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Invited Review

Evidence-based Psychopharmacological Treatments for Pediatric Bipolar Disorder

Pediatrik Bipolar Bozukluk için Kanıta Dayalı Psikofarmakolojik Tedaviler

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ABSTRACT

Bipolar disorder is a chronic illness that often onsets in early stages of life, and the first episode of bipolar disorder frequently occurs in adolescence. Pediatric bipolar disorder (PBD) has more severe symptoms and a poorer prognosis compared to bipolar disorder in adults. Due to limited data on the psychopharmacological treatment of PBD, children and adolescents have been treated primarily in consideration of the findings obtained from clinical studies performed in adults. The efficacy of the psychotropic agents seems to differ in children and adolescents compared to adults. The evidence-based psychopharmacological treatment modalities of PBD are of growing interest in children and adolescents. This review discusses current Food and Drug Administration approved medications for PBD and guidelines for PBD. The psychopharmacologic evidence and algorithms of PBD treatment relevant to different stages of bipolar disorder, including acute manic/mixed episodes, bipolar depression, and maintenance treatment are examined in this review article.

Keywords: Bipolar disorder, mania, psychopharmacology, mood disorders, child and adolescent, bipolar depression

ÖZ

Bipolar bozukluk sıklıkla yaşamın erken dönemlerinde başlayan kronik bir hastalıktır ve bipolar bozukluğun ilk atağı sıklıkla ergenlik döneminde ortaya çıkar. Pediatrik bipolar bozukluk (PBB), yetişkinlerdeki bipolar bozukluğa göre daha şiddetli semptomlara ve daha kötü prognoza sahiptir. Çocuklar ve ergenler, PBB'nin psikofarmakolojik tedavisine ilişkin verilerin sınırlı olması nedeniyle, öncelikle yetişkinlerde yapılan klinik çalışmalardan elde edilen bulgulara göre tedavi edilmektedir. Psikotrop ajanların etkinliği çocuklarda ve ergenlerde yetişkinlere göre farklılık gösteriyor gibi görünmektedir. PBD'nin kanıta dayalı psikofarmakolojik tedavileri çocuklarda ve ergenlerde giderek artan bir ilgi görmektedir. Bu derlemede PBB için mevcut Amerikan Gıda ve İlaç İdaresi onaylı ilaçlar ve PBB ile ilgili kılavuzlar tartışılmaktadır. Ayrıca, akut manik/karma dönemler, bipolar depresyon ve idame tedavisi dahil olmak üzere bipolar bozukluğun farklı evrelerine bağlı olarak PBB tedavisine ait psikofarmakolojik kanıtlar ve algoritmalar incelenmektedir.

Anahtar kelimeler: Bipolar bozukluk, mani, psikofarmakoloji, duygudurum bozuklukları, çocuk ve ergen, bipolar depresyon

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INTRODUCTION

Bipolar disorder is a chronic, severe psychiatric condition associated with poor outcomes and it frequently requires lifelong treatment consisting of pharmacotherapy and psychosocial interventions[1]. Bipolar disorder affects over 1% of the global population, regardless of nationality, ethnicity, or socioeconomic status, and stands as one of the primary contributors to disability among the youth population[2]. Early diagnosis of pediatric bipolar disorder (PBD) in youth is crucial because nearly 60% of individuals with PBD are affected before the age of 21 years[3].

Diagnostic criteria for PBD in children and adolescents are the same as for adults, but diagnosis of early-onset PBD is more challenging than late-onset PBD. Temper outbursts and irritability commonly develop in youth and more frequently cause mixed or rapid-cycling presentations compared to adults[4]. Moreover, symptoms of mania and hypomania that overlap with symptoms of other psychiatric disorders such as attention deficit and hyperactivity disorder (ADHD), personality disorders, and behavioral problems in young people complicate the diagnosis of PBD[5]. Disruptive mood dysregulation disorder (DMDD) was included in the Diagnostic and Statistical Manual of Mental Disorders-The Fifth Edition

(DSM-5) to address concerns "about the appropriate diagnosis and treatment of children and adolescents who present with chronic, persistent non-episodic irritability relative to children and adolescents who present with classical bipolar disorder" and to put right what was evaluated as an inappropriate overdiagnosis of BPD in some children[6,7]. Youngsters with DMDD who have higher psychiatric comorbidity rates are also debilitated and have functional impairments in different areas[8]. Although the inclusion of the diagnostic criteria of DMDD in DSM-5 has reduced the incidence of overdiagnosis in youth with BPD, antipsychotics and polypharmacy have been started to be used more frequently in these children and adolescents[6]. It is important to emphasize that while there are no treatment guidelines for DMDD, children and adolescents with persistent aggression and non-episodic irritability remain a challenging group[9]. Episodes of acute mania correlate with engaging in high-risk activities, including gambling, substance abuse, accidents, and hazardous behaviors. Episodes of depression are linked to a heightened risk of suicide[4]. PBD is associated with more severe symptoms, suicide risk, and poorer prognosis compared with the late- onset PBD. The efficacy of psychopharmacological treatments seems to differ in children and adults. Therefore, there is a growing interest in identifying effective and safe psychopharmacological treatments for PBD in children and adolescents[10].

Pharmacotherapy of bipolar disorder in children can be challenging. The crucial step in the pharmacotherapy of PBD is to confirm the PBD episodes and define the patient's mood status because medical approach to mania, hypomania, and depression changes considerably[11]. Thus, the choice of pharmacotherapy is generally based on the presentations of PBD (manic/mixed, depressive, or maintenance). Children and adolescents have been treated primarily by adjusting findings from clinical studies in adults due to limited data on the psychopharmacological treatment of PBD in children. The National Institute for Health and Care Excellence (NICE) proposes recommendations on treating specific conditions covered by The National Health Service in the United Kingdom. Relevant NICE guidelines published in 2014 cover management strategies for patients with bipolar disorders in adults, children, and adolescents in primary and secondary care[12]. In 2018, the last updates of The Canadian Network for Mood and Anxiety Treatments (CANMAT) were published in collaboration with the International Society for Bipolar Disorders (ISBD). CANMAT 2018 guidelines have used recommendations for the first, second, and third-line treatments, considering levels of evidence for efficacy and clinical support based on experience[13]. The latest American Academy of Child and Adolescent Psychiatry (AACAP) algorithm for the psychopharmacological treatment of PBD was still based on the results of randomized controlled trials (RCTs) performed in adult patients, data from open-label trials and retrospective studies conducted in children and adolescents[14]. Since 2005, an increasing number of RCTs have been performed to investigate the efficacy of psychotropic drugs in the treatment of PBD. Recently, Hobbs et al.[15] have proposed a comprehensive update to the AACAP's 2005 algorithm for PBD treatment.

This review discusses FDA approved medications for PBD and current guidelines related to PBD. Moreover, we have examined the psychopharmacologic evidence and algorithms of PBD treatment depending on the manifestations of illness.

FDA-approved Psychotropic Drugs for The Treatment of Pediatric Bipolar Disorder

Most of the RCTs of psychotropic agents used in the treatment of PBD have been reported, especially in the last two decades. Medications superior to placebo in the treatment of BPD patients presenting with acute manic or mixed episodes include aripiprazole[16], asenapine[17], risperidone[18], quetiapine[19], and olanzapine[20]. FDA has approved aripiprazole, asenapine, risperidone, or quetiapine for their use in the management of acute mania or mixed episodes in PBD for patients aged ≥10 years and olanzapine for adolescents aged 13-18 years. The FDA has approved lithium for the treatment of manic or mixed episodes of PBD in individuals aged 7-17 years, supported by favorable outcomes observed in RCTs performed in children and adolescents[21]. None of the anticonvulsant medications (valproate, carbamazepine, lamotrigine) are currently approved by the FDA for the treatment of PBD[22,23]. Lurasidone and olanzapine/fluoxetine combination have been approved for the treatment of depressive episodes of PBD in children aged 10-17 years[24,25]. Lithium and aripiprazole are the only two medications to be used with an FDA indication for the maintenance treatment of PBD.

Treatment of Acute Manic or Mixed Episodes

Acute episodes have a significant risk of suicide, disinhibition, recklessness, irritability, and threat to family or others. Accordingly, the primary objectives involve ensuring the safety of the patient and those in the community while striving for clinical stability with

minimal adverse effects in the acute management of PBD. Additionally, fostering engagement and establishing a therapeutic agreement are crucial aspects of managing this lifelong condition. Collaborative efforts are vital for long-term adherence to PBD treatment, especially during the initial episode[26].

There are several published guidelines for the treatment of acute PBD episode[12-14]. NICE 2014 guidelines indicate that differences in dosage and side effects of the medications in younger patients compared to the adult population should be taken into account[12]. Mechanisms of action of second-generation antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole) and mood stabilizers (lithium, sodium valproate, lamotrigine, carbamazepine) are thought to be similar in youths and adults[12]. At the time of the publication of NICE 2014 guidelines, only one drug (aripiprazole) was licensed for the treatment of moderate to severe manic episodes in bipolar disorder in children aged 13 years and older for the duration of 12 weeks, and some preparations of lithium were also licensed for use in children aged over 12 years in the UK[27]. At the time of release of NICE guidelines in September 2014, olanzapine, risperidone, haloperidol, quetiapine, lamotrigine, lithium, and valproate lacked UK marketing authorization for use in children and young people for treating mania or hypomania. However, the NICE 2014 guidelines suggested consideration of the recommendations intended for adults in such cases[12]. In accordance with recommendations for adult patients, if a patient experiences mania or hypomania while on antidepressant monotherapy, it is advised to discontinue the antidepressant and consider initiating treatment with an antipsychotic drug such as haloperidol, olanzapine, quetiapine, or risperidone[12]. If the initial antipsychotic drug is poorly tolerated or ineffective at maximum dosage, an alternative antipsychotic drug from the recommended list should be offered[12]. While off-label use of lithium was acknowledged in September 2014, NICE suggested that if a second antipsychotic drug fails to provide sufficient relief at maximum dosage, the addition of lithium may be considered[12]. If the addition of lithium proves ineffective or if lithium is unsuitable due its adverse effects on biochemical parameters detected during routine blood tests, valproate may be considered as an alternative[12]. Furthermore, the updated NICE 2023 guidelines advise against initiating valproate treatment for the first time in patients, regardless of gender, who are younger than 55 years old[28].

The CANMAT and the ISBD 2018 guidelines emphasize the significance of evidence levels with clinical support for efficacy in formulating the final treatment recommendations, as outlined in Table 1[13]. These guidelines recommend lithium, risperidone (level 1 evidence), aripiprazole, asenapine, and quetiapine (level 2 evidence) as the first-line options for acute treatment of PBD[13]. Risperidone is recommended for the treatment of non-obese youth and children with ADHD as a preferred alternative to lithium. Olanzapine (level 2 evidence) and ziprasidone (level 2 evidence) are offered as second-line options in consideration of safety and tolerability concerns. Adjunctive therapy with quetiapine is also recommended as a second-line treatment (level 3 evidence)[13]. Despite insufficient response rates observed with divalproex, positive treatment outcomes documented with this drug in open-label studies involving children, and adolescents together with its extensive history of use among adults with bipolar disorders, position it as a third-line treatment alternative for youths who do not respond to or could not tolerate first or second-line treatment options (level 4 evidence)[29]. Oxcarbazepine has failed to demonstrate superiority over a placebo in a significant RCT (level 2 negative evidence) and has not been endorsed in the CANMAT and ISBD 2018 guidelines[13,30].

