males outnumbering females by a ratio of 1.5:1. Pneumonia was diagnosed in 82.4% of cases, with severe pneumonia/bronchitis comprising 33.3%. The average hospital stay was 7.64±3.72 days, and 64.3% of patients had comorbidities. Cefotaxime was the most commonly prescribed antibiotic (42.1%), with intravenous administration being predominant (62.3%). Positive treatment outcomes were observed in 98.7% of patients, underscoring the efficacy of current regimens.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee in Biomedical Research of Hue University of Medicine and Pharmacy (approval number: H2023/355, date: 02/06/2023).

Footnotes

Informed Consent: Informed consent was obtained from the parents of all patients participating in the study, after they were fully informed about the purpose, procedures, and potential risks associated with the research.

Author Contributions: Thuan NTM: Concept, Design, Data Collection or Processing, Analysis or Interpretation; Binh TD: Data Collection or Processing, Literature Search, Writing.

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

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Evaluation of Psychiatric Consultations Requested from Pediatric Clinics During the COVID-19 Pandemic

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Abstract

We aimed to assess the characteristics of children and adolescents who presented to pediatric clinics and required psychiatric consultation during the Coronavirus disease 2019 (COVID-19) pandemic. This descriptive study employed data derived from a retrospective analysis of medical records for 264 patients under 18 years old who were referred to the Child and Adolescent Psychiatry Department upon their presentation to the Pediatric Emergency and General Pediatric Clinics of Mersin University Hospital between March 11, 2020, and May 5, 2023. The median age of the patients surveyed was 15 years (interquartile range: 12-16), with 168 (63.6%) identifying as female. Among the total, 48 patients (18.2%) were young children (under 10 years), whereas 216 patients (81.8%) were adolescents (10-18 years). The predominant cause for consultation among children was behavioral issues (52.1%), whereas for adolescents, it was suicide attempts (42.1%). Of the young child cases, 29.2% exhibited no significant psychopathology, whereas 70.8% were diagnosed with at least one psychiatric disorder. Attention-deficit/hyperactivity disorder was the most commonly diagnosed psychiatric disorder in young children (25%), followed by generalized anxiety disorder (8.3%) and tic disorder (8.3%). Among the adolescent cohort, 6% exhibited no major psychopathology, whereas 94% received a diagnosis of at least one psychiatric disorder. Major depressive disorder was the most prevalent psychiatric diagnosis in adolescents (39.8%), followed by somatic symptom disorder (8.3%). Anxious mood was observed in 43.7% of young children, whereas 26.8% of adolescents displayed depressive mood. A total of 71.2% of patients received prescriptions for psychotropic medication (39.6% of young children and 78.2% of adolescents). This study, conducted in the fifth year of the pandemic, reviews the impact of COVID-19 on young children's and adolescents' mental health. It aims to enhance the awareness and knowledge of pediatricians, child and adolescent psychiatrists, and policymakers in our country regarding this issue.

Keywords: Adolescent, young child, COVID-19 pandemic, psychiatric consultations

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Introduction

Childhood and adolescence represent critical developmental stages marked by significant biological, psychological, cognitive, and social transformations. During these critical phases, 50% to 75% of mental disorders typically emerge[1,2]. Mental disorders constitute a significant global disease burden in this population, with the continuation of mental health issues into adulthood associated with considerable long-term adverse effects throughout the lifespan. Consequences encompass heightened mortality from suicide, diminished academic performance, and reduced economic mobility[2,3].

Highlights

- There has been a tendency for declining psychological well-being and a rise in mental health issues among children and adolescents during the Coronavirus disease 2019 (COVID-19) pandemic.
- The predominant cause for psychiatric consultation among young children was behavioral issues, whereas for adolescents, it was suicide attempts during the COVID-19 pandemic.
- During the COVID-19 pandemic, attention-deficit/hyperactivity disorder was the most commonly diagnosed psychiatric disorder in young children, followed by generalized anxiety disorder and tic disorder.
- Major depressive disorder was the most prevalent psychiatric diagnosis in adolescents, followed by somatic symptom disorder during the COVID-19 pandemic.

Epidemiological studies and meta-analyses indicate that mental health issues among children and adolescents constituted a major public health concern before the Coronavirus disease 2019 (COVID-19) pandemic. A meta-analysis of research conducted from 1985 to 2012 found a 13.4% prevalence of mental disorders in individuals aged 5 to 18 years.[1] Pre-pandemic data from the Global Burden of Disease Study revealed that around 10% of individuals aged 5 to 24 years experienced at least one mental disorder, with an average prevalence of 11.6%. Age-specific prevalence rates were 6.8% for those aged 5-9 years, 12.4% for 10-14 years, and 13.9% for 15-19 years[4]. The COVID-19 pandemic has been correlated with a rise and continuation of the symptoms of mental disorder in many children and adolescents[1-3].

COVID-19 usually progressed as a mild acute illness or was asymptomatic in children. Severe pneumonia and post-acute illnesses such as Multisystem Inflammatory Syndrome in Children have also been observed[5-7]. Besides the effects on physical health, changes in children's nutrition, eating behavior, and mental health occurred during the pandemic[8,9]. The COVID-19 pandemic has caused substantial interruptions in everyday activities. Quarantines, social distancing, and the cancellation of in-person school and community events have adversely affected the mental health of children and adolescents. Mental health issues, including anxiety, depression, suicide attempts, and eating disorders, have risen among young children and adolescents beyond pre-pandemic forecasts[10,11]. The COVID-19 pandemic has correlated with a decline in psychological well-being and an increase in mental health issues among children and adolescents[12]. The COVID-19 pandemic has significantly impacted young child and adolescent mental health, with anxiety, depression, loneliness, and stress being the most commonly reported issues[13]. Data reveal a rise in diagnoses of anxiety disorders and major depressive disorder among individuals under 18 in our country post-COVID-19 pandemic when compared to the pre-pandemic period[14].

Research is needed to investigate the epidemiology and developmental trajectory of mental health issues among young children, adolescents, and young adults during crisis situations, including pandemics[4]. Research findings in this domain can aid in the formulation of effective, evidence-based interventions aimed at preventing mental health issues and their related negative consequences. This study evaluates the demographic and clinical characteristics of young children and adolescents requiring psychiatric consultation who presented to Pediatric Emergency and General Pediatric clinics during the COVID-19 pandemic.

Material and Method

This descriptive study's data were acquired through a retrospective examination of the medical records of patients under 18 years old who were referred to the Child and Adolescent Psychiatry Department, upon their presentation at the Pediatric Emergency or General Pediatric Clinics of Mersin University Hospital, from March 11, 2020, to May 5, 2023. This research encompasses data from the initial verified COVID-19 case in Türkiye until the World Health Organization's declaration of the pandemic's conclusion. The data were obtained at the pediatric clinics inside our hospital that maintained full-time operating hours and did not adopt a flexible schedule throughout the pandemic.

The departments seeking consultation were documented by examining the consultation requests and response notes. Patient presentation dates (consultation dates) were categorized into three roughly one-year intervals: March 11, 2020-March 31, 2021; April 1, 2021-April 30, 2022; and May 1, 2022-May 5, 2023. Descriptive data were gathered on patient age, gender, existence of chronic systemic or mental conditions, grounds for consultation, detected psychiatric issues, and treatment and follow-up strategies. Out of 269 patient files with consultation requests, 264 were incorporated into the study. Five patients of international nationality were omitted. Subsequent visits for patients already assessed for identical concerns and referred for follow-up were excluded. Approval for this study was secured from the Mersin University Clinical Research Ethics Committee (approval number: 2024/415, date: 14.05.2024).

Diagnoses were reviewed based on anamnesis, physical examination, and psychiatric examination findings in pediatric clinics and the child and adolescent psychiatry clinic. Psychiatric disorders were diagnosed by a child and adolescent psychiatrist based on the

criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders-5[15].

Statistical Analysis

Statistical analysis of the data was conducted using SPSS version 21.0.0. Continuous variables are expressed as median with interquartile range (IQR), whereas categorical variables are represented as frequency (n) and percentage (%). Results for the young child (<10 years) and adolescent (≥10 years) cohorts were reported as descriptive statistics.

Results

This study evaluated 264 consultations. The timeframe with the greatest number of consultations occurred from May 1, 2022, to May 5, 2023, accounting for 45.5%, while the period with the fewest consultations was from March 11, 2020, to March 31, 2021, representing 23.9%. **Figure 1** illustrates the periodic distribution of consultations. Of the departments requesting consultations, 176 (66.7%) originated from the pediatric emergency department, while 88 (33.3%) were from the general pediatrics department.

The median age of the consulted patients was 15 years, with an IQR of 12 to 16 years; 168 patients, representing 63.6%, were female. The ages of patients varied from 1 to 18 years. Among the patients, 48 (18.2%) were young children aged under 10 years, while 216 (81.8%) were adolescents aged between 10 and 18 years. Of the patients, 87.5% were enrolled in school, whereas 11.7% were of school age but not enrolled. Two patients (0.8%) who had completed high school were preparing for university entrance examinations, while one patient, aged 16, was employed. **Table 1** presents the sociodemographic characteristics of the patients.

Among the patients, 17.8% were previously diagnosed with a mental disorder, while 6.4% had a chronic systemic illness. The prevalence of mental disorder was 22.3% among the mothers of the patients and 7.2% among their fathers. **Table 2** presents the clinical characteristics of the patients.

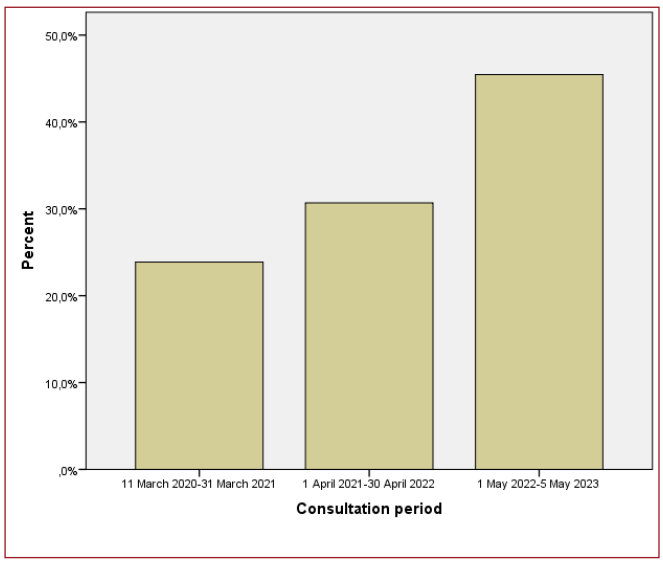

Figure 1. Distribution of consultations by period

Table 1.
Sociodemographic characteristics of the patients (n=264)

	n (%)
Age groups	
Young child	48 (18.2)
1-3 years of age	18 (6.8)
4-6 years of age	14 (5.3)
7-9 years of age	16 (6.1)
Adolescent	216 (81.8)
10-13 years of age (early adolescence)	54 (20.5)
14-16 years of age (middle adolescence)	114 (43.2)
17-18 years of age (late adolescence)	48 (18.2)
Gender	
Girl	168 (63.6)
Boy	96 (36.4)
Residence	
Living with family	257 (97.3)
Childcare institution/residential care	7 (2.7)
Birth order	
First-born	120 (45.5)
Second-born	83 (31.4)
Third-born or later	61 (23.1)
Mother's age (year)	41 (37-45)
Father's age (year)	44 (40-50)
Mother's education level	
Non-literate	16 (6.1)
Literate	7 (2.7)
Primary/Middle School	133 (50.4)
High School	54 (20.4)
Higher education	54 (20.4)
Father's education level	
Non-literate	3 (1.2)
Literate	4 (1.5)
Primary/Middle School	130 (49.2)
High School	66 (25.0)
Higher education	61 (23.1)

Table 2.
Clinical characteristics of the patients (n=264)

	n (%)
Pre-pandemic mental disorder diagnosis	47 (17.8)
Major depressive disorder	18 (6.8)
ADHD	15 (5.7)
Generalized anxiety disorder	9 (3.4)
Obsessive-compulsive disorder	4 (1.5)
Stuttering	1 (0.4)
Presence of chronic systemic disease	17 (6.4)
Epilepsy	10 (3.8)
Hypertension	2 (0.7)
Chronic kidney disease	2 (0.7)
Congenital heart disease	1 (0.4)
Systemic lupus erythematosus	1 (0.4)
Sickle cell disease	1 (0.4)

ADHD: Attention-deficit/hyperactivity disorder

The median age (IQR) of the young child cases was 5 (3-7) years, with 24 (50%) identified as female. The median age (IQR) of the adolescent cases was 15 (13.5-16) years, with 144 (66.7%) identified as female. Behavioral problems were the most common reason for consultations in young child cases (52.1%), whereas suicide attempts were the predominant reason for consultations in adolescent cases (42.1%) (**Table 3**). Among the 92 adolescent cases of suicide attempts, 85 (92.4%) involved medication ingestion, 5 (5.4%) involved jumping from a height, and 2 (2.2%) involved wrist cutting. The primary reasons for suicide attempts included, ranked by frequency, conflict with family (n=67, 72.8%), conflict with friends or a romantic partner (n=13, 14.1%), impulsivity and behavioral disorder (n=8, 8.7%), death of a family member (n=2, 2.2%), depression (n=1, 1.1%), and abuse (n=1, 1.1%).

