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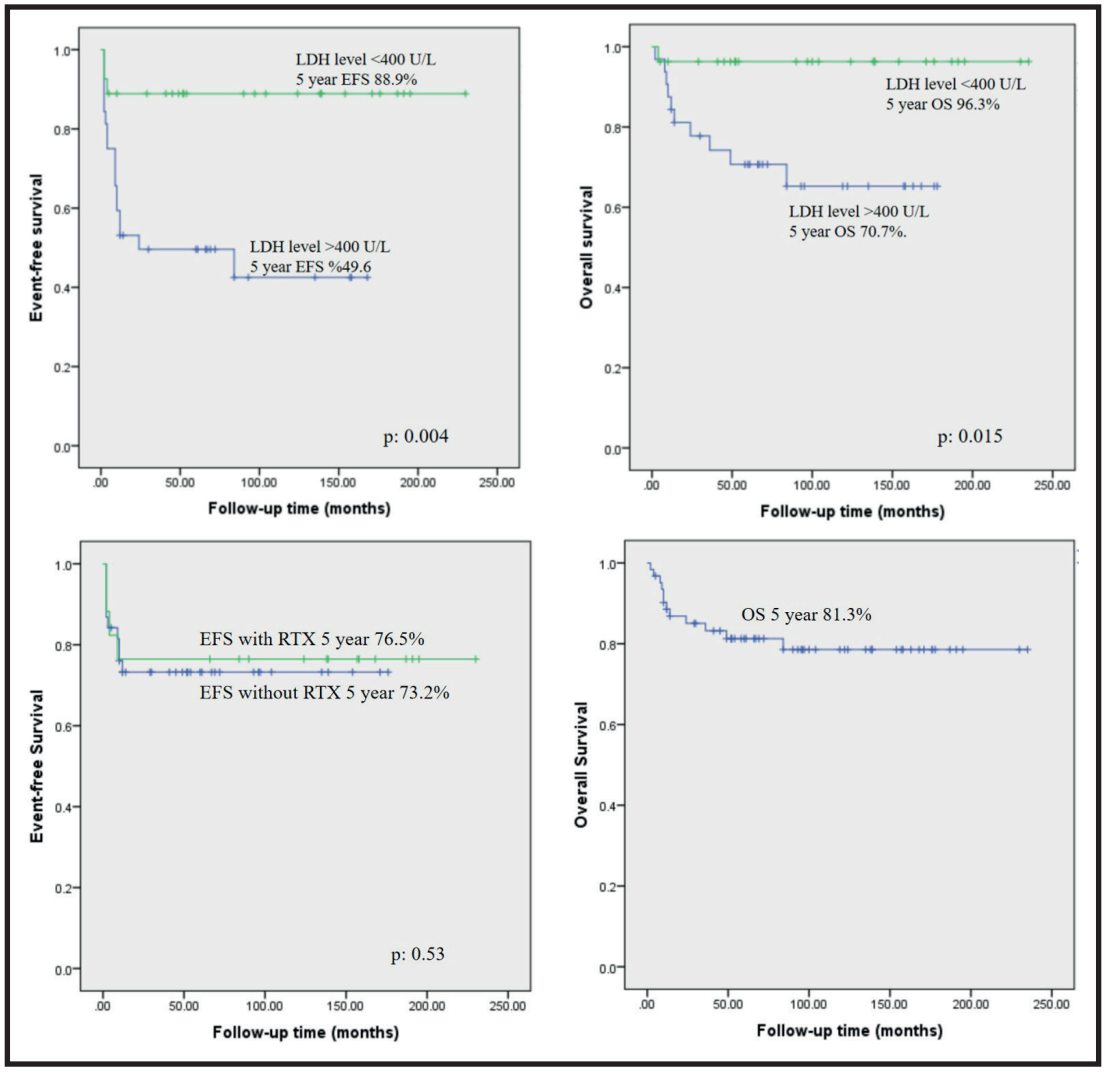

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Review

Autoinflammatory bone diseases: Genetic mutations, clinical manifestations, and modern therapeutic approaches

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ABSTRACT

Autoinflammatory bone diseases result from dysregulation of innate immune responses, leading to systemic inflammation and sterile inflammatory bone lesions. These disorders primarily affect children and adolescents but can persist into adulthood or present later. Chronic nonbacterial osteomyelitis (CNO) and its severe form, chronic recurrent multifocal osteomyelitis (CRMO), are the main phenotypes associated with these conditions. CNO serves as an umbrella term encompassing various presentations characterized by the insidious onset of local bone pain, typically exacerbated at night, with or without fever. Affected lesions commonly involve the metaphyseal regions of long bones, clavicle, spine, and pelvis, although any bone segment can be implicated. The etiology of CNO remains unclear, although familial predisposition exists, and a notable association with other inflammatory conditions, such as psoriasis, inflammatory bowel disease, and spondyloarthropathies, has been observed among sporadic CNO patients and their first-degree relatives, suggesting a genetic basis. Monogenic disorders, including deficiency of interleukin-1 receptor antagonist (DIRA) and PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum, and Acne), manifest prominent CNO symptoms. Syndromic forms, such as Majeed syndrome and Cherubism, also exemplify this association. CNO is diagnosed through exclusion, with whole-body magnetic resonance imaging (WB-MRI) regarded as the gold standard. MRI findings typically reveal bone cortical thickening, lytic lesions with sclerosis, and bone edema, while differential diagnoses must consider infections and malignancies. First-line treatment typically consists of nonsteroidal anti-inflammatory drugs (NSAIDs), while bisphosphonates and tumor necrosis factor-alpha (TNF-α) inhibitors may serve as effective second-line options. Although CNO is often benign, inadequate or delayed treatment can lead to severe complications, including valgus deformity, vertebral collapse, and limb length asymmetry.

Keywords: autoinflammatory diseases, bone diseases, osteomyelitis, chronic disease

INTRODUCTION

The term “autoinflammatory disease” refers to a group of disorders characterized by recurrent inflammatory episodes that occur without elevated levels of autoantibodies or autoreactive lymphocytes.[1] Autoinflammatory bone diseases primarily affect children and include a subgroup with sterile bone inflammation as the main phenotypic feature.[2] It was first described in 1972 by Giedion et al. in four pediatric patients with subacute and chronic symmetric bone lesions.[3] However, it has been noted that the disease does not consistently manifest symmetrically and may display a recurrent nature over time. In 1980, Probst, Bjorksten, and Gustavson proposed the definition of *CRMO*.[4,5]

CNO/CRMO can be associated with other inflammatory conditions such as palmoplantar pustulosis (PPP), psoriasis vulgaris, severe acne, and Sweet syndrome.[6-9] It has also been reported that CNO/CRMO is linked to inflammatory

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bowel disease (IBD) and spondyloarthropathies.[10-13] CNO/CRMO is considered part of the spondyloarthropathy disorder family.[11]

The most common form of autoinflammatory bone disease is sporadic CNO, while bone involvement in many monogenic diseases can appear as sterile osteomyelitis. Three genetic diseases are prominently linked to CNO: DIRA, PAPA, and Majeed syndrome (LPIN2 mutations).[14-16] Several genes that can cause sterile osteomyelitis in human and animal models have been identified, including LPIN2, IL1RN, Pstpip2 (in mice), and FBLIM1.[17-20] Additionally, Cherubism is considered a syndromic form of CNO.[21,22]

The exact cause of sporadic CNO is not yet known, but the activation of NLRP3 inflammasome and increased proinflammatory cytokines in genetic forms of the disease classify it as an autoinflammatory syndrome.[23] The frequent occurrence of inflammatory diseases among first-degree relatives, as well as the occurrence of inflammatory diseases like IBD in accompanying first-degree relatives, suggests that sporadic CNO/CRMO may have a genetic component.[24,25]

Nomenclature and classification of the disease

Autoinflammatory bone diseases have historically been referred to by various names. However, the term CNO has become the preferred, more inclusive designation, reflecting the disease's variable presentation, which is not always symmetric or multifocal. CRMO is considered a more severe and recurring form of CNO, characterized by multifocal and serious lesions.

The classification of autoinflammatory bone diseases also includes specific conditions with known genetic mutations, such as Majeed syndrome, DIRA, and PAPA syndrome. These genetically linked conditions help further elucidate the disease mechanisms in CNO/CRMO and provide insights into its pathophysiology (Table 1).[26-40]

Epidemiology

CNO/CRMO are rare diseases. The exact frequency of the disease is not known, but in Germany, it affects 2 to 80 out of 100,000 people.[24,41] It has been reported to be more common in Europe and Scandinavian countries.[41] CNO/CRMO is an autoinflammatory disease, primarily in childhood. It is most commonly seen between the ages of 7 and 12.[41,42] Girls are affected 2 to 4 times more than boys.[41-43] While it is mainly observed during childhood, the condition can manifest as SAPHO syndrome in adulthood, especially when skin involvement is present.[40] It is rare to see it in children under 2 years old. In such cases, the condition may have a genetic cause, including DIRA, PAPA, Majeed syndrome, or part of a syndromic CNO, and should be investigated from this perspective.

Table 1. Genetic and Clinical Spectrum of Autoinflammatory Bone Diseases

Disease/Disorder	Genetic Cause	Clinical Features
Chronic Nonbacterial Osteomyelitis (CNO)	Unknown genetic etiology in sporadic cases, potential genetic predisposition in some	Sterile bone inflammation and chronic bone pain can be associated with skin conditions and IBD
Chronic Recurrent Multifocal Osteomyelitis (CRMO)	Similar to CNO, may be more severe and recurrent	Multifocal, recurring sterile bone lesions, systemic inflammation
Majeed Syndrome	LPIN2 mutation	CRMO, congenital dyserythropoietic anemia, neutrophilic dermatosis
Deficiency of Interleukin-1 Receptor Antagonist (DIRA)	IL1RN mutation	Pustulosis, osteitis, periostitis, systemic inflammation, potentially life-threatening
Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne (PAPA)	PSTPIP1 mutation	Sterile arthritis, cystic acne, pyoderma gangrenosum
Cherubism	SH3BP2 mutation	Mandibular and maxillary bone lesions, jaw enlargement, tooth misalignment
SAPHO Syndrome	Unknown	Synovitis, acne, pustulosis, hyperostosis, osteitis, more common in adults

CNO: chronic nonbacterial osteomyelitis; CRMO: chronic recurrent multifocal osteomyelitis; IBD: inflammatory bowel disease; IL1RN: gene encoding interleukin-1 receptor antagonist, related to DIRA; LPIN2: gene associated with Majeed syndrome; PSTPIP1: gene encoding proline-serine-threonine phosphatase interacting protein 1, related to PAPA syndrome; SAPHO: synovitis, acne, pustulosis, hyperostosis, osteitis; SH3BP2: gene encoding SH3-domain binding protein 2, related to cherubism

Etiology and Pathogenesis

The irregular expression of pro and anti-inflammatory cytokines plays a central role in the pathophysiology of CNO/CRMO. There is evidence linking the development of the Interleukin-10 (IL-10) pathway with CNO. Hofmann et al. have reported that peripheral blood monocytes stimulated with the Toll-like receptor 4 (TLR-4) agonist lipopolysaccharides (LPS) secrete significantly less in IL-10 than healthy control monocytes.[44,45] In patients with CNO/CRMO, levels of regulatory IL-10 and interleukin 19 (IL-19) are decreased in peripheral blood monocytes, while levels of proinflammatory cytokines interleukin 1 beta (IL-1B), interleukin 6 (IL-6), TNF-α , interleukin 8 (IL-8), and macrophage inflammatory protein (MIP) have been found to increase.[44,45] Therefore, one scenario in the pathogenesis of the disease involves increased NOD-like receptor protein 3 (NLRP3) activation due to decreased regulatory cytokines, with their mRNA products initiating the inflammatory process.[46] This cytokine dysregulation leads to an imbalanced resorption environment in the bone through the receptor activator of nuclear factor-kappa B (NF-kB) (RANKL) and soluble RANKL receptors responsible for osteoclast activation and differentiation.[47]

The triggering factors for this condition can be an infection or trauma in genetically predisposed individuals. In a study conducted by Bjorksten et al., 25% of patients with CNO/CRMO experienced trauma before the onset of the disease.[5]

CNO/CRMO is characterized as an autoinflammatory bone disease. Patients' bone cultures show no growth, indicating sterility in the affected areas. Antibiotics are ineffective during disease activation, but anti-inflammatory treatments have shown benefits.[48] In a small group of cases, it was demonstrated that azithromycin improved the radiological and clinical signs and symptoms of CNO.[49] This improvement may be due to the anti-inflammatory properties of azithromycin rather than to antimicrobial properties. Adults with SAPHO syndrome and children with CNO/CRMO often have lesions in their skin and bones that test negative on polymerase chain reaction (PCR) and culture tests.[43,49] In one series of adult patients with SAPHO, *Propionibacterium acnes* were cultured from the bone of 7 out of 15 patients tested.[50] In addition, some studies have isolated *Propionibacterium acnes*, *Mycoplasma*, and *Staphylococcus* in bone lesions, but a clear distinction between contamination and true infection could not be made.[51-53]

In recent years, there has been increasing support for the idea that CNO might be a genetic disease within the range of autoinflammatory disorders. Furthermore, in the largest groups of CNO patients, the prevalence of the disease among patients' relatives was higher. Some reports have also described families with multiple affected members or have reported a high incidence of psoriasis, IBD, and other chronic inflammatory conditions in first-degree family members of individuals with CNO, suggesting that there is a significant genetic component to disease susceptibility.[54]

Previous discoveries have identified several single gene defects (LPIN2, Pstpip2, and IL1RN) that cause interleukin 1 (IL-1) mediated sterile multifocal osteomyelitis.[55-57] Lorden et al. demonstrated that LIPIN2 deficiency activates the NLRP3 inflammasome through altered P2X7 receptor function, supporting the classification of Majeed syndrome as an NLRP3 inflammasomopathy.[58] Recent gene discoveries have identified FBLIM1 as a susceptibility gene for CRMO, with mutations detected in a consanguineous family exhibiting the condition.[59] FBLIM1 is one of the most significantly differentially expressed genes in the bones of CRMO mice, playing a crucial role in IL-10-mediated anti-inflammatory responses and bone remodeling physiology.[45] Moreover, chronic osteomyelitis is a common characteristic of two monogenic diseases caused by mutations in genes related to the activation of the NLRP3 inflammasome or in the homeostasis of IL-1.[54] These diseases are known as PAPA and DIRA, respectively.[14,15] There may be a genetic association locus at chromosome 18q21.3–18q22 and CRMO.[60] This genetic association has not yet been linked to the pathophysiological development of CNO. Beginning in 2010, several case reports suggested a connection between CNO and familial Mediterranean fever (FMF)/MEFV gene mutations and the potential use of colchicine as a treatment option for CNO.[61]

Many animal models with autoinflammatory bone lesions result in genetic defects. Two mouse models have been developed: *CRMO mice* and *Lupo mice*. Both of these mouse models have mutations in pstpip2 and exhibit similar clinical features seen in humans. CRMO mice typically develop a severe clinical presentation.[62,63] Mouse pstpip2 shares similarities with human PSTPIP1 and PSTPIP2. PSTPIP1 modulates the NLRP3 inflammasome through its interaction with pyrin and is associated with genetic defects in the autosomal dominant autoinflammatory syndrome known as PAPA.[64,65]

Clinical manifestations of CNO/CRMO

The disease typically begins insidiously, with the main clinical symptom being localized bone pain.[41] This pain

can be sporadic or constant, often worsening at night and causing the person to wake up. Bone lesions typically cluster around the metaphysis, may present in atypical sites for bacterial osteomyelitis, such as the clavicle, and often show a symmetrical distribution when multiple.[11] Seventy-five percent of bone lesions occur in the perimetaphyseal region. All bones can be affected, but the metaphyseal regions of long bones are the most commonly affected. The long bones of the lower extremity are affected three times more frequently than the long bones of the upper extremity. The most frequent sites for CNO lesions include the femur, tibia, pelvis, calcaneus, ankle, vertebrae, and clavicle.[66-68] CNO is the most common cause of disease that affects the middle third of the clavicle in people of all ages.[69] Although vertebral involvement is less common, it is still important because it can lead to complications such as fractures, spinal cord compression, kyphosis, and scoliosis.[24,35] It typically affects the thoracic vertebrae most often. It may also present as unilateral sacroiliitis in the pelvis bones. Involvement of the small bones in the hands and feet is less common.[66-68]

Symmetric bone involvement is observed in 25-40% of patients.[41,42] Involvement is multifocal in up to 85% of all cases.[24] The number of osteomyelitis lesions can vary from one to at least 18 at any given time.[42] In a German study, the authors reported that patients with multifocal bone inflammation only experienced clinical symptoms at a median of one lesion.[24] In the study conducted by Girschick et al. 30 patients with CNO were followed for 5.6 years.[25] It was stated that the patients were divided into four groups: unifocal non-recurrent (30%), unifocal recurrent (10%), multifocal non-recurrent (30%), and multifocal recurrent (30%).

Additionally, a study reported that arthritis occurs in 40% of cases of chronic nonbacterial osteomyelitis.[41,68] In these cases, arthritis was found in 60% of adjacent joint lesions and 40% of distant joint lesions.[41,68] Clavicular lesions typically present with noticeable swelling, tenderness, and pain, while vertebral lesions may have a more gradual and subtle onset. Vertebral fractures and neurological deficits may arise. Pelvic involvement usually presents with unilateral sacroiliitis. Pain is a common symptom in all cases; fever may accompany pain in 17% to 33% of cases.[68] Constitutional symptoms such as weakness, fatigue, and weight loss may be present in approximately 15-20% of patients, but most patients with CNO appear clinically well except for pain.[70,71]

CNO is a systemic disease that affects the skin, joints, gastrointestinal tract, and lungs, and patients often show coexisting chronic inflammatory conditions.[41,68] In one study, 20–50% of patients were found to have or develop another autoimmune or inflammatory disease.[68,72] The most prevalent associated autoimmune and inflammatory diseases include arthritis, psoriasis, inflammatory bowel disease, vasculitis, myositis, fasciitis, and parotitis. Patients with these conditions generally present a higher number of bone lesions compared to those without concurrent inflammatory diseases.[68] These diseases may occur simultaneously or subsequently before the diagnosis of CNO. Studies have detected psoriasis in 2-17% of patients, palmoplantar pustulosis in 3-20%, and inflammatory bowel diseases in 3-7%.[73,74] Another disease commonly seen with CNO is FMF. Recently, cases demonstrating the link between FMF and CNO have been reported.[61]

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), markers of inflammation, are typically within normal limits or only slightly elevated. In patients with chronic nonbacterial osteomyelitis, higher levels of CRP and ESR indicate a greater likelihood of involvement in multiple sites.[68]

Chronic anemia caused by the disease can be identified during a blood test. The white blood cell count is typically within the normal range or slightly elevated, with a slight increase in either monocytes or neutrophils.[41,42] Autoantibodies usually test negative, and the condition is not linked to HLA B27.[25,42] High levels of TNF-α and IL-6 in the blood indicate dysregulation of cytokines in the development of the disease.[42,75] Additionally, to make a clear diagnosis, it is important to ensure that serum lactate dehydrogenase, uric acid, calcium, phosphorus, and alkaline phosphatase levels in patients are all within normal limits.

Diagnostic imaging studies

The diagnosis of chronic nonbacterial osteomyelitis largely depends on radiological findings. The most commonly used initial imaging study is conventional radiography, followed by MRI if the radiographic findings are inconclusive. MRI is considered the standard technique due to its high specificity in characterizing CNO lesions, non-invasive nature, and lack of exposure to ionizing radiation.[76]

In a child suspected of having CNO/CRMO, the first step should be to take a plain radiograph of the area of pain, as it is low-cost and non-invasive. In the early stages of

the disease, findings may not be visible on radiography. In a longitudinal case series involving 31 children diagnosed with CRMO, as confirmed by Falip et al. it was found that 40% of long bone lesions, 55% of vertebral lesions, and 75% of pelvic lesions appeared normal on plain radiographs.[77] In some patients, a radiolucent appearance may be present due to bone lesions. In the chronic stages, the lesions become sclerotic as new bone forms, resulting in a dense radiopaque appearance on X-rays. Mixed osteolytic and sclerotic lesions at the metaphysis of the long bones are one of the most common radiological findings.[78] Epiphyseal and diaphyseal involvement is unusual but may occur. The radiographic presentation of CNO typically includes focal mixed, lytic, or sclerotic lesions, as well as hyperostosis and periosteal reactions.[77,78] Involvement of the clavicle and vertebrae typically starts as a destructive lesion in the bone, with progressive sclerosis and hyperostosis noted during periods of healing and recurrence of attacks.[35,71] Involvement in the pelvic bones is often characterized by a sclerotic appearance and may manifest as sacroiliitis.[78]

Exposure to ionizing radiation, along with difficulty distinguishing between active CNO lesions and inactive disease, limits the usefulness of Computed Tomography (CT) imaging as a diagnostic method, particularly in the pediatric population.[76]

MRI is considered the best imaging technique for CNO and the most appropriate method for both diagnosing and monitoring the condition over time. It has a high sensitivity, with the ability to detect lesions in the lower limbs up to 100% of the time.[79,80] WB-MRI has been recognized as the preferred imaging method for monitoring disease. If the WB-MRI is not available, regional MRIs can be used. It is recommended to scan sequences of the entire body using fat-suppressed short tau inversion recovery (STIR) or T2-weighted sequences turbo inversion recovery measurement (TIRM) with the coronal window and also to scan the vertebrae using the sagittal window. Active CNO lesions may display signs of bone marrow edema, which can appear as hypointense (dark) on T1-weighted MRI but hyperintense (bright) on STIR and T2-weighted sequences. The importance of a WB-MRI scan lies in its ability to detect lesions that may be asymptomatic in many patients. In the context of disease monitoring, hyperostosis and osteitis may signify the progression of CNO and frequently manifest as hypointense areas on both T1- and T2-weighted MRI scans.[76] Additionally, at the time of diagnosis, WB-MRI (TRIM/STIR) is usually used to identify inflammatory bone lesions and periosteal and soft tissue involvement and to exclude diseases in the differential diagnosis.

Technetium-99m bone scintigraphy has traditionally been utilized to detect asymptomatic lesions initially. However, it should not be used if WB-MRI is accessible because MRI is significantly more effective at identifying clinically silent chronic nonbacterial osteomyelitis lesions. Moreover, in the pre-pubertal period, the metaphyseal and epiphyseal regions are already highly vascularized in bone scintigraphy, which could result in misinterpretation of a lesion in a non-lesioned area or physiological involvement in a patient with bilateral metaphyseal involvement.[81] Additionally, scintigraphy is not recommended for pediatric patients due to the risk of radiation exposure.

Histology

A bone biopsy should be considered as it can be very helpful in making a differential diagnosis but not necessarily for confirming a diagnosis. Confirming the diagnosis of CNO is often necessary. This is especially important because bone malignancies sometimes resemble CNO in isolated bone lesions. Clavicular and multifocal involvement or accompanying conditions such as palmoplantar pustulosis or psoriasis vulgaris can strongly indicate CNO. Some experts argue that a biopsy may not be necessary in these cases of CNO. However, if there is insufficient evidence for a diagnosis of CNO, caution should be exercised as serious conditions like intraosseous lymphoma and other neoplasms can sometimes mimic CNO. A biopsy is recommended in cases with a significant and persistent increase in acute phase responses, alongside hematological abnormalities such as anemia, leukopenia, or thrombocytopenia, especially in patients with atypical localization and poor overall health. This is particularly important to rule out malignancy.

In a typical CNO biopsy, the early stages may show an abundance of neutrophils, while the later stages may reveal an increase in lymphocytes and plasma cells, indicating chronic inflammation.[82]

Diagnostic challenges in CNO/CRMO

CNO is diagnosed by exclusion, relying on clinical symptoms, imaging investigations, and a bone biopsy that yields negative cultures. Currently, there are no validated or widely accepted clinical criteria for the disease. The diagnosis is confirmed by ruling out other bone-related diseases. Jansson et al. introduced a clinical scoring system to assist in diagnosis and treatment.[41] Roderick et al. suggested using the Bristol criteria to reduce the need for biopsy in certain patients.[83] The validity of these diagnostic criteria for pediatric patients is crucial, particularly since

the Bristol stool form scale is used exclusively to assess children and adolescents. 3% of the patients involved in Jansson's study were over 18 years old. For both criteria, radiological imaging is the essential method for diagnosis. The typical appearance on a radiological image (such as multifocal or clavicular) accompanying localized bone pain is usually enough to make a diagnosis.

In the differential diagnosis of the disease, malignancy and infections should be ruled out first. Malignant bone tumors such as leukemia, lymphoma, primary bone lymphomas, osteosarcoma, and Ewing sarcoma, as well as bone metastases of tumors (especially neuroblastoma), are some of the malignant causes. The main infectious causes include acute/subacute/chronic infectious osteomyelitis, septic arthritis, and bone involvement of mycobacterial diseases. Other conditions: Langerhans cell histiocytosis, avascular necrosis, scurvy, hypophosphatasia, cherubism, skeletal dysplasia, benign bone tumors (osteoid osteoma, enchondroma, osteoblastoma), fibrous dysplasia, and growing pains listed in the causes (Table 2).

Treatment

In practice, NSAIDs are commonly the first-line treatment for patients without vertebral involvement. They provide quick symptom relief and control bone inflammation in some CNO/CRMO patients. However, over 50% of patients experience flare-ups within two years of treatment.[84] Beck et al. conducted a prospective study involving a cohort of German children with CRMO and assessed their response to NSAIDs over a one-year treatment period.[85] In this group, arthritis was initially diagnosed in almost 40% (14 out of 37) of patients. All of these patients had arthritis at 3 months, 50% at 6 months, and 21% at 12 months. Vertebral involvement was found in nearly 20% (7 out of 37) of patients. Three out of 37 patients experienced pathological fractures during the study, including 2 out of 7 patients with spine involvement.[85] NSAIDs inhibit cyclooxygenase (COX) enzymes and reduce inflammasome assembly.[86] Commonly used NSAIDs include naproxen, indomethacin, and sulfasalazine, especially in patients with concurrent inflammatory bowel disease.