The most recent update in psychopharmacological treatments for PBD highlighted the evidence that

Table 1. Definitions for line of treatment ratings in guidelines

Treatment	Evidence levels
First-line	Level 1 or level 2 evidence for efficacy plus clinical support for safety/ tolerability and no risk of treatment-emergent switch
Second-line	Level 3 or higher evidence for efficacy plus clinical support for safety/ tolerability and low risk of treatment-emergent switch
Third-line	Level 4 evidence or higher for efficacy plus clinical support for safety/ tolerability
Not recommended	Level 1 evidence for lack of efficacy, or level 2 evidence for lack of efficacy plus expert opinion

Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders 2018 guidelines[13]

has emerged since the AACAP 2005 algorithm was published for managing manic or mixed episodes in children and adolescents[15]. Hobbs et al.[15] suggested use of second-generation antipsychotic agents (SGAs) as the first-line treatment of acute manic or mixed episodes, with the specific choice of antipsychotic agent left to the discretion of the clinician. The latest update has emphasized better efficiency of SGAs compared to other agents used in RCTs for the treatment of mixed or manic episodes of PBD[15]. For the treatment of manic or mixed episodes of PBD associated with psychosis, the initial approach involves using one of the FDA-approved SGAs such as aripiprazole, asenapine, olanzapine, quetiapine, or risperidone[15]. If there is no response to the priorly preferred SGA, another FDA-approved SGA can be used as monotherapy[15]. Lithium augmentation may be considered in case of partial response to two SGAs. In cases of acute manic or mixed episodes without psychosis, lithium may be considered as an augmentation therapy to an SGA or as monotherapy if two different SGAs[15] fail to provide an adequate response[15]. During acute manic or mixed episodes with psychotic or non-psychotic manifestations it is advisable to contemplate incorporating lamotrigine as an adjunctive therapy alongside an SGA and/or lithium[15]. If tolerance to lithium and lamotrigine is not encountered, it is advisable to consider enhancing the treatment regimen by combining an SGA with second-line agents such as divalproex, carbamazepine, or oxcarbazepine[15]. If patients do not respond to these agents, electroconvulsive therapy (ECT) or clozapine can be considered for both psychotic and nonpsychotic groups of acute manic or mixed episodes[15]. Even though lithium has showed a smaller effect size compared to SGAs in RCTs performed for the treatment of manic or mixed episodes of PBD[15], it remains as an important treatment option due to its unique features which include reducing suicidality in adults and children and providing neuroprotective advantages both *in vivo* and *in vitro*[31].

Treatment of Depressive Episodes

Children with PBD usually exhibit depression as the initial mood episode; however, a diagnosis of PBD requires a history or presence of mania/hypomania associated with an elevated risk of self-harm and suicide[32]. The Course and Outcome of Bipolar Youth study has revealed that, during follow-up, the majority of recurrences after an initial episode of BPD were major depressive episodes (60%), followed by hypomanic (21%), manic (15%), and mixed (5%) episodes[4]. Patients with depressive episodes of PBD are more frequently inclined to exhibit more severe psychiatric comorbidity, atypical features, psychotic features, a heightened risk of suicide, subsyndromal manic symptoms, and a higher prevalence of positive family history compared to those with unipolar depression[33]. While selective serotonin reuptake inhibitors (SSRIs) can enhance depressive symptoms in bipolar disorder, they also elevate the risk of triggering a manic episode[34]. In addition, some reports indicate a higher occurrence of antidepressant-induced switching to mania in children and adolescents compared to adults[35]. Healthcare providers should approach the use of antidepressants in depressive episodes of PBD with caution[14,34].

The 2014 NICE guidelines indicate lack of empirical data on the treatment of depressive episodes in PBD among children and adolescents[12]. When the NICE 2014 guidelines were released, there were no trials of SSRIs in bipolar depression. However, it was noted that open-label treatment trials of lithium[36] and lamotrigine[37] might be effective in addressing depressive episodes in PBD. The NICE 2014 guidelines propose referring to the recommendations for adults when addressing depressive episodes in PBD[12]. According to the adult recommendations, in cases of moderate or severe bipolar depression and the absence of bipolar disorder treatment, fluoxetine combined with olanzapine or quetiapine alone can be offered based on the individual's preference and prior treatment response[12]. If there is no response to fluoxetine-olanzapine or quetiapine combination, the consideration of lamotrigine monotherapy is advised[12].

Data on pediatric populations are limited, and their interpretation is complicated by the presence of elevated placebo-response rates obtained in RCTs. In other words, the observed improvements in symptoms might be influenced by the placebo effect rather than the actual effectiveness of the tested treatment. As a result, the CANMAT and ISBD 2018 recommendations primarily rely on the clinical experience and results obtained from adult studies[13]. In an RCT study, DelBello et al. found that lurasidone induced a higher response rate than placebo (level 2 evidence) in alleviating depressive symptoms in the pediatric population with acute bipolar depression[25]; but still we have insufficient clinical data regarding its use in the pediatric population. Due to clinical experience and its effectiveness in adult patients, lurasidone is suggested as a first-line treatment for depressive episodes in PBD[13]. Meanwhile, lithium

and lamotrigine are proposed as first-line treatment options for bipolar depression in adults[13]. Despite the limited RCT data, there is extensive clinical experience with these medications. Results of open-label studies with lithium (level 4 evidence)[36] and lamotrigine (level 4 evidence)[37] in children and adolescents are available. Based on the robust evidence in adults, lithium and lamotrigine are advised as second-line treatment options for PBD depression. Additionally, there is RCT level 1 evidence supporting the theraupetic effectiveness of the olanzapine-fluoxetine combination for PBD depression[24]. However, concerns about the metabolic effects of olanzapine and insufficient clinical experience with this combination treatment in pediatric patients have led to the classification of this option as a third-line treatment alternative[13]. Considering the negative results in children and adolescents (level 2 negative evidence)[38,39], quetiapine is recommended as the third-line treatment for the pediatric population due to evidence supported by significant clinical experience from studies performed in adults. Observational studies advocate for the cautious use of antidepressants in PBD and suggest their combination with mood stabilizers (level 4 evidence)[40,41]. Oxcarbazepine is not approved for the management of depressive episodes of PBD and has not been found to have a higher response rate than placebo (level 2 negative)[13]. However, a large-scale RCT has showed its effectiveness in younger children rather than older individuals[30].

The most recent update of AACAP 2005 proposes lurasidone as a first-line treatment for depressive episodes of PBD[15]. Lurasidone (effect size, 0.45) and olanzapine-fluoxetine (effect size, 0.46) combination are both FDA-approved drugs. However, lurasidone has a lower metabolic side effect burden than olanzapine-fluoxetine combination[24,25]. This updated review suggests that lurasidone, if partially effective, can be combined with lamotrigine[15]. If depressive symptoms persist during adjunctive therapy with lamotrigine, adding an FDA approved SSRI such as escitalopram or fluoxetine may be considered; however, caution is warranted due to the risk of a manic switch[15]. If lurasidone fails to elicit a response, cross-tapering to the olanzapine-fluoxetine combination should be considered[15]. Despite evidence of efficacy and FDA approval, the underuse of olanzapine-fluoxetine persists in clinical practice. For partial responders to olanzapine-fluoxetine combination, augmentation with lamotrigine is recommended[15]. If FDA-approved agents have failed, non-FDA-approved treatments like quetiapine, risperidone, asenapine, aripiprazole, bupropion, other SSRIs, and lithium should be considered [15]. SSRIs should be used along with mood stabilizers to mitigate the risks of manic switch. Clinicians should note that quetiapine is FDA-approved only for adults; in children and adolescents with bipolar depression, it showed similar efficacy to placebo in two RCTs[38,39]. While not recommended as a first-line medication for youths, quetiapine remains an acceptable choice for older adolescents suffering from bipolar depression[15]. In cases where other treatments prove ineffective, ECT may be considered as an alternative option[15].

Maintenance Treatment

PBD presents a chronic illness trajectory with a high susceptibility to relapse and permanent disability. A 5-year prospective follow-up study on adolescents with bipolar disorder reported relapse rates of 44%[42]. Effective long-term treatments of bipolar disorder are essential, particularly in youths. Despite the severity and chronicity of PBD, research in the psychopharmacology of maintenance treatment of PBD has provided insufficient evidence than in adult bipolar disorder[43].

In clinical practice, long-term treatment of PBD often includes the off-label use of antipsychotics and anticonvulsants since there is a paucity of randomized data available on maintenance treatment in youths with PBD[44]. There are several published guidelines for the maintenance treatment of PBD. For long-term pharmacological treatment, the 2014 NICE guidelines advise considering medications that have demonstrated efficacy during episodes of PBD[12]. The NICE guidelines advise engaging in a discussion with the individual about their preference to either continue with this treatment or switch to lithium therapy[12]. NICE guidelines recommend the use of lithium as a first-line maintenance treatment of PBD[12]. If lithium is ineffective, poorly tolerated, or not suitable, an antipsychotic (asenapine, aripiprazole, olanzapine, quetiapine, or risperidone) may be considered[12]. If the initial antipsychotic is not well tolerated at any dosage or proves ineffective at the highest dosage, it is advisable to contemplate using a second antipsychotic from the list of recommended medications[12]. According to the NICE guidelines, if the second antipsychotic is ineffective, a combination of valproate with either an antipsychotic or lithium should be considered[12]. It is recommended that when long-term pharmacological treatment is terminated, the patient should be educated on how to recognize early signs of relapse and what to do at the time of recurrence [12]. Additionally, the NICE guidelines suggest continuing

to monitor symptoms, mood, and mental status for two years after the medication is completely discontinued[12].

CANMAT and ISBD 2018 guidelines recommend aripiprazole (level 2 evidence)[45,46], lithium (level 2 evidence)[47], and divalproex (level 2 evidence)[48] as first-line maintenance treatment alternatives of PBD. The CANMAT guidelines indicate that a minority of patients continue to do well after switching to either lithium or divalproex monotherapy, and the majority respond positively when the combination therapy is reintroduced [13]. Additionally, studies have suggested the effectiveness of combination therapy, such as risperidone plus lithium or divalproex[49], and lithium plus divalproex or carbamazepine[50], in achieving and sustaining remission. Use of lamotrigine may also be considered as an adjunctive therapy for those aged ≥13 years (level 2 evidence)[51]. However, there is no recommendation with level ≥3 evidence for second-line maintenance therapy. As for asenapine, there is limited data for its use as long-term PBD treatment alternative. Nonetheless, an open-label study suggests gradual tapering of its dose during treatment of manic symptoms over 50 weeks in the pediatric patients (level 4 evidence). Additionally, a RCT conducted in adult patients has validated the effectiveness of asenapine in preventing the recurrence of mood episodes. Clinical observations and open-label studies suggest that quetiapine, risperidone, or ziprasidone may serve as alternative third-line alternatives for maintenance treatment, especially for patients who has shown positive responses during acute episodes of PBD (level 4 evidence)[52-54].

The AACAP 2005 guidelines suggest that mood stabilizers (carbamazepine, lamotrigine, lithium, and valproate) along with SGAs can be used as first-line and combinations of these medications as second-line treatment alternatives[14,22]. The AACAP 2005 guidelines suggest use of SGAs as adjunctive agents or alternatives to lithium and valproate[1]. According to AACAP practice parameters, maintenance treatment for at least 12-24 months following the initial episode is recommended [14]. For patients with severe symptoms and a history of recurrent episodes, lifelong treatment with psychotropic medications should be considered[14]. Monotherapy with either lithium or divalproex in pediatric patients is associated with a comparatively shorter median time to relapse[55]. Furthermore, discontinuation of lithium has been demonstrated to elevate relapse rates in adolescents diagnosed with bipolar disorder[56]. Hence, gradual tapering, and finally discontinuation of maintenance therapy is recommended over a period of time devoid of significant anticipated stressors[14]. The American Psychiatric Association's Practice Guideline for the Treatment of Patients with Bipolar Disorder in adults advises that maintenance therapy with an agent should persist for at least 18 months following the stabilization of a manic episode[57]. Since definitive answers are not available on the exact duration of maintenance treatment, clinicians must navigate the balance between the potential harm of symptom recurrence and the side effects of mood stabilizers and antipsychotics. This uncertainty persists due to the lack of conclusive information regarding the long-term effects of these medications[1].