Table 4 presents the mental disorders identified through pediatric and psychiatric examinations. Of the young child cases, 29.2% exhibited no significant

Table 3.
Reasons for psychiatric consultation

Young children	n (%)	Adolescents	n (%)
Behavioral problems	25 (52.1)	Suicide attempt	92 (42.1)
Speech delay	7 (14.6)	Behavioral problems	45 (20.8)
Attention problems	3 (6.3)	Seizure	36 (16.7)
Anxiety attack	3 (6.3)	Anxiety attack	12 (5.6)
Feeding problems	2 (4.2)	Eating problems	7 (3.2)
Learning difficulties	2 (4.2)	Dyspnea	5 (2.3)
Drug poisoning	1 (2.1)	Tobacco, substance, and alcohol use	4 (1.9)
Suspected abuse	1 (2.1)	Speech disorder	3 (1.4)
Dyspnea	1 (2.1)	Emotional problems	2 (0.9)
Dizziness	1 (2.1)	Dizziness	2 (0.9)
Headache	1 (2.1)	Numbness in the body	2 (0.9)
Excessive crying	1 (2.1)	Family problems	1 (0.5)
Total	48 (100.0)	Suspected abuse	1 (0.5)
		Attention problems	1 (0.5)
		Headache	1 (0.5)
		Vision loss	1 (0.5)
		Death of a family member	1 (0.5)
		Total	216 (100.0)

Table 4.
Psychiatric conditions identified at consultation

Young children	n (%)	Adolescents	n (%)
No major psychopathology	14 (29.2)	Major depressive disorder	86 (39.8)
ADHD	12 (25.0)	Somatic symptom disorder	18 (8.3)
Generalized anxiety disorder	4 (8.3)	ADHD	17 (7.9)
Tic disorder	4 (8.3)	Generalized anxiety disorder	15 (6.9)
Intellectual disability	3 (6.3)	No major psychopathology	13 (6.0)
Autism spectrum disorder	3 (6.3)	Impulsive suicide attempt	13 (6.0)
Specific learning disorder	2 (4.2)	Psychotic disorder	12 (5.6)
Psychotic disorder	2 (4.2)	Eating disorder	7 (3.2)
Adjustment disorder	1 (2.1)	Obsessive-compulsive disorder	6 (2.8)
Conduct disorder	1 (2.1)	Borderline personality disorder	5 (2.3)
Obsessive-compulsive disorder	1 (2.1)	Alcohol and substance use disorder	5 (2.3)
Somatic symptom disorder	1 (2.1)	Conduct disorder	4 (1.9)
Total	48 (100.0)	Intellectual disability	4 (1.9)
		Panic disorder	4 (1.9)
		Social anxiety disorder	2 (0.9)
		Adjustment disorder	1 (0.5)
		Autism spectrum disorder	1 (0.5)
		Specific learning disorder	1 (0.5)
		Gender dysphoria	1 (0.5)
		Post-traumatic stress disorder	1 (0.5)
		Total	216 (100.0)

ADHD: Attention-deficit/hyperactivity disorder

psychopathology, whereas 70.8% received a diagnosis of at least one mental disorder. Attention-deficit/hyperactivity disorder (ADHD) was the most commonly identified psychiatric disorder in young children, occurring in 25% of cases, followed by generalized anxiety disorder and tic disorder, each at 8.3%. Among the adolescent cases, 6% did not exhibit major psychopathology, whereas 94% received a diagnosis of at least one mental disorder. Major depressive disorder was the most commonly identified psychiatric disorder in adolescents, occurring in 39.8% of cases, followed by somatic symptom disorder at 8.3%.

Euthymic mood was observed in 54.2% of young child cases and 21.3% of adolescent cases. Anxiety was observed in 43.7% of the young children, while depressive symptoms were noted in 26.8% of the adolescents. **Table 5** presents the mood types of the patients.

In terms of treatment and follow-up plans, 60.4% (n=29) of the young child cases commenced non-pharmacological clinical follow-up, 35.4% (n=17) initiated psychopharmacological treatment with a single medication, and 4.2% (n=2) began psychopharmacological treatment involving at least two different medications. No child cases required hospitalization. Among the adolescent cases, 21.8% (n=47) received non-pharmacological clinical follow-up, 58.8% (n=127) commenced treatment with a single psychopharmacological medication, and 19.4% (n=42) began treatment with at least two different psychopharmacological medications. Three adolescents diagnosed with major depressive disorder who had attempted suicide were hospitalized.

Discussion

The COVID-19 pandemic presented a significant challenge to global mental health. Children and adolescents are particularly susceptible to the mental health effects of the pandemic, attributable to their developmental stages, fear of infection, lockdown measures, cessation of educational and extracurricular activities, social distancing mandates, and the global economic decline[10]. In this study, psychiatric consultations requested from Pediatric Emergency and General Pediatric clinics during the COVID-19 pandemic were evaluated. The study also reviewing the topic of the COVID-19 pandemic and child mental health.

Survey studies on children and adolescent mental health during the COVID-19 pandemic indicated that the most frequently reported issues included anxiety (28%), depression (23%), loneliness (5%), stress (5%), fear (5%), tension (3%), anger (3%), loss of appetite (3%), confusion (3%), dizziness (3%), and worry (3%)[10]. All these symptoms were reported with varying frequencies in relation to our reasons for consultation and primary diagnoses. A study involving 1004 children aged 7-18 years in Tokat, Türkiye, conducted from July 1 to October 1, 2021, revealed that 60.8% experienced changes in anxiety levels during the pandemic, 54.1% reported an increased fear of death, 28.9% noted a negative impact on familial relationships, 12.3% identified as becoming impatient or intolerant, and 7.2% reported feelings of irritability[16]. In our study, anxiety and behavioral issues were the reasons for psychiatric consultation in both young children and adolescents, whereas family-related issues were a reason for consultation only among adolescents. A study involving 535 patients with a mean age (standard deviation) of 10.8 (4.5) years, conducted at a University Hospital Child Psychiatry Outpatient Clinic in Afyonkarahisar, Türkiye, from September 1, 2020, to March 1, 2021, revealed that 27.2% were diagnosed with ADHD, 19.5% with an anxiety disorder, and 5.6% with an autism spectrum disorder. In comparison to the pre-pandemic era, there was a reduction in ADHD diagnoses and an escalation in the diagnoses of anxiety disorders and severe depressive disorders among patients during the pandemic, with 58.8% of patients receiving prescriptions for psychiatric medication[14]. Our findings indicate that during the pandemic, the predominant primary diagnosis for children under 10 referred from pediatric clinics was ADHD, while for adolescents, it was major depressive disorder. Psychotropic medication was prescribed in 71.2% of all our cases, with 39.6% for young children and 78.2% for adolescents.

A systematic review investigating the effects of COVID-19 lockdowns on the mental health of children and adolescents, involving 54,999 participants (mean age=11.3 years, 49.7% female), found that anxiety symptoms had a prevalence between 1.8% and 49.5%, while depression symptoms ranged from 2.2% to 63.8%. This review indicates that irritability was reported in 16.7% to 73.2% of cases, while anger was reported in 30.0% to 51.3% of cases[17]. In the present study, major depressive disorder was identified in 32.6% (86/264) of cases, while generalized anxiety disorder was identified in 7.2% (19/264). Anxious or depressive mood was the most frequently observed presentation in our study.

Suicidal ideation, suicide attempts, and non-suicidal self-injury have significantly increased as mental health consequences of the pandemic, in children and adolescents. The COVID-19 pandemic has led to an increase in non-suicidal self-injury behavior and suicidal ideation among Chinese adolescents, as well as heightened suicidal ideation among Canadian and American adolescents; and rising suicide rates among Japanese young children and adolescents[18]. Our study found that behavioral problems, including self-harm, were the predominant reason for consultation in young child cases; whereas suicide attempts were the leading reason for consultation in adolescent cases.

The prevalence of mental health problems during the COVID-19 pandemic varied by age group[19,20]. Research indicates that during the pandemic, young children

Table 5.
Mood types of the patients

Young children	n (%)	Adolescents	n (%)
Euthymic	26 (54.2)	Depressive	58 (26.8)
Anxious	21 (43.7)	Anxious	57 (26.4)
Anhedonic	1 (2.1)	Anhedonic	55 (25.5)
Total	48 (100.0)	Euthymic	46 (21.3)
		Total	216 (100.0)

(under 7 years) exhibited excessive attachment to parents, heightened fear for safety, maladaptive and anxious behaviors, boredom, attention-seeking, and reported anxiety[20]. Research indicates that school-aged children (7-13 years) exhibit elevated rates of anxiety and depression compared to pre-pandemic levels, with severe depressive symptoms reported between 2.2% and 11.8% and severe anxiety symptoms ranging from 1.8% to 23.9%. Additionally, there is an increase in inattention, increased need for reassurance, academic challenges, inappropriate behavior, and social isolation.[20] Our study identifies psychiatric problems in children under 10 years of age, which aligns with existing literature. Notably, our findings include diagnoses of tic disorder and obsessive-compulsive disorder. Adolescents during the pandemic have exhibited a heightened risk for internalizing disorders, including depression (prevalence 17.3-22.3%) and anxiety (prevalence 10.4-29.3%). Additionally, they have shown increased incidence of stress, sadness, worry, externalizing disorders such as violence and defiance, somatic symptoms, attention problems, impulsivity, hopelessness, substance use, suicidal ideation, and suicide. Furthermore, challenges in peer relationships and academic performance, sleep disturbances, sedentary lifestyle, and elevated screen time have also been reported[20,21]. The psychiatric issues observed in the adolescent cases of our study align with the current literature. In our study, notable diagnoses include eating disorders, obsessive-compulsive disorder, autism spectrum disorder, and gender dysphoria.

Children and adolescents with physical health conditions are at an increased risk for mental health disorders. 2,12 In this study, 6.4% (17/264) of the subjects presented with a chronic systemic disease, and only 5.9% (1/17) of these cases had a euthymic mood. Conversely, euthymic mood was noted in 28.7% (71/247) of the subjects devoid of a chronic disease. During crises like the pandemic, the psychological condition and emotional well-being of at-risk pediatric groups, particularly those with chronic conditions, must not be disregarded.

Children and adolescents possess diminished autonomy relative to adults, rendering them more vulnerable to their surroundings. The resilience of children and adolescents relies on the well-being of the people in their environment[2]. Our study found that 100% of individuals with fathers having a mental disorder and 91.5% of those with mothers having a mental disorder were diagnosed with a psychiatric disorder during the pandemic. Furthermore, 77.1% of participants with parental mental disorder did not display a euthymic mood. Pre-existing mental disorders are significant risk factors for the development of anxiety during the COVID-19 pandemic[18]. In our study, 91.5% of cases with a pre-existing, physician-diagnosed mental disorder did not display a euthymic mood during the pandemic; 38.3% exhibited anxious mood, 31.9% showed depressive mood, and 21.3% experienced anhedonic mood. Effective communication between parents and children has been shown to mitigate anxiety and depression during the pandemic[12,18]. In our study, familial conflict was the predominant cause of suicide attempts, with 66.3% of patients classified as having severe depressive disorder.

Pre-pandemic data from our country reveal that 93.7% of psychiatric consultations for hospitalized children and adolescents were initiated by the pediatrics department. The age of the consulted cases ranged from 2 to 17 years, with 78.7% being adolescents, 21.3% children under 10, and 66.9% female[22]. The present study's findings, which assessed psychiatric consultations requested from the pediatrics department for outpatient and inpatient cases during the pandemic, show a profile comparable to pre-pandemic inpatients in terms of age group, and gender distribution of cases. It is essential to analyze both the short-term health impacts of the pandemic, as well as its long-term effects on mental health. The pandemic has led to a rise in mental health-related emergency department visits among adolescents over time[12,19]. The increasing number of our consultations, which reached the highest number in the 2022-2023 period, across the one-year periods between 2020 and 2023 supports this inference in the literature.

Considering the high incidence of mental health issues in children and adolescents, it is crucial for pediatricians to be vigilant in early and precise diagnosis[2]. Our findings demonstrate that pediatricians accurately recognized that the majority of cases for which they sought psychiatric consultations showed abnormal mental status; specifically, 89.8% of the psychiatric consultation requests made by pediatricians during the pandemic period led to a diagnosis of a psychiatric disorder.

Study Limitations

The pandemic has adversely affected the mental health of young children and adolescents. To effectively plan and implement interventions that address both short- and long-term effects, it is essential that our findings are corroborated by multi-center incidence and longitudinal study designs. Future research should aim to produce generalizable results for the broader population. The study's limitations encompass its single-center and retrospective design, the absence of comparison with pre-pandemic data, the exclusion of cases that directly presented to child and adolescent mental health outpatient clinics, and consultations requested from clinics outside of pediatric emergency and general pediatrics.

Conclusion

There has been a decline in psychological well-being and a rise in mental health issues among young children and adolescents during the COVID-19 pandemic. Empirical research indicates that both preventive measures and infection dynamics correlate with the degree of psychopathology. Literature identifies factors such as age, gender, socioeconomic level, prior mental and physical health, parental mental health, positive parenting, and family environment as determinants of mental health. We assert that our study, conducted in the fifth year of the pandemic, which reiterates this information, will enhance the knowledge of pediatricians, child psychiatrists, and policymakers in our nation concerning child and adolescent mental health during pandemic periods.

Ethics

Ethical Approval: Approval for this study was secured from the Mersin University Clinical Research Ethics Committee (approval number: 2024/415, date: 14.05.2024).

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

Footnotes

Author Contributions: Durak F: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Literature Search, Writing; Tezol Ö: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Literature Search, Writing; Güler Aksu G: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Writing; Bozlu G: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Writing.

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Association of SNP (rs1360780) in *FKBP5* Gene and Plasma Cortisol Levels in Children with Autism Spectrum Disorder

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Abstract

The inconsistent results about cortisol levels in individuals with autism spectrum disorder (ASD) may be suggestive of other factors like gene polymorphisms rather than the disorder itself. We aimed to investigate the rs1360780 polymorphism in the *FK506 binding protein 5* (*FKBP5*) gene and its relation to ASD and cortisol levels. Eighty-nine children with ASD ranging in age from two to fifteen years were selected for the study group, and eighty-six healthy children were selected for the control group. Blood samples were collected between 10 and 12 am in the morning. Enzyme linked immunosorbent assay and polymerase chain reaction were used to assay serum cortisol levels and genotyping, respectively. The mean cortisol levels for the study and the control groups were 8.5±3.6 µg/dL and 6.1±3.5 µg/dL, respectively. Cortisol levels were significantly higher in the study group compared to the control group ($p<0.001$). There was no statistically significant difference in terms of allele and genotype frequencies between the groups ($p>0.05$). Carrying the C allele was found possibly to increase the cortisol levels in the study group. This is the first clinical study to evaluate the association between rs1360780 polymorphism in the *FKBP5* gene and serum cortisol levels in children with ASD compared to those of healthy participants. Since the prevalence of ASD is gradually increasing in recent years, possible endocrine and related genetic factors should be borne in mind while examining this population.

Keywords: Autism, cortisol, *FKBP5* gene, rs1360780 polymorphism

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Introduction

Autism spectrum disorder (ASD) is a phenotypically heterogeneous group of neurodevelopmental syndromes, with polygenic heritability, characterized by a wide range of impairments in social interaction, communication, and stereotypic behaviors[1]. Because individuals with ASD often experience poor adaptation to change, examination of the hypothalamic-pituitary-adrenal (HPA) axis via cortisol has been a growing area of research interest.

Highlights

- This is the first clinical study to evaluate the association between rs1360780 polymorphism in the *FKBP5* gene and serum cortisol levels in children with autism spectrum disorder (ASD) compared to those of healthy controls.
- Cortisol levels were found to be significantly higher in children with ASD than in their healthy peers.
- No significant allele and genotype differences were found between the groups, and no genotype effect on cortisol levels was observed between children with ASD and healthy controls.
- Since the prevalence of ASD is gradually increasing in recent years, possible endocrine and related genetic factors should be born in mind while examining this population.
- More research is also needed to further explore the relationship between ASD and these factors.

The majority of the studies concerning the HPA axis reactivity and diurnal fluctuations in ASD have been conducted on children. While lower functioning children with ASD have been shown to exhibit atypical diurnal regulation of the HPA axis, higher functioning children with ASD have been reported to have a normal secretion pattern of cortisol[2-5]. The rhythm tends to be much more variable from day to day compared to that of typically developing (TD) children, especially in terms of morning values[3,6]. Evening values have been found to be higher and are also associated with increased stress related to a poor response to changes throughout the day[6,7]. However, almost all studies suggest greater circadian dysregulation in ASD groups relative to age-matched TD controls.