Table 2. Comprehensive Differential Diagnosis Framework for CNO/CRMO: A Systematic Approach to Exclude Infections, Malignancies, and Genetic Disorders

Disease Groups	Conditions
Infections	• Osteomyelitis • Bacterial • Mycobacterial • Fungal
Malignant Bone Tumors	• Osteosarcoma • Ewing sarcoma • Bony Metastases (Neuroblastoma)
Benign Bone Tumors	• Osteoid osteoma • Osteoblastoma • Fibrous dysplasia • Enchondromatosis • Hemangiomatosis • Bone Cysts
Hematological Malignancies	• Leukemia • Lymphoma • Langerhans cell histiocytosis
Metabolic Bone Disorders	• Hypophosphatasia
Genetic Disorders	• DIRA • PAPA • Majeed syndrome • Cherubism
Primary Immune Deficiency	• Defects of IFN-gamma/IL-12 axis (favoring mycobacterial infections)
Miscellaneous	• Hypovitaminosis C (Scurvy)

DIRA: Deficiency of Interleukin-1 Receptor Antagonist, PAPA: Pyogenic Arthritis, Pyoderma gangrenosum, Acne syndrome, IFN: Interferon, IL-12: Interleukin-12

Corticosteroids, like NSAIDs, reduce prostaglandin production by inhibiting phospholipase A2.[87] Corticosteroids also suppress proinflammatory cytokines (IL-1, IL-6, TNF-α), regulated by NFκB[87]. Corticosteroids rapidly control inflammation in 79% of cases but often fail to achieve long-term remission. Low-dose prednisone (0.1-0.2 mg/kg/day) can be used as a 'bridging therapy' until disease-modifying antirheumatic drugs (DMARD) take effect. While corticosteroids are effective in controlling inflammation, the majority of cases do not achieve long-term remission.[84,87] Traditional non-biologic DMARDs like methotrexate (MTX) and sulfasalazine can be effective, though data remains conflicting.[88] In patients who do not respond to NSAIDs treatment, non-biological DMARDs such as methotrexate and sulfasalazine can be used.

TNF-α plays a key role in CNO by activating osteoclasts.[41,75] In the last years, successful use of biological agents like TNF-α inhibitors has been reported. In a study by Borzutzky et al., 10 out of 11 patients using TNF-α antagonists responded positively, with a 46% remission rate.[68] Eleftheriou et al. assessed three pediatric patients receiving TNFα-blocking agents for CRMO or SAPHO.[89] All three patients showed clinical improvement. However, one patient had to stop the therapy early due to an invasive fungal infection. Catalano-Pons et al. reported findings from a cohort of 40 pediatric cases in a French dataset, in which two patients had been treated with TNFα antagonists.[72] However, the specifics of the treatment response were not thoroughly outlined. Similarly, a case report of five children with refractory CNO/CRMO showed radiological improvement during ongoing treatment, and another recent report found similar effects in four children who were treated with etanercept.[90,91] In the large French cohort, which included 178 patients with CRMO, 8 out of 9 patients who received anti-TNF therapy achieved remission.[92]

Induction of clinical and radiological remissions in response to cytokine blockade has been reported, especially in patients with extraosseous manifestations who may benefit from cytokine blockade therapy. The blockade of IL-1 using anakinra has shown positive outcomes in managing osteitis and arthritis; however, its effects on mucocutaneous manifestations remain inconsistent.[93,94] Given the clinical parallels between SAPHO syndrome and psoriasis, the interleukin 17A (IL-17A) neutralizing antibody secukinumab has been effectively used in treating patients with SAPHO.[95] IL-6 inhibitors are another promising therapy, but there is currently inadequate research on the drug's effectiveness and reliability. Other biologic medications have been used in case reports that include interferon alpha (INF-α) and gamma (INF-γ).[96,97]

Bisphosphonates inhibit osteoclast activity. Intravenous pamidronate has shown positive outcomes[97-100]. This therapy likely treats CNO by inactivating osteoclasts, reducing pain, and possibly through anti-inflammatory effects.[87] Pamidronate can be administered in two protocols: 0.5 mg/kg/day initially, followed by 1 mg/kg/day (maximum 60 mg) on days 2 and 3 every 3 months for 3-4 courses, or 1 mg/kg monthly for 1-6 months. Symptom improvement is often observed after the first infusion.[100] Bisphosphonates show effects within a few weeks, and the duration of intravenous treatment in case reports varies from 1 to 4 years, averaging 1.5 years.[101,102] Recent studies involving pediatric patients with osteogenesis imperfecta have demonstrated that oral alendronate and intravenous pamidronate exhibit equivalent efficacy.[44,90] In studies by Miettunen et al. and Hospach et al., clinical and radiological improvement was seen in 100% of patients (9/9 and 7/7, respectively) after pamidronate treatment.[98,100]

Roderick et al., Gleeson et al., and Simm et al. reported over 80% clinical improvement with pamidronate.[101-103] The most frequently observed adverse events are mild flu-like symptoms lasting one day post-infusion. Osteonecrosis of the jaw is a potential but currently unreported side effect of pamidronate in children with CNO. To mitigate this risk, pediatric patients should undergo dental screening and have wisdom teeth extracted before initiating pamidronate treatment. Furthermore, elective dental procedures should be deferred for at least six months following therapy.[100]

Compared to adult CNO/CRMO treatment, a higher percentage of children with CNO were treated with anti-TNFs and bisphosphonates, while more adults received traditional DMARDs. Recent reports show promise in using non-TNF biologic DMARDs (bDMARDs) for treating CNO, more commonly in adults than children. In adults with CNO, the primary non-TNF agents utilized are anakinra, ustekinumab, secukinumab, and tocilizumab.[104,105]

Promising studies on protein kinases and the microbiome are emerging. Changes in the gut microbiome affect disease outcomes in CMO mice. Acne and IBD are also linked to imbalanced microbiomes in humans with CNO/CRMO. Therefore, modifications made to the microbiome could potentially manage CNO/CRMO in genetically susceptible individuals or even prevent the development of the disease. Differences in microbiomes may explain

why antibiotics have been effective in certain CNO/CRMO patients, as reported in early studies.[106,107]

In conclusion, NSAIDs are the first-line treatment for CNO but are insufficient for remission. If unresponsive to treatment, non-biological DMARDs (methotrexate, sulfasalazine) can be used. Temporary use of low-dose steroids is an option. For spine or growth plate involvement, bisphosphonates (pamidronate, zoledronic acid) or biologics (etanercept, adalimumab, infliximab) should be initiated early due to the risk of long-term effects.

Childhood Arthritis and Rheumatology Research Alliance (CARRA) treatment plan, along with our clinical experience and literature data, forms the basis for our clinical practice treatment scheme, as presented in Table 3.

Treatment duration, monitoring, and long-term outcomes

There is a lack of large prospective cohort studies on CNO patients from childhood to adulthood. Retrospective studies show that early, adequate treatment and follow-up lead to positive outcomes in CNO. Although there is no consensus on when to stop treatment, a long-term plan is essential due to the disease's fluctuating course.[98,100]

Studies show CNO may resolve within 12-18 months, but 50% of patients experience flare-ups around 29 months on average. These findings emphasize the necessity of long-term monitoring of CNO patients.[84,108] Remission rates are favorable (50-80%), but more than half of CNO children experience a flare-up within the first year.[109,110]

Current literature suggests that symptoms typically improve slowly over time, with the majority of children making a full recovery. However, some children may experience persistent disease activity despite intensive treatment.[72] Delayed, inadequate, and prematurely terminated treatment can lead to complications related to the disease. Complications in CNO may already be present at the time of diagnosis or accumulate over time. Wipff et al. found that of the 178 pediatric patients studied, 25% experienced lasting effects after an average follow-up duration of three years.[92] The most common complication is vertebral compression fractures, seen in about 10% of patients at diagnosis.[111] Jansson et al. reported that 50% of vertebrae showed pathological fractures.[41]

European cohorts generally show better outcomes, but functional and cosmetic issues from hyperostosis are common. Scoliosis, kyphosis, leg length discrepancy, and growth problems are common long-term issues in CNO.[41,112] Complications related to the disease in the musculoskeletal system include malocclusion, valgus deformity, muscle atrophy, thoracic outlet syndrome, chronic arthritis, and spondyloarthropathies.[111]

CNO patients had significant limitations in their quality of life; a study using Pediatric Quality of Life Inventory Generic Core Scales 4.0 (PedsQL4.0) found that physical and school functions deteriorate as CNO progresses.[113]

A Turkish study reported that, despite treatment, CNO negatively affected patients' quality of life. These effects impacted patients' physical, social, emotional, and academic lives.[114]

Table 3. Comprehensive treatment approaches for CNO/CRMO: From first-line therapies to advanced biologic interventions

Treatment Stage	Options
First-Line Treatment (NSAIDs)	• Naproxen • Indomethacin
Non-Responsive Cases (Spinal involvement or Resistant Cases)	• DMARDs (Methotrexate, Sulfasalazine (especially in the presence of IBD)) • Corticosteroids (Low-dose bridging therapy)
Biologic Agents	• TNF-α inhibitors (Etanercept, Adalimumab) • IL-1 blockade (Anakinra) • IL-17A (Secukinumab) • IL-6 inhibitors
Bisphosphonates	• Pamidronate • Zoledronic acid

DMARDs: disease-modifying antirheumatic drugs; IBD: inflammatory bowel disease; IL-1: interleukin-1; IL-17A: interleukin-17A; IL-6: interleukin-6; NSAIDs: nonsteroidal anti-inflammatory drugs; TNF-α: tumor necrosis factor-alpha

Genetic autoinflammatory syndromes with bone inflammation

Majeed syndrome

Majeed Syndrome is an uncommon autosomal recessive condition first identified by Majeed in 1989. The classic triad in Majeed Syndrome includes early onset CRMO, congenital dyserythropoietic anemia, and neutrophilic dermatosis. The mutation responsible for Majeed syndrome is in LPIN2, which encodes LIPIN2.[16,17] LIPIN2 is a member of the LIPIN family, which is involved in glycerolipid biosynthesis as a phosphatidate phosphatase (PAP). Homozygous mutations in LPIN2 have been identified in seven unrelated families featuring five distinct mutations.[115] The LPIN2 mutation in humans does not appear to produce lipid abnormalities.[17] The phenotypic characteristics of Majeed syndrome are proposed to arise from the loss of PAP activity in LIPIN2.[116] This mutation appears to impact the PAP activity without affecting other lipid and metabolic functions of lipin2. Lorden et al. defined Majeed syndrome as an inflammasomopathy by demonstrating that LIPIN2 is a negative regulator of the NLRP3 inflammasome.[58]

CRMO typically begins in infancy but can present as late as 6 years old. Severe bone pain, soft tissue swelling, and fever are typical features of exacerbation. Flares occur every 3 or 4 months. There is a significant increase in acute phase response during attacks. Its histology and radiology are identical to CRMO. Similar to CRMO, it does not respond to antibiotics. Neutrophilic dermatosis, a phenotypic feature of the disease, is reported in only 14% of patients.[117,118] Psoriasis has also been reported in carrier patients.[2]

Children with Majeed syndrome experience varying degrees of anemia, from mild to severe, sometimes requiring transfusions. The anemia is typically microcytic. A bone marrow biopsy shows dyserythropoiesis with abnormal normoblasts.[117,118] Corticosteroids partially improve bone and skin inflammation, but anemia is less responsive. NSAIDs help with pain relief, while colchicine is ineffective.[117] Two brothers did not respond to TNF inhibitors but showed improvement with IL-1 beta-blockade in clinical, laboratory, and radiologic outcomes.[118] This supports the idea that Majeed syndrome is an autoinflammatory condition.

Deficiency of the interleukin-1 receptor antagonist

DIRA is an autosomal recessive autoinflammatory disorder. Prose and colleagues first described DIRA in 1994, and it was recognized as a distinct syndrome in 2009.[14] DIRA is caused by a mutation in IL1RN, and symptoms typically present within the first week of life. DIRA can be life-threatening, mimicking neonatal sepsis. Early recognition is crucial to prevent organ damage and death.[119-121]

The typical clinical features consist of widespread pustulosis, osteitis, periostitis, and systemic inflammation.[119-121] Skin inflammation occurs in 95% of affected infants, and cultures of the lesions are negative.[119-121] Within the first few weeks after birth, a pustular rash and signs of inflammation throughout the body develop. Despite high systemic inflammation markers, fever is usually absent. Osteitis is then detected weeks after the rash appears.[119-121]

As the disease progresses, destructive multifocal bone involvement, widespread osteitis in long bones, rib epiphyseal enlargement, and significant bone deformities occur.[119-121] These bony lesions typically affect long bones and vertebral bodies, with a preference for the proximal femur. Vertebral collapse due to osteolytic lesions may occur, leading to cervical fusion. Pulmonary involvement occurs in approximately 50% of infants with DIRA. In two infants, interstitial lung disease has been reported, and another infant died of respiratory failure due to systemic inflammatory response syndrome (SIRS).[119-121] Another life-threatening complication is central nervous system vasculitis. The disease is potentially fatal, with a 30% mortality rate. Antibiotics are ineffective in DIRA.[122] Most patients improved with high doses of corticosteroids. Genetic understanding has improved outcomes with IL-1 blockers like anakinra. Anakinra treatment leads to rapid and dramatic improvement within days.[14]

Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA)

PAPA is an autoinflammatory disease with autosomal dominant inheritance caused by mutations in PSTPIP1, which encodes the PSTPIP1 protein. Affected patients present with sterile erosive arthritis in childhood. Synovial fluid taken shows a significant increase in polymorphonuclear cells.[15] Cystic acne and pyoderma gangrenosum are the typical skin manifestations of the disease.[15] In the literature, a patient with PAPA disease was reported to have CNO/CRMO and clinical improvement in lesions was observed 6 months after starting treatment with the IL-1 receptor antagonist anakinra for bone lesions.[123]

Cherubism

Cherubism is a genetic bone disorder that affects the mandible and maxilla.[21,22] It was first described by Jones in 1933. Most children with this disorder are aged 2 to 7.[21,22]

The condition is marked by symmetrical, progressive, and extensive multilocular cystic lesions primarily affecting the mandible, although the maxilla can also be involved, albeit less frequently. [21,22] Similar multilocular cysts are observed in Noonan syndrome and are regarded as part of the Noonan spectrum.[124] This enlargement can lead to misalignment of the teeth, tooth loss, and difficulties with chewing. Jaw enlargement typically regresses after puberty begins. In 2001, heterozygous mutations in the SH3BP2 gene were identified in 12 affected families.[124]

In numerous immune cells, particularly osteoclasts, SH3BP2 can induce phosphorylation, thereby influencing signaling pathways. Mutations in this regulatory protein lead to unregulated bone resorption in the jaw.[124] Cherubism remains challenging to manage. Recently, two patients underwent treatment with adalimumab, but it was ineffective.[125] Another recent case reported no improvement in a patient treated with adalimumab and oral bisphosphonates.[126]

CONCLUSION

Sterile bone inflammation is a defining characteristic of autoinflammatory bone disorders such as CNO and CRMO. These conditions are frequently linked with skin and gastrointestinal tract inflammatory disorders, suggesting common immunological mechanisms. Familial cases of CNO/CRMO have shed light on the underlying pathophysiology. Clinically, the presentation of CNO/CRMO ranges from mild, self-limiting episodes to severe, recurrent manifestations. WB-MRI is a crucial diagnostic tool, enabling the identification of asymptomatic lesions without the risks associated with radiation exposure. Nevertheless, the optimal management strategies for CRMO remain unclear, underscoring the need for prospective studies to compare therapeutic interventions and assess the long-term safety and efficacy of biological treatments in pediatric populations.

Author contribution

The authors declare contribution to the paper as follows: Review conception and design: KB; literature review: HMK; draft manuscript preparation: HMK. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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Research Article

Evaluation of biochemical markers in relation to psychological well-being in adolescents with polycystic ovary syndrome

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ABSTRACT

Objective: This study examines psychological well-being levels among adolescents with polycystic ovary syndrome (PCOS) by levels of biochemical markers used for their diagnoses.

Methods: A cross-sectional study involved 45 adolescent females with PCOS at a pediatric endocrinology outpatient clinic. Data, including demographics, clinical exams, and lab results, were recorded at enrollment. Initial blood samples included metabolic and hormonal markers. Mental health was assessed using the Depression Anxiety Stress Scale (DASS)-42 questionnaire.

Results: The study provides valuable insights into the possible metabolic and hormonal influences on mental health in adolescents with PCOS, detecting that total testosterone (TT) exhibits high sensitivity for depression, while aspartate transaminase (AST) presents notable specificity for stress. Anxiety did not show a significant link with laboratory data.

Conclusion: TT exhibits high sensitivity for depression, while AST presents notable specificity for stress. Both markers suggest diagnostic potential in their respective categories, necessitating further research for validation.

Keywords: adolescents, polycystic ovary syndrome, mental health, depression, stress

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a hormonal disorder in women of reproductive age. Its exact cause remains elusive, but it is understood to be multifactorial, stemming from genetic and environmental influences. Factors such as heredity, hormonal imbalance, obesity, and insulin resistance are associated with an elevated risk of PCOS, though they do not directly induce the condition.[1] PCOS presents a spectrum of immediate and long-term complications, ranging from infertility and endometrial anomalies (hyperplasia and cancer) to metabolic challenges such as type 2 diabetes, gestational diabetes, pregnancy-induced hypertension, non-alcoholic fatty liver disease, dyslipidemia, and obesity, alongside manifestations like acne and psychological disturbances including depression and anxiety.[2] Given the breadth of these potential complications, early diagnosis, regular monitoring, and appropriate management of PCOS are crucial.

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Numerous studies exist regarding preventing, detecting, and monitoring complications associated with PCOS. Clinical practice appears to prioritize the evident complications of PCOS, including metabolic, cardiovascular, and gynecological concerns. Although PCOS is primarily a hormonal and metabolic disorder, it can also significantly affect a woman's mental health. The psychological dimensions of the disease present potential risks, which may be overlooked unless the patient exhibits significant distress or impairment in this domain. Multiple studies have reported a higher prevalence of psychological disorders and symptoms among women with PCOS than those without.[3,4] It is well-documented that women with PCOS generally have higher rates of depression, anxiety, and stress than the general population.[5] This can be attributed to hormonal fluctuations, the cumulative stress of dealing with symptoms, and the challenges of managing a chronic health condition. It is believed that the hormonal imbalances inherent in PCOS might directly influence mood and psychological well-being. For example, elevated androgens might be associated with mood disturbances.[6]

Various measurement tools have been used to detect these psychological aspects of PCOS in patients, including other self-report questionnaires and clinical interviews.[4] Although self-report questionnaires have their uses, they may be insufficient in accurately assessing mental health. On the other hand, the evaluation process of these patients by mental health professionals is only when the patient reports a psychological complaint. During the diagnosis and follow-up of PCOS, a number of blood laboratory values are examined. However, no marker is used to determine the psychiatric or psychological effects of the disease. Thus, the complication of psychological involvement in PCOS remains clinically and laboratory in the background. This study sought to elucidate the relationship between the parameters employed as diagnostic adjuncts for PCOS and patients' psychological well-being, suggesting that the extant blood sample results might offer insights into the potential psychological ramifications of the disease.

MATERIALS AND METHODS

Adolescents diagnosed with PCOS were recruited for the study after informed consent was obtained from both them and their parents.

Selection and Identification of Cases

This study enrolled 45 adolescent females with PCOS, selected through continuous sampling after referral to the Health Sciences University Bursa Yüksek Ihtısas Education and Researh Hospital pediartic endocrinology outpatient clinic. Based on the Rotterdam criteria of 2003, PCOS was diagnosed in the patients.[2] Exclusion criteria included metabolic syndrome, conventional medication (e.g., oral contraceptives, metformin, and medication's effects on sleep or mental status), chronic disease history, alcohol consumption, pregnancy, and lactation.

Data collection

Clinical and anthropometric data were collected during enrollment. Researchers recorded demographic information, clinical examination results (height, weight, Body mass index (BMI), hyperandrogenism features), and laboratory test results in a questionnaire for each patient. Income levels were determined based on the official starvation and poverty limits of 2023.

Anthropometric measurements

Using a daily calibrated stadiometer (Seca 703, SecaGmBH&Co Kg, Hamburg, Germany) that ensures accuracy of 0.1 cm for height and 0.1 kg for weight, patients were assessed for their body weight and height while dressed in their underwear and without shoes or outer clothing. The BMI was computed as the weight in kilograms divided by the square of the height in meters. A BMI over the 85th percentile was classified as overweight, while one above the 95th percentile was classified as obese.[7]

Physical examination parameters

Blood pressure was measured twice at rest with a 15-minute interval to screen all patients for hypertension. Any patients with hypertension (n=2) were excluded from the study.

The modified Ferriman-Gallwey (mFG) scoring system was used to diagnose hirsutism, evaluating hair growth in nine regions (upper lip, chin, chest, back, waist, upper abdomen, lower abdomen, arm, and thigh) and scoring each region from 0 to 4 according to the terminal hair growth rate. The total score is calculated, and females with an FG score of 8 or higher are considered hirsute.[8]

Laboratory-derived metrics

During their first visit to the endocrinology clinic, blood samples were taken to diagnose PCOS. The samples included metabolic (fasting glucose, serum insulin, alanine transaminase (ALT), aspartate transaminase (AST), lipids;

triglycerides (TG), high-density cholesterol (HDL-C), low-density cholesterol (LDL-C), and total cholesterol (TC) and hormonal (luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), prolactin (PRL), thyrotropin (TSH), free thyroxine (fT4), total and free testosterone, dehydroepiandrostenedione sulfate (DHEAS), Δ4-androstenedione, and 17 OH progesterone) measurements. The insulin resistance index was calculated using the homeostatic model assessment–insulin resistance (HOMA-IR) formula, equal to (fasting plasma glucose x fasting serum insulin) divided by 22.5.[9]

Mental health assessment

The Depression Anxiety Stress Scale (DASS)-42 assessed participants' mental health. The DASS-42 is widely used in clinical and non-clinical populations, including adolescents. The method was developed by Lovibond and Lovibond in 1995 and adapted for Turkish use by Bilgel and Bayram in 2010.[10,11] It displayed high levels of internal consistency reliability, with Cronbach's alpha coefficients of .96 for depression, .89 for anxiety, and .93 for stress. In the Turkish version of the DASS-42, the Cronbach alpha coefficients for depression, anxiety, and stress were .92, .86, and .88, respectively. This self-report questionnaire includes 42 items to measure depression, anxiety, and stress. Respondents rate 14 items on a 4-point severity/frequency scale, with options ranging from '0' (not suitable) to '3' (completely suitable) to indicate how often they experienced each state over the past week. The scale measures depression, anxiety, and stress, with scores ranging from 0 to 42 for each sub-dimension. These categories express the severity of the conditions: normal, mild, moderate, severe, and very severe. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. For anxiety, scores of 8-9, 10-14, 15-19, and ≥20 are mild, moderate, severe, and severe, respectively. The Stress scale is sensitive to levels of chronic non-specific arousal, assessing difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive, and impatient. Mild stress is 15-18, moderate stress is 19-25, severe stress is 26-33, and ≥34 is extremely severe. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. Mild depression is 10-13, moderate depression is 14-20, severe depression is 21-27, and very severe depression is ≥28. This study compared patients with normal scores with those outside the normal range.

Ethical approval

The study was approved by the local ethics committee of Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki (Ethical approval number: 2011-KAEK-25 2023/02-16). Adolescents diagnosed with PCOS were recruited for the study after informed verbal and written consent was obtained from both them and their parents.

Statistics

The Shapiro-Wilk test examined the data to determine whether it presented a normal distribution. The results were presented as mean ± standard deviation, median (minimum-maximum), or frequency and percentage. Mann-Whitney U test was used to compare the two groups. The Pearson correlation coefficient was calculated for the relationship between variables. Statistically, the significance level was accepted as α=0.05. Statistical analyses were performed with IBM SPSS ver.28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.).

Receiver operating characteristics (ROC) curve analysis was performed to determine optimal cut-off values for the significant variables of triglyceride according to depression and stress. The area under the curve (AUC) with a confidence interval, sensitivity, and specificity values were given for optimal cut-off value. MedCalc Statistical Software version 22.006 was used for ROC analysis (MedCalc® Statistical Software version 22.006 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023).

RESULTS

Demographics and clinical features

The study involved 45 PCOS adolescents with a mean age of 16.17±1.4 years. The BMI of the participants was 27.02±6.04. Twelve (26.6%) patients were obese, and 16 (35.6%) were overweight. The sociodemographic characteristics of the study subjects are summarized in Table 1.

Presenting symptoms

Patients applied to the hospital with four different symptoms. The most common complaint of the patients

Table 1. Socio-demographics and characteristics of the patients		
Age, year		16.17±1.4
Delivery mode	NVD	29 (64.4%)
	C/S	16 (35.6%)
BMI, kg/m^2		27.02±6.04
BMI sds		1.48±1.63
Underweight		2 (4.4%)
Normal		15 (33.3%)
Overweight		16 (35.6%)
Obese		12 (26.6%)
Socio-economic status	low	2 (4.4%)
	medium	40 (88.9%)
	good	3 (6.7%)
Presenting Symptoms	menstrual irregularity	23(51.1%)
	weight gain	8(17.8%)
	acne	2(4.4%)
	hair growth	12(26.7%)

NVD; normal vaginal delivery, C/S; cesarean section, BMI; body mass index

at hospital admission was menstrual irregularity (n=23, 51.1%). The others were as follows: weight gain (n=8, 17.8%), acne (n=2, 4.4%), and hair growth (n=12, 26.7%).

Psychological assessments

Participants were divided into two groups based on their scores on the DASS-42 subscales: normal range (NR) and high score (HS). The groups were then compared based on their laboratory values. Table 2 displays participants' laboratory values and DASS-42 subscale results.