Only lithium[47] and aripiprazole[45,46] have been approved by FDA for the maintenance treatment of PBD. Numerous international treatment guidelines advocate initiating treatment for PBD with monotherapy and suggest that the drug combinations are considered only after multiple conservative treatment approaches have proven ineffective[1,13]. A recent meta-analysis examining long-term treatment trials for PBD has revealed that combination treatments, which typically involve use of lamotrigine, lithium, or valproate combined with a SGA, yield superior outcomes compared to monotherapy trials[44]. This meta-analysis has formulated the apparent order of efficacy as follows: combined agents > anticonvulsants ≥ lithium ≥ antipsychotics[44]. Nevertheless, conduction of further RCTs is necessary to evaluate long-term safety and effectiveness of these psychopharmacologic agents used for the treatment of PBD. In the context of maintenance treatment for bipolar disorder, the polarity index (PI) serves as a metric indicating the relative preventive efficacy of drugs against manic versus depressive episodes[58]. The PI is derived by calculating the ratio of the Number Needed to Treat (NNT) for the prevention of depression to the NNT for the prevention of mania, as evidenced by results from RCTs performed in adult populations. A PI value exceeding 1.0 signifies relatively greater prophylactic efficacy against manic episodes, while a value below 1.0 suggests relatively greater efficacy in preventing depressive episodes. In the context of maintenance therapy for bipolar disorder, the PI values are as follows: 12.09 for risperidone, 4.38 for aripiprazole, 3.91 for ziprasidone, 2.98 for olanzapine, 1.39 for lithium, 1.14 for quetiapine, and 0.40 for lamotrigine. The reliability of the PI values for valproate and oxcarbazepine may be compromised due to their ineffectiveness in trials of maintenance therapy. Notably, quetiapine and lithium exhibit a PI close to 1, indicating their nearly equal efficacy in preventing both manic and depressive episodes[58]. Indeed, although PI values are derived from adult RCTs, they may still be

clinically beneficial in providing information for the selection of an appropriate maintenance treatment for bipolar disorders in adolescents.

CONCLUSION

This article reviews evidence from different guidelines and algorithms formulated for the psychopharmacological treatment of PBD, acute manic or mixed, depressive episodes, and maintenance therapy. At present, there is still a lack of sufficient double-blind, RCTs involving pediatric and adolescent patients with bipolar disorders. The existing guidelines have predominantly relied on studies conducted on adult patients with bipolar disorders. However, the clinical characteristics and presentation of bipolar disorder in children and adolescents differ significantly from those in adults. This fact highlights the necessity for the conduction of further psychopharmacological trials specifically tailored to this younger age group. As ongoing RCTs are carried out, the body of evidence regarding psychopharmacological treatment in children and adolescents will accumulate. Consequently, there is an ongoing need for updated and evidence-based guidelines that specifically address the treatment of PBD.

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REFERENCES

1. McClellan J, Kowatch R, Findling RL; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(1):107-25. doi: 10.1097/01.chi.0000242240.69678.c4.
2. Alonso J, Petukhova M, Vilagut G, Chatterji S, Heeringa S, Üstün TB, et al. Days out of role due to common physical and mental conditions: results from the WHO World Mental Health surveys. Mol Psychiatry. 2011;16(12):1234-46. doi: 10.1038/mp.2010.101.
3. Duffy A. The early course of bipolar disorder in youth at familial risk. J Can Acad Child Adolesc Psychiatry. 2009;18(3):200-5.
4. Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. Am J Psychiatry. 2009;166(7):795-804. doi: 10.1176/appi.ajp.2009.08101569.
5. Connor DF, Ford JD, Pearson GS, Scranton VL, Dusad A. Early-Onset Bipolar Disorder: Characteristics and Outcomes in the Clinic. J Child Adolesc Psychopharmacol. 2017;27(10):875-83. doi: 10.1089/cap.2017.0058
6. Findling RL, Zhou X, George P, Chappell PB. Diagnostic Trends and Prescription Patterns in Disruptive Mood Dysregulation Disorder and Bipolar Disorder. J Am Acad Child Adolesc Psychiatry. 2022;61(3):434-45. doi: 10.1016/j.jaac.2021.05.016.
7. Association AP. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: American Psychiatric Association; 2013.
8. Uran P, Kılıç BG. Family Functioning, Comorbidities, and Behavioral Profiles of Children With ADHD and Disruptive Mood Dysregulation Disorder. J Atten Disord. 2020;24(9):1285-94. doi: 10.1177/1087054715588949.
9. Treatment Options for the Cardinal Symptoms of Disruptive Mood Dysregulation Disorder. J Can Acad Child Adolesc Psychiatry. 2015;24(1):41-54.
10. Sun AY, Woods S, Findling RL, Stepanova E. Safety considerations in the psychopharmacology of pediatric bipolar disorder. Expert Opin Drug Saf. 2019;18(9):777-94. doi: 10.1080/14740338.2019.1637416.
11. Stepanova E, Findling RL. Psychopharmacology of Bipolar Disorders in Children and Adolescents. Pediatr Clin North Am. 2017;64(6):1209-22. doi: 10.1016/j.pcl.2017.08.002.
12. National Collaborating Centre for Mental Health (UK). Bipolar Disorder: The NICE Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care. London: The British Psychological Society and The Royal College of Psychiatrists; 2014 Sep.
13. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97-170. doi: 10.1111/bdi.12609.
14. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M, et al. Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005;44(3):213-35. doi: 10.1097/00004583-200503000-00006.
15. Hobbs E, Reed R, Lorberg B, Robb AS, Dorfman J. Psychopharmacological Treatment Algorithms of Manic/Mixed and Depressed Episodes in Pediatric Bipolar Disorder. J Child Adolesc Psychopharmacol. 2022;32(10):507-21. doi: 10.1089/cap.2022.0035.
16. Findling RL, Nyilas M, Forbes RA, McQuade RD, Jin N, Iwamoto T, et al. Acute treatment of pediatric bipolar I disorder, manic or mixed episode, with aripiprazole: a randomized, double-blind,

placebo-controlled study. J Clin Psychiatry. 2009;70(10):1441-51. doi: 10.4088/JCP.09m05164yel.

17. Stepanova E, Grant B, Findling RL. Asenapine Treatment in Pediatric Patients with Bipolar I Disorder or Schizophrenia: A Review. Paediatr Drugs. 2018;20(2):121-34. doi: 10.1007/s40272-017-0274-9.
18. Haas M, DelBello MP, Pandina G, Kushner S, Van Hove I, Augustyns I, et al. Risperidone for the treatment of acute mania in children and adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled study. Bipolar Disord. 2009;11(7):687-700. doi: 10.1111/j.1399-5618.2009.00750.x.
19. Delbello MP, Kowatch RA, Adler CM, Stanford KE, Welge JA, Barzman DH, et al. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. J Am Acad Child Adolesc Psychiatry. 2006;45(3):305-13. doi: 10.1097/01.chi.0000194567.63289.97.
20. Tohen M, Kryzhanovskaya L, Carlson G, Delbello M, Wozniak J, Kowatch R, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. Am J Psychiatry. 2007;164(10):1547-56. doi: 10.1176/appi.ajp.2007.06111932.
21. Findling RL, Robb A, McNamara NK, Pavuluri MN, Kafantaris V, Scheffer R, et al. Lithium in the Acute Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Study. Pediatrics. 2015;136(5):885-94. doi: 10.1542/peds.2015-0743.
22. Cox JH, Seri S, Cavanna AE. Clinical Guidelines on Long-Term Pharmacotherapy for Bipolar Disorder in Children and Adolescents. J Clin Med. 2014;3(1):135-43. doi: 10.3390/jcm3010135.
23. Díaz-Caneja CM, Moreno C, Llorente C, Espliego A, Arango C, Moreno D. Practitioner review: Long-term pharmacological treatment of pediatric bipolar disorder. J Child Psychol Psychiatry. 2014;55(9):959-80. doi: 10.1111/jcpp.12271.
24. Detke HC, DelBello MP, Landry J, Usher RW. Olanzapine/Fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2015;54(3):217-24. doi: 10.1016/j.jaac.2014.12.012.
25. DelBello MP, Goldman R, Phillips D, Deng L, Cucchiaro J, Loebel A. Efficacy and Safety of Lurasidone in Children and Adolescents With Bipolar I Depression: A Double-Blind, Placebo-Controlled Study. J Am Acad Child Adolesc Psychiatry. 2017;56(12):1015-25. doi: 10.1016/j.jaac.2017.10.006.
26. Berk L, Hallam KT, Colom F, Vieta E, Hasty M, Macneil C, et al. Enhancing medication adherence in patients with bipolar disorder. Hum Psychopharmacol. 2010;25(1):1-16. doi: 10.1002/hup.1081.
27. Uttley L, Kearns B, Ren S, Stevenson M. Aripiprazole for the treatment and prevention of acute manic and mixed episodes in bipolar I disorder in children and adolescents: a NICE single technology appraisal. Pharmacoeconomics. 2013;31(11):981-90. doi: 10.1007/s40273-013-0091-0.
28. NICE guideline CG185. Bipolar disorder: assessment and management: Evidence review for changes to valproate recommendations after revised MHRA safety advice December 2023. Available from: https://www.nice.org.uk/guidance/cg185/evidence/evidence-review-for-changes-to-valproate-recommendations-after-revised-mhra-safety-advice-pdf-13257358093.
29. Kowatch RA, Findling RL, Scheffer RE, Stanford K. (2007, October). Pediatric bipolar collaborative mood stabilizer trial. In 54th Annual Meeting of the American Academy of Child and Adolescent Psychiatry. pp. 23-8.
30. Wagner KD, Kowatch RA, Emslie GJ, Findling RL, Wilens TE, McCague K, et al. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. Am J Psychiatry. 2006;163(7):1179-86. doi: 10.1176/ajp.2006.163.7.1179.
31. Ochoa ELM. Lithium as a Neuroprotective Agent for Bipolar Disorder: An Overview. Cell Mol Neurobiol. 2022;42(1):85-97. doi: 10.1007/s10571-021-01129-9.
32. Goldstein TR, Ha W, Axelson DA, Goldstein BI, Liao F, Gill MK, et al. Predictors of prospectively examined suicide attempts among youth with bipolar disorder. Arch Gen Psychiatry. 2012;69(11):1113-22. doi: 10.1001/archgenpsychiatry.2012.650.
33. Yang R, Zhao Y, Tan Z, Lai J, Chen J, Zhang X, et al. Differentiation between bipolar disorder and major depressive disorder in adolescents: from clinical to biological biomarkers. Front Hum Neurosci. 2023;17:1192544. doi: 10.3389/fnhum.2023.1192544.
34. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry. 2013;170(11):1249-62. doi: 10.1176/appi.ajp.2013.13020185.
35. Lim CJ, Leckman JF, Young C, Martin A. Antidepressant-induced manic conversion: a developmentally informed synthesis of the literature. Int Rev Neurobiol. 2005;65:25-52. doi: 10.1016/S0074-7742(04)65002-1.
36. Patel NC, Delbello MP, Bryan HS, Adler CM, Kowatch RA, Stanford K, et al. Open-label lithium for the treatment of adolescents with bipolar depression. J Am Acad Child Adolesc Psychiatry. 2006;45(3):289-97. doi: 10.1097/01.chi.0000194569.70912.a7.
37. Chang K, Saxena K, Howe M. An open-label study of lamotrigine adjunct or monotherapy for the treatment of adolescents with bipolar depression. J Am Acad Child Adolesc Psychiatry. 2006;45(3):298-304. doi: 10.1097/01.chi.0000194566.86160.a3.
38. DelBello MP, Chang K, Welge JA, Adler CM, Rana M, Howe M, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. Bipolar Disord. 2009;11(5):483-93. doi: 10.1111/j.1399-5618.2009.00728.x.
39. Findling RL, Pathak S, Earley WR, Liu S, DelBello MP. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial. J Child Adolesc Psychopharmacol. 2014;24(6):325-35. doi: 10.1089/cap.2013.0105.
40. Goldsmith M, Singh M, Chang K. Antidepressants and psychostimulants in pediatric populations: is there an association with mania? Paediatr Drugs. 2011;13(4):225-43. doi: 10.2165/11591660-000000000-00000.
41. Bhowmik D, Aparasu RR, Rajan SS, Sherer JT, Ochoa-Perez M, Chen H. Risk of manic switch associated with antidepressant therapy in pediatric bipolar depression. J Child Adolesc Psychopharmacol. 2014;24(10):551-61. doi: 10.1089/cap.2014.0028.
42. Strober M, Schmidt-Lackner S, Freeman R, Bower S, Lampert C, DeAntonio M. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. J Am Acad Child Adolesc Psychiatry. 1995;34(6):724-31. doi: 10.1097/00004583-199506000-00012.
43. Nazeer A, Hashemi N, Imran N, Naveed S, Azeem MW, Skokauskas N. Pediatric bipolar disorder. Journal of Alternative Medicine Research. 2022;14(3):257-66.

44. Yee CS, Hawken ER, Baldessarini RJ, Vázquez GH. Maintenance Pharmacological Treatment of Juvenile Bipolar Disorder: Review and Meta-Analyses. Int J Neuropsychopharmacol. 2019;22(8):531-40. doi: 10.1093/ijnp/pyz034.