The FK506 binding protein 5 (*FKBP5*), encoded by the *FKBP5* gene, is a co-chaperone of heat-shock protein 90, which regulates glucocorticoid receptor (GR) sensitivity[8]. It has been reported that overexpression of FKBP5 was associated with glucocorticoid resistance and high cortisol levels, suggesting an involvement of FKBP5 in the HPA axis as a determinant of the negative feedback regulation[8-10]. Single nucleotide polymorphisms (SNPs) within the *FKBP5* gene are known to influence GR sensitivity and thus HPA axis regulation, which has been discussed as a key endocrine marker for several psychiatric disorders, such as major depression and posttraumatic stress disorder[11,12]. The most consistent findings have been reported for rs1360780, a SNP located in the second intron of the *FKBP5* gene. The T allele of this SNP forms a putative transcription start site[13].

A recent study reported higher messenger RNA (mRNA) levels of FKBP5 in the postmortem middle frontal gyrus tissues of ASD subjects[14]. To the best of our knowledge, no previous study has directly examined the association between *FKBP5* gene polymorphisms and ASD. The inconsistent results about cortisol levels in individuals with ASD may be suggestive of other factors like gene polymorphisms rather than the disorder itself. Therefore, we aimed to investigate the rs1360780 polymorphism in the *FKBP5* gene and its relation to ASD and cortisol levels compared to those of healthy participants.

Materials and Methods

Participants

We have included two main groups as study and control groups in the present study. Subjects in the study group were recruited among children and adolescents who were referred to the child and adolescent psychiatry in two centers during a period of one year. Eighty-nine children with ASD, ranging in age from 2 to 15 years, were selected for the study group, with diagnosis of ASD based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. Subjects with any genetic syndrome (e.g., Down syndrome, Fragile X, Rett syndrome), any medical disorder (e.g., epilepsy, clinically active infection, Cushing syndrome, hypothyroidism, vitamin deficiencies, and morbid obesity), or with a history of past or current cortisol therapy or vitamins were excluded from the study group. Healthy children without any neurodevelopmental disorder (e.g., ASD, intellectual disability, communication disorders), without any neurological disorder or clinically active infection, and without a history of past or current cortisol therapy or vitamin use were selected as the healthy control group. The study protocol was approved by the Non-invasive Clinical Research Ethics Committee of Gaziosmanpaşa University (approval number: 15-KAEK-226, date: 05.01.2016), and written informed consent was obtained from both parents before starting any study-related procedure.

Measures

Autism Behavior Checklist

Autism behavior checklist (ABC) was developed by Krug et al.[15] It has been used to evaluate the severity of autism symptoms. ABC consists of five subscales with a 57-item scale, including sensory, relationship building, the use of the body and objects, language skills, social and self-care skills. The lowest score of the scale is 0 and the highest score is 159. The scale has been adapted to Turkish by Irmak et al.[16]

Biochemical Analysis

Peripheral venous blood samples were collected postprandial, between 10 and 12 a.m. The samples were stored at room temperature for 15 minutes for

coagulation. Then, blood samples were centrifuged to separate serum from clot at 1000 g for 10 minutes. The sera were stored at -80 °C until the time of analysis. The sera of the study and control groups were measured together using the same plate. Serum cortisol levels were determined with the enzyme linked immunosorbent assay (ELISA) method (Shanghai LZ Biotech Co., Ltd, China, catalogue number is YHB0851Hu), according to the manufacturer's instructions. These kits include a double-antibody sandwich ELISA to assay the level of cortisol in samples. Briefly, samples were added to wells that are pre-coated with monoclonal antibody, and incubated. Then, antibodies labeled with biotin were added and combined with Streptavidin-HRP to form an immune complex. Incubation and washing steps were then carried out. Then the chromogen solutions were added to the wells, and the yellow color was finally observed under the effect of the stop solution. We measured the optical density (OD) of each well at a wavelength of 450 nm within 10 minutes after adding stop solution. According to standard concentrations and corresponding OD values, we calculated the linear regression equation of the standard curve, and we determined the cortisol concentration of the samples.

DNA Isolation and Genotyping

A whole blood sample (200 µL) was taken into ethylenediaminetetraacetic acid-treated tubes, and genomic DNA was isolated using a commercially available kit according to the manufacturer's instructions, (QIAamp DNA Mini Kit, Qiagen, Hilden, Germany). The SNP rs1360780 was genotyped using the TaqMan 5'-exonuclease allelic discrimination assay (assay ID: C ___8852038_10), and StepOnePlus real-time polymerase chain reaction (PCR) system (ThermoFisher Scientific, MA, USA). PCR conditions were 60 ºC for 30 seconds, 95 ºC for 10 min, followed by 40 cycles of 15 seconds at 95 ºC and 1 minute at 60 ºC. Lastly, a temperature of 60 °C was applied for 30 seconds during the post-PCR reading. The fluorescent signal was detected at pre-PCR, amplification (at the end of each cycle), and post-PCR reading steps.

Procedure

Firstly, the diagnostic process of ASD was conducted in referred subjects. The severity of autistic symptoms was assessed with the ABC scale. Hearing tests were applied to all participants. Blood samples for detecting cortisol levels were collected between 10 am and 12 noon once a day. ELISA and PCR were used to assay serum cortisol levels and genotyping, respectively.

Statistical Analysis

The Student's t-test was used to compare normally distributed variables in independent groups, and the Mann-Whitney U test was used to compare nonparametric or ordinal variables. The cortisol levels were not normally distributed. For this reason, the data were transformed to the log base 10 of the values. The effects of age, gender, ABC scores, and genotypes on cortisol levels were evaluated using two-way ANOVA and ANCOVA tests. Pearson's test was used to evaluate correlation coefficients and the statistical significance of normally distributed variables, and Spearman's test was used to evaluate non-normally distributed variables. The values were given as mean ± standard deviation. We have compared the genotype distribution and allele frequencies of rs1360780 between the study and control groups using chi-square or Fisher's exact tests. A value of $p<0.05$ was considered statistically significant.

Results

The study group consisted of 89 children (76 males, 13 females) with a mean age of 43.9±25.7 months, and the control group consisted of 86 healthy children (61 males, 25 females) with a mean age of 47.7±14.2 months. Mean number of siblings in the study and control groups was 2.7±1.2 and 3.0±1.5, respectively. 26.9% of parents in the study group were found to have consanguineous marriages, while 26.7% in the control group had consanguineous marriages. There was no significant difference between the groups regarding mean age of the participants, number of siblings, and the rates of consanguineous marriage ($p>0.05$). A significant difference was found between the groups for gender ($p<0.05$).

The mean cortisol level for the study group was 8.5±3.6 µg/dL, while the mean cortisol level for the control group was 6.1±3.5 µg/dL. Cortisol levels were significantly higher in the study group compared to the control group ($p<0.001$). **Table 1** shows the socio-demographic attributes and cortisol levels in the study and control groups.

The mean total ABC score was 79.5±21.4 in the study group. The ABC subscale scores were found to be 9.5±3.9 for sensory, 20.1±5.6 for relating, 17.9±5.8 for body and object use, 18.5±5.5 for language, and 12.6±3.6 for social and self-help. Regressive autism was observed in 23.6% of the subjects with ASD (n=21). The total ABC scores and language, social and self-help subscale scores were significantly higher in subjects with regressive autism than those without regression ($p<0.05$).

Table 1.
Socio-demographic variables and cortisol levels in the study and control groups

	Study group (n=89)	Control group (n=86)	t	p
Age (months)	43.9±25.7	47.7±14.2	-1.195	0.23
Gender (male/female)	76/13	61/25		**0.03**
Number of siblings	2.7±1.2	3.0±1.5	-1.267	0.20
Consanguineous marriage (yes/no)	24/65	23/63		1.00
Cortisol (µg/dL)	8.5±3.6	6.1±3.5	4.195	**<0.001**

Two-way analyses of variance (ANOVA or ANCOVA) were conducted in order to assess the contribution of age, gender, ABC total and subscale scores, and regressive type of autism on cortisol levels of the study group. There was a statistically significant negative correlation between age and cortisol levels in the study group (r=-0.360, p=0.001). Gender, ABC total and subscale scores, and the regressive type of autism, had no significant effect on cortisol levels.

The *FKBP5* genotype distribution between the study and control groups is shown in **Table 2**. The frequencies of the C and the T alleles in the study group were 72.5% and 27.5%, respectively, while the control group they were 68% and 32%, respectively. *FKBP5* rs1360780 genotype frequencies were CC=46; CT=37; TT=6 for the study group and CC=42; CT=33; TT=11 for the control group. There was no statistically significant difference in terms of allele and genotype frequencies between the groups (p>0.05). Under the recessive model, the mean cortisol levels in the participants of the study group with the CC and CT genotypes were found to be significantly higher than those of the control group with the same genotypes (p<0.001), while there was no statistically significant difference in terms of mean cortisol levels between the study and control groups with the TT genotypes (p>0.05). Under the dominant model, homozygous and heterozygous subjects for the T allele were combined in our analysis, a significant difference between the study and control groups was also found for cortisol levels (p<0.05). The mean cortisol levels were compared between genotypes under the additive, recessive, and dominant models in both the study and control groups separately. No significant difference was found between genotypes in the level of cortisol. **Table 3** displays the comparison of mean cortisol levels based on the genotype models between the groups, and **Figure 1** demonstrates the mean cortisol levels according to genotypes within the groups.

Discussion

The present study investigated the association between *FKBP5* rs1360780 polymorphism and serum cortisol levels in children with ASD. The results suggest that there was no significant difference in terms of allele and genotype frequencies between children with ASD and their healthy peers; however, cortisol levels were significantly higher in children with ASD than their healthy peers. The study also shows no genotype effect on cortisol levels in children with ASD.

Children with ASD often experience poor adaptation to change and exhibit marked stress responses in novel and social situations compared to their typically developed peers. Additionally, sensory hypersensitivity in ASD contributes to the influence of external and internal factors that alter the regulatory system, which in turn leads to greater diurnal variability. Since cortisol secretion is known to be associated with markedly

Table 2.
Genotype distribution and allele frequencies in the study and control groups

Polymorphism		Study group n (%)	Control group n (%)	p	ORs (95%CIs)
rs1360780	Genotype			0.52	
	CC	46 (51.7)	42 (48.9)		
	CT	37 (41.6)	33 (38.3)		
	TT	6 (6.7)	11 (12.8)		
	Allele frequency			0.46	1.23 (0.76-1.98)
	C	129 (72.5)	117 (68)		
	T	49 (27.5)	55 (32)		
	Recessive			0.23	1.88 (0.65-5.46)
	CC+CT	83 (93.3)	75 (87.2)		
	TT	6 (6.7)	11 (12.8)		
	Dominant			0.69	1.13 (0.61-2.1)
	CC	46 (51.7)	42 (48.8)		
	CT+TT	43 (48.3)	44 (51.2)		

OR; Odds ratio, CI; Confidence interval

Table 3.
Mean cortisol levels based on the genotype models between the groups

		Mean cortisol level (± standard deviation)		
Model	**Genotype**	**Study**	**Control**	**p**
Additive	CC	8.2 (±3.3)	6.3 (±3.9)	**0.02**
	CT	9.2 (±3.8)	6.0 (±3.2)	**0.001**
	TT	8.7 (±4.2)	6.0 (±3.9)	0.21
Recessive	CC+CT	8.6 (±3.6)	6.2 (±3.6)	**0.00**
	TT	8.7 (±4.2)	5.9 (±3.9)	0.21
Dominant	CC	8.2 (±3.3)	6.3 (±3.9)	**0.02**
	CT+TT	9.1 (±3.8)	6.0 (±3.4)	**0.00**

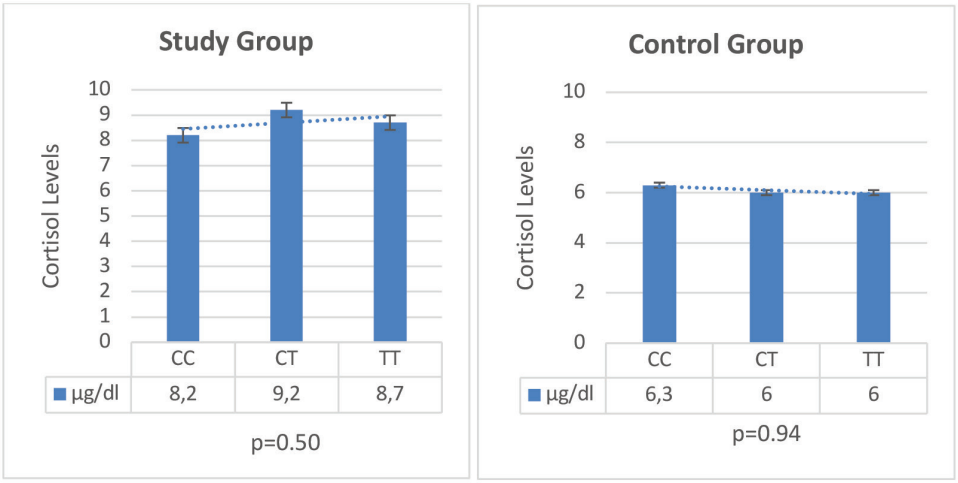

Figure 1. Mean cortisol levels based on the genotypes within the groups

increase in response to stress and greater sensory sensitivity, cortisol levels are more likely to be higher in children with ASD which is in accordance with the present study.

The normal circadian pattern of cortisol is a sharp increase in the morning hours, with a gradual decline throughout the day until it reaches its nadir during nighttime sleep; deviation from this pattern is suggestive of HPA-axis dysregulation[17]. Some studies have focused on specific aspects of this pattern (e.g., cortisol awakening response, daily decline, variability), while others examined cortisol levels once a day, as in our study. In contrast to our findings, Curin et al.[18] and Hamza et al.[19], using plasma cortisol collected in the morning hours, found lower cortisol levels in children with ASD relative to TD controls. However, no difference has been reported in cortisol levels between the ASD group and the TD controls in other studies using the same method[20,21]. Despite the inconsistent results, most of the studies suggest greater circadian dysregulation of cortisol in ASD groups relative to age-matched TD controls[6,7].

It has been shown that age is a critical moderating factor in the activation of the HPA axis in children with ASD. We found a statistically significant negative correlation between age and cortisol levels in the study group. Studies have demonstrated an interaction between diagnosis and age, resulting in significantly higher stress responses in older school-age youth that engage in play with peers. For example, older children with ASD show higher levels of cortisol compared to both younger children with ASD and their TD peers during play[22,23]. The negative correlation between age and cortisol levels in the present study is probably due to the cortisol sampling method, since we did not measure the serum levels in response to a social interaction or a stressful event. Also, no association was shown between cortisol levels and age in other related studies[18,24].