Body mass index (BMI)

There was no statistically significant difference in BMI among groups of depression, anxiety, or stress based on the provided p-values (all > 0.05) (Table 2).

Modified Ferriman Gallwey Score (mFGS)

Of the group, 25 patients (55.55%) had a mFGS score of 8 and above. However, when contrasting the results of patients with mFGS scores below 8 to those scoring eight and above, no statistically significant differences emerged for depression (p=0.46), anxiety (p=0.87), or stress (p=0.72). Further evaluation of patients with mFGS scores ≥8 similarly revealed no significant correlation, as detailed in Table 2.

Blood lipid profiles (TC, LDL-C, HDL-C, and TG)

TC and LDL-C did not exhibit a statistically significant difference in evaluating lipid metrics, as depicted in Table 2. Lower HDL-C levels were associated with higher stress scores (p=0.011). Concurrently, there was a notable elevation in TG levels corresponding to heightened stress and depression scores (p-values < 0.05). Contrastingly, nonHDL-C did not present any variations across the respective sub-scales (Table 2).

The TG levels of 38 patients were within the normal range, defined by an upper limit of 150 mg/dl. No statistically significant difference was found when the sub-scale results of patients with blood TG values below and above 150 mg/dl were compared (p= 0.17 for depression, p=0.07 for anxiety, and p= 0.065 for stress).

Logistic regression analysis

Logistic regression analysis evaluated odds ratios (ORs) for two stress-related variables (TG and HDL-C). The result suggests that for every one-unit increase in TG, the odds of stress increase by 3.1%. HDL-C levels were inversely associated with stress, which indicated that for every one-unit increase in HDL-C, the odds of stress decreased by 6.1% (Table 3).

ROC analysis of depression and stress diagnostic tools

ROC curve analysis of variables for depression and stress is depicted in Figure 1 and Figure 2, respectively. Table 3 presents the ROC curve analysis for various biochemical variables in relation to depression and stress. In terms of depression, TT and TG demonstrated substantial areas under the curve (AUCs) with significance, where TT particularly showcased high sensitivity at 85.71%. For stress markers, AST stood out with the highest AUC of 0.766, signifying its potential diagnostic power, and it also showed an impressive specificity of 93.75%. The results suggest that these specific biochemical markers, especially AST and TT, may be significant in understanding and diagnosing depression and stress.

Examining the multivariate effects of the significant univariate variables from Table 2 on depression, only TT was significant (p=0.027, 0R=0.962).

Table 2. Laboratory profiles of PCOS patients according to the Depression Anxiety Stress Scale

	depression			anxiety			stress		
	NR	**HS (≥9)**	**p**	**NR**	**HS (≥8)**	**p**	**NR**	**≥15 (HS)**	***p***
n (%)	19 (43.2)	25 (56.8)		17 (37.8)	28 (62.2)		16 (37.2%)	27 (62.85)	
BMI	25.25±7.6	27.16±6.5	0.507	25.12±5.2	27.11±7.8	0.237	25.79±5.9	26.44±7.7	0.615
BMI, sd	1.46±1.4	1.48±1.8	0.722	1.02±1.5	1.76±1.6	0.111	1.13±1.6	1.62±1.6	0.327
WC	82.47±22.2	88.5±16.6	0.400	79.68±21.1	89.71±16.9	0.128	84.69±15.2	86.06±21.6	0.669
FG	85.89±8.9	85.72±7.1	0.859	84.76±8.2	86.14±7.7	0.582	86.88±8.7	85.26±7.5	0.615
FI	10.61±5.5	14.99±10.1	0.201	11.72±4.7	13.81±10.2	0.861	10.96±5.2	14.09±10.1	0.400
HOMA-IR	2.46±1.2	3.08±1.9	0.462	2.46±1.19	2.99±1.8	0.708	2.49±1.2	2.95±1.8	0.660
TC	174.58±28.7	173.4±40.0	0.767	171.06±34.8	175.11±35.5	0.665	176.25±36.2	172.59±35.9	0.651
LDL-C	96.08±24.7	92.25±37.4	0.368	93.39±25.5	94.01±35.7	0.888	93.16±30.8	94.3±34.2	0.763
HDL-C	59.22±16.5	51.35±12.4	0.107	60.61±16.8	50.86±11.9	0.075	61.94±14.6	51.07±13.3	**0.011**
TG	85.48±37.6	116.48±56.7	**0.045**	87.07±43.7	113.68±52.8	0.090	75.58±31.9	116.19±53.1	**0.008**
TSH	1.94±0.9	1.51±0.6	0.196	1.56±0.6	1.77±0.8	0.460	1.52±0.5	1.75±0.8	0.505
fT4	1.04±0.1	0.98±0.07	**0.030**	1.01±0.09	1±0.09	0.550	1±0.08	1.02±0	0.847
FSH	5.13±1.4	4.42±1.5	0.083	4.51±1.6	4.92±1.5	0.276	4.53±1.6	4.84±1.4	0.386
LH	6.94±5.01	5.03±4.1	0.188	6.21±5.3	5.53±4	0.944	7.25±5.9	4.99±3.5	0.327
E2	42.69±21.1	35±14.1	0.055	38.47±22.5	37.79±14.2	0.752	41.13±22.2	37.16±14.7	0.352
TT	56.26±28.7	40±19.9	**0.027**	52.12±30.3	44.68±21	0.517	49.13±25.6	47.1±26.5	0.746
PRL	18.92±14.0	14.55±6	0.722	18.22±14.1	15.06±7.1	0.752	16.88±11	15.86±10.2	0.716
DHEAS	338.74±177.2	257.06±104.8	0.166	337.61±165.3	266.26±123.5	0.143	303.71±117	286.71±163.2	0.498
17 OH PG	0.49±0.2	0.47±0.3	0.441	0.58±0.3	0.41±0.2	0.061	0.47±0.2	0.48±0.3	0.497
Androstenedione	1.25±0.5	1.06±0.6	0.168	1.38±0.6	0.99±0.5	0.055	1.25±0.5	1.04±0.6	0.152
LH_FSH_ratio	1.34±0.7	1.16±0.9	0.222	1.3±0.8	1.18±0.9	0.426	1.52±0.9	1.06±0.8	0.067
AST	16.00±4.4	16.08±4.7	0.962	14.71±3.3	16.86±4.9	0.244	13.44±2.5	17.33±4.7	**0.004**
ALT	14.16±8.0	19.00±11.5	0.089	13.00±5.7	19.04±11.7	0.076	12.63±6	18.70±11.2	**0.035**
mFGS ≥8	12 (66.7)	13 (54.2)	0.414	9 (56.3)	16 (59.3)	0.847	8 (53.3)	17 (65.4)	0.446

The values are shown as mean ± standard deviation. NR; normal range, HS; high score (indicative of higher depression, anxiety, or stress). The p-values indicate the statistical significance of the differences between the NR and HS groups for each condition (depression, anxiety, and stress). A p-value less than 0.05 is considered statistically significant. BMI; body mass index (kg/m^2), SD; standard deviation, WC; waist circumference (cm), FG; fasting glucose (mg/dl), FI; fasting insülin (µU/L), HOMA-IR homeostasis model assessment insulin resistance index, TC; total cholesterol (mg/dl), LDL-C; low-density lipoprotein cholesterol (mg/dl), HDL-C; high-density lipoprotein cholesterol (mg/dl), TG; triglyceride (mg/dl), TSH; thyroid stimulating hormone (mIU/L), fT4; free thyroxine (ng/dL), FSH; follicle-stimulating hormone (µU/ml), LH; luteinizing hormone (µU/ml), E2; Estradiol (pg/ml), TT; total testosterone (ng/dl), PRL; prolactin (ng/mL), DHEAS; dehydroepiandrosterone sulfate (µg/dl), 17 OH PG; 17 OH progesterone (ng/ml), Androstenedione; ng/ml, ALT; alanine transaminase (IU/L), AST; aspartate transaminase (IU/L), mFGS; modified Ferriman-Gallwey score.

Thyroid-related measures (TSH and fT4)

TSH levels did not differ significantly between groups, while fT4 levels significantly decreased with higher depression scores (p = 0.030).

Hormonal measures (FSH, LH, E2, TT, PRL, DHEAS, 17 OH PG, Δ4-androstenedione, and LH/FSH ratio)

There were no significant differences in most measures among the groups, except for total testosterone level, which showed a significant decrease for higher depression scores (p = 0.027) (Table 2).

Table 3. Logistic regression analysis of Laboratory profiles in relation to stress and ROC curve analysis for depression and stress variables

	p		OR		95% CI for OR	
TG (*mg/dl*)	0.028		1.045		1.005	1.088
HDL-C (*mg/dl*)	0.037		0.916		0.844	0.995
AST (*IU/L*)	0.023		1.839		1.088	3.106
ALT (*IU/L*)	0.196		0.843		0.652	1.092
	Criterion	**AUC**	**95% CI**	**p**	**Sensitivity (%)**	**Specificity (%)**
Depression						
TG	>81	0.678	0.520-0.811	0.0327	76	57.89
TT	≤58	0.704	0.539-0.838	0.0180	85.71	52.63
fT4	≤0,99	0,696	0.533-0.830	0.0252	58.33	76.47
Stress						
TG	>74	0.744	0.588-0.865	0.0017	85.19	56.25
HDL_C	≤52	0.734	0.577-0.857	0.0038	70.37	75
ALT	>12	0.693	0.534-0.825	0.0221	62.96	75
AST	>16	0.766	0.612-0.882	0.0002	48.15	93.75

OR; odds ratio, CI; confidence interval, TG; triglyceride, HDL-C; high-density cholesterol, AST; aspartate transaminase, ALT; alanine transaminase, TT; total testosteron, fT4; free thyroxine

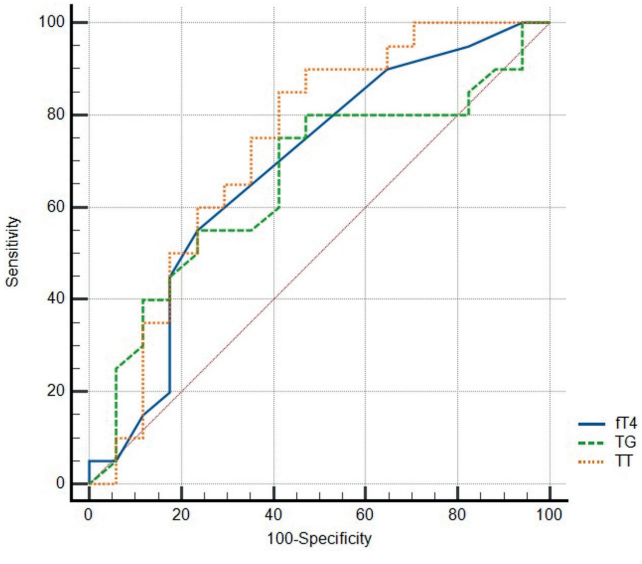

Figure 1. Receiver operating characteristic (ROC) curve analysis for predicting depression in PCOS patients: Evaluating fT4, TG, and TT parameters

fT4: free thyroxine; TG: triglyceride; TT: total testosterone

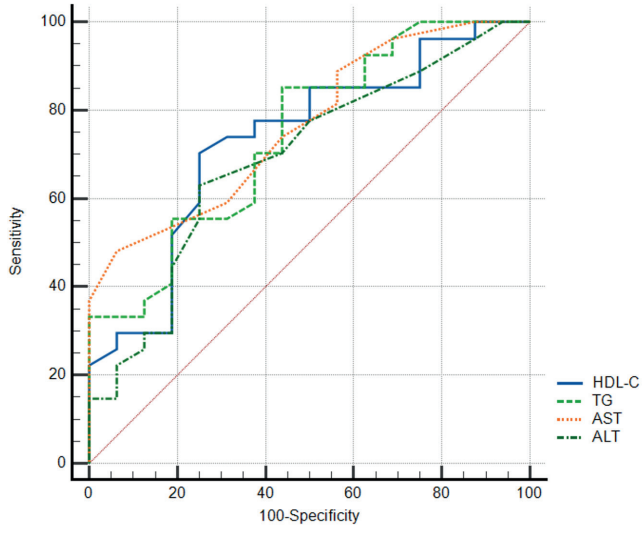

Figure 2. Receiver operating characteristic (ROC) curve analysis of HDL-C, TG, AST, and ALT as predictive markers for stress in PCOS patients

HDL-C: high-density cholesterol; TG: triglyceride; AST: aspartate transaminase; ALT: alanine transaminase

DISCUSSION

This research focuses on the potential link between metabolic and hormone profiles in adolescents with PCOS and their mental health, as quantified by the DASS-42.

Relationship between common characteristics of PCOS and mental health BMI

The relationship between BMI, PCOS, and mental health is complex. Patients with PCOS generally have an increased BMI. Elevated BMI, which indicates overweight or obesity, is associated with an increased risk of various psychological issues, irrespective of PCOS. Being overweight and obese is linked with body image concerns, lower self-esteem, and a higher prevalence of depression, among other concerns.[12] Some research suggests that women with PCOS and a higher BMI have an increased prevalence of depressive and anxiety symptoms compared to women with PCOS and a normal BMI.[7] In the current research, most participants had elevated BMI, placing them in the overweight and obese category, typical of PCOS presentations. However, there was no significant correlation between BMI and mental health indicators such as depression, anxiety, or stress, suggesting that participants' weight alone did not notably impact their mental health outcomes.

Hirsutism defined with mFGS

The mFGS is used to evaluate the degree of hirsutism in patients, a common symptom of PCOS. In this study, over half (55.55%) of the sampled adolescents with PCOS had an mFGS score of 8 or above, suggesting a substantial prevalence of hirsutism. Historically, higher mFGS scores have often been associated with elevated psychosocial distress.[13] The intuitive link is that the aesthetic concerns and stigma of hirsutism may contribute to these psychosocial effects. However, intriguingly, the current study found no statistically significant difference in levels of depression, anxiety, or stress between patients with mFGS scores below eight and those with scores of 8 or above. This result in our study may be related to the fact that body hair is no longer a concern compared to previous years with the developing technology.

The connection between laboratory characteristics of PCOS and mental health

TG and HDL-C

Among blood lipid profiles, TG was a significant predictor for both stress and depression in the present study. TG levels are primarily discussed in the context of cardiovascular health, as elevated levels can serve as a risk factor for heart disease. However, recent research has also begun to explore the potential associations between lipid levels, including triglycerides, and various psychological conditions.[14] In most (84%) participants, the TG level was below 150 mg/dl, considered the pathological laboratory limit. Previous studies have shown a potential link between high TG levels and depression[14], although the nature and direction of this association remain unclear. The mechanisms underlying this relationship have yet to be thoroughly explored. However, it is suggested that systemic inflammation, which can be associated with elevated TG, might play a role in depression. Our study observed that depression and stress scores increased as TG increased, although within normal limits. Although still within the normal range, we saw that the lower HDL-C level affected the stress scores and contributed negatively to this. Higher levels of TG have been associated with cardiovascular risks and other metabolic problems, so it is interesting to note that in our sample, it was also associated with mental health within the normal range. In the current study, the ROC analysis provided cut-off values for TG that might be used to predict the presence of depression or stress. The areas under the curve (AUC) for both were reasonably good (though not outstanding), suggesting that this cut-off might serve as a useful, albeit not definitive, biomarker. The odds of experiencing stress increased by 3.1% for every one-unit increase in TG.

Conversely, an increase in HDL-C led to a decrease in stress odds by 6.1%. This suggests that lipid profiles, particularly TG and HDL-C, could play a role in mental health, at least in terms of stress. Lipids, especially in the context of metabolic syndrome, can influence inflammatory pathways in the body. Chronic inflammation is increasingly recognized as a factor in several psychiatric conditions, including depression and anxiety disorders.[15] On the other hand, HDL-C has anti-inflammatory and antioxidant properties that might offer some neuroprotective effects. HDL-C helps stabilize cell membranes, which could stabilize mood.[16] Given the brain's heavy reliance on cholesterol, balanced HDL-C levels might affect optimal brain health. Some studies have suggested that higher HDL-C levels might be protective against cognitive decline and dementia. Lower HDL-C levels have been observed in some people with depression and anxiety.[17] While the association exists, causality is still a topic of debate. We highlighted that HDL-C levels were inversely associated with stress, implying a potential protective role. One theory is that HDL-C's anti-inflammatory and

antioxidant properties help buffer against some adverse effects of chronic stress on the brain. As PCOS is a chronic disease, we deduced that even within the normal range, TG may potentially boost inflammation, whereas HDL-C could act as a safeguard against inflammation. Being within the normal range for TG does not necessarily imply a significant risk for mental health issues. However, metabolic health is a part of the broader picture of mental health. More extensive cohort studies and more focused research are needed to provide a more definitive answer about the connection between "normal" TG levels and mental health.

fT4

In the current research, low fT4 levels were significantly associated with higher depression scores. The thyroid plays a critical role in metabolism and mood, so imbalances can have various systemic effects. Both low (hypothyroidism) and high (hyperthyroidism) levels of thyroid hormones can be associated with mental health. While the most commonly discussed thyroid hormone in relation to depression is thyroid-stimulating hormone (TSH), altered free T4 levels can also indicate underlying thyroid dysfunction.[18] The relationship between thyroid function and PCOS is complex and still a subject of ongoing research. In some PCOS patients, there may be alterations in thyroid hormone levels.[19] PCOS is often associated with metabolic syndrome, which includes hypertension, dyslipidemia, insulin resistance, and obesity. Changes in metabolism and these associated conditions might indirectly influence thyroid hormone regulation. Many factors affect the levels and effects of free T4 on mental health, including genetics, autoantibodies (as in Hashimoto's thyroiditis or Graves' disease), other medical conditions, and medications. Additionally, the absolute value of free T4 does not always matter. The balance between free T4, free T3, and TSH, as well as how these hormones interact with various systems in the body, can influence mental health outcomes.[20]

TT

In our study, examining the multivariate effects of the significant univariate variables on depression, only TT showed a significant association with depression, revealing a decrease in increased depression.

Testosterone has various effects on the brain, influencing mood, cognition, and behavior. Testosterone might also influence the brain's stress response.[21] Some studies suggest elevated testosterone might contribute to mood dysregulation, but the evidence is inconsistent across all research.[22] While high testosterone levels can negatively impact mood, evidence suggests testosterone might have neuroprotective effects.[23] Testosterone can influence the serotonergic system in the brain, which plays a vital role in mood regulation.[24]

Moreover, testosterone may help in reducing the risk of certain neurodegenerative conditions. Some studies suggest that hormone replacement therapy is effective in reducing depressed mood in menopausal women.[25] However, the relevance of these findings to PCOS patients is still a matter of discussion. It is crucial to understand that while testosterone might play a role in the mental health of women with PCOS, it is just one piece of a complex puzzle. Genetics, lifestyle factors, other hormonal imbalances, and the psychosocial effects of living with a chronic condition like PCOS influence mental health. In conclusion, while testosterone might have some protective effects on the brain and mental health, its role in PCOS is nuanced and can vary among individuals. There are potential benefits and drawbacks to elevated testosterone levels in the context of PCOS and mental health, and more research is needed to understand this relationship fully.

ALT and AST

Our findings suggest that AST has greater specificity in indicating stress, but its sensitivity is lower than ALT. However, both enzymes present potential as stress biomarkers, with AST demonstrating extreme discriminative power. Elevated levels traditionally suggest potential liver damage or inflammation. It is possible that stress, through various mechanisms, impacts liver function or exacerbates pre-existing liver conditions, leading to elevated ALT and AST.[26] Remarkably, ALT and AST are effective in the stress scale, albeit within normal limits, since PCOS patients with metabolic syndrome and cases with ALT and AST values outside the normal range were not included in our study. Even if AST and ALT are within normal ranges, it does not rule out metabolic stress or early metabolic disturbances in PCOS patients. PCOS patients often have underlying insulin resistance, which might not immediately reflect in elevated liver enzymes but could still represent a form of metabolic stress. In summary, while normal levels of AST and ALT are reassuring regarding liver health, they do not directly provide insights into the various forms of stress that a PCOS patient might be experiencing. It is crucial to have a multifaceted approach when evaluating stress and its impacts on PCOS patients.

CONCLUSION

The study provides valuable insights into the possible metabolic and hormonal influences on mental health in adolescents with PCOS, detecting that TT exhibits high sensitivity for depression, while AST presents notable specificity for stress. It should be kept in mind that the correlation between PCOS and mental health is complex and may be influenced by various factors, including hormonal imbalances, symptoms such as weight gain or hirsutism, and the psychological impact of dealing with a chronic illness. The associations discovered offer potential avenues for clinical interventions and further research.

Limitations

It is crucial to consider potential limitations. The study has a relatively small sample size, potentially limiting its statistical power and generalizability to the broader population of adolescents with PCOS. Participants were sourced from a single pediatric endocrinology outpatient clinic, which may introduce selection bias. As a cross-sectional study, it provides a snapshot at one point without elucidating causality or temporal relationships between variables. Unmeasured confounders, like lifestyle or dietary habits, could influence the results despite controlling for certain factors. Moreover, solely using the DASS-42 questionnaire for mental health assessment, though recognized, may not capture the full spectrum of psychological well-being that could be achieved with multiple tools.

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Ethical approval

This study has been approved by the Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (approval date 22.02.2023, number 2011-KAEK-25 2023/02-16). Adolescents diagnosed with PCOS were recruited for the study after informed verbal and written consent was obtained from both them and their parents.

Author contribution

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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Research Article

Neutrophil-lymphocyte ratio as an indicator of recovery phase in children with dengue fever

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ABSTRACT

Objective: Dengue is an infectious disease that burdens global public health, especially children. There are three phases of dengue infection; the last phase is the most expected, namely the recovery phase. One of the signs of this phase is platelet recovery. The platelet recovery time is still unclear because it is greatly influenced by several factors, such as immune response and lymphocyte and neutrophil activity. These factors play an important role in platelet repair and the recovery phase.

Methods: This study was a cohort prospective study. Data were obtained between January and June 2024 in Dr. Moewardi Hospital. The inclusion criteria of this study were pediatric patients diagnosed with dengue and had complete laboratory data (neutrophils, lymphocytes, and platelets) until the fifth day of fever. Data was analyzed using the Mann-Whitney test, Fisher Exact tests, and receiver Operating Characteristic (ROC) method to obtain the Area Under Curve (AUC) value, cut point, sensitivity (Sn), and specificity (Sp).

Results: This study shows absolute lymphocytes (30%; 9/30), predominance of lymphocytes (46.7%; 14/30), and Neutrophil-Lymphocyte Ratio (NLR) (63.3%; 19/30). Statistical analysis results in correlation with platelets improvement: absolute lymphocytes (AUC 77.8%, OR 5.00, Sn 66.7%, Sp 72.7%, p=0.102), predominance of lymphocytes (AUC 73.6%, OR 7.80, Sn 16.7%, Sp 66.7%, p=0.024), and NLR (AUC 78.7%, OR 10.00, Sn 91.7%, Sp 50.0%, p=0.009).

Conclusion: Supporting examination of the neutrophil-lymphocyte ratio (NLR) has been proven to be a better indicator of the recovery phase, especially in monitoring the increase in platelets in children with dengue infection compared to lymphocyte examination.

Keywords: neutrophil-lymphocyte ratio, platelet, children, dengue fever

INTRODUCTION

Dengue incidence occurs in many countries in the world, especially in tropical areas. Dengue is transmitted mainly by the Aedes aegypti mosquito.[1] The spread of dengue fever from year to year is increasingly widespread, and the number of cases is also increasing. In 2017, an estimated 105 million people were infected with dengue, with 41,000 deaths and an estimated incidence of 1,371 per 100,000 population.[2] The dengue virus attacks the immune system when the host's immunity decreases. Symptoms of dengue infection that can be life-threatening are thrombocytopenia or platelet levels below normal. The normal value of platelet levels is 150,000-400,000/microliter; if platelet levels are below 150,000/microliter, intensive treatment is needed.[3]

Dengue infection has three main phases, namely the fever phase, the critical phase, and the recovery phase.[4] The critical phase of dengue infection is the most serious because there is a significant decrease in platelets in the

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blood and plasma leakage, which can lead to shock and severe bleeding.[5] Many studies have been conducted to find factors that can predict this phase. Simple laboratory tests such as hematological examinations are important to help improve the accuracy of the diagnosis, and the critical phase can be passed well.[6] The end of the critical phase includes improvement in hematocrit levels and increased platelet counts.[7]

Lymphocytosis is one of the potential indicators in the healing phase of dengue cases. An increase in the number of lymphocytes is an indicator of the body's response to a viral infection. This is because the body begins to react to the presence of dengue virus infection. However, in-depth research on this in children has not been widely used as a predictor of the healing phase.[8] The change from neutrophil predominance to lymphocytes is also interesting to observe because several studies have shown that this change indicates an increase in the body's immunity to the dengue virus. This change can be measured using the Neutrophil-Lymphocyte Ratio (NLR).[9] NLR, one of the indicators of inflammation, is a predictor for predicting improvement or worsening of infection cases. A decrease in NLR is believed to be a predictor of the recovery phase in dengue infection due to an increase in lymphocyte dominance in several cases of viral infections, especially dengue.[10]

Establishing a diagnosis of dengue virus infection is an important thing to do in health services in hospitals. Several types of examinations can be done in establishing a diagnosis of dengue virus infection such as PCR, serology, and hematology. However, there are still many health facilities that do not have complete laboratory examinations, so simple and accurate supporting examinations are needed so that all health facilities can implement them. The Pediatrician Association has created guidelines for the diagnosis of dengue fever according to WHO, 2009. The guidelines contain simple and accurate clinical and laboratory examinations that can be performed by health services. Examination of clinical symptoms such as fever for 1-7 days, and petechiae examination, accompanied by hematology and serology supporting examinations are examinations of the accuracy of the diagnosis of dengue fever.[11] Decreased platelet count is more specific as a marker of dengue virus infection compared to other viral infections.[12] Serology examination of IgM and IgG antibodies also showed an increased level of accuracy in classifying primary and secondary dengue infections compared to other viral infections.[13]

Simple hematology tests such as lymphocytosis, NLR, and lymphocyte dominance are important laboratory tests to predict the incidence of infection in patients with various cases.[14,5] Increased Absolute Lymphocyte Count (ALC), lymphocyte predominance, and changes in NLR are interesting to study as markers of the recovery phase of dengue infection associated with improvement in thrombocytopenia. This study aims to determine whether lymphocytosis, lymphocyte dominance, and NLR can be used as predictors of improvement in thrombocytopenia in children with dengue. So that it can help reduce mortality due to dengue infection.