45. Findling RL, Correll CU, Nyilas M, Forbes RA, McQuade RD, Jin N, et al. Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study. Bipolar Disord. 2013;15(2):138-49. doi: 10.1111/bdi.12042.

46. Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Wynbrandt JL, Adegbite C, et al. Double-blind, randomized, placebo-controlled long-term maintenance study of aripiprazole in children with bipolar disorder. J Clin Psychiatry. 2012;73(1):57-63. doi: 10.4088/JCP.11m07104.

47. Findling RL, McNamara NK, Youngstrom EA, Stansbrey R, Gracious BL, Reed MD, et al. Double-blind 18-month trial of lithium versus divalproex maintenance treatment in pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2005;44(5):409-17. doi: 10.1097/01.chi.0000155981.83865.ea.

48. Pavuluri MN, Henry DB, Carbray JA, Naylor MW, Janicak PG. Divalproex sodium for pediatric mixed mania: a 6-month prospective trial. Bipolar Disord. 2005;7(3):266-73. doi: 10.1111/j.1399-5618.2005.00204.x.

49. Geller B, Luby JL, Joshi P, Wagner KD, Emslie G, Walkup JT, et al. A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. Arch Gen Psychiatry. 2012;69(5):515-28. doi: 10.1001/archgenpsychiatry.2011.1508.

50. Kowatch RA, Suppes T, Carmody TJ, Bucci JP, Hume JH, Kromelis M, et al. Effect size of lithium, divalproex sodium, and carbamazepine in children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry. 2000;39(6):713-20. doi: 10.1097/00004583-200006000-00009.

51. Findling RL, Landbloom RL, Mackle M, Wu X, Snow-Adami L, Chang K, et al. Long-term Safety of Asenapine in Pediatric Patients Diagnosed With Bipolar I Disorder: A 50-Week Open-Label, Flexible-Dose Trial. Paediatr Drugs. 2016;18(5):367-78. doi: 10.1007/s40272-016-0184-2.

52. Duffy A, Milin R, Grof P. Maintenance treatment of adolescent bipolar disorder: open study of the effectiveness and tolerability of quetiapine. BMC Psychiatry. 2009;9:4. doi: 10.1186/1471-244X-9-4.

53. Findling RL, Pathak S, Earley WR, Liu S, DelBello M. Safety, tolerability, and efficacy of quetiapine in youth with schizophrenia or bipolar I disorder: a 26-week, open-label, continuation study. J Child Adolesc Psychopharmacol. 2013;23(7):490-501. doi: 10.1089/cap.2012.0092.

54. Findling RL, Cavuş I, Pappadopulos E, Vanderburg DG, Schwartz JH, Gundapaneni BK, et al. Efficacy, long-term safety, and tolerability of ziprasidone in children and adolescents with bipolar disorder. J Child Adolesc Psychopharmacol. 2013;23(8):545-57. doi: 10.1089/cap.2012.0029.

55. Findling RL, McNamara NK, Gracious BL, Youngstrom EA, Stansbrey RJ, Reed MD, et al. Combination lithium and divalproex sodium in pediatric bipolarity. J Am Acad Child Adolesc Psychiatry. 2003;42(8):895-901. doi: 10.1097/01.CHI.0000046893.27264.53.

56. Strober M, Morrell W, Lampert C, Burroughs J. Relapse following discontinuation of lithium maintenance therapy in adolescents with bipolar I illness: a naturalistic study. Am J Psychiatry. 1990;147(4):457-61. doi: 10.1176/ajp.147.4.457.

57. Hirschfeld RMA, Bowden CL, Gitlin MJ, Keck PE, Perlis RH, Suppes T, et al. Practice guideline for the treatment of patients with bipolar disorder (revision). Focus. 2003;1:64-110.

58. Popovic D, Reinares M, Goikolea JM, Bonnin CM, Gonzalez-Pinto A, Vieta E. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. Eur Neuropsychopharmacol. 2012;22(5):339-46. doi: 10.1016/j.euroneuro.2011.09.008.

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Original Article

Electrocardiographic Findings in Pediatric MIS-C Patients

Pediatrik MIS-C Hastalarında Elektrokardiyografik Bulgular

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ABSTRACT

Objective: This study investigates electrocardiographic (ECG) findings in pediatric patients diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) during the coronavirus disease-2019 pandemic, offering valuable insights into the diagnostic process.

Method: Demographic, clinical, and laboratory data of 71 MIS-C cases and 27 Kawasaki disease cases between January 2019 and December 2021 were retrospectively collected from hospital records, following ethics committee approval. MIS-C diagnosis adhered to World Health Organization criteria, and Kawasaki disease diagnosis followed American Heart Association guidelines.

Results: Seventy one MIS-C cases and 27 Kawasaki disease cases were included. MIS-C patients exhibited a significantly shorter duration of fever, higher C-reactive protein levels, and elevated serum cardiac troponin T troponin values compared to Kawasaki disease cases. Transthoracic echocardiographic evaluation revealed specific cardiac abnormalities in MIS-C patients, including mitral regurgitation and aortic regurgitation. ST segment changes, T-wave negativity, and QRS changes were observed significantly in MIS-C patients.

Conclusion: Results provide crucial information about the ECG profile of MIS-C cases. Particularly, indicators such as ST segment changes and T-wave negativity play a critical role in distinguishing MIS-C from other similar conditions and understanding its cardiac effects. These data offer valuable clinical markers that can be utilized in the diagnosis and treatment of MIS-C.

Keywords: Electrocardiography, pediatrics, MIS-C, Kawasaki disease

ÖZ

Amaç: Bu çalışma, koronavirüs hastalığı-2019 pandemisi sırasında Multisistem Enflamatuvar Sendromu olan Çocuklarda (MIS-C) elektrokardiyografik (EKG) bulguları araştırarak, tanı sürecine değerli bir bakış sunmayı amaçlamaktadır.

Yöntem: Ocak 2019 ile Aralık 2021 tarihleri arasında 71 MIS-C olgusu ve 27 Kawasaki hastalığı olgusunun demografik, klinik ve laboratuvar verileri, etik kurul onayı sonrasında hastane kayıtlarından retrospektif olarak toplandı. MIS-C tanısı, Dünya Sağlık Örgütü kriterlerine uygun olarak yapılırken, Kawasaki hastalığı tanısı Amerikan Kalp Derneği kılavuzlarına göre yapıldı.

Bulgular: Yetmiş bir MIS-C olgusu ve 27 Kawasaki hastalığı olgusu dahil edildi. MIS-C hastaları, Kawasaki hastalığı olgularına göre belirgin olarak daha kısa süreli ateş, daha yüksek C-reaktif protein seviyeleri ve yüksek cTnT troponin değerleri sergiledi. Transtorasik ekokardiyografik değerlendirme, MIS-C hastalarında özel kardiyak anormallikleri, mitral ve aort regürjitasyonunu içeren belirli kardiyak patolojileri ortaya çıkardı. ST segment değişiklikleri, T dalga negatifliği ve QRS değişiklikleri MIS-C hastalarında belirgin olarak gözlemlendi.

Sonuç: Sonuçlar, MIS-C olgularının EKG profil hakkında önemli bilgiler sağlamaktadır. Özellikle, ST segment değişiklikleri ve T dalga negatifliği gibi göstergeler, MIS-C'yi diğer benzer durumlardan ayırmada ve kardiyak etkilerini anlamada kritik bir rol oynamaktadır. Bu veriler, MIS-C'nin tanı ve tedavisinde kullanılabilecek değerli klinik işaretler sunmaktadır.

Anahtar kelimeler: Elektrokardiyografi, pediatrik, MIS-C, Kawasaki hastalığı

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INTRODUCTION

While the disease process was asymptomatic in childhood at the beginning of the coronavirus disease-2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2, in April 2020, the United Kingdom Pediatric Intensive Care Association

published an article on one deceased and seven survived patients with severe gastrointestinal system symptoms, toxic shock, high fever associated with COVID-19 that presented with a clinical picture similar to atypical Kawasaki disease with severe myocardial involvement[1]. This clinical condition was named "multisystem inflammatory syndrome in children (MIS-C)" by the World Health Organization (WHO) after similar case reports came from other countries.

Kawasaki disease in the differential diagnosis of MIS-C is a frequently confused clinical picture. Although the diagnostic criteria are mostly sufficient to establish a definitive diagnosis and treatment planning, in some cases making an accurate differential diagnosis is almost impossible. Overlapping clinical manifestations are frequently encountered. For the administration of human immunoglobulin and acetylsalicylic acid, which are the first treatment options in Kawasaki disease, a febrile period persisting up to 9 days is an acceptable indication. Since rapid clinical deterioration and shock are more prominent features in MIS-C, early diagnosis, and effective treatment carry vital importance[2].

In this study, we aimed to examine the conventional 12-lead electrocardiographic (ECG) changes detected at the time of admission of MIS-C cases diagnosed and followed up in our clinic during the COVID-19 pandemic.

MATERIALS and METHODS

Demographic, clinical, and laboratory information of cases diagnosed with MIS-C (n=71) and Kawasaki disease (n=27) between January 2019 and December 2021 were retrieved from hospital records after obtaining the necessary ethics committee approval. Ethics committee approval was obtained from the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (decision no: 2022/11-06, date: 09.06.2022).

MIS-C was diagnosed according to the WHO criteria[3]. Patients between the ages of 0-19 years with ≥3 days of fever with at least two of the following diagnostic criteria; rash, conjunctivitis or mucocutaneous lesion, hypotension or shock, cardiac involvement (myocardial dysfunction, pericarditis, valvulitis or coronary artery anomaly), coagulopathy, increased sedimentation rate, C-reactive protein (CRP), and procalcitonin levels with

Table 1. Comparative evaluation of demographic, clinical, electrocardiographic findings, and serum cardiac troponin T levels of the patients

	Multiple systemic inflammatory syndrome	Kawasaki disease	p-value
Gender			
Male, n (%)	52 (73)	13 (48.1)	<0.05
Female, n (%)	19 (26.7)	14 (51.7)	<0.05
Transthoracic echocardiographic findings			
Mitral regurgitation (1-2 degrees), n (%)	19 (26.7)	4 (19)	
Aortic regurgitation, n (%)	4 (5.6)	1 (4.7)	
Pericardial effusion, n (%)	2 (2.8)	0	
LVSD, n (%)	9 (9.1)	0	
Coronary aneurysm, n (%)	0	1 (4.7)	
Normal, n (%)	46	21	
Electrocardiographic findings			
QRS change, n (%)	5 (7)	0	
T-wave change, n (%)	6 (8.4)	0	
ST segment change, n (%)	6 (8.4)	0	
Normal, n (%)	54 (76.2)	27	
Serum cardiac troponin T levels			
1-5 x ULN	6 (6)	1	0.02
5-10 x ULN	2 (2.8)	0	
10 x ULN	17 (23.9)	0	

LVSD: Left ventricular systolic dysfunction, ULN: Upper limit of normal

acute gastrointestinal symptoms were included in the MISC group.

American Heart Association (AHA) guidelines were used for the diagnosis of Kawasaki disease[4]. The diagnosis of Kawasaki disease was based on the presence of ≥5 days of fever and the presence of ≥4 of the 5 principal clinical features including extremity changes, rash, conjunctivitis, oral lesions, and servical lymphadenopathy.

ECG data were obtained retrospectively from conventional standard 12-lead ECG recordings (Philips Medical Systems, Andover, MA, USA) taken at 25 mm/s and 10 mm/mV at admission. PR interval, QRS, and RR measurements were calculated electronically from ECG recordings, and corrected QT interval (QTc) was estimated manually from leads D2 and V5 using Bazett's formula. T-wave amplitude was evaluated from leads D1 and V6, and R and S wave amplitudes were measured manually from leads V1, V4, and V6.

The ECG interpretation was performed according to the guideline published by the AHA Electrocardiography and Arrhythmias Committee[5]. Accordingly, cases with PR >98% according to age and gender were considered to have first-degree AV block. Age-, and gender-adjusted QRS, and QTc intervals >98 were defined as prolonged QRS, and QTc intervals, respectively. ST segment depression was diagnosed when ≥0.05 mV decrease in two or more contiguous leads was observed. ST-segment elevation was defined as ≥0.2 mV in V2/V3, and ≥0.1 mV increase in other leads. T-wave inversion was defined as ≥0.1 mV negativity in any lead, and T-wave negativity between V1-3 was defined as a juvenile pattern (if it was observed in the pediatric age group) was not considered as a pathological finding.