Furthermore, cortisol levels were not significantly associated with ABC total and subscale scores and the regressive type of autism in our study. In an earlier study conducted by Tordjman et al.[24], no significant relationship was reported between autism severity based on the autism diagnostic observation schedule, IQ and cortisol levels, similar to the findings of the present study. However, Hamza et al.[19] reported that autism severity, based on the childhood autism rating scale score, was significantly and negatively correlated with basal and stimulated cortisol levels. In line with this study, Gabriels et al.[25] also reported that children with ASD and high occurrence of repetitive behaviors showed lower diurnal salivary cortisol levels than children with ASD and low occurrence of repetitive behaviors. The authors suggest that repetitive behaviors may serve to mitigate distress or that the glucocorticoid system has been down-regulated, in association with prolonged distress in the children with repetitive behaviors. Further studies are warranted to clarify the inconsistent results regarding the association between autism severity and the HPA axis.

The *FKBP5* protein plays a crucial role in determining sensitivity to glucocorticoid negative feedback, a key mechanism for terminating the HPA axis response to a stressful event. Alterations in the expression or function of FKBP5 could increase cortisol burden and contribute to the allostatic shift in cortisol regulation (Lee et al., 2011). Common SNPs in FKBP5 have been associated with increased FKBP5 protein expression as well as variation in the correlation between plasma cortisol levels and peripheral blood FKBP5 mRNA expression (Binder et al., 2004). The alleles of these polymorphisms are associated with a differential induction of FKBP5 by GR activation and should also be linked to differences in GR sensitivity. In light of this, FKBP5 is considered a promising genetic candidate for vulnerability particularly to stress-related disorders. The rs1360780 polymorphism is among the most common SNPs of FKBP5 that have functional effects. Therefore, we focused on this functional polymorphism in the current study. However, no statistically significant difference was found related to *FKBP5* rs1360780 polymorphism between the study and control groups. To the best of our knowledge, there is no study investigating the FKBP5 associated SNPs, in individuals with ASD in the literature. The link between personality traits and ASD has been demonstrated in several studies[26,27]. Higher harm avoidance and lower cooperativeness were found in individuals with ASD measured by temperament and character

inventory (TCI)[27]. In this context, Shibuya et al.[28] suggested that the T allele of rs1360780 polymorphism in the *FKBP5* gene was associated with higher scores of harm avoidance, and lower scores of cooperativeness, in healthy subjects using TCI. Based on these findings, the personality traits rather than the core features of ASD might be related to *FKBP5* gene polymorphisms. On the other hand, a cohort study using the Neonatal Intensive Care Unit Network Neurobehavioral Scales (NNNS) for evaluating infant neurobehavioral outcomes demonstrated that infants with higher FKBP5 methylation were at increased risk of exhibiting high NNNS arousal scores[29]. The study also found that infants with the TT genotype rs1360780 were more likely to exhibit high NNNS stress response. Since neurobehavioral profiles derived through NNNS have been previously shown to predict neurodevelopmental and cognitive performance in childhood, SNPs in the *FKBP5* gene could serve as biomarkers of neurobehavioral risk, facilitating early screening for neurodevelopmental disorders like ASD. Some forms of SNPs in the *FKBP5* gene were also found to be associated with attention deficit hyperactivity disorder, another neurodevelopmental disorder of childhood, while some forms were not reported to be associated, as observed the present study[30].

We observed significantly higher cortisol levels in the study group with the CC and CT genotypes than in the control group. However, no significant difference was found in terms of mean cortisol levels between the study and control groups among those with the TT genotypes. This finding of the present study is most probably due to the small number of the cases homozygous for the T allele. Carrying the C allele of FKBP5, seems to increase cortisol levels contrary to literature findings. Previous research showed an association of the T allele of the FKBP5 rs1360780 polymorphism with hypercortisolism in the HPA axis[8]. In addition, we compared the cortisol levels among the participants of the study group for the effect of the T allele in the HPA axis. However, we found no significant difference between T allele carriers and non-T allele carriers among the participants in the study group for cortisol levels. Several recent studies also reported no difference in cortisol secretion between the two genotype groups (CC vs. CT/TT) in line with the present study. Fujii et al.[31] indicated no significant difference in any cortisol response value to the dexamethasone suppression test between T allele and non-T allele carriers in young healthy participants, while Höhne et al.[32] suggested that the TT genotype of the FKBP5 rs1360780 polymorphism had no effect on cortisol increase in patients with remitted depression compared to healthy controls.

Study Limitations

Our study has several limitations that should be addressed. The first limitation is the cortisol sampling method since we collected plasma cortisol once a day, and the second is that we did not measure the serum levels in response to a social interaction or a stressful event, and because social impairment is the most critical symptom in children with ASD. Measuring cortisol levels more than once a day in response to a social or stressful trigger could provide accurate cortisol levels. Another limitation is that we investigated only the common functional *FKBP5* variant (rs1360780). The effect of other genotype variants on cortisol levels should be analyzed. Not only do cortisol levels affect the circadian rhythm, but other hormones like melatonin, thyroid-stimulating hormone, and prolactin also play a crucial role in the diurnal rhythm. Evaluating these hormones along with cortisol could provide more information about the circadian dysregulation of ASD. Additionally, not measuring body mass index is a limitation because body weight influences morning cortisol levels.

Conclusion

Despite these limitations, this is the first clinical study to evaluate the association between rs1360780 polymorphism in the *FKBP5* gene and serum cortisol levels in children with ASD compared to those of healthy participants. No significant allele and genotype differences were found between the groups and no genotype effect on cortisol levels between children with ASD and healthy controls. Since the prevalence of ASD is gradually increasing in recent years, possible endocrine and related genetic factors should be born in mind while examining this population. However, more research is needed to further explore the relationship between ASD and these factors.

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We would like to thank all the children and parents who took part in this research for giving us their time.

Ethics

Ethics Committee Approval: The study protocol was approved by the Non-invasive Clinical Research Ethics Committee of Gaziosmanpaşa University (approval number: 15-KAEK-226, date: 05.01.2016).

Footnotes

Informed Consent: Written informed consent was obtained from both parents before starting any study-related procedure.

Author Contributions: Bozkurt H: Concept, Design, Writing; Haktan A: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation; Şimşek Ş: Concept, Literature Search, Writing; Şahin S: Data Collection or Processing, Analysis or Interpretation, Literature Search; Coşkun S: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation.

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

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Clinical Indications and Diagnostic Yield of Transfontanelle Ultrasound in 346 Infants: A Retrospective Single-Center Study

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Abstract

Transfontanelle ultrasonography (TFUSG) is a reliable and non-invasive imaging method used for early detection of cranial abnormalities during the neonatal and infant periods. This study aimed to evaluate the reasons for TFUSG requests, demographic features, and imaging findings in infants under one year of age. In this retrospective study, medical records of 346 infants who underwent TFUSG in the pediatric neurology outpatient clinic of a tertiary hospital between January 1, 2023, and December 31, 2024, were reviewed. Demographic data, TFUSG indications, and imaging findings were analyzed. The study included 346 infants, of whom 214 (61.8%) were male and 132 (38.2%) female, with a mean age of 3.06±2.4 months. A total of 60.1% of the infants were born prematurely. The most common indications for TFUSG were a history of prematurity and/or neonatal intensive care unit admission (56.6%), suspected seizures (20.8%), and clinical findings such as developmental delay, microcephaly, or macrocephaly (12.4%). TFUSG results revealed normal findings in 64.7% of cases, normal variants in 6.4%, and pathological findings in 28.9%. The most common pathologies included increased cerebrospinal fluid spaces (54%), germinal matrix hemorrhage (34%), and hydrocephalus (12%). Abnormal TFUSG findings were significantly more common in male infants, while no significant difference was found concerning gestational age. TFUSG is an effective imaging modality that contributes substantially to the diagnostic process in pediatric neurology outpatient settings. Further studies with larger cohorts are needed to standardize findings and improve diagnostic accuracy.

Keywords: Cranial imaging, prematurity, ultrasonography

Introduction

Transfontanelle ultrasonography (TFUSG) is an effective, safe, and non-invasive imaging technique used to evaluate the anatomy of the developing infant brain[1-3]. It is particularly valuable for assessing high-risk neonates and detecting cranial anomalies that may not appear on clinical examination. With this technique, brain structures can be visualized by applying a small ultrasound probe over the anterior or posterior fontanelle[1]. The procedure is painless and generally does not require sedation or anesthesia.

TFUSG is widely used for the evaluation of premature infants at risk of intraventricular hemorrhage, as well as

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for the diagnosis and follow-up of cranial pathologies such as hydrocephalus, subdural hematomas, and effusions. It also plays a useful role in monitoring various neurological conditions[4]. Due to its practical nature, it is frequently employed in neonatal and pediatric neurology outpatient clinics.

The main advantages of TFUSG include its portability, its ability to be performed at the bedside, the absence of radiation exposure, and its cost-effectiveness. However, the technique also has several limitations, such as reduced usefulness after fontanelle closure, occasionally insufficient anatomical detail, and variability in image quality depending on the device and the operator's experience[5,6].

This study aimed to evaluate the indications for TFUSG, demographic characteristics, and cranial imaging findings in infants aged under one year who underwent the procedure in a pediatric neurology outpatient clinic.

Highlights

- Transfontanelle ultrasonography (TFUSG) is a safe, effective, and non-invasive method for evaluating the infant brain.
- TFUSG was most frequently performed during the first postnatal month (33.5%), highlighting the importance of early cranial imaging.
- In the outpatient setting, TFUSG was commonly used to assess macrocephaly, developmental delay, and suspected seizures.
- A total of 346 infants under one year of age underwent TFUSG in a pediatric neurology outpatient clinic.
- Abnormal findings were detected in 28.9% of cases, including enlarged cerebrospinal fluid spaces, germinal matrix hemorrhage, and hydrocephalus.

Materials and Methods

This retrospective study reviewed the medical records of infants under 12 months of age who were referred for TFUSG to the pediatric neurology outpatient clinic at Kayseri City Hospital, Türkiye, between January 1, 2021, and December 31, 2022. The study commenced after the Non-Interventional Clinical Research Ethics Committee of Kayseri City Hospital granted approval (approval no. 2025/367, date: 11.03.2025). Written informed consent was obtained from the family for the publication of this case report.

Demographic data, including age, sex, gestational age, and clinical indications for TFUSG, were collected and analyzed. In the majority of cases, TFUSG was performed on the same day as the outpatient clinic visit.

Patients were categorized into five age groups based on their age at the time of the TFUSG request: 0-1 month, 1-3 months, 3-6 months, 6-9 months, and 9-12 months. Only examinations performed at our institution were included; TFUSG studies conducted at external centers were excluded.

All TFUSG examinations were conducted by experienced pediatric radiologists using a high-resolution ultrasound system equipped with an 11 MHz sector transducer, optimized for detailed pediatric neuroimaging.

TFUSG findings were classified into three categories: normal, normal variants, and pathological. Normal findings included symmetric lateral ventricles, normal parenchymal echogenicity, and age-appropriate intracranial structures. Normal variants were defined as benign anatomical deviations not associated with clinical or radiological signs of increased intracranial pressure, including cavum septum pellucidum (CSP), mild ventricular asymmetry, isolated septum pellucidum cysts (<10 mm), and mildly widened subarachnoid spaces (≤5 mm). Pathological findings included hydrocephalus, germinal matrix hemorrhage (GMH), congenital malformations, and/or cerebrospinal fluid (CSF) space enlargement exceeding 5 mm with accompanying mass effect or ventricular dilation.

In a subset of patients, additional neuroimaging with magnetic resonance imaging (MRI) or computed tomography (CT) was performed based on clinical indications such as abnormal TFUSG findings or ongoing neurological concerns. As MRI or CT was performed only in selected cases, the classification of findings was based solely on TFUSG results.

Statistical Analysis

Statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables as counts and percentages (%). The chi-square test was used to assess associations between categorical variables. A p-value <0.05 was considered statistically significant.

Results

A total of 373 infants were initially evaluated for inclusion in the study. However, nine patients did not have scheduled appointments , seven underwent the procedure at external centers, six had incomplete medical records, and five were excluded due to inadequate anterior fontanelle opening. As a result, the final study population comprised 346 infants. The recruitment and study flow are presented in **Figure 1**.

Among the 346 patients included, boys constituted 61.8% (n=214), and girls 38.2% (n=132). The patients' mean age was 3.06±2.4 months (minimum 5 days, maximum 12 months). TFUSG was most frequently performed on infants aged 0-1 month at 33.5%. Analysis showed that 52.3% of the patients were born preterm with the majority of this group consisting of late preterm (34-37 weeks) infants. Low birth weight (<2500 grams) was detected in 43.6% of the infants. Head circumference evaluation revealed microcephaly in 6.1% (n=21) and macrocephaly in 9.2% (n=32). The most common reasons for requesting TFUSG were prematurity (32.7%), a history of neonatal intensive care unit (NICU) admission (24.6%), and seizure suspicion (20.5%). Other indications included antenatal cystic lesions (10.1%), abnormal head circumference (8.4%), and developmental delay (4%). **Table 1** summarizes the demographic and clinical characteristics of the study population.

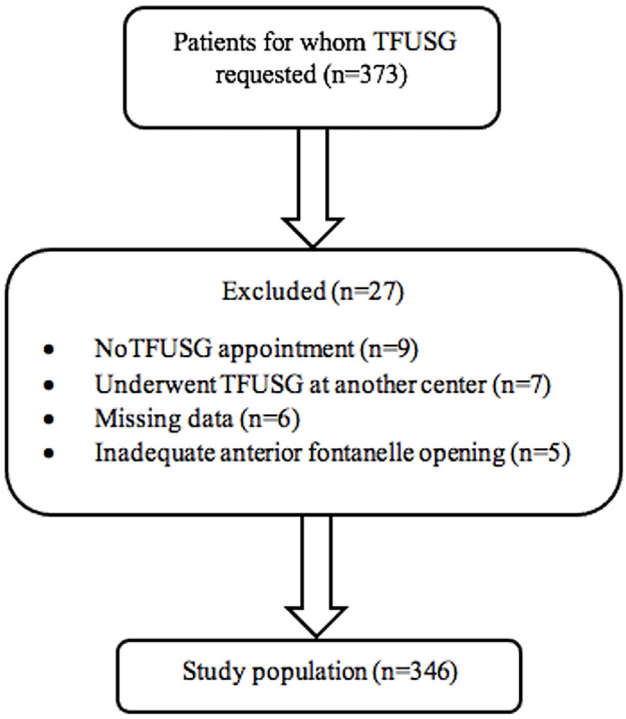

Figure 1. Flowchart of patient recruitment and study inclusion
TFUSG: Transfontanelle ultrasonography

Normal TFUSG findings were observed in 62.4% of the cases, and normal variants, including benign enlargement of the subarachnoid space, mild ventricular asymmetry, isolated septum pellucidum cyst, or CSP, were observed in 6.4%. Pathological findings were identified in 108 infants (31.2%). The most frequently observed abnormality was enlargement of CSF spaces (n=56, 51.9%), typically characterized by widened extracerebral spaces or ventriculomegaly that do not meet the criteria for hydrocephalus.