METHODS

Context

The design of this study is a prospective cohort. The subject was collected from medical records on dengue infection patients treated at Dr. Moewardi Hospital Indonesia from February 2024 to July 2024. The type of data used is secondary data using a total sampling technique, namely, all samples found according to the time and place of study and included in the inclusion criteria.

Inclusion criteria were pediatric patients aged 0–18 years diagnosed with dengue fever and completed routine blood data from the first to the seventh day of fever.". Determination of the diagnosis of dengue fever is based on serological examination of IgM, hematological examination of platelet levels, and physical examination of clinical symptoms. Exclusion criteria were patients with incomplete medical records and comorbid coinfection. A total of 30 pediatric patients were obtained during this study.

Data collection and measurement

The independent variable of this study is thrombocytopenia, while the dependent variables are age, sex, nutritional status, NLR, lymphocyte dominance, and lymphocytosis (day 5). Lymphocytosis (positive ≥ 1472; negative < 1472), predominance of lymphocytes in the number of leukocytes (positive: percentage of lymphocytes that exceeds the rate of other types of leukocytes; negative: percentage of lymphocytes that is lower than the percentage of other types of leukocytes), and NLR (positive < 0.8; negative ≥ 0.8) were explored as indicators of the healing phase of dengue infection. [9] Platelet levels are used as a predictor of thrombocytopenia in Dengue Hemorrhagic Fever (DHF), described using the Receiver Operating Characteristic

(ROC) curve to determine the cut point and Area Under Curve (AUC) presented as the area under the ROC curve. The results were reported as sensitivity, specificity, and positive and negative predictive values.

Analysis

Bivariate data analysis uses the Chi-square test with p>0.05 to see the significance level of the relationship between the independent and dependent variables using the test. If the results do not meet the Chi-square test, then use Fisher's exact test with p>0.05. The strength of the relationship between the variables studied is determined by calculating the Odds Ratio (OR) value.

RESULT

Baseline data

Characteristics of the subjects in 30 pediatric patients with dengue, consisting of 12 subjects in the non-increased platelet group and 18 subjects in the increased platelet group who met the inclusion and exclusion criteria (Table 1).

Based on Table 1. Most respondents with platelets not increasing were aged 5 – 11 years (23.3%; 7/30), followed by those aged 12 – 18 years (13.3%; 4/30), with an average patient age of 8.8 years. The ratio of gender and absolute lymphocytes to platelets does not increase, namely 1:1. The distribution of characteristics of respondents with the most platelets not increasing was good nutritional status (33.3%; 10/30), predominance of negative lymphocytosis (30.0%; 9/30), positive NLR (26.7%; 8/30). The distribution of respondents showed that there were no differences (p-value>0.05) in terms of age, gender, and nutritional status.

Outcome measures

We observed the clinical manifestations of dengue fever patients in 30 pediatric subjects, including general symptoms of dengue cases. All subjects (100%) had a fever, and most (70%) complained of nausea (Table 2).

The clinical manifestations of dengue patients are listed in Table 2. All patients had a fever (100%; 30/30). Headache (40.0%; 12/30), heartburn (13.3%; 4/30), petechiae (23.3%; 7/30), nausea (70.0%; 10/30), vomiting (50.0%; 15/ 30), diarrhea (20.0%; 6/30), seizures (3.3%; 1/30), cough (20.0%; 6/30), cold (13.3%; 4/30), no symptoms (56.6%; 17/30). Average length of stay 5 (1 – 18).

Table 1. Descriptive characteristic of respondent

Variable	Platelet				p-value
	Decrease		Increase		
	n	%	n	%	
Age					
<1 age	0	0.0	3	10.0	1.000*
1 – 4 age	1	3.3	2	6.7	
5 – 11 age	7	23.3	6	20.0	
12 – 18 age	4	13.3	7	23.3	
Gender					
Male	6	20.0	14	46.7	0.120*
Female	6	20.0	4	13.3	
Nutritional status					
Underweight	2	6.7	3	10.0	0.666*
Normal	10	33.3	13	43.3	
Overweight	0	0.0	2	6.7	
Absolute lymphocytes					
Negative	6	20.0	3	10.0	
Positive	6	20.0	15	50.0	
Predominance of lymphocytes					
Negative	9	30.0	5	16.7	
Positive	3	10.0	13	43.3	
Neutrophil-lymphocyte ratio					
Positive	4	13.3	15	50.0	
Negative	8	26.7	3	10.0	

*Mann-Whitney test

Table 2. Clinical manifestations of respondents

Clinical manifestations	n	%
Fever	30	100
Headache	12	40
Heartburn	4	13.3
Petechia	7	23.3
Nauseous	21	70
Vomit	15	50
Diarrhea	6	20
Seizures	1	3.3
Cough	6	20
Have a cold	4	13.3
No symptoms	17	56.6
Average length of stay (days)	5 (1-18)	

The results of observations of increased platelets based on increased lymphocytes on the fourth and fifth days in pediatric patients suffering from DHF (Figure 1). The absolute value of lymphocytes, lymphocyte dominance values, and NLR were analyzed using bivariate analysis, showing an NLR p-value of 0.009 (Table 3).

Based on Table 3. The results of the bivariate analysis show that the most significant variable associated with an increase in platelets is the neutrophil-to-lymphocyte ratio (p-value = 0.009). A negative neutrophil-to-lymphocyte ratio is associated with a tenfold higher likelihood of experiencing an increase in platelets.

The results of further diagnostic tests comparing lymphocytosis to increased thrombosis, NLR to increased thrombosis, and lymphocyte dominance to increased thrombosis are presented with ROC curves (Figure 2, Table 4).

Table 3. Bivariate variable analysis

Variable	p-value	OR	CI 95%
Absolute lymphocytes	0.102	5.00	(0.933 – 26.785)
Predominance of lymphocytes	0.024	7.80	(1.476 – 41.214)
Neutrophil-lymphocyte ratio	0.009	10.00	(1.781 – 56.150)

*Fisher exact test

Table 4. The area under curve ROC

Variable	AUC	Cut-off	Sn	Sp	CI 95%
Absolute lymphocytes	77.8%	2312.75	66.7%	72.7%	(0.611 – 0.945)
Predominance of lymphocytes	73.6%		16.7%	66.7%	(0.548 – 0.924)
Neutrophil-lymphocyte ratio	78.7%	0.4748	91.7%	50.0%	(0.616 – 0.958)

AUC: area under curve; Sn: sensitivity; Sp: specificity

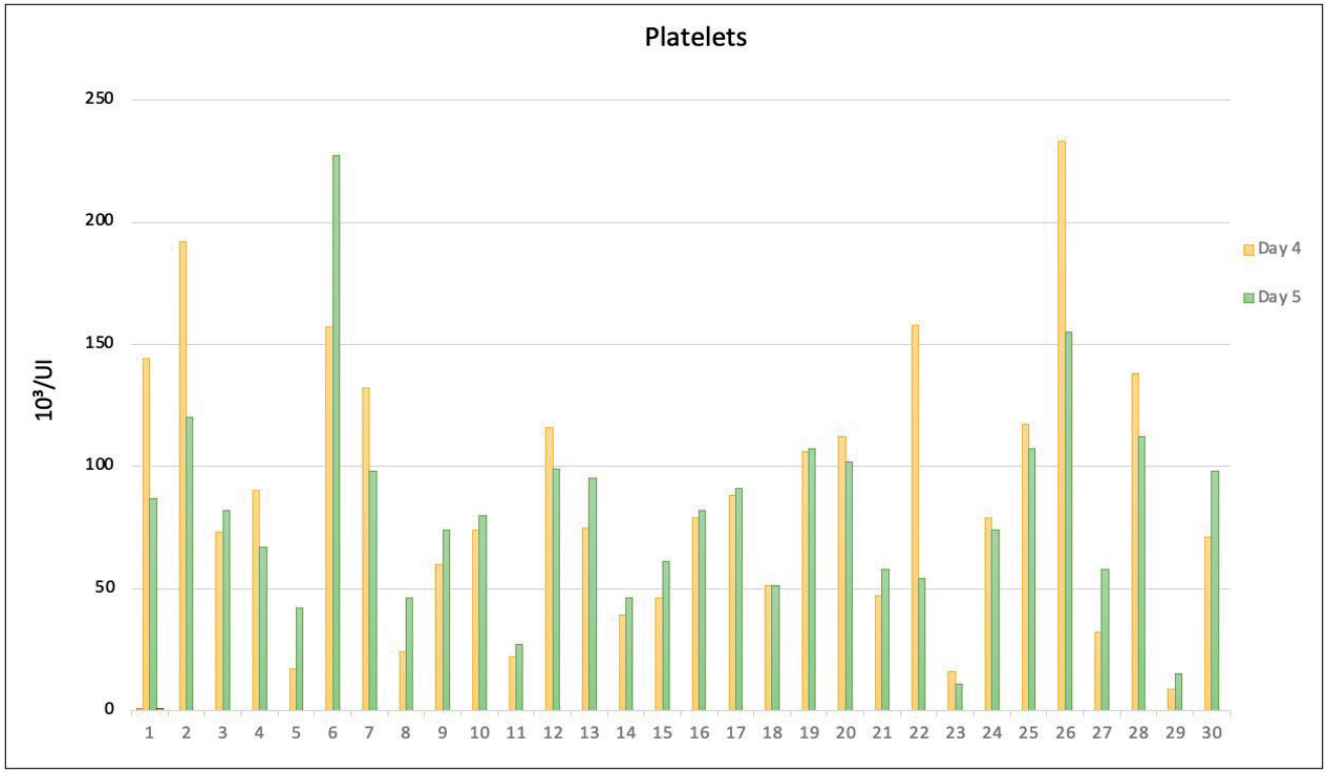

Figure 1. Graph of platelet increase on days 4 and 5 based on the increase in lymphocytes. Based on Figure 1. In this graph, subjects 1-14 show an increase in lymphocyte counts on days 4 to 5, with a trend toward improvement in thrombocytopenia. Meanwhile, subjects 15-30 showed lymphocytes that remained unchanged, and there was a tendency for stagnation or no improvement in platelets

Based on Table 4, a comparison of the ROC curve shows that NLR dominates in terms of sensitivity and specificity with the highest values, namely 91.7% and 50.0%, respectively. This curve also has an AUC value of 78.7% with a cut-off point of 0.4748 (Figure 2).

The results of this study show that the sensitivity in Figure 2 is 66.7%, 16.7%, and 91.7%, respectively. Based on the specificity values, the values obtained are 72.7%, 66.7%, and 50.0%. The AUC results of the three are in the sufficient category, namely 77.8%, 73.6%, and 78.7%. The ROC curve showed that NLR showed better sensitivity and AUC values than absolute lymphocytes and lymphocyte dominance.

DISCUSSION

The subjects of this study were children who had clinical symptoms of dengue fever and showed positive IgM serology results on the 5th to 7th day of fever. IgM examination is one of the important supporting examinations to determine the diagnosis of patients with dengue fever. Positive IgM indicates acute dengue infection.[16]

The results of the study showed that in children infected with the dengue virus in the early stages there were clinical symptoms in the form of fluctuating fever, reddish rash, petechiae, decreased platelets and accompanied by an increase or decrease in leukocytes and neutrophils. In addition, the results of this study showed several clinical symptoms that accompany dengue fever such as headache, heartburn, nausea, vomiting, diarrhea, seizures, cough, and runny nose. Headache was the most common symptom, followed by joint pain and gastrointestinal symptoms.[17,18] Dengue is an acute viral infectious disease caused by the dengue virus, characterized by fever lasting 2–7 days accompanied by manifestations of bleeding, decreased platelets (thrombocytopenia), and hemoconcentration characterized by plasma leakage.[19,20] In the beginning, dengue fever is characterized by leukopenia, where within 24 hours the fever will decrease and the patient will enter a critical period.[21] In the initial fever phase of dengue infection, the leukocyte count can be normal or with an increase in neutrophils, followed by a decrease in the number of leukocytes and neutrophils, which reaches its lowest point at the end of the fever phase. Changes in the number (<5000 cells/mm3) and the ratio between neutrophils and lymphocytes (neutrophils<lymphocytes) are useful in predicting the critical period of plasma permeation.[22,23]

In this study, the sample of dengue fever respondents experienced thrombocytopenia (40%; 12/30) with an average length of hospitalization of 5 days. The risk of thrombocytopenia is directly proportional to age and is related to male gender. The male gender is more sensitive to platelet aggregation than the female.[24] Thrombocytopenia in dengue virus infection causes the formation of antigen-

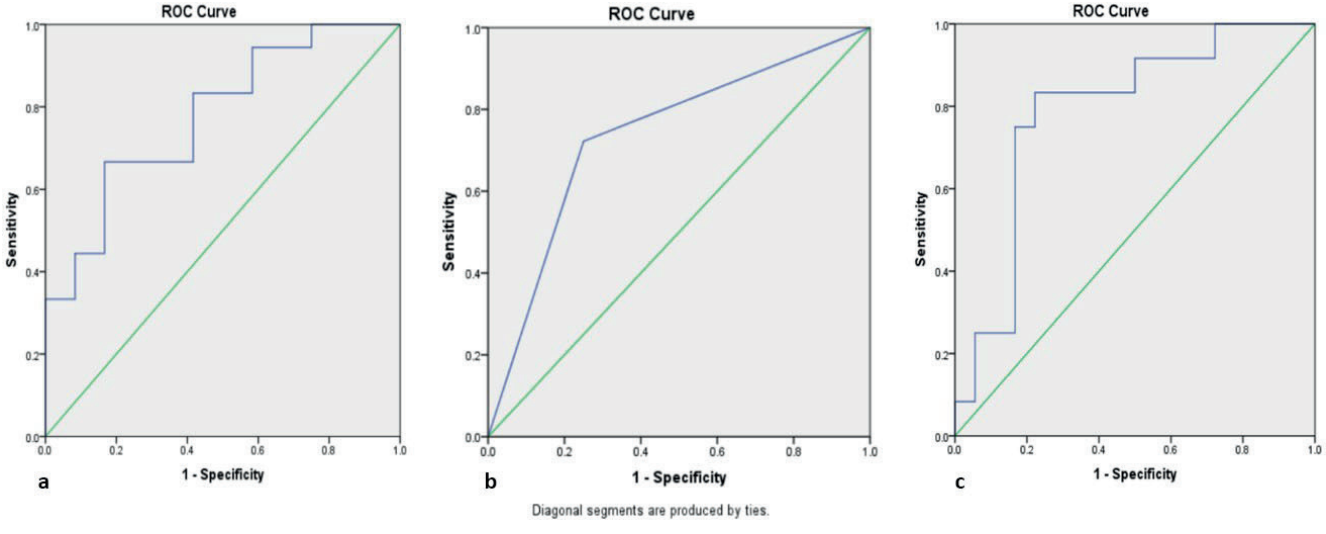

Figure 2. (a) ROC curve of lymphocytosis diagnostic test results on increased platelets. **(b)** ROC curve of diagnostic test results of lymphocyte dominance against Differential Leukocyte Count (DLC) against increased platelets. **(c)** ROC curve of NLR diagnostic test results on the platelet increased

antibody complexes when the dengue virus interacts with the body's immune system. This complex can activate the complement system, which then causes platelet aggregation or clumping. This platelet aggregation occurs because the antigen-antibody complex attaches to the platelet membrane, which triggers the release of adenosine diphosphate (ADP), which causes platelets to stick together. This causes platelets to be destroyed by the Reticuloendothelial System (RES), which results in thrombocytopenia.[25]

The results of this study indicate that there is an increase in the number of platelets marked by lymphocyte predominance, which is a sign of clinical improvement in respondents. The results of the bivariate test support that lymphocyte dominance is related to an increase in platelets. Lymphocytes peaked in the convalescent phase (days 5 to 9 after fever), with the highest number recorded on day 7.[26] The increase in lymphocytes in the convalescent phase is by the theory of pathogenesis involving lymphocytes, especially cytotoxic T cells in the convalescent phase, where the respondent's condition improves.[27]

The absolute number of lymphocytes began to increase since day 4, but in this study there was no significant correlation between the absolute number of lymphocytes and the increase in platelets. Absolute lymphocytes increased along with the development of fever and peaked on day 7 of fever, which is the convalescent phase (days 5 to 9 of fever). The increase in absolute lymphocytes is related to the body's reaction to the increase in the number of platelets and clinical improvement. Previous studies have revealed that although there is an increase in the absolute number of lymphocytes and the number of leukocytes in the critical phase, the increase in the absolute number of lymphocytes is more significant than the number of leukocytes. This is what causes the increase in the relative proportion of lymphocytes in the critical phase.[28,29]

Supporting data from simple laboratory tests with hematology tests is very helpful for fellow doctors to determine a diagnosis quickly. In cases of children with dengue fever, decreased platelets are one of the important things in establishing a diagnosis of dengue fever quickly. However, decreased or increased platelets are not only related to the occurrence of dengue infection, but several other factors can influence such as drug side effects and others. Additional laboratory tests such as NLR can help fellow doctors determine the diagnosis of dengue infection and help observe recovery from dengue fever. In this study, NRL was shown to be significantly correlated with increased platelets in children with dengue fever. Previous studies have shown a significant relationship between NLR and the severity of dengue. There is neutropenia and lymphocytosis at the beginning of fever, which can be used as predictors of infection diagnosis in the first few days of fever.[30] Neutropenia and lymphocytosis can indirectly describe the neutrophil-lymphocyte ratio value; namely, if the neutrophil value is lower, the neutrophil-lymphocyte ratio will also be lower. Conversely, the higher the lymphocyte value, the lower the neutrophil-lymphocyte ratio. Neutropenia and lymphocytes play a central role in the response to dengue infection.[31] Neurophils, as a type of white blood cell, move to the area of infection to fight the causative agent of the disease. After circulating in the blood for 7–10 hours, neutrophils move to the affected infection site to participate in the body's immune response.[32] During dengue virus infection, the bone marrow is suppressed, either directly caused by the virus itself or indirectly through the production of proinflammatory cytokines that inhibit bone marrow activity.[33]

Our study still has some limitations, such as the number of dengue cases treated in the hospital is still small and the treatment time is limited. However, this study is the first study to examine the role of lymphocytosis, lymphocyte dominance, and NLR as predictors of increased platelets and indicators of recovery in pediatric dengue fever. The need for other simple supporting examinations that can be indicators of the recovery phase in dengue diabetes is very much needed by medical colleagues in daily practice, especially in pediatrics. Our further research will focus on tighter control of confounding variables to achieve the best results in dengue infection.

CONCLUSION

On day four, fever, lymphocytosis, lymphocyte predominance, and NLR can serve as predictors of the convalescent phase, especially in monitoring improvement in platelets. NLR has proven to be a better predictor of the convalescent phase, especially in monitoring improvement in platelets in children with dengue infection.

Acknowledgment

We thank the patient and family for allowing us to participate in conducting ancillary examinations to diagnose dengue infection.

Ethical approval

This study has been approved by the Ethics Committee of Dr. Moewardi General Hospital, Indonesia (approval date 15.02.2024, number 422/II/HREC/2024). Written informed consent was obtained from the participant's parent.

Author contribution

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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Research Article

Postnatal growth and extrauterine growth retardation (EUGR) in extremely low gestational age newborns (ELGAN) with a 2-year follow-up

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ABSTRACT

Objective: The primary objective of our study was to investigate the growth patterns of extremely low gestational age newborns (ELGAN) in the Neonatal Intensive Care Unit (NICU), assess the prevalence of Extrauterine Growth Restriction (EUGR) among them, and identify factors influencing its development. Additionally, the study aimed to evaluate the consistency between cross-sectional and longitudinal EUGR in ELGANs and assess catch-up growth at corrected 24 months.

Method: Growth patterns of ELGANs and additional clinical data were retrospectively collected from January 2021 to January 2022 at a single tertiary NICU. EUGR was defined using two methods: cross-sectional EUGR and longitudinal EUGR. Infants were classified into two groups—EUGR and non-EUGR—based on whether their weight z-score was below -1.28 at the time of evaluation (either at a corrected gestational age (CGA) of 36 weeks or at discharge, whichever occurred first) or if the z-score decline (ΔZ score) exceeded 1 standard deviation (SD) between birth and the time of evaluation. According to WHO Child Growth Standards, catch-up growth was assessed at the age of two.

Results: The study included 66 ELGANs. The incidence of EUGR was 51.5% (34 out of 66) based on the cross-sectional definition, increasing to 74.2% (49 out of 66) under the longitudinal definition. Using the criterion of a ΔZ weight < –1, the EUGR group took longer to achieve total enteral nutrition and required more days of total parenteral nutrition than the non-EUGR group. Additionally, the average weight growth velocity (GV) was significantly lower in the EUGR group. Late-onset sepsis (LOS), cumulative antibiotic exposure, and feeding intolerance (FI) were significantly more prevalent in the EUGR group. Among ELGANs discharged with EUGR (based on the longitudinal definition), 53% achieved catch-up growth in weight by one year of age and 77% by two years.

Conclusion: The present study highlights the importance of LOS as an independent risk factor for developing EUGR and underscores the need for interventions to reduce its incidence. Additionally, enhanced enteral nutrition support and strategies to promote higher growth velocity may effectively reduce the incidence of extrauterine growth restriction in ELGANs. Approximately 25% of ELGAN infants are expected to remain underweight by the age of two years, while the majority achieve normalization of head circumference.

Keywords: extremely low gestational age newborns (ELGAN), extrauterine growth Restriction (EUGR), postnatal growth, catch-up growth

INTRODUCTION

Historically, the target growth of preterm infants has been to replicate intrauterine growth patterns, as established by the American Academy of Pediatrics (AAP) in 1977.[1] However, consensus on the optimal growth trajectory for preterm infants and the methodologies for monitoring growth in the neonatal intensive care unit (NICU) remains elusive. The most commonly used growth charts are the cross-sectional charts derived from in-utero growth data.

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Whether preterm infants should be expected to grow at the same rate as their in-utero counterparts is still debated.[2] Extrauterine Growth Restriction (EUGR) refers to inadequate growth in preterm infants in the NICU.[3] EUGR significantly affects multiple aspects of a premature infant's health and development.[4] Research has shown that growth retardation is associated with adverse neurodevelopmental outcomes.[3,5] These findings underscore the importance of monitoring and intervening in the postnatal growth of premature infants to reduce the incidence of EUGR and promote their neurodevelopment and growth. EUGR is classified into two types: Cross-sectional EUGR could be defined as below the 10th percentile or age specific weight Z-score below the −1.28 at a given time. Longitudinal EUGR could be described as an age-specific weight Z-score fall of more than 1 standard deviation (SD) between birth and the given time.[6] The Z-score measures the number of standard deviations an infant's weight and height are from the median, or the 50th percentile, of the reference growth charts for infants of the same age and sex. The World Health Organization (WHO) defines Small for Gestational Age (SGA) as a newborn with a birth weight below the 10th percentile for infants of the same sex and gestational age. EUGR in SGA infants may represent a continuation of intrauterine growth retardation rather than "true EUGR." Hence, it is advised to assess EUGR in SGA infants as a distinct category.[7] Extremely low gestational age newborns (ELGANs) or extremely preterm infants (EPIs) are born before 28 completed weeks of gestation (up to and including 27 weeks and 6 days of gestation).[8] ELGANs are at high risk of unsuccessful postnatal adaptation, including challenges with initiating enteral nutrition, achieving full enteral nutrition, and attaining optimal postnatal growth. While the longitudinal definition of EUGR is generally considered more predictive of long-term outcomes in preterm infants, data on ELGANs is scarce. This study aimed to compare the cross-sectional and longitudinal definitions of EUGR in determining the true prevalence of EUGR in ELGAN infants, the influencing factors, and the growth status at 24 months.

OBJECTIVE AND METHODS

The study included infants born at Tinaztepe University Galen Hospital or transferred there within the first day of life between January 2021 and January 2022. Only ELGANs (infants born before 28 weeks of gestation) were included. Infants with SGA, major birth defects, or congenital anomalies were excluded. Birth weight and weight at the time of evaluation (either at a corrected gestational age (CGA) of 36 weeks or at discharge, whichever occurred first) were converted into age-specific and sex-specific Z-scores using the 2013 Fenton dataset.[9] SGA was defined as an age-specific birth weight Z-score below −1.28, according to the Fenton growth chart.[9] Cross-sectional EUGR is defined as an age-specific weight Z-score below -1.28 at the time of evaluation, either at a CGA of 36 weeks or at discharge, whichever occurs first. Longitudinal EUGR is defined as a decline in the Z-score (ΔZ score) of more than one SD from birth to the specified time.[6]

Perinatal data, maternal and pregnancy complications, growth and nutritional status during hospitalization, treatment conditions, major complications, and other clinical data of ELGANs were retrospectively collected from medical records. Data on growth and nutritional status during hospitalization included maximum weight loss, age at birth, weight recovery, the average weight gain velocity (GV), start time of enteral feeding (excluding colostrum oral care), breast milk volume after the addition of human milk fortifier (HMF), the age of reaching total enteral nutrition and age at reaching the target oral calorie intake (110 kcal/kg/day), the duration of parenteral nutrition (PN). These data were collected from medical records. The average weight GV was expressed as g/kg/day and calculated using Patel's method with the following equation: Growth velocity = 1000 × Ln (Wt2/Wt1)/ (D2 − D1) where Wt_1 and Wt_2 represent the infant's weight measured on days (D) 1 and D2, respectively.[10] The age at which total enteral nutrition was achieved was defined as the number of days required to reach a target oral calorie intake of 110 kcal/kg/day.