Statistical Analysis

For statistical analysis SPSS 18.0 software (SPSS Inc., Chicago, IL, USA) was used. To check for homogeneous distribution of data coming from two independent groups Kolmogorov-Smirnov test was used. Student's t-test was employed to compare homogeneously distributed data, and Mann-Whitney U test to compare data that did not show homogeneous distribution. The chi-square test was used to compare observed results with expected results.

RESULTS

Seventy-one cases with MIS-C (mean age: 8.5±5.1 years) and 27 patients diagnosed with Kawasaki disease (mean age: 2.4±2.1 years) in the same study period were included in the study ($p<0.05$). The MIS-C group consisted of 52 boys (73%), 19 girls (26.7%), and Kawasaki disease group included 13 boys (48.1%) and 14 girls (51.8%) ($p<0.05$).

The febrile period in the MIS-C group was significantly shorter than the Kawasaki disease group monitored during the same study period (4.76 vs. 6.6 days).

CRP levels were higher in MISC patients than those with Kawasaki disease (10.91 vs. 6.02) (CRP normal value <0.5 mg/dL).

Serum cardiac troponin T (cTnT) values increased 10 times the upper limit of normal (ULN) in 17 (23.9%), 5-10 times the ULN in 2 (2.8%), and 1-5 times the ULN in 6 (6%) patients (cTnT n<0.014 ng/dL). The cTnT levels increased in 7 (77.7%) of 9 patients with systolic dysfunction and ECG changes. Only one (4%) Kawasaki patient had a cTnT value between 1-5 times the ULN ($p<0.042$). The cTnT values of MIS-C patients were statistically significantly higher than those with Kawasaki disease ($p=0.02$).

In the transthoracic echocardiographic evaluation of MIS-C patients, mitral regurgitation (1-2 degrees) was found in 19 patients (26.7%), and aortic regurgitation in 4 patients (5.6%). Pericardial effusion was detected in 2 (2.8%) cases. Coronary artery aneurysm (left coronary artery, z+1.6) was detected in 1 (3.5%) Kawasaki disease patient. Left ventricular systolic dysfunction was detected in 9 (9.1%) patients. All patients with left ventricular systolic dysfunction were in the MIS-C group.

Seventeen (23.9%) MIS-C patients including the cases with ST segment changes (n=6; 8.4%), T-wave negativity (n=6; 8.4%), and QRS changes (n=5; 7%) received positive inotropic therapy. QRS fragmentation was observed in one of the patients with ST-segment changes. QRS changes were detected in 2, T-wave changes in 1, and ST segment changes in 4 patients who received positive inotropic therapy. Among 54 patients (76.1%) who did not need positive inotropic therapy alterations in QRS complexes (n=3), T-waves (n=1), and ST segments (n=5) were observed. No pathological ECG changes were detected in patients diagnosed with Kawasaki disease.

DISCUSSION

Although the pathophysiology of MIS-C is not known precisely, the alteration in T cell response after contact with COVID-19, ACE2 receptor-related pathologies, and hyperinflammatory clinical manifestations due to exaggerated interleukin response have been indicated

in its pathogenesis. Unlike Kawasaki disease, in some MIS-C patients, decreased number of naive CD4+ T cells, decreased follicular T helper cell expression, lower IL17A levels, and increased macrophage activation syndrome precursor interferon-γ levels have been detected[6-9]. The clinical findings of MIS-C syndrome, which are observed in clinical practice with the onset of COVID-19 pandemic, show similarities to those of Kawasaki disease[10]. Although history of COVID-19 infection or contact with infected persons is an indispensable diagnostic criterion for MIS-C syndrome, due to its clinical similarity, it is an obvious fact that the physicians caring for these patients need parameters that will help in the decision-making process and arriving at a differential diagnosis.

While Kawasaki disease is typically seen in early infancy (<5 years), MIS-C can be seen at any age, and it is significantly more common in men. Febrile period is shorter in MIS-C patients (4.76 vs. 6.6 days, $p<0.05$) compared to those with Kawasaki disease. In MIS-C patients, left ventricular systolic dysfunction and mitral valve regurgitation were detected by echocardiography at a significantly higher rate compared to Kawasaki disease, and greater number of patients required inotropic treatment and monitoring in pediatric intensive care unit ($p<0.05$). Higher cTnT levels, and more intense inflammation have been detected in MIS-C patients[11], but there was no coronary artery involvement in echocardiographic evaluation, unlike reported by Sperotto et al.[12] in a multicenter study. ST segment changes and T-wave polarization changes were much more frequently detected in our MIS-C patients compared to our patients with Kawasaki disease, which shares similar clinical and biochemical characteristics with MIS-C. We linked the relevant ECG changes to the presence of more extensive systemic involvement and metabolic stress due to the severe inflammatory process in MISC which would increase the possibility of cardiac involvement. We found that the cTnT levels were higher in patients with ST-segment changes and T-wave depolarization disorders detected on ECG. Systolic dysfunction was observed only in MIS-C patients. Cardiac troponin T levels of these patients were significantly higher. However, although few of these MIS-C patients (6%) had troponin positivity and needed inotropic therapy, any pathological change was not observed in ECG. cTnT values were elevated in all patients who needed IV inotropic therapy.

Since our study patients were admitted to our clinic during the pandemic period, the data we obtained during COVID-19 outbreak were of great benefit when evaluating the patients in terms of their exposure to COVID-19 or clinical discrimination of patients with negative COVID-19 IG-G antibodies. In contrast to the case series of Villacis-Nunez et al.[13] in which they detected giant coronary artery aneurysms, coronary artery aneurysms were not detected in any of our MIS-C patients, thanks to the early initiation of medical treatment in our patients diagnosed with MIS-C. The rate of correct diagnosis increased thanks to our criteria for differential diagnosis between MIS-C, and Kawasaki disease which based on number of febrile days, increased CRP, and cTnT levels, presence of systolic dysfunction, and ECG changes. Detecting ECG findings in MIS-C patients that we did not expect to see in cases with Kawasaki disease facilitated our diagnostic process[14].

Study Limitations

The study was conducted in a single clinic, possibly limiting the external validity of the results, as the population characteristics may not represent the broader demographic diversity. The study was conducted during the COVID-19 pandemic, and the unique circumstances of the healthcare system during this period could introduce confounding variables that may impact the internal validity of our study findings.

CONCLUSION

This study delves into the ECG findings in pediatric patients diagnosed with MIS-C during the COVID-19 pandemic, offering valuable insights into the diagnostic process and highlighting differences from Kawasaki Disease. The MIS-C group exhibited distinct clinical characteristics, including a shorter duration of fever, higher CRP levels, and significantly elevated cTnT values. Echocardiographic evaluations revealed more frequent left ventricular systolic dysfunction in MIS-C patients. Importantly, ECG abnormalities, such as ST segment changes and T-wave polarization disorders, were more prevalent in MIS-C, emphasizing the potential for cardiac involvement in this syndrome. The study underscores the significance of considering ECG changes as diagnostic aids in differentiating MIS-C from Kawasaki disease in pediatric populations. The findings contribute to the understanding of unique ECG profile of MIS-C, aiding clinicians in the timely and accurate diagnosis of this syndrome during the ongoing pandemic.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and

Surgery Training and Research Hospital Ethics Committee (decision no: 2022/11-06, date: 09.06.2022).

Informed Consent: Retrospective study.

Author Contributions

Surgical and Medical Practices: M.M.B., Concept: M.M.Y., G.V., Design: M.M., C.D., Data Collection or Processing: C.K., Analysis or Interpretation: M.M.Y., Literature Search: T.M., Writing: M.M.B.

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REFERENCES

1. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, Nguyen EL, Barsh GR, Maskatia S, Mathew R. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. Hosp Pediatr. 2020;10:537-40. doi: 10.1542/hpeds.2020-0123.
2. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):422-6. doi: 10.15585/mmwr.mm6914e4.
3. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Available at: http://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (Accessed on February 12, 2020).
4. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation. 2017;135:e927-99. doi: 10.1161/CIR.0000000000000484. Epub 2017 Mar 29. Erratum in: Circulation. 2019;140:e181-4.
5. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, Rautaharju PM, van Herpen G, Wagner GS, Wellens H; American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53:976-81. doi: 10.1016/j.jacc.2008.12.013.
6. Weisberg SP, Connors T, Zhu Y, Baldwin M, Lin W-H, Wontakal S, et al. Antibody responses to SARS-CoV2 are distinct in children with MIS-C compared to adults with COVID-19. medRxiv [Preprint]. 2020:2020.07.12.20151068. doi: 10.1101/2020.07.12.20151068.
7. Uhlen M, Karlsson MJ, Zhong W, Tebani A, Pou C, Mikes J, et al. A genome-wide transcriptomic analysis of protein-coding genes in human blood cells. Science. 2019;366(6472):eaax9198. doi: 10.1126/science.aax9198.
8. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell. 2020;183(4):968-81. doi: 10.1016/j.cell.2020.09.016.
9. Esteve-Sole A, Anton J, Pino-Ramirez RM, Sanchez-Manubens J, Fumadó V, Fortuny C, et al. Similarities and differences between the immunopathogenesis of COVID-19-related pediatric multisystem inflammatory syndrome and Kawasaki disease. J Clin Invest. 2021;131(6):e144554. doi: 10.1172/JCI144554.
10. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 2004;110(17):2747-71. doi: 10.1161/01.CIR.0000145143.19711.78.
11. Zhang QY, Xu BW, Du JB. Similarities and differences between multiple inflammatory syndrome in children associated with COVID-19 and Kawasaki disease: clinical presentations, diagnosis, and treatment. World J Pediatr. 2021;17(4):335-40. doi: 10.1007/s12519-021-00435-y.
12. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180(2):307-22. doi: 10.1007/s00431-020-03766-6.
13. Villacis-Nunez DS, Hashemi S, Nelson MC, Flanagan E, Thakral A, Rodriguez F, et al. Giant Coronary Aneurysms in Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection. JACC Case Rep. 2021;3(13):1499-508. doi: 10.1016/j.jaccas.2021.06.043.
14. Crystal MA, Syan SK, Yeung RS, Dipchand AI, McCrindle BW. Echocardiographic and electrocardiographic trends in children with acute Kawasaki disease. Can J Cardiol. 2008;24(10):776-80. doi: 10.1016/s0828-282x(08)70683-4.

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Original Article

Our Experiences with Hyperbaric Oxygen Therapy in Paediatric Orthopaedics

Çocuk Ortopedisinde Hiperbarik Oksijen Tedavisi Deneyimlerimiz

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ABSTRACT

Objective: The main uses of hyperbaric oxygen therapy (HBOT) in orthopaedics are acute traumatic ischemia such as crush injuries and compartment syndrome, reimplantations, chronic osteomyelitis, grafts and flaps with suspected involvement, gas gangrene, necrotizing soft tissue infections, avascular necrosis and delayed post-op wound healing. The aim of this study was to determine the most common orthopaedic indications for HBOT in pediatrics. We also aimed to share information about HBOT with pediatric orthopaedic surgeons.

Method: By reviewing our files and system records, we documented all pediatric patients who underwent HBOT between 01.01.2006 and 01.01.2016 with the indications of crush injury, compartment syndrome, chronic osteomyelitis and delayed wound healing. We recorded the demographic characteristics, indications, outcomes, problems encountered, complications and side effects of patients aged 0-18 years who received at least 15 sessions of HBOT.

Results: A total of 1029 HBOT sessions were performed in 31 patients. Treatment was completed as planned in 24 patients (77.4%). Cure was achieved in 19 patients (61.3%). Two patients (6.4%) had improvement with minor morbidity, and three (9.7%) had no improvement as a result of the treatment. Anxiety symptoms were observed in only six patients during the first session (0.6% patient sessions). The sessions did not result in any complications that required treatment to be discontinued.

Conclusion: HBOT in patients with orthopaedic indications was completed without complications. We believe that HBOT can be safely used in pediatric orthopaedics. However, larger patient series are needed.