GMH was the second most common pathology, detected in 38 cases (35.2%). Most GMH cases were low-grade (grade I-II) and typically associated with prematurity. Several patients demonstrated coexisting mild ventricular dilation. Hydrocephalus was diagnosed in 14 infants (13%), most of whom presented with macrocephaly or rapidly increasing head circumference. These cases were referred for further imaging and specialist evaluation, some underwent neurosurgical intervention, including shunt placement.

Follow-up neuroimaging with brain MRI or cranial CT was performed in 81 of 346 patients (23.4%), primarily due to abnormal TFUSG findings or persistent clinical concerns. In 69 of these cases (85.2%), TFUSG findings were confirmed by MRI/CT, including diagnoses of GMH, hydrocephalus, or structural anomalies. Minor discrepancies were observed in 12 cases (14%), such as underestimation of ventricular size, or identification of subtle white matter abnormalities not detected on TFUSG. No clinically significant misdiagnoses were identified.

Statistical analysis revealed a significant association between abnormal TFUSG findings and male sex (p=0.002) as well as prematurity (p=0.029). Notably,

Table 1.
Demographic and clinical characteristics of the study population (n=346, %)

Variable	Category	n	Percentage (%)
Gender	Male	214	61.8%
	Female	132	38.2%
Age at time of TFUSG	0-1 months	116	33.5%
	1-3 months	107	31%
	3-6 months	88	25.4%
	6-9 months	28	8.1%
	9-12 months	7	2%
Gestational week	Premature (<37 weeks)	181	52.3%
	Extreme preterm (<28 weeks)	16	4.6%
	Very preterm (28≤32 weeks)	30	8.7%
	Moderate preterm (32≤34 weeks)	49	14.1%
	Late preterm (34-37 weeks)	86	24.9%
	Term (≥37 weeks)	165	47.7%
Birth weight	<2500 g	151	43.6%
	2500-4000 g	185	53.5%
	>4000 g	10	2.9%
Head circumference	Microcephaly	21	6.1%
	Normocephaly	293	84.7%
	Macrocephaly	32	9.2%
Indications for requesting TFUSG	Prematurity	111	32.1%
	NICU history	85	24.6%
	Seizure suspicion	72	20.8%
	Antenatal cystic lesions	35	10.1%
	Micro--/macrocephaly	29	8.4%
	Developmental delay	14	4%
TFUSG results	Normal	216	62.4%
	Variant of normal	22	6.4%
	Pathological findings	108	31.2%
	Enlargement of CSF spaces	56	16.2%
	Hydrocephaly	13	4%
	Germinal matrix hemorrhage	35	11%

TFUSG: Transfontanelle ultrasonography, CSF: Cerebrospinal fluid, NICU: Neonatal intensive care unit

Table 2.
Demographic analysis of patients with abnormal TFUSG findings

		n	%	p
Gender	Female	29	26.4%	**0.002***
	Male	81	73.6%	
Gestational week	Premature	67	57%	**0.029***
	Mature	43	43%	

TFUSG: Transfontanelle ultrasonography

52.3% of infants with pathological findings were born preterm, and the late preterm group represented the largest proportion (**Table 2**).

Discussion

In this retrospective analysis of 346 infants referred for TFUSG, pathological findings were identified in approximately one-third (31.2%) of the cohort. This is consistent with previous studies reporting cranial abnormalities in 25-35% of similar pediatric populations undergoing ultrasound evaluation[7,8]. The most commonly observed pathology was the enlargement of CSF spaces, accounting for over half of the abnormal cases. While mild subarachnoid space widening (≤5 mm) is considered a benign variant, especially in preterm or low-birth-weight infants, enlargement exceeding 5 mm accompanied by features such as ventricular dilation, cortical thinning, or clinical symptoms was classified as pathological, following published normative data[9-11].

The most frequent indication for TFUSG was evaluation of infants with a history of prematurity and/or NICU admission. This is consistent with previous studies highlighting prematurity as the leading cause for cranial ultrasound referral in early infancy. Additional indications included suspected seizures, abnormal neurodevelopment, and atypical head circumference measurements. These patterns reflect the clinical utility of TFUSG in the initial evaluation of infants with diverse neurological risk factors in the outpatient setting[10,11].

GMH, detected in 35.2% of pathological cases, was primarily low-grade (grade I-II) and strongly associated with prematurity. This aligns with established evidence indicating that the fragile germinal matrix vasculature in preterm neonates predisposes them to hemorrhage, particularly within the first week of life[4,5]. Hydrocephalus was identified in 13% of abnormal cases, often presenting with macrocephaly or rapid increases in head circumference, necessitating neurosurgical evaluation in several instances.

Importantly, 23.4% of patients underwent additional neuroimaging (MRI or CT), primarily due to abnormal TFUSG findings or persistent clinical suspicion. Advanced imaging confirmed TFUSG findings in over 85% of these cases, particularly in the diagnosis of GMH, hydrocephalus, and structural anomalies. These results support the diagnostic reliability of TFUSG as an initial imaging modality. Minor discrepancies, such as the underestimation of ventricular size or subtle white matter abnormalities not detected on ultrasound, highlight the known limitations of ultrasound resolution and the continued role of MRI in comprehensive neuroimaging when clinically indicated[5,6].

The male-to-female ratio in our study was 1.62, within the range reported by previous literature (1.03 to 1.69)[10-13]. Notably, abnormal TFUSG findings were prevalent in male infants, which may reflect sex-specific vulnerabilities in early brain development. Male neonates, especially those born prematurely, are more susceptible to perinatal brain injury due to delayed oligodendrocyte maturation, increased sensitivity to hypoxia-ischemia, and lower levels of neuroprotective hormones such as estrogen[14]. This may explain the higher incidence of GMH and ventricular abnormalities observed in male infants.

Unlike many previous studies, in which term infants formed the majority, our cohort has a nearly equal distribution of preterm and term births. A significant proportion of the abnormalities, including GMH and CSF space enlargement, were observed among late preterm infants (34-37 weeks), suggesting that even marginal prematurity may warrant careful neuroimaging surveillance.

Overall, the findings reinforce the value of TFUSG in early diagnostic workup in pediatric neurology outpatient settings. While it cannot replace MRI in detecting subtle cortical or white matter abnormalities, TFUSG provides a rapid, safe, and cost-effective tool that can guide clinical decision-making, especially when used in conjunction with follow-up imaging in selected cases.

Study Limitations

This study has several limitations. First, its retrospective design may introduce selection and documentation biases, as the analysis relied on the accuracy and completeness of existing medical records. Second, the study was conducted at a single tertiary-care center, which may limit the generalizability of the findings to other populations or clinical settings, particularly in primary care. Third, although all TFUSG scans were interpreted by experienced pediatric radiologists, confirmatory imaging with MRI or CT was used to address the potential for inter-operator variability in TFUSG findings. This may have affected the accuracy of final diagnostic classifications. Lastly, long-term neurodevelopmental outcomes were not assessed, limiting our ability to determine the clinical significance and prognostic implications of some sonographic abnormalities.

Conclusion

TFUSG is a rapid, safe, and non-invasive imaging modality that provides valuable diagnostic information in infants under one year of age without the need for sedation or exposure to radiation. In this retrospective study, TFUSG enabled the identification of pathological cranial findings in approximately one-third of patients, underscoring its diagnostic utility in outpatient pediatric neurology settings. The higher prevalence of abnormalities in male infants and those born preterm may reflect underlying neurodevelopmental susceptibilities, which warrant further investigation. Given the high concordance between TFUSG and advanced imaging in a subset of cases, TFUSG can serve as an effective first-line modality for initial correlation, are needed to refine diagnostic criteira, validate normal variants, and establish standardized protocols for TFUSG interpretation in early childhood.

Ethics

Ethics Committee Approval: The study commenced after the Non-Interventional Clinical Research Ethics Committee of Kayseri City Hospital granted approval (approval no. 2025/367, date: 11.03.2025).

Informed Consent: Written informed consent was obtained from the family for the publication of this case report.

Footnotes

Authorship Contributions: Öztürk S: Concept, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Özgül Gümüş Ü: Concept, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

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Plasma Amino Acid Levels in Obese Adolescents: A Case-Control Study and the Review of the Literature

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Abstract

Optimal balance among amino acids in the circulation is important for body homeostasis. This study aims to evaluate and define the amino acids associated with obesity and insulin resistance. Fifty obese and 42 healthy adolescents aged 10-18 years were included in this study. Fasting plasma glucose, liver enzymes, thyroid function tests, insulin, and lipid levels were studied as routine laboratory examinations, and 26 plasma amino acids were studied as specific laboratory examinations. Isoleucine, leucine, lysine, tryptophan, glutamate, tyrosine, phenylalanine, alanine, methionine, argininosuccinic acid, histidine and valine were significantly higher in patients with obesity. Asparagine and citrulline levels were lower in patients with insulin resistance. The metabolic pathways of various amino acids are significantly impaired in obesity. Plasma concentrations of essential, non-essential, branched-chain, and aromatic amino acids were elevated in this study.

Keywords: Amino acids, adolescent, obesity

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Introduction

Obesity has emerged as a global health issue affecting both children and adults. It increases the likelihood of developing metabolic disorders, including insulin resistance, type 2 diabetes, elevated uric acid levels, abnormal lipid profiles, high blood pressure, and non-alcoholic fatty liver disease. Metabolic complications associated with obesity are important because they cause mortality and morbidity. Understanding the mechanisms could help to identify therapeutic strategies[1,2].

Highlights

- Optimal balance among amino acids in the circulation is important for body homeostasis.
- The metabolic pathways of various amino acids are significantly impaired in obesity.
- Plasma concentrations of essential, non-essential, branched-chain and aromatic amino acids were found to be elevated in our study.

Amino acids (AAs), which contain both an amino and a carboxyl group, undergo metabolic processes that result in the formation of several compounds, including ammonia, fatty acids, glucose, ketone bodies, urea, uric acid, and polyamines. These metabolites take part in various cycles such as the tricarboxylic acid (TCA) and urea cycle, and vital functions such as gluconeogenesis, ketogenesis, acid -base balance, and the synthesis of nucleotides and lipids. Deficiency or excess in plasma AA occurs when these pathways are disrupted. Increased concentrations of AAs and their products can contribute to oxidative stress and associated poor metabolic conditions. Maintaining an appropriate balance of AAs in both the diet and bloodstream is essential for preserving physiological homeostasis[3].

The mechanisms by which AAs contribute to insulin resistance are complex, and studies have been particularly focused on branched-chain amino acids (BCAAs). Leucine is a potent activator of the mammalian target of rapamycin complex 1 (mTORC1). Chronic mTORC1 activation disrupts insulin signaling by enhancing the serine phosphorylation of insulin receptor substrate-1. As a result, cells become less responsive to insulin, leading to insulin resistance**.** In addition, incomplete catabolism of BCAAs results in the accumulation of toxic metabolic intermediates, which can impair mitochondrial function, activate stress-responsive kinases, and promote β-cell dysfunction. Specific BCAA-derived metabolites, such as 3-hydroxyisobutyrate and acetyl-CoA, interfere with fatty acid β-oxidation, leading to the intracellular accumulation of lipids like diacylglycerol and ceramides in skeletal muscle. These lipids activate protein kinases, impair insulin signaling, and exacerbate insulin resistance[4-7].

There are relatively few studies evaluating AA levels in childhood obesity. Butte et al.[8] reported that BCAAs and AAs such as alanine, glutamate, lysine, phenylalanine, and tyrosine were elevated in obese children. McCormack et al.[9] showed that elevations in the concentrations of BCAAs were significantly associated with BMI Z-score and homeostatic model assessment for insulin resistance (HOMA-IR). Elshorbagy et al.[10] demonstrated that total cysteine concentrations are independently related to obesity and insulin resistance. Zhao et al.[11] reported that BCAAs and aromatic AAs were closely related to insulin resistance and future metabolic risk.

The primary objective of this study was to define AAs associated with obesity and insulin resistance. We hypothesized that some AA changes may be biomarkers for metabolic decompensation and could be used in the treatment of childhood obesity.

Material and Method

Study Design

Our study was planned as a case-control prospective observational study.Adolescents with obesity who were evaluated in the pediatric metabolism and endocrinology clinics of the Kayseri Erciyes Training and Research Hospital between November 2017 and May 2018, were included in the study.

Inclusion Criteria

Patient Group

The obesity group consisted of 50 patients aged 10 to 18 years, all with a body mass index (BMI) greater than the 95th percentile and a BMI Z-score above 2. BMI Z-scores were determined using the World Health Organization's data[12]. None of the patients were on a diet and/or exercise. There was no infection or catabolic condition that could affect plasma AAs according to physical examination findings and laboratory results.

Control Group

The control group was selected, consisting of gender and age-matched, completely healthy adolescents with BMI below the 85th percentile, chosen from pediatric policlinics for a check-up or for preoperative evaluation of minor elective surgery. Simple random sampling was used for all subject choices.

Exclusion Criteria

Patients with primary hyperlipidemia, primary liver disease, and secondary obesity were excluded.

Measurements

The height and weight were measured using an automatic device (G-TECH, GL-150). BMI was obtained by dividing the individual's body weight in kilograms by the square of their height, measured in meters (kg/m^2). HOMA-IR was used to determine the IR. HOMA-IR was calculated by multiplying fasting blood glucose (milligrams/dl) by insulin (milliunits/milliliter) and dividing it by 405. A value above 3.16 was accepted as IR[13].

Analyses

All samples were collected after a 12-hour overnight fast. Plasma glucose, liver enzymes, thyroid function tests, insulin, and lipid levels were studied as routine laboratory examinations.

Glucose, triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein were measured

by spectrophotometric methods using an automated clinical chemistry analyzer (C702, Roche Diagnostics, Mannheim, Germany).

Insulin, T4 and thyroid-stimulating hormone levels were measured by electrochemiluminescence assay (E601, Roche Diagnostics, Mannheim, Germany).

A two-milliliter blood sample was taken in a fasting state into EDTA tubes, kept at +4 °C for 15 minutes, and centrifuged at 3500 rpm for 15 minutes in order to study plasma AA levels. All samples were preserved at -80 °C until analysis. Plasma AAs were measured by using Zivak Tandem Gold LC-MS/MS system, in the pediatric metabolism laboratory of Erciyes University Faculty of Medicine. A total of 26 AAs: Alanine, arginine, argininosuccinic acid, asparagine, aspartic acid, cysteine, citrulline, glutamine, glutamate, glycine, homocysteine, hydroxylysine, hydroxyproline, isoleucine, leucine, lysine, methionine, ornithine, proline, serine, threonine, tryptophan, tyrosine, phenylalanine, valine, and histidine were studied.

Ethical Approval

Ethical approval was received from the Ethics Committee of Erciyes University Faculty of Medicine (approval no: 487/2017, date: 27.10.2017).