Data on invasive mechanical ventilation duration, total oxygen use duration, cumulative antibiotic use, postnatal steroid treatment, and hemodynamically significant patent ductus arteriosus (hsPDA) were collected from medical records. Additionally, information on early-onset sepsis (EOS), late-onset sepsis (LOS), feeding intolerance (FI), neonatal necrotizing enterocolitis (NEC) ≥ stage 2 (according to Bell's classification[11]), bronchopulmonary dysplasia (BPD), grade III-IV intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP) requiring intervention based on established diagnostic criteria[12] was also obtained. Bronchopulmonary dysplasia (BPD) was defined as a continuous oxygen requirement for the first 28 days and a need for oxygen at 36 weeks postmenstrual age.[13] The diagnostic criteria for EOS and LOS were established through expert consensus and have been used to diagnose and treat neonatal sepsis.[14] According to the local NICU protocol, feeding intolerance was defined as failure of the feeding

plan, characterized by gastric residue exceeding 50% of the previous feeding amount or gastric residue containing bile, accompanied by vomiting and/or abdominal distension. According to WHO Child Growth Standards, catch-up growth was evaluated at the age of two years. Low weight for age (underweight), low height for age (stunting), and reduced head circumference for age were diagnosed when Z-scores fell below -2 standard deviations. The study was approved by the clinical research ethics committee of Izmir Tinaztepe University with decision no 2024/62. Ethical principles were adhered to, and the research was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Normally distributed measurement data were expressed as mean ± SD, and comparisons between groups were made using independent-sample t-tests. Non-normally distributed quantitative data were reported as median and interquartile ranges (IQRs), with group comparisons performed using the Mann–Whitney U test. Categorical variables were analyzed using the Chi-square test, with Fisher's exact test applied when necessary. Univariate analysis was conducted to identify potential factors influencing clinical outcomes. A p-value < 0.05 was considered statistically significant. All differences among and between groups were considered to be statistically significant at $P < 0.05$

RESULT

Throughout the study period, data were collected on 80 ELGANs. Five cases were excluded due to incomplete information, and an additional nine cases were excluded (eight due to SGA and one due to congenital anomalies). Ultimately, 66 ELGANs were included and assessed in the study (Figure 1). The average birth weight of the infants included in the study was 807 ± 206 grams, and the average gestational age was 25.4 ± 1.2 weeks. The incidence of EUGR among ELGANs was 74.2% (49 out of 66 cases) when assessed using the longitudinal definition based on infant weight at 36 weeks of CGA or at discharge. In contrast, when assessed using the cross-sectional definition, the incidence of EUGR was 51.5% (34 out of 66 cases). Figure 2 presents a scatterplot of the weight-for-age Z-score plotted against the change in weight-for-age Z-score (ΔZ). Using the $\Delta Z < -1$ criterion, birth weight and weight Z-score at birth did not differ significantly between the EUGR and non-EUGR groups. Similarly, birth length, birth length Z-score,

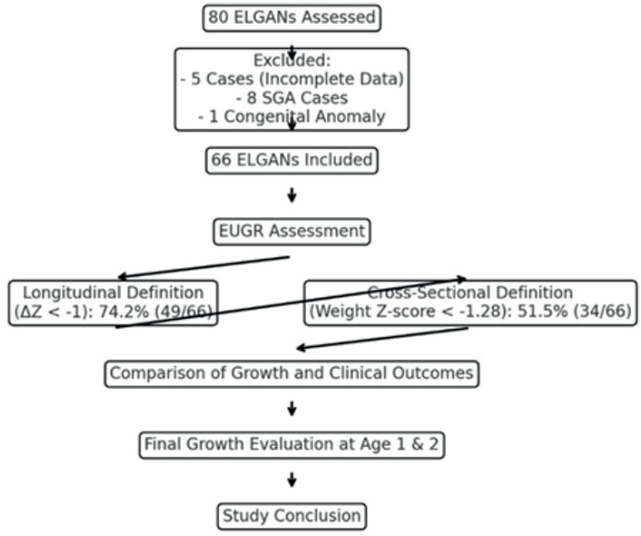

Figure 1. Study flowchart

birth head circumference, and birth head circumference Z-score did not differ significantly between the EUGR and non-EUGR groups. Additionally, factors such as gestational age, the incidence of female infants, 5-minute Apgar scores, and other perinatal and neonatal variables—including pregnancy-induced hypertension, gestational diabetes, mode of delivery, multiple births, and antenatal steroid administration—showed no significant differences between the EUGR and non-EUGR groups ($P > 0.05$), as presented in Table 1.

Following the criterion of ΔZ of weight < –1, a comparison between the EUGR and non-EUGR groups showed no significant differences in maximum physiological weight loss, the age at which birth weight was regained, or the initiation of enteral feeding. However, the average weight GV was significantly lower in the EUGR group (19.5±3.3 vs. 22.6±3). Additionally, the age at which total enteral nutrition was achieved, the number of days required to reach the target oral calorie intake (110 kcal/kg/day), and the duration of parenteral nutrition were all significantly greater in the EUGR group compared to the non-EUGR group ($P < 0.05$), as presented in Table 2. Following the criterion of ΔZ of weight < –1, the LOS, cumulative duration of antibiotics uses, and incidences of FI in the EUGR group were significantly higher than in the non-EUGR group ($P < 0.05$). However, the incidences of complications such as RDS, EOS, HsPDA, IVH grades 3-4, BPD, NEC stage 2 or higher, PVL, and ROP requiring intervention did not differ significantly between the groups ($P > 0.05$) as shown in Table 3.

The discharge weight of the EUGR group was significantly lower than that of the non-EUGR group (2536 ± 287 g vs. 2880 ± 469 g, p = 0.01). Upon evaluating ELGANs for growth at the age of one, it was found that 47% of infants were underweight, 29% experienced stunting, and 38% had a reduced head circumference for their age. By the age of two, these rates had decreased to 23% for underweight, 15% for stunting, and 6% for reduced head circumference.

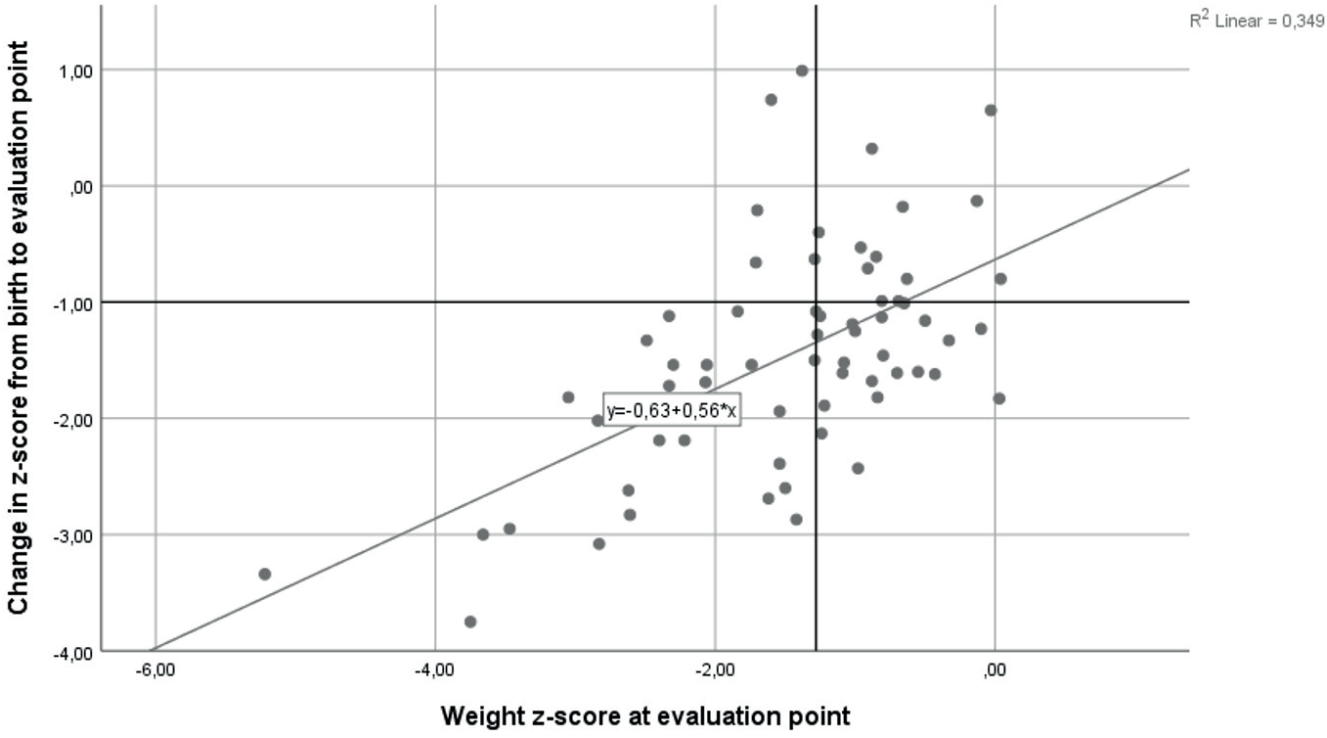

Figure 2. Scatterplot graphic for the weight-for-age z-score plotted against the change in the weight-for-age z-score

Table 1. Comparison of general perinatal and natal characteristics between EUGR and non-EUGR groups

Variable	Non-EUGR n: 27	EUGR n: 39	p
Female [n (%)]	16 (59.2%)	20 (51.2%)	0.52
Gestational weeks (mean±SD)	25.3±1.27	25.5±1.31	0.55
Birth weight, g (mean±SD)	761±187	838±215	0.12
Weight z score at birth (mean±SD)	0.19±0.72	0.24±0.87	0.13
Birth length, cm (mean±SD)	32.69±3.02	33.48±2.72	0.27
Length z score at birth (mean±SD)	0.09±0.94	0.27±0.90	0.4
Birth head circumference, cm (mean±SD)	23.75±2.12	24.06±2.3	0.58
Head circumference z score at birth (mean±SD)	0.46±0.98	0.51±1.09	0.84
Cesarean section [n (%)]	22 (81.4%)	31 (79.4%)	0.36
Multiple births [n (%)]	2 (7.4%)	5 (12.8%)	0.12
Antenatal steroid treatment [n (%)]	15 (55.5%)	23 (58.9%)	0.62
Gestational hypertension [n (%)]	2 (7.4%)	2 (5.1%)	0.53
Gestational diabetes [n (%)]	1 (3.7%)	3 (7.6%)	0.11
Gestational age at discharge (weeks, mean ± SD)	39.18±1.86	39.17±2.07	0.77

EUGR: extrauterine growth restriction

Table 2. Comparison of the nutritional status of ELGANs between the EUGR and non-EUGR groups during hospitalization

Variable	Non-EUGR n:27	EUGR n:39	p
Maximum physiological weight loss, %	10.4±5.1	11.5±3.6	0.3
Age at birth weight recovery (days)	11.2±4.9	13.4±5.6	0.12
Average weight gain velocity (GV) (g/kg/day)	22.6±3	19.5±3.3	0.01*
Initiation of enteral feeding (days)	4±2.4	4.5±3	0.5
Volume of milk fortified with HMF (ml/kg)	87.1±13.9	81.6±12.9	0.11
Time to reach target oral calorie intake (110 kcal/kg/day) (days)	48.2±15.4	55.7±17.6	0.01*
Duration of parenteral nutrition (days)	39.4±13.8	45.4±18.5	0.03*

ELGAN: extremely low gestational age newborns; EUGR: extrauterine growth restriction; HMF: human milk fortifier
*p<0.05

Table 3. Comparison of the main treatments and complications related to hospitalization of ELGANs between the EUGR and non-EUGR groups

Variable	Non-EUGR n:27	EUGR n:39	p
Invasive ventilation duration (days)	42.9±33.6	29.8±30.4	0.11
Total oxygen therapy duration (days)	64.1±35.2	57.8±36.2	0.48
Cumulative duration of antibiotic use (days)	14.8±6.5	20.8±8.3	0.04*
Postnatal steroid treatment [n (%)]	15 (55.5%)	22 (56.4%)	0.78
Hemodynamically significant PDA (hsPDA) [n (%)]	21 (77.7%)	28 (71.7%)	0.58
Early-onset sepsis (EOS) [n (%)]	5 (18.5%)	11 (28.2%)	0.36
Feeding intolerance (FI) [n (%)]	15(55.5%)	32(82%)	0.03*
Late-onset sepsis (LOS) [n (%)]	14 (51.8%)	34 (87.2%)	0.02*
Necrotizing enterocolitis (NEC ≥ stage 2) [n (%)]	2 (7.4%)	3 (7.7%)	0.96
Bronchopulmonary dysplasia (BPD) [n (%)]	12 (44.4%)	10 (25.6%)	0.11
Periventricular leukomalacia (PVL) [n (%)]	2 (7.4%)	3 (7.7%)	0.96
Intraventricular hemorrhage (IVH, grade 3-4) [n (%)]	1 (3.7%)	4 (10.3%)	0.32
Retinopathy of prematurity (ROP, requiring intervention) [n (%)]	2 (7.4%)	3 (7.7%)	0.96

ELGAN: extremely low gestational age newborns; EUGR: extrauterine growth restriction; PDA: patent ductus arteriosus
*p<0.05

DISCUSSION

The Fenton growth curves, revised in 2013 and based on data from a large cohort of preterm infants, are widely used to evaluate both intrauterine and extrauterine growth in this population.[9] Our study identified a significant discrepancy in EUGR assessment depending on whether it was based on the p-value or the ΔZ-score on the growth curve, either at the adjusted 36th week or at discharge, within the same population. Specifically, the incidence of EUGR among ELGANs was 74.2% when defined by a ΔZ-score of less than –1, compared to 51.5% when defined by a discharge weight p-value of less than 10%. This discrepancy of 22.7% highlights the impact of varying EUGR definitions within the same population. Although various studies have reported a higher incidence of EUGR when using the cross-sectional definition based on a discharge weight Z-score < –1.28 (equivalent to a p-value < 10th percentile) compared to the longitudinal definition, longitudinal assessment is considered a more accurate reflection of neonates' true growth trajectories. [6,15] Since the p-value evaluation method is based on the horizontal analysis of group data, whereas the ΔZ score is derived from the analysis of individual data.[16] Simon et al. proposed that the change in Z scores from birth weight to weight at discharge (ΔZ score) be incorporated into the longitudinal definition for assessing EUGR in premature infants to more accurately reflect their postnatal growth status.[17] De Rose et al. proposed that a longitudinal definition for EUGR is more effective than a cross-sectional definition in predicting adverse neurodevelopmental outcomes at a two-year follow-up.[18] Therefore, the definition based on the ΔZ score is thought

to be more effective in predicting the long-term outcomes for preterm infants. In our research, we employed the longitudinal definition of EUGR, which is based on the ΔZ score, to compare the EUGR and non-EUGR groups in ELGANs. Numerous studies have indicated that higher birth weights and male gender may act as protective factors against EUGR.[19-21] Nevertheless, our research revealed no significant differences in birth weight and gender between the EUGR and non-EUGR groups. Postnatal nutritional status is closely linked to the incidence of EUGR. Current guidelines indicate that premature infants need careful monitoring of their growth and the proper and consistent provision of nutrients. This includes supplementation with breast milk, provided both parenterally and enterally, particularly in the first weeks of life.[22] In our study, the univariate analysis revealed that the non-EUGR group exhibited a higher average weight GV (p=0.01), achieved the target oral calorie intake earlier (p=0.01), and had a shorter duration of parenteral nutrition (p=0.03) compared to the EUGR group. Oral calorie intake reaching 110 kcal/kg has been shown to be protective against EUGR in ELGANs, and this is associated with shorter TPN duration and higher GV. Although the HMF initiation time did not differ between the groups in our study, HMF is quite important in reaching the target oral calorie target in preterm infants. Studies have also found that infants experiencing EUGR received fewer calories and less protein than recommended during the transition from parenteral to enteral feeding.[23] The findings indicate that increased focus on enteral nutrition support for ELGANs is warranted. Such factors are crucial in diminishing the occurrence of EUGR. European Milk Bank Association (EMBA) recommends using individualized fortification to optimize nutrient intake.[24] In this study, all ELGANs utilized the individualized fortification method based on blood urea nitrogen (BUN) levels as the standard protocol for HMF. Our study indicated that the occurrence of LOS, the overall length of antibiotic therapy, and instances of feeding intolerance were more prevalent in infants with EUGR compared to their counterparts without this condition. The increased incidence of LOS in ELGANs with EUGR may be linked to feeding intolerance, which is often a consequence of extended antibiotic treatment and significant disruption of intestinal microbiota. Major morbidities linked to prematurity, including PDA, BPD, NEC, the requirement for assisted ventilation, exposure to postnatal steroids, and severe brain lesions, substantially impact the incidence of growth restriction and increase the risk of developing extrauterine growth restriction.[25,26] Greenbury et al.'s extensive study demonstrated significant growth restriction in extremely premature infants who suffer from these major morbidities.[27] Our study revealed no significant differences in major morbidities between the EUGR and non-EUGR groups, except LOS. These morbidities might simply indicate the severity of illness; sick infants tend to be fed less than their healthier counterparts, face higher metabolic demands, and often have unmet nutritional needs, leading to malnutrition and stunted growth. In 2021, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (EPSGHAN) emphasized that to catch up with growth in preterm infants with major morbidity, ongoing energy and protein needs must be met during this period. It has been recommended that critically ill premature newborns replace nutritional and energy deficiencies by increasing calories to 160 kcal/kg/day, protein to 4.5 g/kg/day, glucose to 12.5 g/kg/day, and fat to 8 g/kg/day during the recovery phase.[28] There is limited information on the amount of energy and nutrients that should be provided to meet the increased metabolic requirements due to major morbidities in a specific group, including ELGANs. Given the increasing rates of extremely premature survivors, a universal definition of EUGR and guidelines on neonatal feeding are essential.

The limitations of this study include a single-center design, a small sample size, variability in results due to different EUGR definitions, the absence of long-term neurodevelopmental data, and the lack of detailed evaluation of nutritional and environmental factors. However, we believe it will contribute to the literature by presenting data on a subject for which there is limited information, such as extrauterine growth patterns and catch-up growth in the first 2 years of life in extremely preterm infants. The present study highlights the importance of LOS as an independent risk factor for the development of EUGR and the need for interventions aimed at reducing its incidence.

Ethical approval

This study has been approved by the Tınaztepe University Ethics Committee (approval date 10.10.2024, number 2024-62). Written informed consent was obtained from the participants.

Author contribution

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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Research Article

Retrospective analysis of sleep-disordered breathing in pediatric neuromuscular disease

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ABSTRACT

Objective: Sleep-disordered breathing (SDB) is a prevalent concern in individuals with neuromuscular diseases (NMD), significantly impacting respiratory function and sleep quality. This study aimed to retrospectively evaluate the demographic, clinical, and baseline polysomnographic data of children with NMD to investigate the guiding effect of the Pediatric Sleep Questionnaire (PSQ) and the modified Epworth Sleepiness Scale (ESS-CHAD) in detecting SDB.

Method: A retrospective analysis was conducted on children aged 2-18 years with NMD who underwent polysomnography (PSG) between January 2012 and January 2024. The study assessed various clinical parameters, including age, gender, BMI, underlying disease, PSG results, the PSQ and ESS-CHAD scores, and treatment methods. Statistical analyses were conducted to compare those with and without obstructive sleep apnea syndrome (OSAS).

Results: Of the 174 patients included in the study, 90 patients (51.7%) had normal PSG, 56 patients (32.2%) had mild (OSAS), 12 patients (6.9%) had moderate OSAS, and 16 patients (9.2%) had severe OSAS. PSQ and ESS-CHAD were not significantly different between patients with and without OSAS ($p>0.05$). The most common treatment initiated was noninvasive ventilation (NIV), recommended for 23% of patients.

Conclusion: PSG is the gold standard for diagnosing SDB in children with NMD. While PSQ and ESS-CHAD may be useful for screening in the general pediatric population, they are inadequate in identifying OSAS in children with NMD. Early diagnosis and treatment of SDB are crucial for improving outcomes in this patient group.

Keywords: sleep-disordered breathing, neuromuscular diseases, polysomnography, pediatric sleep questionnaire

INTRODUCTION

Sleep-disordered breathing (SDB) is a group of conditions characterized by abnormal breathing patterns during sleep, affecting both adults and children.[1] SDB represents a significant concern in individuals with neuromuscular diseases (NMD), impacting both respiratory function and sleep quality. Individuals with NMD often face respiratory complications due to weakness of respiratory muscles, leading to an increased risk of SDB.[1]

Untreated SDB can result in cardiovascular side effects, metabolic disorders, and neurocognitive issues, all of which can be exacerbated by innate NMD symptoms.[2] Cognitive impairments, attention deficit/hyperactivity disorders, and social disabilities that may be difficult to cope with have

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been reported in SDB that are not detected early and treated.[3] Therefore, SDB should be screened and treated early in children with NMD.

Polysomnography (PSG), the gold standard for assessing SDB, offers valuable insights into respiratory and sleep parameters.[1] However, PSG is time-consuming, technician-dependent, and not widely accessible.[4] Consequently, pediatric prediction tools for SDB aim to detect obstructive sleep apnea syndrome (OSAS) and identify children needing further evaluation.[4] The Pediatric Sleep Questionnaire (PSQ) and the modified Epworth Sleepiness Scale (ESS-CHAD) serve as reliable SDB screening tools.[5] The PSQ demonstrates 85% sensitivity and 87% specificity for detecting PSG-confirmed SDB in healthy children aged 2-18 years.[5] The ESS-CHAD, a self-report questionnaire, assesses daytime drowsiness in eight daily scenarios.[6] Initially validated for OSAS patients, it is now widely used to identify various conditions causing excessive sleepiness in the general population.[7]

This study aimed to retrospectively evaluate the demographic, clinical, and baseline polysomnographic data of children with NMD to investigate the guiding effect of PSQ and ESS-CHAD in detecting SDB.

METHODS

We analyzed children aged 2-18 years with NMD who underwent PSG in our pediatric sleep laboratory between January 2012 and January 2024. Clinical data, including age, gender, BMI, underlying disease, PSG indications, the result of carbon dioxide in venous blood gas, and treatment methods were collected. Ethics committee approval was obtained from the ethics of Marmara University (Protocol no:28.06.2024.757). Parental informed consent was obtained for the patients.

Polysomnography

Polysomnography (Alice 5, Respironics, Murrysville, PA) was performed to assess respiratory parameters, sleep architecture, and treatment modalities. The following instruments were employed: electroencephalogram (EEG), electrooculography (EOG), chin and diaphragm electromyograph (EMG), thoracic and abdominal effort respiratory inductance plethysmography (RIP) bands, nasal airflow, thermistor, body position, electrocardiogram (ECG), SpO2, and a complete audio and video recording. The PSGs were manually scored by a qualified pediatric sleep physician using the American Academy of Sleep Medicine (AASM) 2012 pediatric criteria.[1,8] The apnea-hypopnea index (AHI) was calculated by dividing the total number of obstructive, central, and mixed apneas and hypopneas by the number of hours of uninterrupted sleep.[8] Obstructive AHI (oAHI) was determined by measuring the total number of obstructive apnea and hypopnea events per hour of sleep, and the oxygen desaturation index (ODI) was measured by the number of oxygen desaturations of P3% per hour of sleep.[8] Based on the patients' oAHI, the severity of OSAS was assessed.[8,9] When the oAHI is ≤ 5 events per hour but >1 event per hour, it is considered mild; when it is ≥5 events per hour but ≤ 10 events per hour, it is considered moderate; and if it is >10 events per hour, it is considered severe.[8,9] When the central apnea index (CAI) is >5 events per hour, central apnea is diagnosed.[8,9] The normal value of carbon dioxide in venous blood gas in children is usually between 35 and 45 mmHg, and above 45 mmHg was considered carbon dioxide retention.[10]

Pediatric sleep questionnaire

The Pediatric Sleep Questionnaire (PSQ) is designed to assess breathing disorders related to sleep-related symptoms.[5] This parent-reported survey includes 22 questions about snoring, observed apneas, difficulty breathing while sleeping, and other characteristics of OSAS. For pediatric SDB, a threshold of 0.33 is used to determine elevated risk.[5]

The modified epworth sleepiness scale

The Modified Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) is a validated, simple scale including eight questions with four-point Likert scale answers and aims to assess excessive daytime sleepiness (EDS) for children> 12 years old.[6,11] The ESS-CHAD score, which ranges from 0 to 24, reflects the degree of sleepiness, with higher scores indicating greater sleepiness. Scores exceeding 10 suggest excessive daytime sleepiness and potential underlying sleep disorders.[6]

Statistical analysis

Analyses were performed using Statistical Package for the Social Sciences (version 16.0; SPSS Inc.; Chicago, IL, USA). Demographic and clinical information for all patients were reported using mean and standard deviation for continuous variables and median with interquartile range. For categorical variables, frequencies and percentages were used. The Mann–Whitney U and Kruskal–Wallis tests were used to compare the study groups for data that did

not follow a normal distribution. Additionally, a chi-square test was used to compare the differences in proportions between the two independent groups. Statistical significance was set at $P < 0.05$.

RESULTS

Baseline PSG was performed in 174 patients during the study period. The median age was 10 years (25-75p, 5.1-13.5), and 124 patients (71.3%) were male. Fifty-four (31%) patients had Duchenne muscular dystrophy (DMD), 23 (13.2%) had spinal muscular atrophy (SMA), and 64 (36.8) had other myopathies. The most common indication for PSG was pCO2 retention in venous blood gas analysis, and 49 (28.2%) patients underwent PSG to assess OSAS symptoms, including snoring and open mouth breathing. Table 1 shows the clinical and demographic characteristics of all patients as well as groups according to the presence of OSAS.