Keywords: Hyperbaric oxygen therapy, pediatric, safety, side effects

ÖZ

Amaç: Hiperbarik oksijen tedavisi (HBOT) ortopedide başlıca crush yaralanmalar ve kompartman sendromu gibi akut travmatik iskemiler, reimplantasyonlar, kronik osteomyelit, tutması şüpheli greft ve flepler, gazlı gangren, nekrotizan yumuşak doku enfeksiyonları, avasküler nekrozlar ve post-op yara iyileşmesinin geciktiği durumlarda kullanılmaktadır. Bu çalışmanın amacı çocuklarda en çok hangi ortopedik endikasyonlarda HBOT uyguladığımızı belirlemektir. Ayrıca çocuk ortopedisi ile ilgilenen hekimlerle HBOT konusunda bilgi paylaşmayı amaçladık.

Yöntem: Dosya ve sistem kayıtlarımızı inceleyerek 01.01.2006 ile 01.01.2016 tarihleri arasında crush yaralanma, kompartaman sendromu, kronik osteomyelit ve gecikmiş yara iyileşmesi endikasyonlarıyla HBOT uyguladığımız tüm çocuk hastaları belgeledik. 0-18 yaş arasında ve yukarıda sayılan endikasyonlarda en az 15 seans HBOT gören hastaların demografik özellikleri, endikasyonları, tedavi sonuçları, karşılaştığımız sorunlar, komplikasyon ve yan etkileri kayıt altına aldık.

Bulgular: Otuz bir hastaya toplam 1029 seans HBOT uyguladık. Hastalardan 24'ünün tedavisi planlandığı şekilde tamamlandı (%77,4). Hastaların 19'unda (%61,3) şifa sağlandı. İki hastada (%6,4) tedavi sonucunda minor morbidite ile düzelme oldu, üç hastanın (%9,7) tedavi sonucunda ise herhangi bir düzelme olmadı. Altı hastada ilk seans sırasında anksiyete bulguları gözlendi (%0,6 hasta seansı). Seanslar sırasında tedavinin kesilmesini gerektirecek bir komplikasyona rastlanmadı.

Sonuç: Ortopedik endikasyonlarla tedaviye alınan hastaların HBOT'si herhangi bir komplikasyon olmadan tamamlanmıştır. HBOT'nin çocuk ortopedisinde güvenli bir şekilde kullanılabileceğini düşünmekteyiz. Ancak bu konuda daha geniş hasta serilerine ihtiyaç vardır.

Anahtar kelimeler: Hiperbarik oksijen tedavisi, çocuk, güvenlik, yan etkiler

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INTRODUCTION

Hyperbaric oxygen therapy (HBOT) is a medical treatment based on the inhalation of 100% oxygen at atmospheric pressures greater than 1 atmospheric absolute (ATA), with a minimum of 1.4 ATA for effectiveness. Treatment is administered in monoplace or multiplace HBOT chambers by delivering 100% oxygen via a mask, hood or endotracheal tube (Figure 1). The duration of treatment varies between 1.5 and 2 hours in routine HBOT sessions, and the treatment pressure varies between 2 and 2.8 ATA[1].

The effect of HBOT is achieved by two different mechanisms. The first mechanism is related to the effect caused by the increase in the atmospheric pressure which is used in the treatment of decompression sickness and arterial gas embolism. The second mechanism concerns with the effect of increasing the partial pressure of oxygen inhaled under high pressure. In this way, hypoxia is eliminated thanks to the increased partial oxygen dissolved in the tissues, which has antitoxic, antibacterial and anti-edema effects. In addition, wound healing processes are also supported by high partial oxygen levels[2-6].

Figure 1. Multiplace pressure chamber, a) interior view, b) exterior view (University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital, Clinic of Underwater Medicine and Hyperbaric Medicine)

In 2001, the indications for HBOT according to the "Regulation on Private Health Institutions Applying HBOT" guideline published by the Turkish Ministry of Health are shown in Table 1[7]. Indications for HBOT have been specified by the Undersea and Hyperbaric Medical Society and the European Committee of Hyperbaric Medicine, and consensus reports with levels of evidence were published[1,8]. There are no randomised controlled trials in the literature on indications and treatment protocols in children. Indications and protocols in adults are being used for HBOT in children.

Indications for HBOT in pediatric orthopedics include crush injuries, compartment syndromes, avascular necrosis, necrotizing soft tissue infections, gas gangrene, chronic osteomyelitis, grafts and flaps suspected of being infected or impaired, and conditions where postoperative wound healing is delayed[9].

There are a limited number of studies in the literature on HBO treatment in children[10-14]. In addition, there are no case series on the use of HBOT in pediatric orthopedics. In this study, we reported the indications for HBOT in pediatric orthopedics, the treatment outcomes and the difficulties we encountered during treatment. We compared our data with those of other studies in the literature. We aimed to share this information with pediatric orthopedic surgeons in particular.

Table 1. Indications for hyperbaric oxygen therapy[7]
Decompression sickness
Air or gas embolism
Carbon monoxide, cyanide poisoning, acute smoke inhalation
Gas gangrene
Necrotizing infections of soft tissues (subcutaneous, muscle, fascia)
Crush injuries, compartment syndrome and other acute traumatic ischaemias
Delayed wound healing conditions (diabetic and non-diabetic)
Chronic refractory osteomyelitis
Excessive blood loss
Radiation necrosis
Skin flaps and grafts with suspected involvement
Thermal burns
Brain abscess
Anoxic encephalopathy
Sudden hearing loss
Retinal artery occlusion
Acute osteomyelitis of the skull, sternum and vertebrae

MATERIALS and METHODS

Approval for this retrospective study was obtained from the Ethics Committee of the University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital on 17.05.2021 with the decision number 2021/05-16. We recorded demographic data, indications, HBOT protocol and number of sessions, problems encountered during treatment, complications and outcomes. Chest radiographs were taken before treatment and the lesions that could cause air trapping were assessed. Consent for treatment was obtained from the children's families. A hyperbaric nurse was present during treatment sessions. However, children who did not want to enter the hyperbaric chamber and showed signs of anxiety were allowed to be accompanied by a family member. Ear equalization manoeuvres were explained and demonstrated to the children. Young children were induced to perform ear equalization manoeuvres in the hyperbaric chamber by playing yawning games. HBOT sessions were performed in a multi-place hyperbaric chamber (Barotech-Istanbul) at 2-3 ATA pressures for 2 hours. Oxygen was administered by mask and hood in children too young to adapt to the mask. Toys that did not pose a fire risk were allowed in the hyperbaric chamber as a distraction for young children. During treatment sessions, the hyperbaric chamber was monitored and recorded by external cameras, and verbal communication was provided by an intercom system. Because of the risk of fire, electrical appliances and flammable objects were not allowed in the hyperbaric chamber. In addition, the oxygen level in the chamber was strictly controlled by oxygen sensors.

Statistical Analysis

Data were entered into a Microsoft Excel (Microsoft, US) spreadsheet under the categories of complete recovery, healing with minor morbidity (minor amputation, skin graft or surgical debridement), no recovery, withdrawal from treatment, and complications related to HBOT. These data were statistically analyzed with Microsoft 365 Excel 2021 software program.

Patients

A total of 31 pediatric patients aged 5-18 years (median 12 years) referred from orthopedic clinics were treated over a 10-year period. Patient demographics by indications and number of sessions performed are shown in Table 2. A total of 1029 HBOT sessions were delivered (mean ± standard deviation number of therapy sessions per patient: 33.2±16.4).

Eighteen patients received HBOT for delayed wound healing. Nine of these patients underwent surgery after trauma and developed infection or necrosis in the surgical field. Nine patients who presented with ulcers due to foot deformity with sequelae of meningomyelocele were school-aged and mobile patients. Eight patients were treated with a diagnosis of chronic osteomyelitis. Patients had femural osteomyelitis (n=1), humeral osteomyelitis (n=1), and tibial-fibular osteomyelitis (n=6). Five patients were treated with the diagnosis of crush injury and compartment syndrome, due to traffic accidents (n=3) and compression between objects (n=2).

RESULTS

Over a 10-year period, we treated a total of 31 patients aged 5-18 years with five different indications. Treatment outcomes are shown in Table 3. Cure was achieved in 19 patients (61.3%) (Figures 2, 3). Two (6.4%) patients had a minor morbidity, and three (9.7%) patients did not recover despite treatment.

None of the patients refused treatment because of claustrophobia. Anxiety was observed in only six out of 1029 sessions (0.6%). Anxiety symptoms disappeared when a family member entered the hyperbaric chamber with his/her children. No barotrauma or oxygen toxicity that would interrupt or terminate treatment was observed during HBO sessions.

DISCUSSION

Indications and levels of evidence for HBOT have been defined by international organizations[1,8]. In the absence of specific HBOT guidelines for children,

Table 2. Indication, demographics and number of sessions

Indication	n	Mean (SD) Age	Sex (F:M)	Median (SD) Session
Delayed wound healing	18			
Operation wounds	9	9.7 (4.0)	4:5	32.9 (13.3)
MMC	9	12 (4.7)	7:2	35.6 (18.8)
Chronic osteomyelitis	8	14.1 (4.0)	3:5	33.4 (21)
Crush injury, compartment syndrome	5	11.8 (4.8)	1:4	31 (12.5)
Total	31	12.2 (4.5)	15:16	33.2 (16.4)

F: Female, M: Male, SD: Standard deviation, MMC: Meningomyelocele

Table 3. Treatments outcomes					
Indication	**n**	**Complete recovery**	**Recovery with minor morbidity**	**No recovery**	**Withdrawal from treatment**
Delayed wound healing	18				
Operation wounds	9	5	1	1	2
MMC squealae	9	6	0	0	3
Chronic osteomyelitis	8	4	0	2	2
Crush injury, compartment syndrome	5	4	1	0	0
n (%)	31	19 (61.3)	2 (6.45)	3 (9.68)	7 (22.6)
MMC: Meningomyelocele					

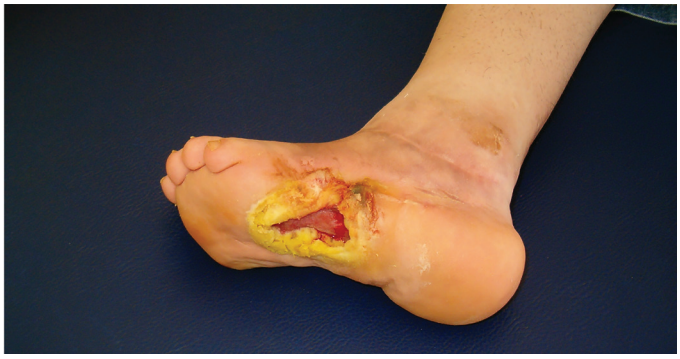

Figure 2. Sixteen year-old female patient, foot deformity due to meningomyelocele, before HBOT

HBOT: Hyperbaric oxygen therapy

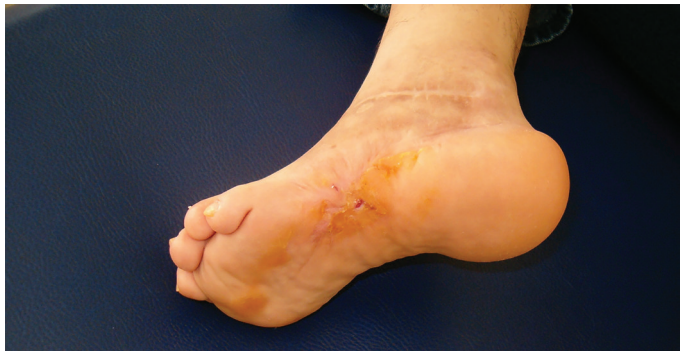

Figure 3. After 60 sessions of HBOT

HBOT: Hyperbaric oxygen therapy

current indications for adults were also used in our study for pediatric patients.

In our study, most commonly patients with delayed wound healing (n=18) received HBOT. Nine of these patients had chronic ulcers occurring in the deformed foot as a result of meningomyelocele. These patients were school-aged children with no activity limitations. Treatment regimens included HBOT, wound care and off-loading. The remaining nine patients were admitted for failure of the surgical site to heal after surgery for various reasons.