Statistical Analysis

Statistics were analyzed using SPSS version 26. Data with a normal distribution were presented as mean, ± standard deviation, while non-normally distributed variables were expressed as median and interquartile range (25^{th}-75^{th} percentile). For comparisons between two groups, the independent samples t-test was used for normally distributed variables, and the Mann-Whitney U test was applied to non-parametric data. Categorical variables were analyzed using the chi-square test. Spearman's correlation was employed to evaluate relationships between non-parametric variables. Multiple linear regression analysis of the association of AAs with BMI change was used to identify the AAs associated with obesity. A p-value of less than 0.05 was indicative of statistical significance throughout all analyses.

Results

The study consisted of 50 (23 M/27 F) adolescents with obesity and 42 (16 M/26 F) healthy controls. The mean ages of the obese group were 13.4±2.0 years and of the healthy controls were 13.7±2.0 years. The AAs: isoleucine, leucine, lysine, tryptophan, tyrosine, phenylalanine, alanine, methionine, glutamate, argininosuccinic acid, histidine, and valine were significantly higher in the obese group than healthy controls. Only glycine levels were lower in the obese group. Comparison of the variables between the obese and control groups is shown in **Table 1**.

Alanine, glutamate, methionine, phenylalanine, isoleucine, leucine, valine, tyrosine, tryptophan, proline, and lysine levels were positively correlated; serine and glycine levels were negatively correlated with obesity-related parameters. Correlation of AAs with obesity related parameters is shown in **Table 2**.

The relationship between AAs that may influence BMI changes was examined with a multivariate linear regression model. We did not observe any autocorrelation, and there was no multicollinearity problem. Alanine, glutamate, glycine, isoleucine, and valine levels were statistically significantly associated with BMI change. The results of multiple linear regression analysis relating AAs to BMI are shown in **Table 3**.

Twenty-eight percent of adolescents with obesity had IR. The mean age was 13.6±2.2 in the group with IR and 13.0±1.8 in individuals without IR. The asparagine and citrulline levels were lower in individuals with IR. Comparison of the variables between two obese groups is shown in **Table 4**.

Discussion

The relationships between obesity, IR, diabetes, cardiovascular diseases, and plasma AAs have been shown in various studies for adults[14-16]. There are relatively few studies evaluating AAs in adolescents with obesity.

BCAAs represent around 20% of the body's protein composition and comprise one-third of the essential AAs. Butte et al.[8] and Ye et al.[6], reported that BCAAs were significantly increased in children with obesity. Similar to previous studies, our research revealed that plasma BCAA levels were elevated in children and adolescents with obesity.

BCAAs have been shown to contribute to early diagnosis, and they can be used as a biomarker to show complications that may develop in obesity[7,17,18]. Although previous studies[19-22] have established a connection between BCAAs and IR, our findings did not show any difference in BCAA levels between obese adolescents with or without IR.

This can be explained by the small number of patients due to the fact that the HOMA-IR value is taken as (3.16). Bi et al.[15] reported that they did not observe any difference in BCAAs between patients with or without IR, as observed in our study.

Phenylalanine is an essential aromatic AA that has an effect on BH4 activation, tyrosine synthesis and neurological development[3]. Bi et al.[15] reported that the increase in phenylalanine, tyrosine, methionine, and alanine was strongly associated with hyperinsulinemia. Similarly, when comparing plasma alanine, tyrosine, methionine, and phenylalanine levels in our patients with obesity to healthy controls, these levels were found to be high, but there was no difference in these AAs between individuals with or without IR.

Glutamate is a non-essential AA that acts as a bridge between urea and TCA cycles. After the increase in plasma glutamate, genes related to the TCA cycle are downregulated, and gluconeogenesis is increased with increased levels of glucagon, and pyruvate is converted to alanine. Glucose levels increase as a result[3]. Glutamate levels weren't associated with IR in our study.

Glycine is a non-essential AA and is involved in the synthesis of glutathione, purine, serine, and porphyrins.

Table 1.
Comparison of the variables between obese and control group

Variable		Obese group (n=50)	Control group (n=42)	p
Gender (F/M)	n	(27/23)	(26/16)	**0.445**^{x2}
Age (years)	Mean ± SD	13.4±2.0	13.7±2.0	**0.515**^{t}
Weight (kg)	Mean ± SD	79.0±19.6	48.8±12.6	**0.000** ^{t}
BMI (kg/m^2)	Median (25-75p)	30.6 (27.7-33.7)	20.0 (17.7-22.2)	**0.000**^{m}
Insulin (mu/L)	Median (25-75p)	15.5 (9.2-25.2)	10.5 (8.1-12.5)	**0.000**^{m}
HOMA-IR	Median (25-75p)	3.3 (2.3-5.8)	2.5 (1.8-2.8)	**0.000**^{m}
BMI Z-score	Median (25-75p)	2.85 (2.4-3.2)	0.05 (0.3-0.9)	**0.000**^{m}
ALT (U/L)	Median (25-75p)	23.0 (18.0-31.5)	15.0 (12.0-18.2)	**0.000**^{m}
HDL (mg/dL)	Mean ± SD	43.8±8.1	47.3±3.5	**0.008**^{t}
Alanine	Median (25-75p)	437.5 (379.7-502.1)	379.1 (306.7-455.8)	**0.002**^{m}
Glutamate	Median (25-75p)	25.1 (15.8-120.1)	17.5 (12.5-65.2)	**0.009**^{m}
Glycine	Median (25-75p)	228.5 (205.2-259.4)	252.3 (230.6-306.0)	**0.007**^{m}
Methionine	Mean ± SD	32.1±8.3	28.8±7.1	**0.047**^{t}
Isoleucine	Mean ± SD	78.9±20,4	64.3±17.2	**0.000**^{t}
Leucine	Mean ± SD	154.5±33.7	122.1±26.9	**0.000**^{t}
Tyrosine	Mean ± SD	81.7±20.0	65.2±16.2	**0.000**^{t}
Valine	Mean ± SD	280.8±59.9	212.5±49.8	**0.000** ^{t}
ASA	Median (25-75p)	0.20 (0.05-0.5)	0.08 (0.01-0.3)	**0.013**^{m}
Lysine	Median (25-75p)	178.2 (155.8-200.3)	148.7 (132.1-175.4)	**0.000**^{m}
Phenylalanine	Median (25-75p)	73.5 (60.2-86.3)	63.9 (54.2-70.8)	**0.002**^{m}
Tryptophan	Mean ± SD	46.7±10.7	39.2±10.2	**0.001**^{t}
Histidine	Median (25-75p)	91.5 (82.8-102.4)	82.7 (77.4-93.7)	**0.018**^{m}

^{m}; Mann-Whitney U test/^{t}; Independent samples-2 test/^{x2}; Chi-square test
ASA; Argininosuccinic acid, SD; Standard deviation, BMI; Body mass index, ALT; Alanine aminotransferase, HOMA-IR; Homeostatic model assessment for insulin resistance, HDL; High-density lipoprotein, F; Female, M; Male

This indicates that the human body can synthesize the required glycine internally through *de novo* synthesis. Low plasma glycine levels have been associated with obesity, type 2 diabetes, and non-alcoholic fatty liver disease[23]. Guevara-Cruz et al.[24] showed that plasma alanine, asparagine, proline, and tyrosine increased while glycine levels decreased in patients with obesity. Okekunle et al.[25] showed that isoleucine, valine, glutamate and proline increased, and glycine decreased in patients with obesity and diabetes. Similar to previous studies, we observed a reduction in plasma glycine levels in adolescents with obesity compared to healthy controls.

Xu et al.[26] demonstrated that asparagine enhances mTORC1 signaling, thereby promoting glycolysis in adipose tissue. They showed that dietary supplementation with asparagine led to marked reductions in serum insulin and triglyceride levels, suggesting improved systemic regulation of glucose and lipid metabolism. Also, Tosur et al.[27] showed that pediatric type 2 diabetes patients had lower arginine, citrulline, glutamine, glycine, phenylalanine, methionine, threonine, and asparagine levels than those with type 1 diabetes. Bugajska et al.[28] reported that plasma levels of leucine, isoleucine, valine, phenylalanine, tyrosine, glutamic acid, and alanine were significantly higher and that the mean values of serine, asparagine, glutamine, and citrulline were significantly lower in overweight and obese children. Our findings showed that plasma asparagine and citrulline concentrations remained normal in obese adolescents, but they were reduced in those exhibiting insulin resistance. Reduced asparagine and citrulline levels may serve as early indicators of an increased risk for developing type 2 diabetes mellitus.

Hellmuth et al.[29] conducted a study involving 80 obese children who participated in a one-year lifestyle intervention program**.** The program led to a substantial weight loss, defined as a reduction of more than 0.5 BMI standard deviation scores in 40 of the children. Among the metabolites analyzed, only tyrosine showed a significant association with insulin resistance at baseline and after the intervention.

Table 2.
Correlation of amino acids with obesity-related parameters

		Weight	BMI	HOMA-IR	BMI Z-score
Alanine	ro p	0.268 0.01	0.267 0.01	0.274 0.008	0.243 0.02
Glutamate	ro p	-	0.214 0.041	-	0.255 0.014
Glycine	ro p	-0.208 0.047	-0.294 0.004	-0.230 0.028	-0.348 0.001
Methionine	ro p	0.223 0.032	-	0.222 0.034	-
Phenylalanine	ro p	0.241 0.021	0.219 0.036	-	-
Isoleucine	ro p	0.287 0.005	0.283 0.006	0.234 0.02	0.266 0.01
Leucine	ro p	0.289 0.005	0.312 0.002	0.207 0.048	0.330 0.001
Lysine	ro p	0.345 0.001	0.355 0.001	0.272 0.009	0.360 0.000
Proline	ro p	0.242 0.02	-	0.282 0.006	-
Serine	ro p	-	-0.257 0.013	-	-0.310 0.003
Tryptophan	ro p	0.266 0.01	0.261 0.012	0.239 0.022	0.254 0.015
Tyrosine	ro p	0.256 0.014	0.334 0.001	-	0.348 0.001
Valine	ro p	0.354 0.001	0.412 0.000	0.269 0.01	0.425 0.000

BMI; Body mass index, HOMA-IR; Homeostatic model assessment for insulin resistance

Table 3.
The results of multiple linear regression analysis of amino acids with BMI

	Unstandardized coefficients		Standardized coefficients		95% confidence interval for B		p value
	B	Standard error	β	t	Lower Limit	Upper Limit	
Constant	18.501	3.460		5.347	11.620	25.381	0.000
Alanine	0.019	0.009	0.292	2.124	0.001	0.037	**0.037**
Glutamate	0.025	0.012	0.186	2.023	0.000	0.049	**0.046**
Glycine	-0.039	0.010	-0.413	-3.742	-0.060	-0.018	**0.000**
Methionine	0.141	0.128	0.151	1.106	-0.113	0.395	0.272
Phenylalanine	-0.014	0.041	-0.041	-0.344	-0.096	0.068	0.732
Valine	0.064	0.021	0.555	3.040	0.022	0.105	**0.003**
Isoleucine	-0.148	0.063	-0.402	-2.345	-0.273	-0.022	**0.021**

BMI; Body mass index
The relationship between amino acids that may affect the change in BMI was examined with a multivariate linear regression model. The Durbin Watson value was determined as 1.857. We observed any autocorrelation. The condition index value 27.7 and the VIF value was 1.604. We observed that there was no multicollinearity problem. The regression model was statistically significant, R=0.601, R^2=0.361 Adjusted R^2=0.308, F=(7-84)=6.783 p<0.001. A p value below 0.05 was considered statistically significant.

Lee et al.[30] reported that children with BCAA concentrations above the median at baseline exhibited an approximately threefold higher risk of developing insulin resistance and metabolic syndrome during a two-year follow-up.

In conclusion, the metabolic pathways of various AAs are significantly impaired in obesity. Isoleucine, leucine, lysine, tryptophan, tyrosine, phenylalanine, alanine, methionine, argininosuccinic acid, histidine, and valine were significantly higher in patients with obesity than healthy controls in our study. The metabolism of people with obesity is affected by many factors. There is little information about the causes, and there is a need for more studies on metabolomics of obesity in adolescents.

Study Limitations

Our study does not include longitudinal data on plasma AAs. This restricts our ability to track the progression of metabolic changes related to obesity over time. Various studies have applied different cut-off values for HOMA-IR. Factors like age, gender, and pubertal stage play a role in determining insulin resistance. Plasma AA levels are also influenced by the nutritional habits of the individuals. However, our study does not include the nutritional habits of the participants.

Table 4.
Comparison of the variables between two obese groups

Variable		Insulin resistance	Without insulin resistance	p
Gender (F/M)	n	(16/12)	(11/11)	0.615^{x2}
Age (years)	Mean ± SD	13.6±2.2	13.0±1.8	0.293^{t}
Weight (kg)	Mean ± SD	84.3±21.6	72.3±14.6	**0.031**^{t}
BMI (kg/m^2)	Median (25-75p)	32.0 (28.2-35.2)	29.1 (27.5-31.4)	0.068^{m}
Insulin (mu/L)	Median (25-75p)	21.9 (17.6-33.4)	9.1 (6.9-12.4)	**0.000**^{m}
HOMA-IR	Median (25-75p)	5.2 (3.6-8.4)	2.0 (1.4-2.7)	**0.000**^{m}
BMI Z-score	Mean ± SD	3.0±0.8	2.7±0.4	0.068^{t}
ALT (U/L)	Median (25-75p)	25.0 (18.2-38.2)	21.5 (17.7-28.2)	0.538^{m}
HDL (mg/dL)	Mean ± SD	42.7±6.4	45.3±9.9	0.270^{t}
Alanine	Median (25-75p)	446.5 (417.2-574.7)	419.7 (366.2-481.8)	0.197^{m}
Methionine	Mean ± SD	32.7±8.6	31.4±8.2	0.588^{t}
Isoleucine	Mean ± SD	81.1±23.1	76.2±16.4	0.413^{t}
Leucine	Mean ± SD	158.0±37.0	150.0±29.2	0.413^{t}
Tyrosine	Mean ± SD	83.4±22.9	79.6±15.9	0.508^{t}
Valine	Mean ± SD	290.3±68.9	268.7±44.6	0.186^{t}
Asparagine	Mean ± SD	60.4±16.7	71.1±19.7	**0.045**^{t}
Lysine	Median (25-75p)	183.9 (159.0-204.2)	171.2 (154.9-199.2)	0.538^{m}
Phenylalanine	Median (25-75p)	75.6 (60.7-86.9)	71.4 (59.1-80.6)	0.379^{m}
Tryptophan	Median (25-75p)	49.5 (38.8-55.7)	44.7 (38.2-48.9)	0.171^{m}
Citrulline	Median (25-75p)	21.2 (17.5-26.5)	27.3 (22.2-39.8)	**0.043**^{m}

^{m}; Mann-Whitney U test/^{t}; Independent samples-2 test/^{x2}; Chi-square test
SD; Standard deviation, BMI; Body mass index, ALT; Alanine aminotransferase, HOMA-IR; Homeostatic model assessment for insulin resistance, HDL; High-density lipoprotein, F; Female, M; Male

Ethics

Ethics Committee Approval: Ethical approval was received from the Ethics Committee of Erciyes University Faculty of Medicine (approval no: 487/2017, date: 27.10.2017).