According to the oAHI, 90 patients (51.7%) had normal PSG, 56 patients (32.2%) had mild OSAS, 12 patients (6.9%) had moderate OSAS, and 16 patients (9.2%) had severe OSAS. Eight patients also had central apnea, seven of whom had mixed apnea.

No statistically significant differences were observed in PSQ scores between individuals with and without OSAS. Similarly, for patients aged ≥ 12 years, ESS-CHAD scores demonstrated no significant variation between those diagnosed with OSAS and those without the condition. There was no significant difference between those with and without OSAS in terms of age, sex, BMI, and blood venous gas PCO2 results. The median AHI, OAHI, and ODI were significantly higher in the subjects with OSAS than those without OSAS ($p<0.005$). In both groups, with and without OSAS, REM stage AHI, OAHI, and ODI were higher compared to the non-REM stage. However, the differences were not statistically significant in either group ($p>0.005$).

Table 2 lists the respiratory and sleep parameters of all patients. The median OAHI was found to be 0.85 (25-75p, 0-3.1). The median OAHI was significantly higher (1.7, 0.1-3.7) in patients with OSAS symptoms compared with those

Table 1. Demographic and clinical features of the patients (n: 174)	
Age (years), median (25-75p)	10 (5.1-13.5)
Male, n (%)	124 (71.3)
Body Mass Index, median (25-75p)	17.9 (13.9-20.8)
Blood venous gas PCO_2 (mm-Hg), mean±SD	45.7±9.1
PSQ, median (25-75p)	0.28 (0.13-0.45)
ESS-CHAD, median (25-75p)	3 (1-6)
The underlying disease of the patients	
* Duchenne muscular dystrophy, n (%)	54 (31)
* Myasthenia gravis, n (%)	26 (14.9)
* Spinal muscular atrophy, n (%)	23 (13.2)
- Spinal muscular atrophy Type 2, n (%)	14 (8)
- Spinal muscular atrophy Type 1, n (%)	8 (4.6)
- Spinal muscular atrophy Type 3, n (%)	1 (0.6)
* Peripheral neuropathies, n (%)	7 (4)
* Other myopathies n (%) (congenital, metabolic, and other dystrophies, etc.)	64 (36.8)
PSG indications	
*pCO_2 retention in venous blood gas analysis, n (%)	52 (29.9)
*Snoring and open mouth breathing, n (%)	49 (28.2)
*Evaluation of respiratory muscle involvement due to neuromuscular disease without any complaint n (%)	43 (24.7)
*Witnessed apnea, n (%)	20 (11.5)
*Pre-decannulation evaluation, n (%)	6 (3.4)
*Evaluation for desaturation, n (%)	4 (2.3)

PSQ, pediatric sleep questionnaire; ESS-CHAD, modified epworth sleepiness scale; PSG, polysomnography

Table 2. Respiratory and sleep parameters from PSG (n: 174)	
AHI, median (25-75p)	1.65 (0.6-3.7)
CAI, median (25-75p)	0.3 (0-0.9)
OAHI, median (25-75p)	0.85 (0-3.1)
ODI, median (25-75p)	1.9 (0.6-5.8)
The lowest O2 saturation, median (25-75p)	92 (88.5-94)
N1 Ratio, median (25-75p)	3.7 (1.7-8.2)
N2 Ratio, median (25-75p)	53.5 (44.9-59.1)
N3 Ratio, median (25-75p)	33.5 (25-41.5)
REM Ratio, median (25-75p)	5.2 (0.2-12.7)
TST, median (25-75p)	354.1 (213-414)
WASO, median (25-75p)	30 (8.8-60)
SL, median (25-75p)	19.1 (9.4-37.9)
SE, median (25-75p)	83.7 (71.5-92)
REM Latency, median (25-75p)	129.5 (81.7-216.7)

PSG, polysomnography; AHI, apnea-hypopnea index; CAI, central apnea index; OAHI, obstructive apnea-hypopnea index; ODI, oxygen desaturation index; REM, rapid eye movement sleep; TST, total sleep time; WASO, waking up after sleep onset; SL, sleep latency; SE, sleep efficiency

with no OSAS symptoms (0.6, 0-2.4) (p=0.044). Among the patients who underwent PSG because of pCO2 retention in venous blood gas analysis (n:37), mild OSAS was found in 11 patients and severe OSAS was found in two patients. However, PSG results of 24 patients were normal.

The study's primary patient groups were DMD, SMA type 2, and myasthenia gravis (MG). The MG group had younger patients and higher BMI, but the difference was insignificant (p>0.05). OSAS was found in 59.2% of DMD patients, 55.5% of SMA type 2 patients, and 46.1% of MG patients, with no significant difference between groups (p>0.05). Age, PSQ and ESS-CHAD scores, BMI, and blood venous gas pCO2 results showed no significant differences across the groups (p>0.05), except for gender (p=0.007). Additionally, no significant differences were noted in other PSG parameters (p>0.05).

PSQ and ESS-CHAD scores did not exhibit statistically significant differences between DMD and MG patients with and without OSAS (p>0.05) (Table 3). In patients with DMD who were diagnosed with OSAS, age was significantly higher, and the venous blood gas pCO2 value was significantly elevated and exceeded 45mmHg (p<0.05) (Table 3).

After the study, treatment was initiated in 25.3% of patients (n=44). The most recommended treatment method was noninvasive ventilation (NIV) (n=37, 21.3 %). One of the six patients with a decannulation plan was decannulated, and the remaining five patients continued invasive ventilation (Table 4).

DISCUSSION

Our investigation revealed that SDB is common in patients with NMD. The PSQ and ESS-CHAD provided inadequate for diagnosing OSAS in NMD patients. PSG remains the most reliable diagnostic tool for SDB. Despite PSG being the gold standard, there is ongoing exploration of alternative diagnostic methods due to the limited availability of PSG-equipped sleep centers and the need for specialized expertise. As a result, symptom scores and questionnaires have often been used but are insufficient for detecting SDB.

Children with NMD frequently have a higher incidence of SDB compared to the general population, with estimates ranging from 27% to 62%.[12,13] Labanowski et al. reported a 42% prevalence of SDB in their study of children and adults with NMD.[14] Oros et al. found an 80.5% rate of OSAS, attributing the higher rate to PSGs conducted during the second decade of life and respiratory failure from scoliosis.[3] Our study identified OSAS in 48.3% of patients, consistent with previous findings.[13,14]

Table 3. The characteristics of DMD and MG patients with and without OSAS (n: 80)						
	Duchenne muscular dystrophy (n:54)			**Myasthenia gravis (n:26)**		
	OSAS + (n: 32)	**No OSAS (n: 22)**	**P value**	**OSAS + (n: 12)**	**No OSAS (n: 14)**	**P value**
Age (years), median (25-75p)	12.7 (10.1-14.5)	8 (7.2-11.1)	0.000*	5.5 (3.5-12.7)	7.9 (3.9-14.9)	0.410
Male/female	31/1	18/4	0.063	9/3	7/7	0.200
BMI, median (25-75p)	17.9 (14.8-22.3)	17.9 (14.9-22.7)	0.740	20.3 (17-22.7)	23 (18.7-24.5)	0.272
Blood venous gas PCO_2 (mm-Hg), mean±SD	47.8±6.4	41.8±8	0.046*	46.4±6.6	46.9±4.9	0.863
PSQ, median (25-75p)	0.2 (0.1-0.4)	0.2 (0-0.4)	0.965	0.1 (0-0.3)	0.2 (0.1-0.5)	0.347
ESS-CHAD[a], median (25-75p)	2.5 (0-6)	2 (0-6)	0.817	1 (0-4)	6 (1-9)	0.092

Duchenne muscular dystrophy, DMD; Myasthenia gravis, MG; BMI, Boddy Mass Index; PSQ, pediatric sleep questionnaire; ESS-CHAD, modified Epworth Sleepiness Scale; OSAS, obstructive sleep apnea; * Mann-Whitney U test, [a]: for aged ≥ 12 years (n: 29)

Table 4. Treatment modalities of the patients (n: 44)	
	n (%)
Noninvasive ventilation (NIV)	37 (21.3)
* Duchenne muscular dystrophy, n (%)	12 (32.4)
* Spinal muscular atrophy type 2, n (%)	3 (8.2)
* Myastenia gravis, n (%)	4 (10.8)
* Other myopathies n (%) (congenital, metabolic, and other dystrophies etc.)	12 (32.4)
* Others, n (%)	6 (16.2)
Continuation of Invasive Ventilation, n (%)	5 (2.9)
Decannulation, n (%)	1 (0.6)
Supplemental Oxygen, n (%)	1 (0.6)

The PSQ has shown differing efficacies in detecting OSAS across various patient groups. In healthy children, it demonstrated high sensitivity for moderate OSAS.[15] Bamaga et al. found that the PSQ detected OSAS in 36.7% of children with DMD.[16] In our center's comorbid patients, the PSQ's sensitivity and specificity were 71.8% and 40.4%, respectively.[17] EDS is a key OSAS symptom in adults, and the ESS is a validated screening tool for this condition.[18] However, EDS is not common in children, and ESS-CHAD does not correlate with pediatric OSAS.[19] Our study found that PSQ and ESS-CHAD were inadequate for predicting OSAS in children. While the PSQ is effective for screening healthy children, it was less successful in identifying those with underlying diseases.[20] Solis et al.'s findings in syndromic patients also support our results.[21]

DMD and SMA patients exhibited a higher incidence of pediatric OSAS compared to healthy controls.[22,23] Chacko et al. noted that SMA types 1 and 2 are more prone to SDB, while type 3 is less affected.[24] Our patient group, primarily with SMA type 2, similarly showed a higher occurrence of OSAS (55.5%). Suresh et al. found OSAS in 31% of DMD patients, whereas our study detected it in 59.2% of DMD patients.[25] Our study detected OSAS in 59.2 % of DMD patients. The higher OSAS rate in our study may be due to the use of PSG in younger patients (first decade), which increases detection rates. Conversely, Suresh's study mainly performed PSG in patients in their second decade of life, noting a higher frequency of nocturnal hypoventilation.

Respiratory muscle involvement in DMD worsens with age. Our study found that DMD patients with OSAS were older than those without OSAS. M. Romei et al. also noted age-related increases in respiratory muscle involvement.[26] Additionally, pCO2 retention in venous blood gas may indicate respiratory muscle involvement in NMD. In our study, DMD patients with OSAS had venous blood gas pCO2 values exceeding 45 mmHg. Hukins et al. identified a venous blood gas pCO2 value ≥45 mmHg in DMD patients as a sensitive and specific indicator of SDB.[27] These findings suggest that respiratory muscle involvement may begin around age 10 years, coinciding with the expected loss of ambulation, indicating the need for PSG at this age.[28]

In patients with NMD, SDB may develop prior to the onset of respiratory failure symptoms and present as daytime hypercapnia.[29] In our study, the most common indication for PSG was pCO2 retention in the venous blood gas analysis, and this indication was most common in the SMA group. Labanowski et al. reported that nocturnal hypoventilation and daytime hypercapnic respiratory failure are frequently observed in patients with NMD, particularly in SMA type 2 patients.[14] Although the most common indication was pCO2 retention in our patients, PSG findings were normal in 26 patients. This may be because capnography cannot be performed simultaneously with PSG, and nocturnal hypoventilation cannot be evaluated.

Noninvasive ventilation (NIV) is crucial for managing respiratory involvement in NMD.[30] In our study, 25.2% of patients received treatment, with NIV being the most common method. Oros et al.'s study on 108 NMD patients showed a higher NIV rate of 36.8%.[3] The lower treatment rate compared to the OSAS rate is due to the mild OSAS patient group being ambulatory, young, and under close monitoring. There are no established clinical criteria for initiating NIV support for NMD. Thus, close monitoring and NIV initiation based on clinical suspicion are planned for these patients.[12]

Our retrospective study may have limitations, such as incomplete patient data and a small number of individuals with specific conditions like myopathies. Nonetheless, the

findings could guide the design of future, more refined research.

CONCLUSION

Our single-center study indicates that the PSQ and ESS-CHAD are ineffective for identifying SDB in children with NMD, with PSG remaining the gold standard for diagnosis. OSAS is a significant and common condition in pediatric NMD patients, exacerbating symptoms and diminishing quality of life. Early diagnosis and treatment of OSAS are crucial, necessitating a comprehensive understanding of its diagnosis, technology, prognosis, and long-term care.

Ethical approval

This study has been approved by the Marmara University Ethics Committee (approval date 28.06.2024, number 2024.757). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: MYK, APE, EEE; data collection: EEB, FÖ, MAY, CAY, NMÇ, MS, ŞK; analysis and interpretation of results: MYK, EEE, YG, BK; draft manuscript preparation: MYK. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Research Article

Can SLS-free toothpastes help children with Behçet's disease and recurrent oral aphthae?

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ABSTRACT

Objective: Sodium Lauryl Sulfate (SLS), a synthetic detergent commonly used in toothpaste, has been implicated in various studies as a cause or trigger of Recurrent Oral Ulcers (ROU). This study aimed to assess the efficacy of SLS-free toothpaste recommendations in pediatric cases with isolated ROU and Behçet Disease (BD). As a secondary aim, we also evaluated whether BD developed during the follow-up of cases with ROU.

Method: This is a retrospective cohort study. Patients who received SLS-free oral care recommendations due to ROU or BD and had at least six months of follow-up data were included between February 2023 and August 2023. The clinicians did not recommend specific brands for the SLS-free oral care products. The follow-up parameters included the visual analog scale (VAS, 0-10), the total number of attacks over three months, the average number of ulcers per attack, and the average duration.

Results: The follow-up data included 78 patients with ROU and 14 patients diagnosed with BD. The mean follow-up duration was 23 ± 7 months. None of the patients referred for ROU developed BD during the follow-up. The initial VAS scores, number of attacks, number of ulcers per attack, and attack duration were higher in BD patients than in ROU patients. During the follow-up visit after initiating SLS-free toothpaste (at least three months), 38 (48.7%) ROU patients reported lower VAS scores. Six patients with BD reported a decrease in the frequency of attacks. However, there were no statistically significant differences between the baseline and 6-month data regarding the number of ulcers, VAS scores, number of attacks, or attack duration.

Conclusion: SLS-free toothpaste could be a good recommendation for ROU cases. Although our limited number of BD cases did not yield statistically significant results, as previously mentioned, some patients reported lower pain scores and fewer attacks.

Keywords: sodium lauryl sulfate, aphthous ulcer

INTRODUCTION

Recurrent oral ulcer (ROU) is the most common inflammatory disease of the oral mucosa, affecting 5%-25% of the pediatric population.[1] It is characterized by one or more painful ulcers covered with a white or grayish pseudomembrane and surrounded by a well-defined erythematous halo. These ulcers typically heal spontaneously within 4-7 days.[2] However, their painful nature can impair speaking, swallowing, and chewing, thereby affecting quality of life. The etiology of ROU has not yet been clarified. Immune issues, vitamin deficiencies, stress, local trauma, infections, and diet are implicated in its etiology.[3] The high prevalence of ROU in the parents of children with ROU suggests a potential genetic predisposition. ROU is also a common reason for referral to pediatric rheumatology clinics because it can be a symptom of rheumatologic diseases like Behçet's disease (BD) and Periodic Fever, Aphthous Stomatitis, Pharyngitis,

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and Cervical Adenitis (PFAPA) syndrome. Increasing shared single nucleotide polymorphisms (SNPs) in ROU, PFAPA, and BD indicate that some cases may be on a shared spectrum.[4] Although variable rates have been reported in the literature, recurrent oral aphthae in BD have been reported with a rate of 97%.[5] However, ROU is rarely caused by underlying BD, and PFAPA is distinguished from isolated ROU by its characteristic features.

Sodium Lauryl Sulfate (SLS), a synthetic detergent commonly used in toothpaste, has been implicated in various studies as a cause or trigger of ROU.[6] It is thought to increase the penetration of exogenous antigens into the oral mucosa by affecting the barrier function.[7] It is also known to cause contact dermatitis by increasing epidermal water loss. The literature contains conflicting results from studies evaluating the frequency of ROU with SLS-free toothpaste. However, the efficacy of SLS-free toothpaste recommendations has yet to be evaluated in BD. In this study, we aimed to assess the efficacy of SLS-free toothpaste recommendations in pediatric cases with isolated ROU and BD. As a secondary aim, we also evaluated whether BD developed during the follow-up of cases with ROU.

MATERIAL AND METHODS

This study is a retrospective cohort analysis. Patients who received SLS-free oral care recommendations due to ROU or BD and had at least six months of follow-up data were included between February 2023 and August 2023. BD patients met the PEDBD (Pediatric Behçet's Disease Criteria)[8] and ICBD[9] (International Criteria for Behçet's Disease). Before diagnosing recurrent oral ulcers (ROU), the following conditions were excluded based on clinical examination, patient history, or laboratory tests: (Immunological deficiencies, hormonal disorders, hematological deficiencies, trauma, medications, microorganisms, oral streptococci, helicobacter pylori (H. pylori), herpes viruses). The clinicians did not recommend specific brands for the SLS-free oral care products. Patients with ROU who simultaneously started vitamin replacement therapy due to deficiencies were excluded. Additionally, cases in which patients had never brushed their teeth or brushed irregularly were excluded. Only BD patients received colchicine treatment. No other medication was used in both groups. Those who had a simultaneous colchicine dose adjustment or were initiated on immunosuppressive therapy to their treatment were excluded. Incomplete patients were excluded from the study. The follow-up parameters included the visual analog scale (VAS, 0-10), the total number of attacks over three months, the average number of ulcers per attack, and the average duration. The follow-up frequency for patients with BD was every three months. Patients with ROU had follow-up visits every three months. The aim was to evaluate the baseline and 6th-month data for patients with BD and the baseline, 3rd-month, and 6th-month data for patients with ROU.

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 26.0, and JASP Version 0.18.3. The normality of the data was assessed using graphical methods, the Shapiro-Wilk test, and the Kolmogorov-Smirnov test, while Levene's test was used to determine the homogeneity of variances. Non-parametric tests were utilized for non-normally distributed data. Descriptive statistics included median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. The Mann-Whitney U test compared two independent groups, the Wilcoxon signed-rank test compared baseline and follow-up measurements in the same sample, and the Friedman test evaluated more than two related groups. Post-hoc analyses, employing the Wilcoxon signed-rank test with Bonferroni correction, were conducted when the Friedman test indicated significant differences. A significance level of $p<0.05$ was used for all statistical analyses. The Ethics Committee approved the study, and written informed consent was obtained from the patients or parents per the Helsinki Declaration.

RESULTS

The follow-up data included 78 patients with ROU and 14 patients with BD. Among the ROU patients, 35 (44.9%) were female. The mean age at presentation was 9.1 ± 3.4 years. Among the patients diagnosed with BD, nine were male, and five were female. The mean age was 13 ± 3.7 years. All patients had oral aphthae, genital aphthae, and skin findings (erythema nodosum), with no additional findings. The minimum follow-up duration was nine months, and the maximum was 37 months. None of the patients referred for ROU developed BD during the follow-up. The initial VAS scores, number of attacks, number of ulcers per attack, and attack duration were higher in BD patients than in ROU patients (Table 1, Figure 1).

During the follow-up visit after initiating SLS-free toothpaste (at least three months), 38 (48.7%) ROU patients reported reduced VAS scores. Additionally, 42 (53.8%) patients had fewer attacks over the three months. The decrease in VAS scores and attacks in the third month was statistically

Table 1. The patients' initial VAS scores, frequency of attacks, number of ulcers per attack, and duration of each attack			
Variable	**Group**	**n**	**Mean Rank / P-value**
Visual Analog Scale	ROU	78	41.46
	BD	14	74.57
			p < 0.001*
Number of Episodes	ROU	78	41.26
	BD	14	76.68
			p < 0.001*
Number of Ulcers	ROU	78	43.75
	BD	14	61.82
			p = 0.014*
Duration of Episode	ROU	78	43.71
	BD	14	62.04
			p = 0.013*

ROU: recurrent oral ulcers; BD: Behçet disease

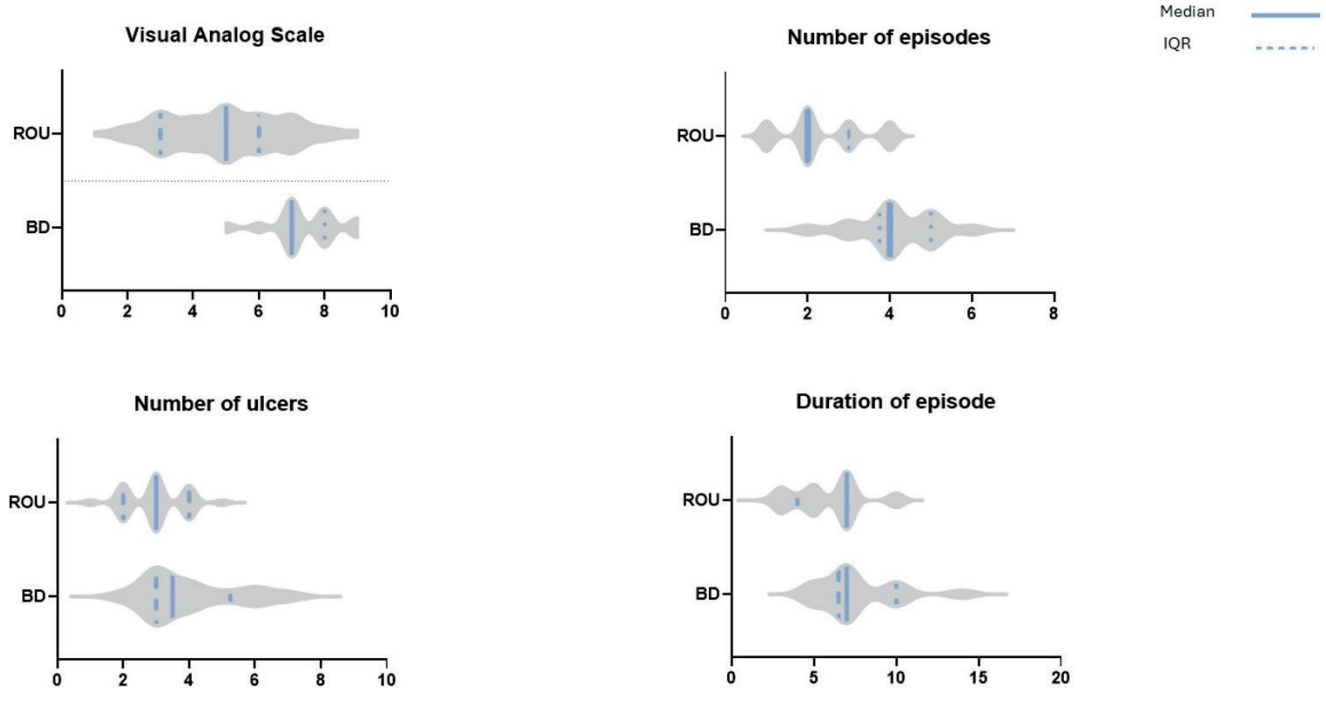

Figure 1. The patients' initial VAS scores, frequency of attacks, number of ulcers per attack, and duration of each attack

ROU: recurrent oral ulcers; BD: Behçet disease

significant. In contrast, the average number of ulcers per attack and the attack duration remained unchanged (Table 2, Figure 2).

Twenty-nine patients were lost to follow-up the 6-month follow-up after the initial change. Of these, 15 patients reported reductions in VAS scores and the number of attacks at the 3-month follow-up. Five patients had a reduction in VAS scores, while nine patients showed no decrease in either attack frequency or VAS scores. Of the 49 patients with follow-up data, 13 experienced a reduction in VAS scores during the follow-up despite no reduction in the first three months. Six patients reported lower VAS

Table 2. Baseline and 3-month parameters of patients with recurrent oral aphthae					
Variable	**Group**	**n**	**IQR**	**Mean ± SD**	**p-value**
Visual Analog Scale	SLS Paste	78	5 (3-6)	4.99 ± 1.82	<0.01*
	SLS-free Paste	78	2 (3-5)	3.78 ± 1.95	
Number of Episodes	SLS Paste	78	2 (2-3)	2.38 ± 1.02	<0.01*
	SLS-free Paste	78	2 (1-3)	1.87 ± 0.97	
Number of Ulcers	SLS Paste	78	3 (2-4)	2.97 ± 0.91	0.483
	SLS-free Paste	78	3 (3-4)	3.14 ± 0.87	
Duration of Episode	SLS Paste	78	7 (4-7)	5.88 ± 2.09	0.187
	SLS-free Paste	78	5 (4-7)	5.68 ± 2.17	

SLS: sodium lauryl sulfate
*P value was considered significant when < 0.05.