In addition to HBO treatment, wound care, appropriate antibiotherapy based on tissue culture results, and minor debridement of ulcers were performed. Traffic accidents were the most common cause of chronic osteomyelitis in eight cases. One of the four crush injury cases required a minor amputation. In the remaining cases, treatment achieved healing of wounds. One case of compartment syndrome was treated with HBO. This patient's treatment resulted in complete healing at the end of the 15th session of HBO without need for surgical intervention.

In the patient series of Frawley et al.[10] and Frawley and Fock[12], cases of delayed wound healing were treated with HBO. In a series of 112 patients, 13 patients were treated with a diagnosis of chronic osteomyelitis. Complete recovery was reported in 10 and recovery with minor sequelae in 3 cases[10]. In a series of 139 patients by Waisman et al.,[11] five cases of chronic osteomyelitis were treated and cured without the need for surgical intervention after an average of 32 sessions of HBOT. Another series of patients reported two cases of chronic osteomyelitis without any mention of the outcomes of the cases[12]. A total of 27 cases including 14 cases with crush injuries and 13 cases with compartment syndromes were reported. Three of these patients recovered with major disability and 15 with minor disability. The average number of 7.2 HBO sessions were used in these patients[10]. In the study by Waissman et al.,[11] 13 cases with acute traumatic and crush injuries were reported. Two patients recovered completely and five patients partially. Six patients did not benefit from the treatment.

The most common side effect of HBOT is ear and sinus barotrauma[15-18]. Side effects of HBOT have not been investigated in studies performed on pediatric patients.

However, the incidence of barotrauma in the general population has been reported to be 1.9-3% in various studies[16,17].

Complications requiring discontinuation of HBOT were not observed in our study. Anxiety was observed in only six (0.6%) sessions and these symptoms disappeared when the parents entered the hyperbaric chamber with their children. The rates of anxiety in the study by Frawley and Fock[12] were reported to vary between 2, and 3.2%. In the study by Plafki et al.[16] the rate of anxiety in the general population, was reported to be 4.3%, and in 1.3% of the cases treatment was discontinued because of anxiety. We believe that if a family member accompanies his/her child during therapy sessions, anxiety of these children will be relieved, and the treatment process will not be interrupted or discontinued.

Study Limitations

This study has some limitations. The main limitations are its retrospective nature, and the small number of patients included in the study population. We also did not have information on the outcomes of seven patients whose treatment was discontinued at the request of their families. The other limitation is the lack of a control group which prevents intergroup comparison of treatment outcomes.

CONCLUSION

HBOT is an adjunctive treatment modality that can be used for several indications in pediatric orthopedics. We believe that HBOT can be safely used in pediatric patients for the same indications as in adults. Large patient series are needed to provide more detailed information on the efficacy and side effects of HBOT in pediatric orthopedics.

Ethics

Ethics Committee Approval: Approval for this retrospective study was obtained from the Ethics Committee of the University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital on 17.05.2021 with the decision number 2021/05-16.

Informed Consent: Retrospective study.

Author Contributions

Surgical and Medical Practices: F.A., M.İ., Concept: F.A., Design: F.A., Data Collection or Processing: F.A., Analysis or Interpretation: F.A., M.İ., Literature Search: F.A., M.İ., Writing: F.A.

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REFERENCES

1. Moon RE. Indications for Hyperbaric Oxygen Therapy. 14 ed. Moon RE, editor. Florida USA: Best Publishing Company; 2019.
2. Hammarlund C. The physiologic effects of hyperbaric oxygenation. In: Kindwall EP, Whelan HT (ed). Hyperbaric Medicine Practice. Best Publishing Company. USA, 2nd Revised Edition, 2002:39-70.
3. Mathieu D, Favory R, Collet F, Linke JC, Wattel F. Physiologic Effects of Hyperbaric Oxygen on Hemodynamics and Microcirculation. Springer. 2006. doi: 10.1007/1-4020-4448-8_6.
4. Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. Plast Reconstr Surg. 2011;127 Suppl 1(Suppl 1):131S-41S. doi: 10.1097/PRS.0b013e3181fbe2bf.
5. Jain KK. Physical, physiological and biochemical aspects of hyperbaric oxygenation. Textbook of Hyperbaric Medicine. 2017:9-19. doi: 10.1007/978-3-319-47140-2_2.
6. Çimşit M. Hiperbarik Oksijenin Etki Mekanizması Hiperbarik Tıp-Teori ve Uygulama. Eflatun Yayınevi. 2009:35-58.
7. Hiperbarik Oksijen Tedavisi Endikasyonları Resmî Gazete Tarihi: 01.08.2001 Sayısı: 24480 Available from: https://www.mevzuat.gov.tr/mevzuat?MevzuatNo=4809&MevzuatTur=7&MevzuatTertip=5
8. Mathieu D, Marroni A, Kot J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. Diving Hyperb Med. 2017;47(1):24-32. doi: 10.28920/dhm47.1.24-32.
9. Jeyaraman M, Sami A, Nallakumarasamy A, Jeyaraman N, Jain VK. Hyperbaric Oxygen Therapy in Orthopaedics: An Adjunct Therapy with an Emerging Role. Indian J Orthop. 2023;57(5):748-61. doi: 10.1007/s43465-023-00837-2.
10. Frawley G, Bennett M, Thistlethwaite K, Banham N. Australian paediatric hyperbaric oxygen therapy 1998-2011. Anaesth Intensive Care. 2013;41(1):74-81. doi: 10.1177/0310057X1304100113.
11. Waisman D, Shupak A, Weisz G, Melamed Y. Hyperbaric oxygen therapy in the pediatric patient: the experience of the Israel Naval Medical Institute. Pediatrics. 1998;102(5):E53. doi: 10.1542/peds.102.5.e53.
12. Frawley GP, Fock A. Pediatric hyperbaric oxygen therapy in Victoria, 1998-2010. Pediatr Crit Care Med. 2012;13(4):e240-4. doi: 10.1097/PCC.0b013e318238b3f3.
13. Siewiera J, Mews J, Królikowska K, Kalicki B, Jobs K. Hyperbaric oxygenation in pediatrics: indications in the light of evidence - based medicine. Dev Period Med. 2019;23(2):142-8. doi: 10.34763/devperiodmed.20192302.142148.
14. Canaz Z. Hiperbarik Oksijen Tedavisi Uygulanmış 0-14 Yaş Grubu Hastaların Değerlendirilmesi, (Uzmanlık Tezi), İÜ İstanbul Tıp Fakültesi Sualtı Hekimliği ve Hiperbarik Tıp Kliniği 2021.
15. Camporesi EM. Side effects of hyperbaric oxygen therapy. Undersea Hyperb Med. 2014;41(3):253-7.
16. Plafki C, Peters P, Almeling M, Welslau W, Busch R. Complications and side effects of hyperbaric oxygen therapy. Aviat Space Environ Med. 2000;71(2):119-24.
17. Fitzpatrick DT, Franck BA, Mason KT, Shannon SG. Risk factors for symptomatic otic and sinus barotrauma in a multiplace hyperbaric chamber. Undersea Hyperb Med. 1999;26(4):243-7.
18. Heyboer M 3rd, Sharma D, Santiago W, McCulloch N. Hyperbaric Oxygen Therapy: Side Effects Defined and Quantified. Adv Wound Care (New Rochelle). 2017;6(6):210-24. doi: 10.1089/wound.2016.0718.

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Original Article

Evaluation of Infectious Complications and Their Causative Agents in Pediatric Cancer Patients: A Prospective Single-center Cohort Study

Pediatrik Kanser Hastalarında Enfeksiyonlar ve Etken Ajanların Değerlendirilmesi: Prospektif Tek Merkezli Kohort Çalışması

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ABSTRACT

Objective: This study aimed to evaluate the epidemiological, microbiological, clinical characteristics of the patients followed up with different types of underlying hematologic malignancies and solid tumors.

Method: This cohort study included patients with pediatric malignancy. Eighty-eight patients who were followed up for two years were included. The number of days from the first diagnosis, recurrent infectious episodes, number of days with fever, presence of neutropenia and nonneutropenic episodes, chemotherapy regimens, antimicrobial agents, blood and urinary tract culture samples were recorded.

Results: A total of 149 infectious episodes were observed. The median age was 5.08 years. The mean age was 9.02±5.17 years in patients who had no infectious episodes during the follow-up and 5.70±4.60 years in patients with two and more infectious episodes and was significantly lower (p=0.024). In total, 264 microbial cultures were retrieved from different locations during these infectious episodes. Regarding all the cultures, 27% of blood cultures and 9% of urinary tract cultures were positive. The most commonly isolated microorganism were Gram-positive bacteria (n=23, 57.5%).

Conclusion: Younger children with cancer are at higher risk of infection complications compared to children of older ages. Children with hematologic malignancies are more likely to develop a neutropenic fever during the consolidation and induction periods. Regarding the high rate of FUO in our study, more attempts to increase microbiological diagnosis in this patient population.

Keywords: Febrile neutropenia, cancer, pediatrics

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ÖZ

Amaç: Bu çalışmada, altta yatan farklı tipte hematolojik maligniteler ve solid tümörler ile takip edilen hastaların epidemiyolojik, mikrobiyolojik, klinik özelliklerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Bu kohort çalışmasına pediatrik maligniteli hastalar dahil edilmiştir. İki yıl takip edilen 88 hasta çalışmaya dahil edildi. İlk tanıdan itibaren gün sayısı, tekrarlayan enfeksiyöz ataklar, ateşli gün sayısı, nötropeni ve nötropenik olmayan atak varlığı, kemoterapi rejimleri, antimikrobiyal ajanlar, kan ve idrar yolu kültür örnekleri kaydedildi.

Bulgular: Toplam 149 enfeksiyöz epizod gözlendi. Takipte enfeksiyöz epizodu olmayanlarda yaş ortalaması 9,02±5,17 yıl iken, iki ve daha fazla enfeksiyöz epizodu olanlarda 5,70±4,60 yıldı ve anlamlı olarak daha düşüktü (p=0,024). Bu enfeksiyöz epizodlar sırasında farklı yerlerden toplamda 264 mikrobiyal kültür alındı. Tüm kültürlerde kan kültürlerinin %27'si ve idrar yolu kültürlerinin %9'u pozitifti. En sık izole edilen mikroorganizma Gram-pozitif bakterilerdi (n=23, %57,5).

Sonuç: Pediatrik çağdaki kanserlerde yaş azaldıkça daha yüksek enfeksiyon komplikasyonları riski izlenmiştir. Hematolojik maligniteleri olan çocukların konsolidasyon ve indüksiyon dönemlerinde nötropenik ateş geliştirme olasılığı daha yüksektir. Çalışmamızdaki nedeni bilinmeyen ateş oranlarından da yola çıkarak bu grup hastalıklarda daha iyi mikrobiyolojik tanı için daha fazla çalışma gerekmektedir.

Anahtar kelimeler: Febril nötropeni, kanser, çocuk

INTRODUCTION

Children treated for cancer develop serious complications even death during episodes of infectious complications, most of them being associated with neutropenic fever[1]. Studies have revealed that during the last 50 years survival rates increased from 25% to 80%[2], especially due to intensive chemotherapy and evolving treatment modalities. Improvement in survival rates is achieved with repeated use of multi-agent courses, which resulted in recurrent episodes of severe and prolonged neutropenia. Eight percent of neutropenic episodes due to intensive chemotherapy which persists more than one week are complicated by fever, and about 60% of them have an infectious etiology[3].

The infectious complications are mainly influenced by the type of primary disease. For instance, severe bloodstream infections have been reported in the children with hematologic malignancies compared to cases with solid tumors[4]. The treatment modalities of neutropenic fever include hospitalization, intravenous administration of broad-spectrum empirical antibiotics, and also antifungal and antiviral treatment for some selected patients[5]. Better understanding of the malignancy-specific infectious complications and the time when the risk of infection is increased during the intensive chemotherapy might additionally contribute to the clinical management of these patients.

We have aimed to evaluate the infections and causative microorganisms that emerged during episodes of febrile neutropenia in patients with malignancy.

MATERIALS and METHODS

This prospective cohort study wascarried out between February 2018 and May 2020 in a 28-bed oncology-hematology department of a 400-bed pediatric teaching hospital. The patients aged 1 month to 18 years with the diagnosis of malignancy who were followed up from the time of diagnosis of the primary disease until termination of the study or completion of the primary treatment for malignancy were analyzed retrospectively. The patients who were not followed up for at least three months were not included in the final analysis. Patients were divided into groups of hematologic malignancies including acute lymphoblastic leukemia (ALL), acute myelocytic leukemia (AML) and solid tumors.