Informed Consent: Informed consent was obtained from the parents of all patients participating in the study.

Footnotes

Authorship Contributions: Soylu Üstkoyuncu P: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Doğan D: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Literature Search, Writing; Kardaş F: Concept, Design, Literature Search, Writing; Kendirci M: Concept, Design, Data Collection or Processing, Literature Search, Writing; Dündar MA: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation, Canpolat A: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation, Literature Search; Altuner Y: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Literature Search.

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Pancreaticopleural Fistula: A Rare Complication of Pancreatitis in Children - A Case Report

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Abstract

Pancreaticopleural fistula (PPF) is a rare complication of pancreatitis, which can present as massive pleural effusion. We herein report a six-year-old male, a follow-up case of acute pancreatitis, who later presented with bilateral pleural effusion due to PPF. Initially, tuberculosis was suspected as the cause of pleural effusion due to the patient's maternal history of contact with tuberculosis and chronic history and chronic history. However, further investigations revealed a diagnosis of PPF. Management and outcome: He was managed conservatively for a prolonged period, following which there was a complete resolution of pleural effusion. This pediatric case highlights a rare complication of acute pancreatitis and the role of early initiation of management in these patients, thereby resulting in good outcomes even in a resource-limited setting.

Keywords: Pancreaticopleural fistula, high pleural fluid amylase, octreotide

Introduction

Pancreaticopleural fistula (PPF) is a rare complication of pancreatitis in children. The actual pediatric incidence of PPF is not known. In children, available literature is limited to case reports and case series. In adults, as is reported in 0.4% of cases of pancreatitis and 4.5% of patients with pancreatic pseudocyst[1]. A PPF develops when a pancreatic collection, usually a pseudocyst, ruptures into the pleural space, most commonly through the aortic or esophageal hiatus in the diaphragm, causing pancreatic fluid to leak directly into the pleural cavity due to a disruption in the pancreatic duct, leading to pleural inflammation and fluid accumulation; this is typically a complication of pancreatitis, with the most common underlying cause being chronic pancreatitis.

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Many times, diagnosis is delayed due to its presentation exclusively with pulmonary symptoms[2]. We report a case of a six-year-old boy with PPF who showed complete resolution of the condition on prolonged medical management in our resource-limited settings.

Clinical Description

A six-year-old boy who was previously diagnosed as a case of acute pancreatitis with pseudocyst eight months ago and was asymptomatic during follow-up with a diminishing pseudocyst size for the last 2 months from last discharge. He presented with sudden-onset breathlessness, chest pain (right-sided), and cough for 5 days. Dyspnea was present at rest as well as when lying down. Chest pain was bilateral, dull, aching, and non-radiating. The cough was non-productive and intermittent. There was a history of continuous, diffuse, non-radiating, dull aching abdominal pain for the last three days. There was no associated history of fever, hemoptysis, vomiting, loose stools, abdominal distension, decreased urine output, rash, abnormal body movement, and cyanosis. His past medical and treatment history revealed that he was diagnosed with seizure disorder at age five and was on treatment with sodium valproate. He had a history of severe abdominal pain and vomiting eight months ago, for which he was diagnosed with acute pancreatitis secondary to sodium valproate based on high serum amylase, serum lipase, and ultrasound findings. After the onset of pancreatitis, he had three short admissions over the course of next three months for which he was managed conservatively with analgesics, dietary management, proton pump inhibitors and antibiotics. During that time on ultrasound examination, pseudocyst formation was noted after 1 month of onset of acute pancreatitis. The serial sizes of pseudocyst on follow-up ultrasounds done at 4 weeks, 8 weeks and 16 weeks post-illness were as follows: 5×4×5 cm; two ppc of size 4.9×4.6×6 cm & 3.1×3.1×2.7 cm and 3.1×5.3×3 cm respectively. He was on conservative pain and dietary management along with vitamins and calcium supplements. There was a history of tuberculosis contact in the mother 2 years ago. The social, birth and developmental history were non-contributory. He consumed a mixed diet, which was deficient in both calories and proteins. On examination, there was tachypnea, tachycardia, and respiratory distress characterized by subcostal retractions and nasal flaring. The child was hemodynamically stable. His height and weight were less than the 3rd centile and body mass index was 11.2 kg/m^2. He appeared pale, but there was no icterus, clubbing, edema, lymphadenopathy, or rash. The trachea was deviated to the left with reduced chest movements on the right side. Stony dull percussion was present in bilateral subscapular, right infra-axillary, and axillary regions. Air entry was reduced in the lower part of the chest bilaterally with no added sound. Abdomen examination showed mild distension without any guarding, rigidity, organomegaly, fluid thrill and shifting dullness. Bowel sounds were normal. The rest of the systemic examination was unremarkable. A clinical diagnosis of bilateral pleural effusion was made. Since the child was afebrile and was a follow-up case of acute pancreatitis with pseudocyst, and also had a history of tuberculosis in the mother, clinically an etiological diagnosis of pleural effusion secondary to acute pancreatitis, tuberculosis or malignancy was made.

Management and Outcome

His initial investigations were as follows. Complete blood counts: Hemoglobin - 9.2 gm%. Total leukocyte count - 13,400/mm^3, differential leukocyte count - P62%/L32%, and platelet count - 2.7×10^5/mm^3. The Kidney Function test, Lipid profile, vitamin D, calcium, and phosphate levels were normal. The liver function tests showed the following: total bilirubin - 0.9 mg/dL; serum glutamic-oxaloacetic transaminase - 57 IU; serum glutamic pyruvic transaminase - 48 IU; alkaline phosphate - 208 IU. Serum amylase was 1032 IU/L and lipase was 730 IU/L. Chest X-ray showed massive bilateral pleural effusion (**Figure 1A**). Ultrasonography showed a bulky pancreas with an obscured tail, a peripancreatic fluid collection measuring 5×4×5 cm, bilateral B/L pleural effusion (with separations of 5 cm on the right side and 3 cm on the left side) and mild ascites. Diagnostic or therapeutic paracentesis was performed. Pleural fluid analysis showed cytology 10-12 RBCs/HPF, with no atypical cells, and 250 WBCs/mm^3 with 85% lymphocytes. Pleural fluid biochemistry showed a sugar level of 50 mg/dL, proteins at 5.2 g/dL, and albumin at 2 g/dL. The pleural fluid amylase level was high (32,962 U/L). A provisional diagnosis of PPF with bilateral pleural effusion and an underlying acute pancreatitis with pseudocyst was made. He was kept nil per os and was started on proton pump inhibitors, antibiotics, and octreotide infusion. Due to the non-availability of endoscopic retrograde cholangiopancreatography (ERCP) or surgical intervention for a small child, he was managed with conservative therapy over the course of three months only. During this period, a chest tube was inserted on the right side. Calories and proteins were optimised for his age, to avoid delayed improvement. There was subsequent improvement, marked by a reduction in drain output, prompting the removal of the chest tube after 10 days (**Figure 1B**). Octreotide infusion was continued as part of the treatment plan. Although efforts were made to introduce NG feeds, the patient struggled to tolerate them, necessitating the initiation of total parenteral nutrition (TPN). After three weeks of sustained improvement in pleural effusion and symptoms, the octreotide infusion was gradually tapered off and eventually stopped. Magnetic resonance cholangiopancreatography (MRCP) done during this time revealed walled-off necrosis in a peripancreatic region of size 5.9×6.7×6.3 cm near the tail of the pancreas, with extensions into the lesser sac anteromedially and cranially, and posteriorly to the right retrocrural region, and a fistulous tract (18 mm) originating from the pseudocyst and extending to the right hemithorax (**Figure 2**). A diagnosis of PPF was confirmed.

However, symptoms of respiratory distress along with pleural effusion reappeared within one week of the discontinuation of octreotide, prompting the reintroduction of octreotide infusion and chest tube drainage. This regimen was continued for another three weeks before being tapered off and discontinued. Following this, he was watched for the presence of any adverse reactions.

The patient had not experienced abdominal pain, vomiting or respiratory distress for about next five days. A chest X-ray done before discharge showed complete resolution of effusion (**Figure 1C**). On subsequent follow-up at 1 week, 1 month, 2 months, visits, the child was gaining weight and had no further symptoms. Pancreatic pseudocyst size on follow-up on abdominal ultrasound had also decreased to 3x3x2.5 cm. The patient's prolonged illness, presence of an indwelling ICD, and pancreatic pseudocyst led to early satiety, restricting oral intake. Consequently, the patient remained on a liquid diet for an extended period, resulting in nutritional deficiencies. However, as the pancreatic pseudocyst gradually decreased in size and nutritional deficiencies were corrected, the child began to gain weight.

Discussion

PPF is a unique complication of pancreatitis occasionally reported in adults and rarely in pediatric patients. On review of literature, only 33 cases of PPF have been reported amongst pediatric patients, whereas more than 300 cases of PPF have been reported amongst adults[1]. PPF is significantly rarer in children compared to adults, with the primary difference being that in adults, PPF is most commonly associated with chronic alcoholic pancreatitis, while in children, the cause is often unclear and may be related to genetic mutations causing chronic pancreatitis or trauma, making the diagnosis and management in children more complex; additionally, children may present with less typical symptoms due to their age and developmental stage. While adults may present with classic symptoms of chronic pancreatitis like abdominal pain, along with respiratory symptoms such as chest pain and shortness of breath due to pleural effusion, children may have less prominent abdominal pain. They may present primarily with respiratory symptoms like cough or difficulty breathing, which can lead to delayed diagnosis. When disruption of the pancreatic duct occurs posteriorly, amylase-rich pancreatic secretion can enter the retroperitoneal space, entering through various diaphragmatic orifices into the mediastinum, and further rupture into the pleural space to form PPF[1-3]. PPF usually presents as rapidly accumulating massive pleural effusion and is resistant to therapeutic thoracentesis. It needs to be distinguished from the self-limiting pleural effusion which is seen in 3% to 17% of cases of acute pancreatitis, that is unilateral, of mild to moderate volume and often resolves on its own during conservative management[4]. The major clinical symptoms of PPF are dyspnoea (52%), cough (24%), and chest pain (20%). Pulmonary symptoms create a diagnostic challenge and delay timely diagnosis. Other symptoms include abdominal pain (20%), vomiting (8%), and anorexia (8%). The most characteristic feature of PPF is a high pleural amylase level which can also be observed in tuberculosis, oesophageal perforation, lymphoma, liver cirrhosis or malignancy. The amylase level of PPF is grossly elevated, as seen in previously reported case series, ranging from 1200 U/L to 156,200 U/L[5].

For diagnosing PPF, imaging is essential. Due to bowel gas artifacts and inadequate respiratory cooperation, transabdominal ultrasound has limited effectiveness for diagnosing PPF[6]. Abdominal computed tomography is a commonly used imaging method in evaluating pancreatic parenchymal atrophy, pseudocyst, calcification, and ductal dilatation. But its sensitivity in diagnosing PPF is low ranging from 33% to 47%. MRCP has been recommended as the first-choice imaging modality for diagnosing PPF as it can visualize pancreatic duct anatomy (stricture or obstruction) in 80% of cases. ERCP can help in identifying precise pancreatic ductal anatomy and any duct disruption, but the major limitation is its low diagnostic sensitivity (38.5%)[7,8].

There is no well-established treatment for PPF in the pediatric population and management is limited to previously reported cases in pediatrics and adults. Initial management includes conservative therapy with medications received for 10 to 60 days (average 2 to 3 weeks), followed by endoscopic procedures or surgery for those failing conservative management. Medical therapy including, octreotide which is the mainstay acts by reducing large-volume pancreatic secretion, therefore, helping in the closure of disrupted pancreatic duct is seen in 31% to 65% of PPF patients combined with TPN also recognised in the index case after 3 weeks. The children usually

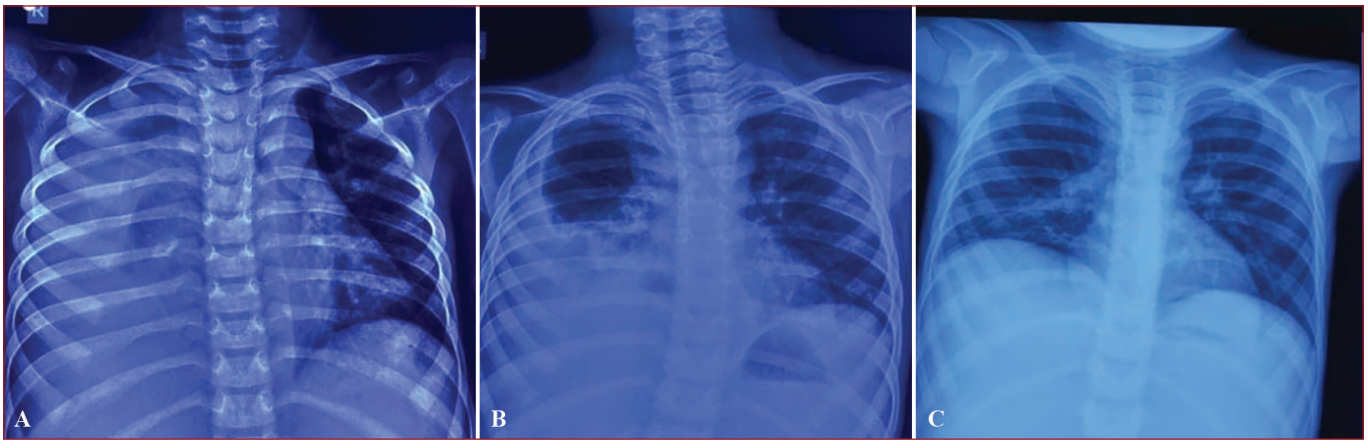

Figure 1. (A) Chest X-ray at the time of admission showing a large volume right sided pleural effusion presenting clinically as dyspnoea, **(B)** reducing pleural effusion during treatment in hospital, **(C)** significant improvement noticed before discharge