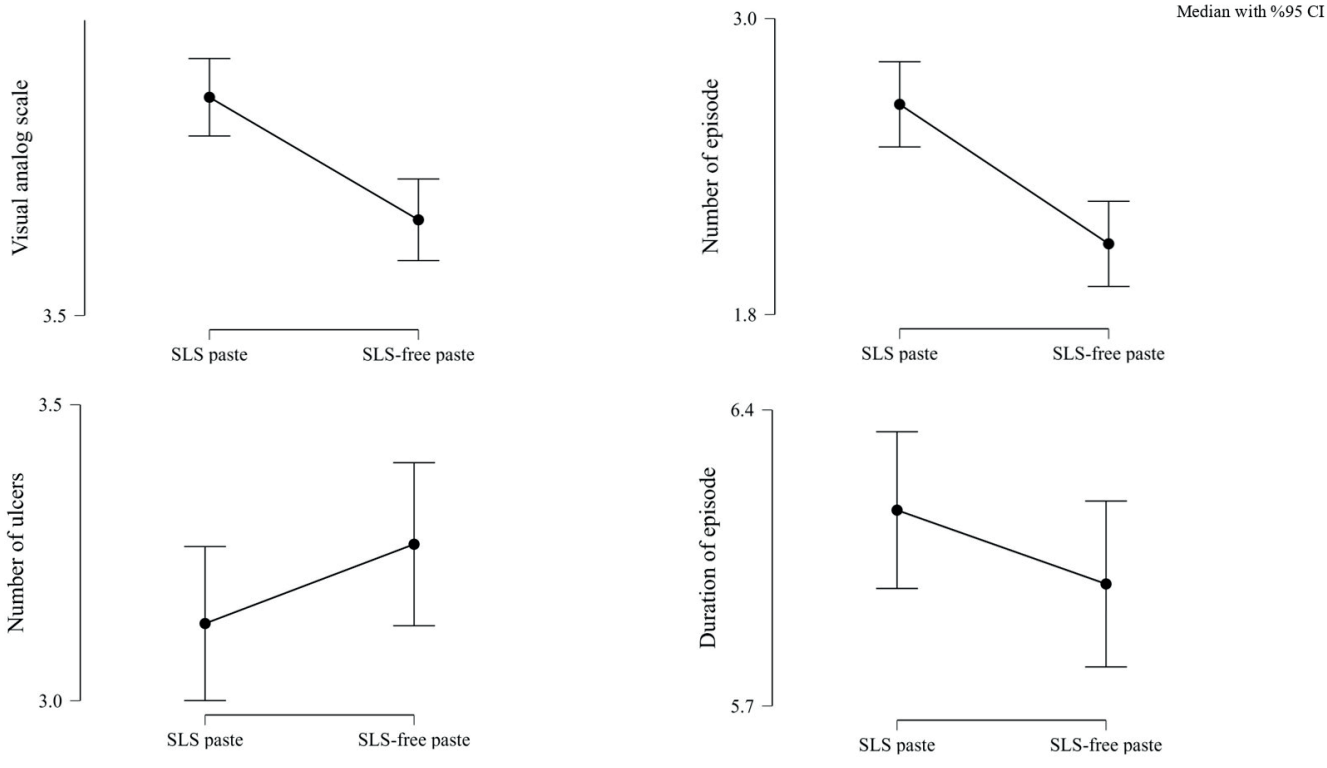

Figure 2. Baseline and 3-month parameters of patients with recurrent oral aphthae

SLS: sodium lauryl sulfate

scores at the 6-month follow-up than the 3-month follow-up. When comparing VAS scores at baseline, three months, and six months, the 6-month scores were significantly lower than the baseline scores. The number of attacks also significantly decreased between the baseline and 6-month follow-up data (Table 3, Figure 3). The number of ulcers per attack and attack duration were not reassessed for these patients.

Six patients with BD reported a decrease in the frequency of attacks. However, there were no statistically significant differences between the baseline and 6-month data regarding the number of ulcers, VAS scores, number of attacks, or attack duration (Table 4).

Table 3. Baseline, 3-month, and 6-month parameters of patients with recurrent oral aphthae

Variable	n	Friedman p-value	Pairwise Comparisons (Wilcoxon)	Wilcoxon Test (Wi)	p-value	Bonferroni Adjusted p-value
Visual Analog Scale	49	0.001*	Baseline	99.500,	0.006a-b*	0.017 a-b*
			3M	149.000	0.001a-c*	0.004 a-c*
			6M	252.000	0.606b-c	1.000 b-c
Number of Episodes	49	0.016*	Baseline	198.000	0.023a-b*	0.070a-b*
			3M	89.000,	0.004a-c*	0.012a-c*
			6M	95.500	0.160b-c	0.480b-c

M: months; a: baseline; b: 3 months; c: 6 months
Pairwise comparisons: Baseline, 3 Months, and 6 Months. Significant differences are marked with * (Bonferroni-adjusted p < 0.05). Non-significant comparisons are also shown for completeness.
*P value was considered significant when < 0.05.

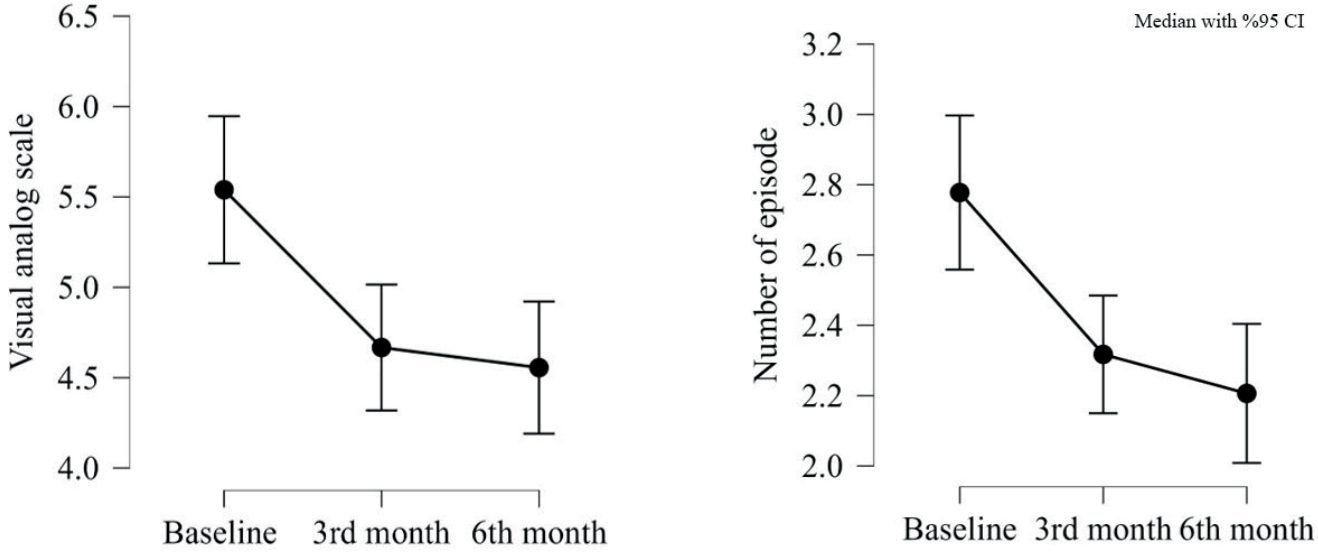

Figure 3. Baseline, 3-month, and 6-month parameters of patients with recurrent oral aphthae

Table 4. Baseline and 6-month data on the number of ulcers, VAS scores, frequency of attacks, or attack duration in Behçet's patients

Variable	Group	n	IQR	Mean ± SD	p-value
Visual Analog Scale	SLS Paste	78	5 (3-6)	4.99 ± 1.82	<0.01*
	SLS-free Paste	78	2 (3-5)	3.78 ± 1.95	
Number of Episodes	SLS Paste	78	2 (2-3)	2.38 ± 1.02	<0.01*
	SLS-free Paste	78	2 (1-3)	1.87 ± 0.97	
Number of Ulcers	SLS Paste	78	3 (2-4)	2.97 ± 0.91	0.483
	SLS-free Paste	78	3 (3-4)	3.14 ± 0.87	
Duration of Episode	SLS Paste	78	7 (4-7)	5.88 ± 2.09	0.187
	SLS-free Paste	78	5 (4-7)	5.68 ± 2.17	

SLS: sodium lauryl sulfate
*P value was considered significant when < 0.05.

DISCUSSION

Sodium Lauryl Sulfate is a detergent and foaming agent widely used in toothpaste. The foam facilitates the spreading of the toothpaste in the oral cavity and provides a sense of cleanliness.[10] SLS also serves as a plaque-cleaning agent by loosening and emulsifying plaque deposits, which aids in their removal and may help prevent periodontal diseases.[11] Lastly, it exhibits antimicrobial effects by disrupting bacterial cell integrity and inhibiting their metabolic activities.[12]

Despite these beneficial effects, the weakening of membrane integrity makes the oral mucosa more vulnerable to trauma and irritants. This can lead to apoptosis and inflammatory reactions.[13] In patients with ROU, elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 have been observed, exacerbating the inflammatory response and prolonging ulcer healing.[14]

Mouth rinses containing concentrations higher of Sodium Lauryl Sulfate (SLS) than those found in commercially available toothpaste have been shown to cause prolonged burning sensations and mucosal erosion. Barkvoll and Rolla were the first to demonstrate in the literature that using SLS-free toothpaste significantly reduced ulcer incidence.[15] In a randomized controlled trial, the use of SLS-free toothpaste was associated with lower pain scores and ulcer incidence; however, no changes were observed in ulcer count or healing time.[16] Another study, primarily involving adult patients, found no benefits for any parameter.[17] However, a systematic review analyzing the results of four studies found that SLS-free paste usage was associated with reductions in all four parameters.[18]

This study is the first to evaluate the effectiveness of SLS-free toothpaste in pediatric BD and ROU. Due to the high prevalence of BD in Turkey, oral aphthae in pediatric cases are a significant source of stress for families. During our 9–37-month follow-up period, patients referred for isolated ROU did not develop other clinical features of BD. Notably, patients with BD (though the number of observations was limited) reported more frequent attacks, a higher number of ulcers, and higher VAS scores.

While nearly half of the patients reported lower attack frequency and VAS scores, the number of ulcers and the duration of attacks did not change, suggesting that SLS might contribute as a potential exacerbating factor in the multifactorial process.

CONCLUSIONS

SLS-free toothpaste may be recommended for ROU cases. Although our limited number of BD cases did not yield statistically significant results, as previously mentioned, some patients reported lower pain scores and fewer attacks. It is not a medication and is cost-effective, so it can be tried while adhering to existing treatment algorithms. Well-designed studies are warranted for BD cases as well. Clinicians recommended SLS-free oral care without endorsing a specific brand, and patients might have eliminated other toothpaste ingredients through different brand preferences. This was not scrutinized in our routine evaluations. The small number of patients, particularly in the BD cohort, might have prevented the detection of potential clinical efficacy statistically. Due to the retrospective nature of the study, there is a possibility of recall bias.

Ethical approval

This study has been approved by the Hacettepe University Health Sciences Research Ethics Committee (approval date 08.10.2024, number 2024/17-48). Written informed consent was obtained from the participants.

Author contribution

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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Research Article

Rituximab in pediatric B-cell Non-Hodgkin Lymphoma: Clinical outcomes and prognostic implications

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ABSTRACT

Objective: B-cell Non-Hodgkin Lymphoma (B-NHL) is an aggressive malignancy in children requiring prompt multidisciplinary management. This retrospective cohort study aims to evaluate the clinical characteristics, treatment outcomes, and impact of rituximab (RTX) in pediatric B-NHL patients.

Methods: We retrospectively analyzed 62 pediatric B-NHL patients treated at tertiary centers. Patient demographics, clinical presentation, histopathological subtypes, disease stage, treatment regimens, and survival outcomes were assessed. Event-free survival (EFS) and overall survival (OS) rates were analyzed based on lactate dehydrogenase (LDH) levels and RTX administration.

Results: The mean age at diagnosis was 8.73±4.3 years, with a male predominance (79%). The most common histological subtype was Burkitt lymphoma (BL) (53.2%), followed by diffuse large B-cell lymphoma (DLBCL) (33.8%). Advanced-stage disease (III-IV) was observed in 74.1% of cases. RTX was administered in 72.5% of patients, with a mean of 5.1±2.7 doses. Febrile neutropenia (FEN) was noted in 74.1%, with intensive care unit (ICU) admission required for seven patients. Mortality was observed in 12 (19.3%) patients, including all patients with primary immunodeficiency (PID). The 5-year EFS for the entire cohort was 67.2%, and OS was 81.3%. Patients with LDH <400 U/L had superior 5-year EFS (88.9%) and OS (96.3%) compared to those with LDH >400 U/L (EFS: 49.6%, OS: 70.7%; p=0.004 and p=0.015, respectively). In RTX-treated patients without PID, EFS was 76.5% versus 73.2% in those without RTX, but the difference was not statistically significant (p=0.53).

Conclusions: Although not statistically significant, EFS was found to be higher in the RTX-treated group, suggesting that adding RTX to standard chemotherapy regimens may improve survival, particularly for high-risk patients, though its benefit in low-risk cases remains uncertain. Despite improved survival, patients with PID had poor outcomes, likely due to increased infections and disseminated disease. Risk-adapted, targeted treatment strategies are essential for optimizing outcomes in pediatric B-NHL. Further large-scale, randomized controlled trials are needed to confirm the efficacy of RTX in different risk groups and to optimize treatment regimens for pediatric B-NHL.

Keywords: rituximab, non-hodgkin lymphoma, primary immunodeficiencies

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INTRODUCTION

Non-Hodgkin lymphoma, accounting for only 7% of cancers in the pediatric population younger than 20 years old, is an important tumor due to its high grade.[1] Certain variables, such as geographical location, age, gender, race, whether the patient is infected with Ebstein-Barr virus or diagnosed with an inherited disease associated with cancer development, and the patient's immune status impact incidence.[2]

Despite the improved survival rates, as high as ≥95% 5-year event-free survival (EFS) rate and 80-90% 5-year overall survival (OS), the outcome depends on many factors, including stage and histology of the disease. It should be underlined that, except for anaplastic large cell lymphoma, regardless of histology, response failure to first-line therapy is an independent prognostic factor.[3] In addition to this, toxicities experienced during the courses are still a matter of debate.[2,4]

Mature B cell lymphomas account for nodal marginal zone lymphoma (NMZL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), primary mediastinal (thymic) large B-cell lymphoma, ALK (anaplastic lymphoma kinase) positive large B-cell lymphoma, Burkitt Lymphoma (BL), and B-cell lymphoma unclassifiable (B-NHL, NOS). Among them, low-grade NHL, such as FL and NMZL, are rare in childhood.[2] B-cell NHLs are commonly treated with regimens containing corticosteroids, high-dose methotrexate and cytarabine, alkylating agents, prophylactic/intense (in the presence of central nervous system involvement) intrathecal injections. The protocols frequently consist of short, however intensive chemotherapy cycles. Therefore, the frequency of short-term toxicities is increased for patients with B-NHL. Although long-term toxicity incidence is still acceptable, precautions should be undertaken to reduce the risk of cardiovascular complications and secondary malignancies.[5,6]

In recent years, Rituximab (RTX) (Anti-CD20 monoclonal antibody) has been proven to have an efficacy both on EFS and OS in large-scale phase 3 trials, whilst it has been utilized in the standard care of patients with B-NHL in adulthood, combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) regimen.[7] The present study is designed as a retrospective cohort evaluating the effects of RTX on both EFS and OS.

MATERIAL AND METHOD

In the current study, 62 patients diagnosed with B-NHL who had been admitted to the Pediatric Hematology and Oncology Departments of Erciyes, Van Yüzüncü YIl, Sakarya, Dicle, Hasan Kalyoncu Universities and Gaziantep City Hospital between the years 2005 and 2024 were enrolled in the study. The demographical data, stage, and histology of the disease, treatment regimens, and treatment outcomes were obtained from the patient files. Besides, the frequency of treatment-related complications, for example, febrile neutropenia and fungal infections, intensive care unit admission, and the necessity of granulocyte-macrophage colony-stimulating factor and/or immunoglobulin utilization in the periods of severe infections were evaluated.

The staging and risk group stratification were assessed in accordance with the NHL-BFM protocol designed by the Berlin-Frankfurt-Münster Group. According to this protocol, risk group stratification depends on the resection status of the tumor, stage, and serum lactate dehydrogenase (LDH) level on admission. The staging system is primarily based on St Jude's staging.[8-10] R1 risk group is defined as the completely resected tumor, R2 is defined as stage I or II disease with an incomplete resected tumor, or stage III disease with an LDH level of <500 U/L. Whereas R3 is defined as stage III disease with an LDH level equal to or higher than 500 U/L and lower than 1000 U/L, or stage IV Burkitt Leukemia with an LDH level <1.000 U/L and no involvement of central nervous system (CNS). R4 is defined as stage III disease with an LDH level of >1.000 U/L or stage IV Burkitt leukemia with an LDH level of ≥1.000 U/L in the presence of CNS negativity. In the presence of CNS involvement, cases are classified as R4 CNS+.[8-10]

The primary endpoint of this retrospective cohort was to achieve information on event-free (EFS) and overall survival rates (OS). Besides, the effect of monoclonal anti-CD20 antibody RTX on survival and side effects was evaluated.

Continuous data were compared using the Student t-test if normally distributed; if not, they were compared using the Mann-Whitney U test. Also, proportions were compared with the x2 test and Fisher exact test. Survival was evaluated with Kaplan Meier and Log-rank tests. A p-value<0.05 was considered statistically significant. Results were analyzed using SPSS version 22.0 software.

RESULTS

Of the 62 patients enrolled in the study, only 13 (21%) were female and 49 (79%) were male. Regarding the subtypes of B-NHL, 33 patients (53.2%) were diagnosed with BL, 21 (33.8%) with DLBCL, 2 (3.2%) with ALBCL, and 1 (1.6%) with FL, 1 (1.6%) with plasmoblastic lymphoma, and B-cell lymphoblastic lymphoma (BCLL, NOS) with indistinguishable subgroup was detected in 4 patients (6.4%). Four patients were solid organ transplanted (3 of them liver and one kidney transplantation). Of which two were diagnosed with BL, whereas two were diagnosed with DLBCL. The mean age was 8.73 (±4.3) years, whereas the median age was 8.9 years (minimum 6 months - maximum 17 years) on admission. The most common signs and symptoms on admission were swelling in the cervical area and palpable lymphadenomegaly observed in 25 (40.3%) patients, followed by abdominal distension and pain in 27 (43.5%) patients. Of the patients admitted with cervical lymphadenomegaly, 6 had shortness of breath, 5 had cough, and 4 had hoarseness. Among the patients with abdominal symptoms, 4 of them had been admitted with the clinical findings of intussusception, requiring urgent surgical intervention.

Regarding the primary sites of disease, 31 patients (50%) had abdominal, 23 (37%) had cervical, and 8 (12.9%) had mediastinal involvement. CNS involvement was present in only 2 (3.2%) patients. 5 (8%) had bone marrow involvement. Three patients (4.8%) had both bone and bone marrow disease. In contrast, four patients (6.4%) had effusions and organ involvements like liver and kidney. Considering the stages of disease according to St Jude's staging system; 16 patients (25.8%) had stage II, 34 (54.8%) had stage III, and 12 patients (19.3%) had stage IV disease. Seventeen patients (27.4%) were stratified in R2, 30 (48.4%) in R3, and 15 (24.2%) in R4 risk group.

Table 1. Baseline characteristics of the patients

Characteristics	**N: 62 (%)**
Gender	
Female	13 (21%)
Male	49 (79%)
Age	
Mean±SD	8.73 (±4.3) years
Median (min-max)	8.9 years (minimum 6 months - maximum 17 years)
Diagnosis	
Burkitt Lymphoma	33 (53.2%)
Diffuse large B-cell lymphoma	21 (33.8%)
B-NHL, not otherwise specified	4 (6.4%)
Follicular Lymphoma	1 (1.6%)
Plasmoblastic Lymphoma	1 (1.6%)
Risk group	
R2	17 (27.4%)
R3	30 (48.4%)
R4	15 (24.2%)
Stage of disease (Murphy)	
Stage II	16 (25.8%)
Stage III	34 (54.8%)
Stage IV	12 (48.4%)
Primary site	
Abdomen	31 (50%)
Mediastinum	8 (12.9%)
Cervical lymph nodes	23 (37%)

SD: standard deviation; NHL: non-hodgkin lymphoma; R2: risk group 2; R3: risk group 3; R4: risk group 4

Table 2. Diagnosis of patients with primary immunodeficiencies

No	Primary Diagnosis	Type of NHL
1	Nijmegen Breakage Syndrome	BL
2	XLF deficiency	DLBCL
3	CD137 deficiency	DLBCL
4	TNFRSF13B mutation	DLBCL
5	MSH6 mutation	DLBCL
6	FCHO1 deficiency	DLBCL
7	FCHO1 deficiency	DLBCL
8	RASGRP1 mutation	DLBCL
9	DIAPH1-Deficiency	Plasmoblastic Lymphoma
10	IL-2 gamma receptor deficiency	DLBCL

BL: burkitt lymphoma; DLBCL: diffuse large B cell lymphoma

Considering the treatment regimens utilized in therapy, NHL-BFM protocol was initiated in 42 patients (67.7%) based on the risk groups, EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) in 5 patients (8%), CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in 11 patients (17.7%) with primary immunodeficiency (PID), and LMB89 protocol in 4 patients (6.4%). The demographical data of the whole cohort and the exact diagnosis of the 10 (16.1%) patients with PID are available in Table 1 and Table 2, respectively.

RTX was utilized in 45 (72.5%) patients with a mean number of applications of 5.1±2.7 times and a median of 5 times (minimum 1- maximum 17 times) with the dose of 375 mg/m.^{2} All the patients with PID received RTX. Before the intravenous administration of RTX, premedication with antihistamine and analgesic drugs was utilized. No adverse events related to administration were observed. Twenty-three patients (51.1%) had intravenous immunoglobulin (IVIG) in addition to RTX treatment.

Regarding the laboratory evaluation on admission, five patients (8%) had leukopenia with WBC <5000/ mm^3 and three patients (4.8%) had PLT levels < 100,000/ mm^3. Neutropenia was present in 2 patients (3.2%) and lymphopenia in 6 patients (9.6%). Impaired renal functions were detected in only two patients (3.2%) and elevation in transaminases in 12 (19.3%) patients. Mean LDH level was 655 U/L ±915 U/L and median 428 U/L (minimum 191 U/L-maximum 6564 U/L). The mean uric acid level was 5.6 mg/dl ±3.7 mg/dl, and the median was 5.4 mg/dl (minimum 1mg/dl- maximum 29 mg/dl). Regarding LDH levels, patients with LDH levels below 400 U/L (n:27, 43.5%) had 5-year EFS and OS of 88.9% and 96.3%, respectively. Whereas patients with LDH levels >400 U/L (n:32, 51.6%) had 5-year EFS of 49.6% and OS of 70.7%. The differences between the groups were statistically significant, with p level of 0.004 for EFS and 0.015 for OS, and available in Figure 1.

Febrile neutropenia (FEN) was determined in 46 patients (74.1%). The mean number of FEN episodes was 2.8±1.2, and the median number was 1 (minimum 0- maximum 4). Seven patients with FEN had intensive care unit (ICU) admission. Documented fungal infections were observed in 3 of the patients. One of them was the patient with PID who died owing to Candida parapsilosis sepsis. The second patient's primary diagnosis was cystic fibrosis (CF), and had recovered from DLBCL. Candida albicans sepsis resulted in the mortality of this patient. The third one was diagnosed with BL; no underlying disease was present. The blood cultures resulted in Candida parapsilosis in this patient as well.

Twelve of the patients (19.3%) died. All of these patients had RTX in treatment. Of them, seven patients had the diagnosis of primary immunodeficiency, and one was presented as a posttransplant lymphoproliferative disease owing to immunosuppression after liver transplant. Regarding the rest of the patients, 2 of them had disseminated disease with bone and bone marrow involvement, 1 CNS involvement, and 1 had refractory ALBCL.

5-year EFS for the whole group was 67.2%, whereas 76.5% in the group received RTX, excluding the patients with PID and 73.2% who did not. The difference was not statistically significant, with a p-value of 0.53. The mean follow-up time was 7.2 (±5.3) years. 5-year OS was 81.3% in the whole cohort. Survival analyses are available in Figure 2.

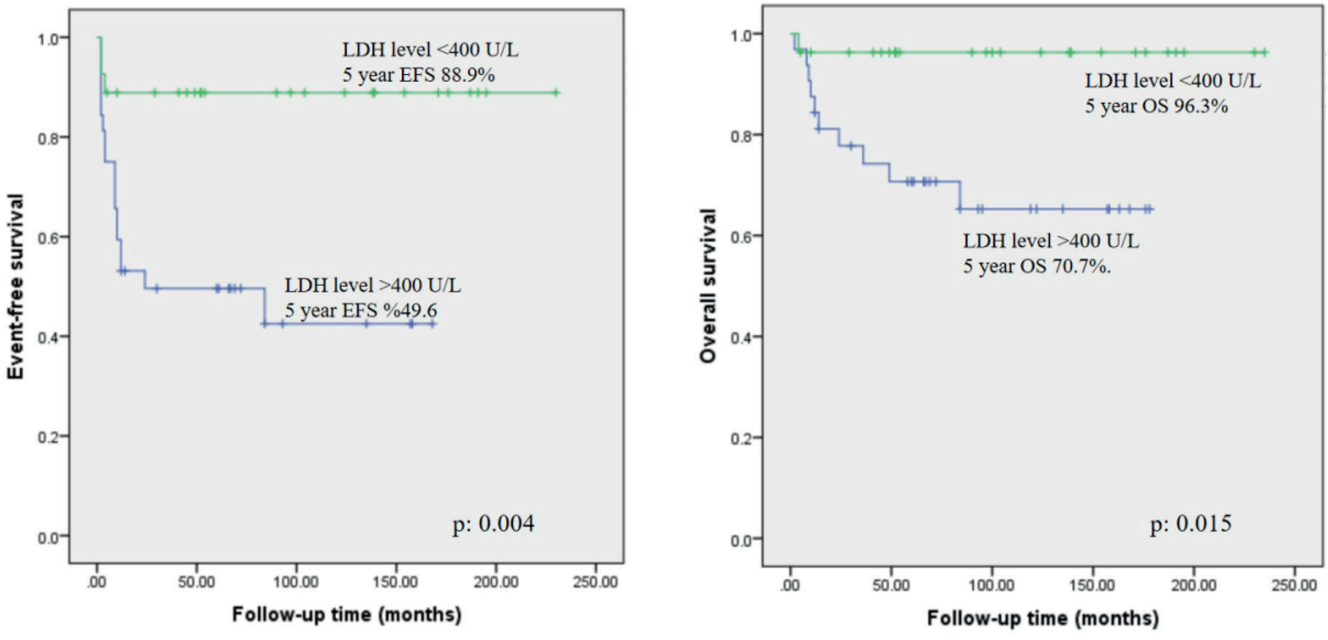

Figure 1. Event-free and overall survival depending on the LDH levels on admission

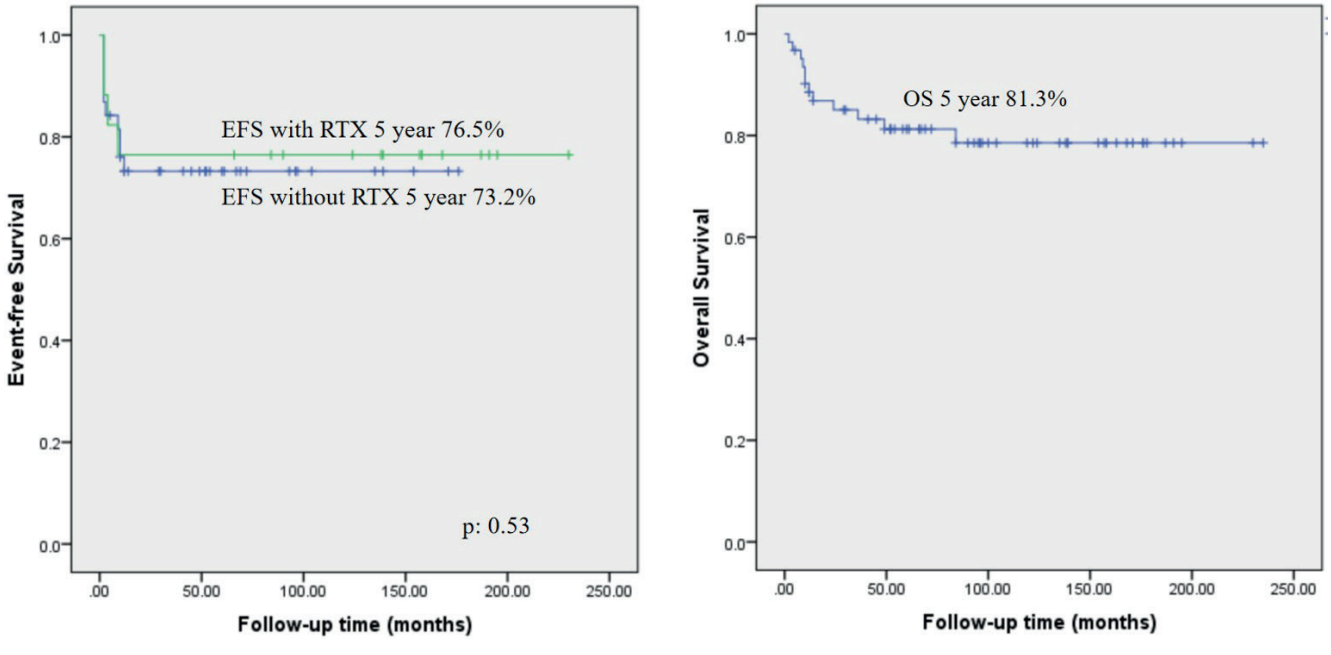

Figure 2. a. Event-free survival for the groups with and without RTX, excluding the patients with primary immunodeficiency. **b.** Overall survival for the whole cohort

DISCUSSION

Rituximab has been widely recognized for its efficacy in treating B-NHL, significantly improving OS and EFS rates in various histological subtypes. B-NHL, one of the highest-grade diseases in childhood, needs prompt management with a multidisciplinary approach. The mean age at onset is reported to be around 10 years in literature, which was 8.73 years for our retrospective cohort.[10] Our cohort demonstrated a male dominancy, similar to the literature, except for primary mediastinal B-cell Lymphoma.[2,10] The effects of age and gender have been evaluated in large-scale cohorts in literature. These studies disclosed that age and gender have impacts on both OS and EFS based on the histological subtype.[11]

In literature, both acquired and inherited immunodeficiencies are disclosed to be related to malignancy predisposition. Regarding the PIDs, NHL is the most common malignancy, followed by Hodgkin Lymphoma.[12-18] Comparing the immunocompetent patients, patients with underlying immunodeficiency have dismal survival rates. However, in the era of targeted therapies and monoclonal antibodies, the survival rates and toxicities related to chemotherapy courses have been improved.[19,20] Our results in the present cohort are compatible. The patients enrolled in the study with PID had a quite high mortality rate even with the treatment of RTX. These results can be attributed to the high rates of febrile neutropenia episodes, delayed diagnosis, and disseminated disease.[13-18]

In the present study, the most frequent pathologic subtype was BL, which is compatible with the literature.[10] Besides, as expected, the most common site of BL was the abdomen, detected in 23/33 cases (69.6%). Most of our patients were diagnosed at advanced stages, such as stage III and IV determined in 46 patients (74.1%). This can be attributed to our small sample size, which cannot represent the national data. Besides, since the contributing centers are tertiary reference centers, patients with advanced diseases were consulted.

Over the last century, survival rates of mature B-cell NHL have improved significantly, with an OS of over 90%.[21] The prognostic factors that have a dismal effect on survival account for high-stage, elevated LDH levels and involvement of bone marrow and/or CNS on admission. Besides, unresponsiveness to therapy is a poor prognostic factor. RTX has been proven efficient in treating adults NHL and is considered a standard of care.[21,22] However, the prognosis and response rates can differ in adults and children, depending on molecular anomalies or different subtypes arising in different ages. Also, compared to adults, treatment with chemotherapy alone still has superior outcomes in children and adolescents. Despite a better prognosis, life-threatening complications may arise due to intensive chemotherapy regimens, resulting in treatment failure. Besides, RTX is a highly specific and sensitive monoclonal antibody against CD20 antigen, which is expressed in the mature B cells homogeneously. Owing to these reasons, RTX has been evaluated in the first-line therapy in addition to chemotherapy with reduced intensity both in terms of efficacy and toxicities in childhood.[23,24] In our retrospective cohort study, RTX was administered as an adjunct to standard treatment in high-risk patients to facilitate rapid and effective disease control and in conjunction with low-intensity chemotherapy in immunocompromised patients to achieve disease control. Minard-Colin et al.[21,22] conducted a large-scale, international, randomized phase 3 trial and disclosed that integration of RTX to standard lymphoma regimens provides a survival advantage in both EFS and OS, especially in high-risk patients defined as stage III disease with an elevated LDH or stage IV disease.[22-24] Consistently, the efficacy and safety of rituximab in combination with LMB chemotherapy for children with high-risk mature B-NHL have been further supported by a Japanese multicenter trial, demonstrating a three-year event-free survival of 97.7% and an overall survival of 100%, reinforcing the robustness of RTX-based regimens in diverse populations.[25] Although not statistically significant, an EFS advantage can be attributed to the RTX in the current retrospective cohort when the patients with PID are excluded. On the other hand, adverse events, hypogammaglobulinemia, and infectious episodes were increased in the RTX arm, which is not comparable with our cohort.[21-24] Prior to this phase 3 international trial, a phase 2 study was conducted to search for the effect of utilizing RTX alone in newly diagnosed patients. It was disclosed that 21% of the patients responded within the 5 days before the chemotherapy regimen was initiated.[23] Also, primary mediastinal B-cell lymphomas have a dismal outcome compared to other B-cell NHL subtypes. Recently, Knörr et al. disclosed that implementing RTX with the EPOCH regimen has resulted in better survival rates. On the other hand, owing to the CNS relapses in their cohort, they addressed that large-scale randomized, controlled, and collaborative trials are needed to prevent CNS disease and improve outcomes.[8] Despite the promising and significantly improved outcomes, the accessibility can be a limitation owing to the economic burden on individual

centers, highlighting a critical challenge in the broader implementation of this treatment in low- and middle-income countries.[26]

Standard and low-risk NHL patients have almost 97% OS after chemotherapy alone, which is a great response, so initiation of RTX in these patients is debated owing to reported increased adverse events.[23,24] However, in our small-scale retrospective cohort, no elevation in adverse events was observed. Despite the fact that our study has major limitations, such as its retrospective nature and insufficient number of patients, it is obvious that RTX may has a survival advantage in the high-grade B-cell NHL. The addition of RTX to the cytotoxic treatment is safe in terms of side effects and is likely to contribute to event-free survival. Risk based and tailored treatment options are gaining importance in treating high-grade B-cell NHL.

Ethical approval

This study has been approved by the Erciyes University Faculty of Medicine (approval date 09.10.2024, number 224/07). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: ŞA, TG, DKG, AÖ; data collection: TG, MFO, EY, BD; analysis and interpretation of results: SK, VHÜ, MÖ, MK, MB, EÜ, KK; draft manuscript preparation: ŞA, EÜ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

B-cell lymphoblastic lymphoma in a 10-year-old boy with complaints of arthralgia: A case report

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ABSTRACT

Lymphoma represents a common type of cancer among pediatric populations, exhibiting a range of identifiable symptoms. The aim of this study is to present a case involving a 10-year-old male patient who displayed symptoms of bone pain and arthralgia, ultimately leading to a confirmed diagnosis of B-cell lymphoblastic lymphoma. The patient was admitted to Ali Asghar Hospital in in Tehran, Iran, presenting with complaints of swelling and pain in the right wrist and right ankle that had persisted for six months. Additionally, he developed intermittent fever and bone pain as new symptoms, prompting a series of medical evaluations. Initially, the child was diagnosed with brucellosis, systemic lupus erythematosus, and juvenile idiopathic arthritis six months prior to the final diagnosis of B-cell lymphoblastic lymphoma. Following the commencement of pharmacological treatment, the patient was discharged in stable condition and is currently undergoing chemotherapy.

Keywords: lymphoma, B-cell lymphoblastic, pediatric, case report

INTRODUCTION

Lymphomas are cancers originating from well-developed B and T lymphocytes, often appearing as malignant growths in lymphoid tissues.[1]

Lymphoma is a frequently occurring type of cancer in children, appearing in different recognizable forms.[2] Non-Hodgkin's lymphoma (NHL) is identified as the fourth most prevalent neoplasm in pediatric populations. In pediatric patients, high-grade histological variants are found in over 90% of NHL instances, in contrast to adults, who predominantly present with low- or intermediate-grade lymphomas.[3] NHL encompasses a heterogeneous group of lymphoproliferative disorders that are less clearly defined than Hodgkin lymphomas and exhibit a greater propensity for extranodal dissemination. NHL is classified into four primary categories: diffuse large B-cell lymphoma (DLBCL), which includes primary mediastinal B-cell lymphoma (PMBL), Burkitt lymphoma (BL), lymphoblastic lymphoma (LL), and anaplastic large cell lymphoma (ALCL).[2]

In the United States, NHL is identified as the seventh most common cancer and the ninth leading cause of cancer-related mortality. NHL constitutes approximately 90% of all lymphoma cases within the country, with its prevalence differing across age demographics; specifically, it represents 62% of lymphoma cases in children aged 0-14 years and 25% in adolescents aged 15-19 years. Furthermore, leukemia accounts for roughly 29% of all cancer diagnoses in the pediatric population.[1]

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Certain B-cell neoplasms may share visual features with BL but have distinct genetic or phenotypic traits. These cases tend to be more aggressive than diffuse large B-cell lymphoma. Pediatric hematologists customize chemotherapy for aggressive B-cell lymphomas based on clinical factors like stage, LDH levels, and bone marrow or CNS involvement rather than histological characteristics.[4]

Certain signs and symptoms of NHL can include fever, night sweats, weight loss, loss of appetite, and swollen lymph nodes in areas like the neck, axillary, and groin. Lymph nodes may also be visibly enlarged. In some cases, patients may experience symptoms related to areas outside of the lymph nodes, such as gastrointestinal bleeding from stomach lymphoma.[5] Common indications include continuous migraines, nausea, increased inflammation and discomfort in the skeletal structure, presence of a growth or accumulation in the abdominal or cervical area, frequent infections, a pale appearance in the eye, queasiness, persistent paleness, changes in eye or vision capabilities, recurrent or prolonged fever with joint inflammation, bleeding gums and nose, as well as swollen eyeballs.[6]

The aim of this study is to report a case of a 10-year-old boy presenting with symptoms of bone pain and arthralgia, leading to the final diagnosis of B-cell non-Hodgkin lymphoma.

CASE PRESENTATION

A 10-year-old male patient was admitted to Ali Asghar Hospital in Tehran, Iran, presenting with primary complaints of swelling and pain in the right wrist and right ankle that had persisted for six months. Over this period, the symptoms intensified, necessitating the administration of analgesics and the application of a cast. Additionally, the patient developed intermittent fever and bone pain, which prompted further medical interventions. One month prior to the current evaluation, the patient reported experiencing pain in the lower right jaw and observed two nodules on both elbows. Upon examination, vital signs were within normal limits, although swelling was noted in the lower right jaw region. Two nodular masses in both elbows (15*15 mm) were noted without erythema or tenderness. Swelling in multiple joints, including both elbows, right wrist, and right ankle was present. Joints were sensitive to touch and had a limited range of motion. Hepatosplenomegaly was detected on sonography. The initial diagnoses made six months ago for this child were brucellosis, systemic lupus erythematosus (SLE), and juvenile idiopathic arthritis (JIA). Laboratory findings included: WBC: 4500/L (PMN: 41.7%, Lymph: 45.06%, MONO: 10.80%, EO: 10.52%, BA: 0.42%), RBC: 4.02 *10^6 /microL, Hb: 10.3 g/dL, MCV: 77.4 FL, MCH: 25.6 pg, MCHC: 33.1 g/dL, PLT: 183000/mL, ESR: 70, CRP: 40, Wright agglutination: Negative, Coombs Wright: Negative, 2ME: Negative, FANA: Negative, Anti-dsDNA: Negative, ANCA: Negative, Anti-PR3 (C.ANCA): Negative, R.A. Factor: 10 (Negative), VDRL: Non-Reactive, C3, C4, CH50: Normal, LDH: 1540, D-dimer: 4508 ng/dl, CD4/CD8: 0.3%, CD19: 14.9%, CD56: 25.6%.

Right foot MRI showed an Abnormal increase *T2/STIR* signal intensity in the talus, lateral cuneiform, and tibial epiphysis is noted. Also, a 40×10 mm well-defined *T1, T2* lesion was identified at the lateral border of the tibial diaphysis. Mild fusion of the anterior and posterior talus joint and subcutaneous swelling in the lateral and medial ankle were observed. The Right-hand MRI showed without gadolinium (GAD) indicated normal bone structures without destructive processes or signs of osteomyelitis.

Spiral thoracic CT scan with and without contrast showed focal pleural thickening in the posterolateral aspect of the base of right hemothorax, and in visualized cuts of lower neck, a lytic lesion of mandibular body was found. Also, there was a homogenous axillary lymph node with a Short Axis Diameter (SAD) of 16 mm on the right side.

Spiral Abdominopelvic CT scan with and without contrast showed the spleen with a craniocaudal diameter of 165 mm was larger than normal with homogenous parenchymal density. There were multiple homogenous lymphadenopathies in bilateral iliac chains, with a maximum SAD of 21 mm on the left and 15 mm on the right side. Few homogenous paraaortic lymph nodes with SAD up to 6mm and scattered homogenous mesenteric lymphadenopathies with a maximum SAD of 10 mm and retrocrural lymph nodes with SAD of 5 mm were also found.

Spiral Brain CT scan with and without contrast showed mild mucosal thickening of visualized paranasal sinuses was found.

The radiography picture showed the lytic lesions characterized by a permeative appearance were identified in various locations, including the proximal and distal metaphysis of the left humerus, the distal metaphysis of the right humerus, the proximal metaphysis of both sides, the diaphysis of the left ulna, and the distal meta diaphysis of the radius bilaterally. Additionally, a lytic lesion exhibiting a deformed and sclerotic margin, measuring approximately 20×50mm, and situated eccentrically and intracortically, was observed in the lateral aspect of the distal metaphysis of the right tibia (Figure 1).

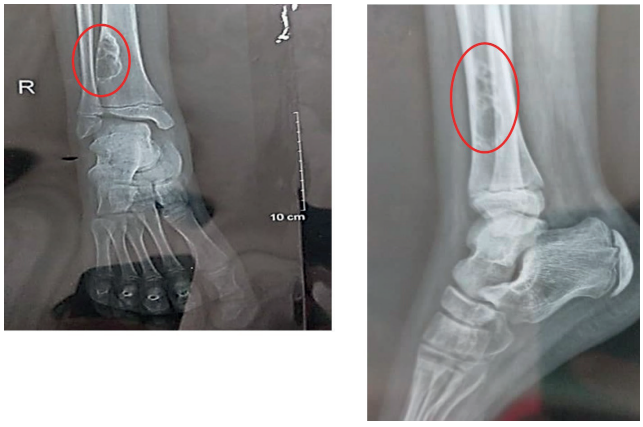

Figure 1. Right foot X-ray (Before treatment)

The sonography pictures showed the suspected lymph nodes (16×15mm) were observed in the right elbow and (14×10mm) in the left elbow. Also, the presence of numerous enlarged pelvic lymph nodes bilaterally, measuring up to 19×27mm on the right side and 25×42mm on the left side, exhibited a highly concerning appearance indicative of potential malignancy infiltration.

A biopsy was conducted on the lymph nodes located in the elbow, specifically from the epitrochlear region, which ultimately led to the diagnosis of B-cell lymphoblastic lymphoma based on the pathological analysis of the biopsy specimen. The bone marrow aspiration yielded normal results. Considering the clinical findings, which included the involvement of cervical lymph nodes and the epitrochlear region, the condition was classified as stage 3 non-Hodgkin's lymphoma.

Treatment

Management of the patient prior to the establishment of the main diagnosis of the condition (B-cell lymphoblastic lymphoma), the patient was administered co-trimoxazole and rifampin for a duration of six weeks as part of the treatment for brucellosis. Additionally, he received prednisolone for two weeks in relation to the diagnosis of GIA. Following the diagnosis of B-cell lymphoblastic lymphoma, the patient received a treatment regimen consisting of the BFM 2009 protocol. Following the initiation of pharmacological therapy, the patient was released from the medical facility in a favorable overall state and is presently undergoing treatment with chemotherapeutic agents. Following the initiation of treatment, there was a complete resolution of all lymphadenopathies. Additionally, the patient experienced a total alleviation of joint and bone pain; no active bone lesions were detected in the tibia of the right foot, and the previously identified lytic lesions have transformed into sclerotic areas (Figure 2).

Ethical disclosure

The Ethics Committee of Iran University of Medical Sciences (Tehran, Iran) approved this study, which was performed under the approved guidelines (Ethical code: IR.IUMS.REC.1402.1093). For this case report, informed consent has been obtained, and their parents have been assured that their child's name will not be included in the article and all their information is confidential.

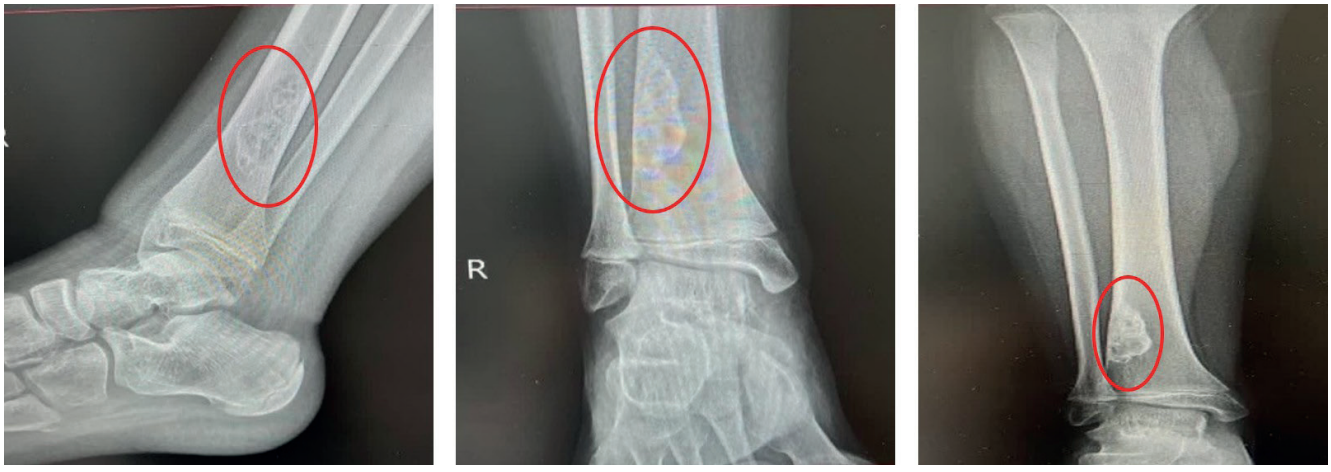

Figure 2. The absence of bone lytic lesions following treatment and their subsequent transformation into sclerotic regions in the right tibial area (After treatment).

DISCUSSION

The case report discussed in this document involves a patient displaying symptoms indicative of arthritis who was later diagnosed with non-Hodgkin's Lymphoma. This case study signifies a significant progression in delivering precise clinical care and treatment for patients presenting with similar clinical symptoms. As with numerous other malignancies, the economic ramifications related to lymphomas can vary considerably.[7]

In the case study conducted by Delavarian et al., a 6-year-old male was observed to exhibit bilateral gingival swelling in the mandible, along with swelling of the right testicle. Ultimately, he was diagnosed with NHL[8] in our study; the child patient presented at the medical facility exhibiting symptoms of swelling and discomfort in the right wrist and right ankle.

In a case study conducted by Chaudhary and Borker, a 3-year-old female patient was admitted to the hospital with severe pain and swelling in her right knee joint, which persisted for three months. Radiographic imaging revealed a notable lytic lesion in the supracondylar region of the right femur, along with pathological fractures and multiple lytic lesions in both femurs. The imaging results did not show any signs of lymphadenopathy or organomegaly. Hematological assessments, including peripheral blood smear analysis and bone marrow examination, returned normal findings. A biopsy of the right supracondylar region confirmed the diagnosis of B-cell precursor lymphoblastic lymphoma. Additionally, a computed tomography scan detected a dense and faint lesion in the left adnexal area, which ultimately contributed to the diagnosis of B-cell lymphoblastic lymphoma.[9]

In a case study conducted by Fujita et al., a 3-year-old female patient was discharged from the hospital with complaints of pain in the right knee following a previous discharge one month earlier due to pain and swelling in the wrist. The patient exhibited limitations in leg mobility. The initial diagnoses included rheumatism and juvenile idiopathic arthritis, which were established based on observations from a T1-weighted MRI scan that revealed abnormally low signal intensity in the femur, tibia, fibula, and bone marrow of the leg. A subsequent contrast-enhanced T1-weighted MRI indicated enhancement of the synovial contrast and the presence of synovial fluid accumulation in the right ankle joint. Laboratory blood tests indicated a white blood cell count of 40,000/μL, with 66% of these cells identified as blasts, alongside a monoclonal increase in lymphoblasts. As a result, the patient was diagnosed with B-cell progenitor acute lymphoblastic leukemia.[10]

In a study conducted by Marina Boushra, a case report is presented regarding a 2-year-old female diagnosed with isolated torticollis who underwent multiple evaluations in the emergency department and outpatient clinic. During the first three visits, the patient exhibited no associated neurological abnormalities. He was discharged with supportive therapeutic treatment and a probable diagnosis of viral lymphadenitis. Notable findings included swelling of the right wrist and left foot, along with a lytic lesion observed in the initial radiograph of the right ulna. An iliac biopsy yielded non-diagnostic results. On the second day of hospitalization, the patient developed a scalp rash. Subsequent biopsy and flow cytometry of the nodules were consistent with B-cell lymphoblastic lymphoma.[11]

In a case study conducted by Yan et al., the authors documented a primary lymphoma of the bone localized in the tibial epiphysis, which initially manifested as knee pain. Diagnostic imaging techniques, including X-ray, MRI, CT, and PET-CT, were utilized, followed by a bone biopsy that confirmed the presence of diffuse B-cell lymphoma. Additionally, the patient exhibited a concurrent lesion in the left iliac bone, which upon biopsy, was also identified as diffuse large B-cell lymphoma.[12]

Compression of the spinal cord caused by NHL is a rare event, as evidenced by a study conducted by Acquaviva et al., the research documented a case involving a 5-year-old female patient who initially complained of pain, which progressed to hyposthenia and post-traumatic paraplegia. Imaging examinations revealed that the compression spanned from the T2 to L4 vertebrae, completely occupying the vertebral canal and extending into the surrounding soft tissues. An emergency surgical procedure was performed, leading to swift tumor regression and eventual full recovery of the patient 42 months after the initial diagnosis. The authors recommend a neurosurgical intervention only in cases where symptoms deteriorate rapidly or for diagnostic purposes, as chemotherapy has shown efficacy in managing such instances.[13]

In a case study carried out by Ishizuka et al., a 14-year-old female patient presenting with a palpable mass in her right breast was diagnosed with B-lymphoblastic lymphoma at stage I, as determined by immunohistochemical analysis and flow cytometric evaluation.[14]

In a separate case study conducted by Al Masroori et al., a 5-year-old male patient was admitted to the hospital with

symptoms of right knee arthritis and left ankle pain. The patient did not exhibit lymphadenopathy, organomegaly, skin rash, or fever. He experienced difficulty bearing weight and nocturnal pain, initially diagnosed as Juvenile Idiopathic Arthritis. Subsequent bone biopsy of the left femur revealed marrow infiltration by immature blasts. Further diagnostic tests, including blood film analysis, bone marrow aspiration, and flow cytometry indicated 66% blasts with characteristics consistent with B cell progenitors, leading to a final diagnosis of acute lymphoblastic leukemia with B immunophenotype.[15]

CONCLUSION

According to the description given, B-cell lymphoblastic lymphoma is the predominant malignant hematologic disorder globally, manifesting in diverse recognizable manifestations as outlined, and some patients may present with extranodal involvement. Based on the provided information, the confirmation of B-cell lymphoblastic lymphoma in pediatric patients (particularly pediatric patients presenting with symptoms of joint pain and inflammation) necessitates thorough examination and accurate analysis of laboratory and imaging findings to establish a definitive diagnosis and treatment plan.

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Ethical approval

This study has been approved by the Iran University of Medical Sciences (approval date 03.02.2024, number IR.IUMS.REC.1402.1093). Written informed consent was obtained from the participant.

Author contribution

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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