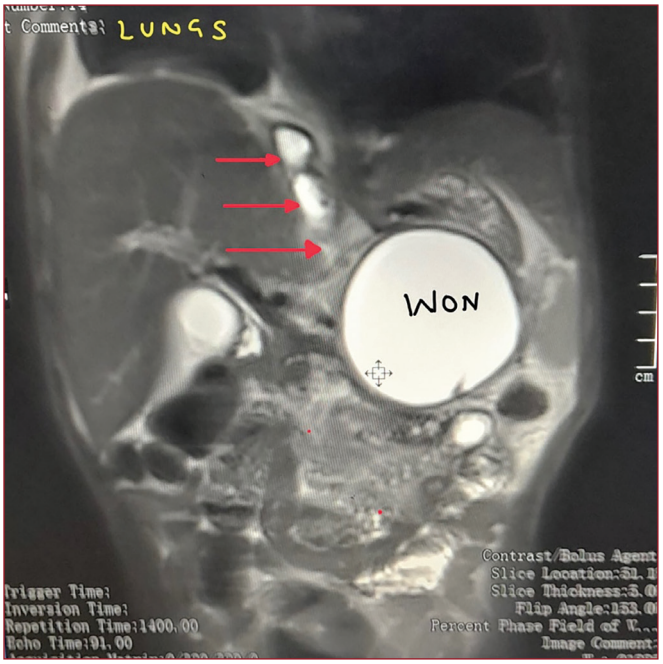

Figure 2. MRCP showing a well-defined thick-walled collection (WON) noted in region of tail of pancreas. The collection is extending into lesser sac anteromedially, cranially and posteriorly to right retrocrural region. A communication tract (PPF) seen crossing the crura and opening in right pleural cavity as shown with red arrow head

MRCP: Magnetic resonance cholangiopancreatographic

respond to standard octreotide therapy in 3 weeks in the presence of a closed thoracic drainage tube[9,10]. During conservative therapy, the child may develop malnutrition, septicemia, and other complications that need to be dealt with utmost priority[11]. Children who fail conservative management may further require endoscopic or surgical management with varying success rates. Endoscopy therapy includes placement of an ERCP stent, an evolving non-surgical method of management of PPF with an excellent success rate of 100% and 96.4% as reported by Khan et al.[12] and Pai et al.[13] respectively. ERCP is a less invasive procedure with shorter postoperative recovery time and with fewer complications (infections, bleeding, damage to the pancreatic duct, repeated accumulation of fluid and pancreatitis) is gradually developing as a procedure of choice which was comparable to surgical success rate of 94% reported by King et al.[8] with the only limitation of the requirement of substantial technical experience. In our case, PPF was managed in our resource-limited setting. This case highlights the role of clinical examination leading to early initiation of conservative management, resulting in good outcomes. This case presented with bilateral pleural effusion, with a significantly high level of amylase in the pleural fluid. Diagnosis of PPF was confirmed by MRCP. Due to the non-availability of surgical and endoscopic intervention, he was managed conservatively with octreotide infusion, and had a prolonged course lasting nearly six weeks. During the past six months of follow-up after discharge, the child has been in good health and is symptom-free with normalized serum amylase levels.

Conclusion

This case highlights the rare complication of acute pancreatitis and the role of examination, imaging and early initiation of conservative management in a case of PPF resulting in positive outcomes in a resource-limited setting. Illustrates the fact that when a patient has massive pleural effusion. Early diagnosis of these rare lesions is important to avoid a preventable fatal outcome.

Ethics

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

Footnotes

Author Contributions: Mishra NM: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Data Collection or Processing, Literature Search, Writing; Kumar S: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Data Collection or Processing, Literature Search, Writing; Dewan V: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Literature Search, Writing; Mishra VK: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Literature Search, Writing; Mohan N: Surgical and Medical Practices, Analysis or Interpretation, Data Collection or Processing, Literature Search, Writing; Lamba A: Surgical and Medical Practices, Data Collection or Processing, Literature Search.

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Letter to the Editor

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The Radiological Findings in an Infant Suffering from Osteopetrosis Due to a Novel Variant in the *CLCN7* Gene

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Dear Editor,

Osteopetrosis, also known as marble bone disease, is a rare inherited skeletal disorder primarily defined by abnormally increased bone density. Its estimated incidence ranges between 1 in 100,000 and 1 in 500,000 live births.1 Based on the mode of inheritance, the condition is classified into three major types: the benign autosomal dominant osteopetrosis (ADO), the severe autosomal recessive osteopetrosis (ARO), and a less common X-linked variant. ADO is observed in approximately 1 in 20,000 births, while ARO appears in about 1 in 250,000. The autosomal dominant form is typically diagnosed in adulthood and often presents with mild or no symptoms, whereas the recessive infantile form can be life-threatening if not treated promptly[1]. Radiologically, the disease is marked by generalized or localized bone sclerosis, increased bone mass, and a tendency for pathological fractures. Osteopetrosis encompasses a spectrum of clinically and genetically heterogeneous conditions, all linked by a common pathophysiology: impaired bone resorption due to defective osteoclast development or function.

According to the Nosology Group of the International Society of Skeletal Dysplasia, disorders characterized by increased bone density are categorized based on clinical presentation, patterns of inheritance, and their molecular and pathogenic underpinnings[2]. In most cases, the management of osteopetrosis remains supportive, addressing symptoms rather than the root cause. Hematopoietic stem cell transplantation may be considered in selected severe cases, particularly in ARO. However, due to the disease's variable and often non-specific clinical manifestations, misdiagnosis is not uncommon. As a result,

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comprehensive genetic testing and molecular analysis play a crucial role in establishing an accurate diagnosis and may also pave the way for emerging therapeutic approaches, including gene-based interventions[3].

Osteopetrosis results from a disruption in osteoclast differentiation or function, with pathogenic variants in at least 10 genes identified as the underlying cause. These variants account for approximately 80% of cases.1 Genetic variants in the *TCIRG1* and *CLCN7* genes are identified in nearly 70% of ARO individuals. Among these, *CLCN7* variants account for approximately 75% of ADO cases, 10-15% of ARO cases, and are implicated in all currently recognized cases of the intermediate form of the disease. Pathogenic alterations in *CLCN7* impair the osteoclasts' ability to acidify their extracellular environment, thereby hindering effective resorption of the inorganic bone matrix. This functional disruption contributes to the diverse clinical manifestations observed in affected patients[4].

The *CLCN7* gene, part of the CLC gene family in mammals, encodes a chloride channel protein that plays a crucial role in osteoclast function. In osteoclasts, the CLCN7 protein is localized to the membranes involved in the late stages of the endosomal-lysosomal pathway, specifically at the fringe margin, where it contributes to the acidification of resorption lacunae.4 Previous studies elucidated the physiological role of the CLCN7 protein, demonstrating that pathogenic variants in this gene cause severe osteopetrosis in animal models. Accordingly, this protein is regarded as key in the process of acidifying resorption lacunae within the extracellular matrix. The function of these lacunae is to facilitate the process of osteoclast-mediated bone resorption, which is integral to the regulation of bone mass. In summary, the *CLCN7* gene assumes a pivotal role in bone remodeling, and its pathogenic variants are likely to result in fragile, excessively dense bones. In osteopetrosis, increased bone density paradoxically makes fractures more likely, commonly affecting the proximal sections of the femur and tibia[4].

This study reveals an unobserved variant within the *CLCN7* gene in a patient with osteopetrosis and presents evidence for its plausible pathogenicity. A 14-day-old male infant was admitted to our hospital due to respiratory distress and low platelet count. The patient was born at 37 weeks of gestation, weighing 2,780 grams, through a normal spontaneous vaginal delivery during the first pregnancy. Upon examination, it was noted that the patient's lower extremity was immobilized in a plaster cast due to a fracture. Family history revealed consanguinity between the parents. On admission, the patient's general condition was moderately compromised, and a cast was noted on the lower extremity. Physical examination also revealed hepatomegaly and splenomegaly, with both organs palpable 5 cm below the costal margin. Laboratory results showed the following: leukocytes 10,610/mm³, hemoglobin 14.1 g/dL, platelets 45,000/mm³, alanine aminotransferase (SGPT) 40 U/L, aspartate aminotransferase (SGOT) 162 U/L, total bilirubin 1.08 mg/dL, inorganic phosphorus 1.50 mg/dL, direct bilirubin 0.46 mg/dL, glucose 88 mg/dL, albumin 4.3 g/dL, calcium 9.9 mg/dL, sodium 138 mEq/L, uric acid 3.4 mg/dL, urea 11 mg/dL, and alkaline phosphatase 987 U/L. Calcium levels were within normal limits, while phosphorus levels were low. Both alkaline phosphatase and parathyroid hormone levels were elevated. Vitamin D levels were low, and radiographs confirmed the diagnosis of osteopetrosis and rickets. Vitamin D supplementation was initiated, and subsequent radiologic imaging revealed enlargement of the distal metaphyses of the ulna and radius on hand and wrist radiographs (**Figure 1A**).

Coronal temporal computed tomography (CT) showed decreased aeration in the mastoid portions of the bilateral temporal bones and sclerosis in the bony structures of the inner ear (**Figure 1B**). The axial CT section showed sclerosis and cortical thickening in the bilateral orbital bones, the sphenoid bone, and the bones forming the maxillary sinus (**Figure 1C**). Within 15 days, the homozygous NM_001287.6: c.957G>A p.Trp319Ter variant was discovered in the *CLCN7* gene

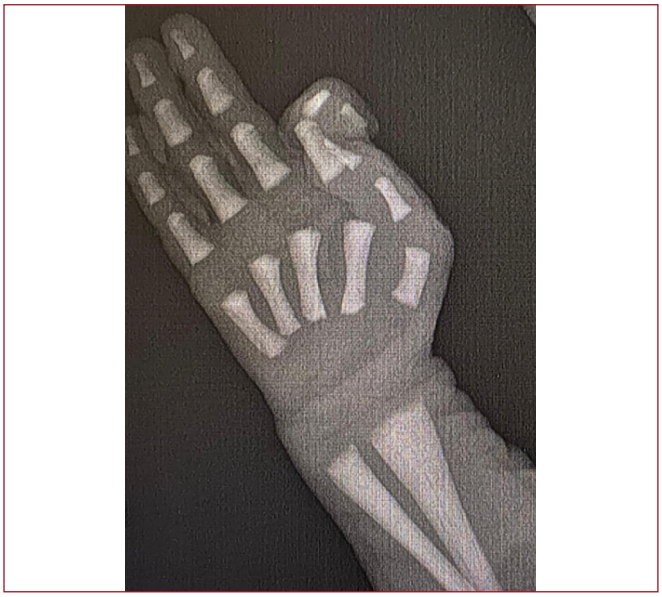

Figure 1A. Widened distal ulna and radius on X-ray due to vitamin D deficiency

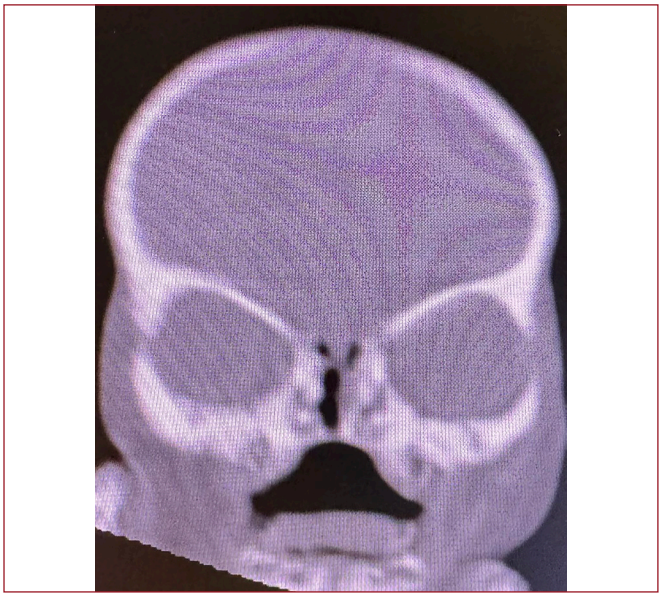

Figure 1B. Coronal CT shows bilateral mastoid hypoaeration and inner ear bony sclerosis

CT: Computed tomography

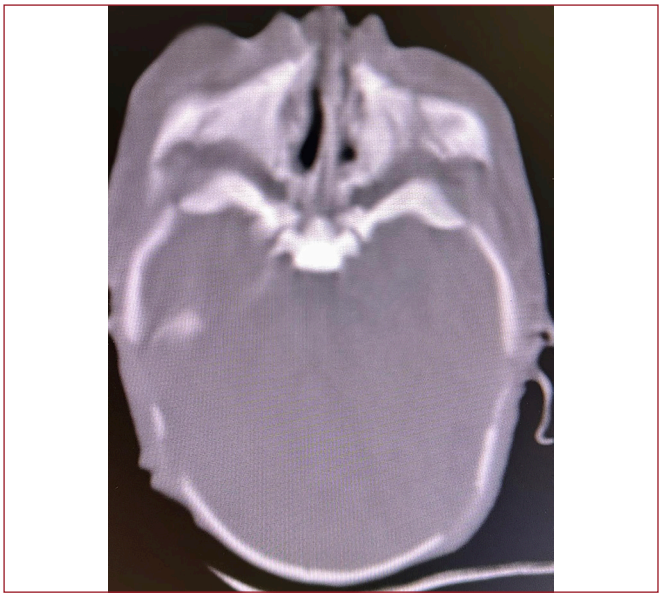

Figure 1C. Axial CT demonstrates cortical thickening and sclerosis of the orbital walls, sphenoid, and maxillary sinus bones
CT: Computed tomography

by rapid whole-exome sequencing. This nonsense variant, previously unreported in both the literature and healthy population databases (gnomAD aggregated allele frequency: not available), was classified as likely pathogenic according to American College of Medical Genetics and Genomics (ACMG) criteria because it is a rare (PM2) truncating variant expected to result in nonsense-mediated decay of the mRNA produced by the *CLCN7* gene (PVS1)[5]. The results were confirmed by targeted variant analysis based on next-generation sequencing, and the variant was found to be heterozygous in both parents. The patient and his family were informed, and an urgent bone marrow transplant was scheduled.

CLCN7-related osteopetrosis is inherited in an autosomal recessive or autosomal dominant manner[6]. As previously mentioned, ARO-as seen in our patient-has an early onset and a malignant course. Additionally, *CLCN7*-related ARO is typically caused by biallelic loss-of-function variants in the gene. Although the identified homozygous nonsense variant has not been previously reported in the literature, its molecular mechanism and consistency with the clinical phenotype support a clear interpretation of its association with ARO.

In this research, we discovered a previously unreported variant in the *CLCN7* gene in a patient with osteopetrosis, suggesting its potential impact. Although various indirect lines of evidence point to the deleterious nature of the newly identified *CLCN7* variant, it has been classified as "likely pathogenic" according to the ACMG guidelines[5]. In conclusion, we have identified a novel likely pathogenic variant in the *CLCN7* gene, explaining its association with ARO through detailed clinical findings.

Footnotes

Author Contributions: Çapkan DÜ: Radiological Practices, Concept, Design, Data Collection or Processing, Literature Search, Analysis or Interpretation, Writing; Demir B: Medical Practices, Concept; Baş H: Genetic Practices, Concept, Literature Search, Writing; Tatlı M: Medical Practices, Concept; Doğan M: Medical Practices, Concept; Ünal E: Medical Practices, Concept, Design, Data Collection or Processing, Literature Search, Analysis or Interpretation, Writing.

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