The infectious episodes in the patients who were diagnosed with malignancy during their therapy starting from the first day to the end of treatment were included in the study. The data concerning the number of days from the first diagnosis, recurrent infectious episodes, number of days with fever, presence of neutropenia and non-neutropenic episodes, chemotherapy regimens, antimicrobial agents, test results of blood culture samples, and positive cultures of species of pathogenic microorganisms (if any) were also recorded. Blood cultures were considered positive if one or more than one microorganism grew in at least one culture set. Positive cultures were considered contaminated if normal flora of the skin, including coagulase-negative staphylococci (CoNS), viridans group streptococci, *Bacillus* species, *Neisseria* species (other than *Neisseria meningitidis* or *Neisseria gonorrhoeae*), *Micrococcus* species, or aerobic Gram-positive rods grew in only one culture set. If the same skin microorganism were identified in two culture sets, then they were considered true positives, and in the presence of positive signal or positive culture, a second set of blood culture set was prepared within the first 24 hours of the first one[6] In case of identification of only one pathogenic agent in urine culture, isolation of a single pathogen with either 100,000 CFU/mL in the cultures of mid-stream urine or bagged urine specimens or ≥50,000 CFU/mL in catheter tip cultures; and if more than one pathogen was isolated, then growth of one bacteria at 100,000 CFU/mL, and the other one at <50,000 CFU/mL in the cultures of mid-stream and bagged urine specimens, finally growth of 50,000 CFU/mL for one, and <10,000 CFU/mL for the other agent in the catheter tip cultures were considered significant.

Isolation of CoNS was accepted as contamination irrespective of catheter-tip or dual inoculation.

Treatment of ALL and AML was performed according to ALL-IC BFM 2009, AML BFM 2004 protocols and in phases of induction, consolidation, reinduction, and maintenance chemotherapy[6,7]. Neutropenia was described as a total number of granulocytes $<0.5\times10^9$/L or leukocytes $<1.0\times10^9$/L without differential counts available[8]. Febrile neutropenia was defined as either absolute neutrophil counts below 500/mm^3 or expected to decrease below 500/mm^3 within 48 hours in the presence of fever of 38.3 °C with single axillary measurement or above 38 °C persisting for one hour or with two measurements above 38 °C within one hour[9]. Antimicrobial therapy was planned according to Infection Diseases of American Association guideline recommendations[10] .

Microbiologically proven infection was defined as isolation of a pathogen from a sterile body site (blood, urine) in the clinical setting of suspected

infection. Clinically proven infection was defined as clinical or radiological findings of infection where the patient shows a prompt response to antimicrobials without any laboratory evidence of an infectious etiology. Fever of unknown origin (FUO) was defined as fever without any focus or etiology identified by clinical history, physical examination, radiological or microbiologic testing during a minimum hospitalization period of three weeks without an established diagnosis despite an intensive one-week investigation. Central venous blood samples were collected twice for aerobic and anaerobic cultures from patients with fever under aseptic conditions and after disinfection of the central venous access device hub, in addition to a blood culture sample drawn from peripheral veins.

Statistical Analysis

Collected data were analyzed with SPSS Software version 20 (IBM Corporation, Armonk, NY, USA). Categorical variables were analyzed using relative frequencies, and numerical variables were expressed as median or mean values depending on whether they showed normal distribution or not. Categorical variables were compared using Pearson χ^2 and Fisher's exact tests, and numerical variables with t-test or nonparametric Mann-Whitney U test. For statistical analysis of quantitative data, t-test, Mann-Whitney U, Kruskal-Wallis, and One-Way ANOVA tests were used. The level of significance was taken as $p \leq 0.05$. Dunn's test was used in the post-hoc analysis of Kruskal-Wallis test. Survival analyzes were performed using Kaplan-Meier method, and log-rank test was used for the comparison of factors. Written consent was obtained from all patients.

RESULTS

Demographic Features

Ninety-two newly diagnosed patients including those with solid tumors and hematologic malignancies were enrolled in this study. The patients with hematologic malignancies were followed up for a mean period of 97.80±18.48 days, and those with solid tumors for a mean period of 170.48±32.69 days. Three patients were not followed up for at least three months and one patient was lost to follow-up due to the city change of the family. In the final analysis, 45 (51.1%) female, and 43 (48.9%) male patients were included in the study. Median age of the patient population was 60 months (interquartile range: 30.50-120.00 months). Primary diagnoses were ALL in 44 (50%), AML in 7 (8.0%), and solid tumors in 37 (42%) patients (Table 1).

Development of Infectious Episodes

Among 88 patients, 67 children (76.2%) experienced at least one infectious episode during chemotherapy, and during the study period we observed a total of 149 infectious episodes (Figure 1). The primary diseases of 21 children in whom infectious episodes were not observed, were ALL (n=9), Hodgkin's disease (n=3), neuroblastoma (n=3), rhabdomyosarcoma (n=3), non-Hodgkin's disease (n=1), Ewing's sarcoma (n=1), and pancreas cancer (n=1).

During the follow-up period, 17.6% of patients with hematologic malignancies, and 32.4% of those with solid tumors had not experienced infectious episodes during the follow-up period without any significant difference regarding percentages of infection-free patients between groups ($p>0.05$). Duration of infection-free periods were 60±4.26 days in all patients, while they were 55±10.20, and 60±8.51 days in cases with leukemia and solid tumors, respectively. According to the Kaplan-Meier method, 49±0.070% of leukemia patients, and 48.6±0.082% of those with solid tumors had not experience any infectious episode on the 55th, and 60th days of follow-up, respectively (Figure 2). Duration of infection-free periods were not statistically significantly different between patients with hematologic and solid tumors ($p>0.05$).

Table 1. The distribution of the underlying malignancies of the patients in the study

Cancer types	(n) %
Leukemia	
Acute lymphoblastic leukemia	50 (44)
Acute myelocytic leukemia	8.0 (7)
Lymphoma	
Hodgkin lymphoma	3.4 (3)
Non-hodgin lymphoma	5.6 (5)
Willms tumor	3.4 (3)
Neuroblastoma	10.2 (9)
Rhabdomyosarcoma	8.0 (7)
Bone tumor	
Osteosarcoma	1.1 (1)
Ewing tumor	2.3 (2)
Central nervous system tumor	
Glioma	1.1 (1)
Ependymoma	1.1 (1)
Ovarian epitelial tumor	1.1 (1)
Hepatoblastoma	1.1 (1)
Endodermal sinus tumor	1.1 (1)
Pancreatic tumor	1.1 (1)

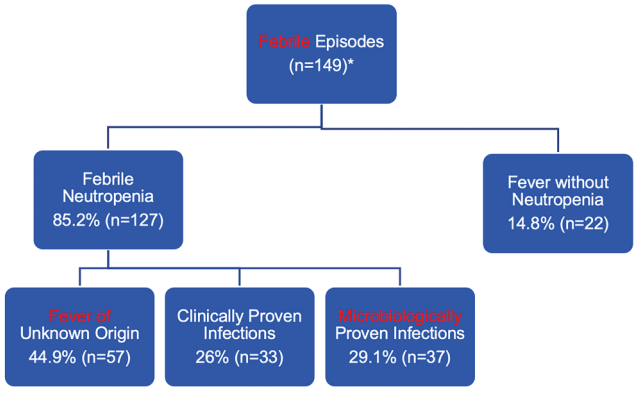

Figure 1. The distribution of the infectious episodes according to the clinical and microbiological features

*Four patients were excluded due to lack of sufficient follow up data

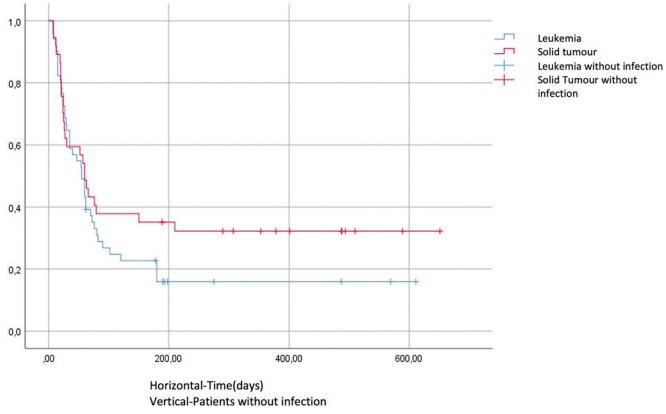

Figure 2. Kaplan-Meier analysis concerning development of infectious episodes, solid tumors and hematologic malignancies

According to the Kaplan-Meier method, 49±0.070% of leukemia patients on the 55th day, and 48.6±0.082% of the patients with solid tumors on the 60th day of the follow-up period had not experienced infectious episodes. A statistically significant difference was not found in terms of time interval passed without infection between patients with hematologic and solid tumors, (p>0.05)

A total of 149 infectious episodes were observed in ALL (n=74; 49.7%), in AML (n=19; 12.8%) patients and in cases with solid tumors (n=56; 37.6%). The number of infectious episodes varied in patients with ALL (0-6), AML (1-5), and solid tumors (0-5) without any significant intergroup difference (p>0.05) (Table 2). The patients who had two or more infectious episodes during follow-up period (mean age: 5.70±4.60; range: 0.75-17.17 years) were statistically significantly younger than those that had not experienced any infectious episodes (mean age: 9.02±5.17 years; range: 2-17.25 years) during that period (p=0.024).

The Characteristics of Infectious Episodes

The patients were neutropenic during 127 (85.2%) and non-neutropenic during 22 (14.8%) episodes. FUO was revealed in 57 (44.9%), clinically confirmed infections in 33 (26%), and microbiologically proven infections in 37 (29.1%) patients during febrile neutropenic episodes (Figure 1).

In our study the number of febrile neutropenic episodes differed between patients with leukemia (n=80; 63%), and the cases with solid tumors (n=47; 37%). Absolute neutrophil counts were ≤100/μL in 69 (54.3%) episodes. In patients with ALL, febrile neutropenic episodes were most frequently observed in the consolidation period (n=38; 29.9%), and in the induction period (n=17; 13.3%). In AML, febrile episodes were detected most frequently during the induction period (n=8; 6.2%). Microbiologically proven infectious episodes lasted significantly longer (14.11±5.55 days) compared to UFO (10.35±3.90 days), and clinically diagnosed infectious episodes (11.12±4.72 days) (p<0.001).

Focus of infection was present in 43 (33.9%), and absent in 84 (66.1%) febrile neutropenic episodes. Patients with febrile neutropenic attacks with identified foci of infection had skin (n=20; 46.6%), lower respiratory tract (n=9; 20.9%), upper respiratory tract (n=6; 13.9%), urinary tract (n=6; 13.9%) and gastrointestinal system (n=2; 4.7%) infections.

Blood cultures were performed either from peripheral vein or catheter tip samples in 97% (n=145), and urine specimens in 79% (n=119) of infectious episodes. A total 264 microbial cultures were performed from different locations during these infectious episodes. Regarding all of the cultures, 27% of blood, and 9% of urine cultures were positive. The most commonly isolated microorganisms were gram-positive bacteria. (n=23, 57.5%) followed by Gram-negative bacteria (n=16, 40%) and fungal agents (n=1, 2.5%). Most commonly isolated bacteria were CoNS (47.5%) followed by *Klebsiella pneumonia* (2.7%), *Staphylococcus aureus* (2.0%), and *Pseudomonas aeruginosa* (2.0%) (Table 3). *Escherichia Coli* was the most common isolated pathogen in urinary tract infections (Table 3).

DISCUSSION

In this cohort study with 2 years of the follow-up period, a total of 88 patients with pediatric hematologic malignancies and solid tumors were monitored for the development of infections. A total of 149 infectious

Table 2. Clinical characteristics associated with infections in children diagnosed with malignancy during the study period

Number of infectious episodes	0	1	>2	p-value
Age (median)	9.01*	6.45	5.70*	0.024*
Gender - n (%)				
Girl	11 (12.5)	7 (8.0)	27 (30.7)	>0.05
Boy	10 (11.4)	14 (15.9)	19 (21.6)	
Diagnosis - n (%)				
ALL	9 (20.5)	12 (27.3)	23 (52.3)	
AML	-	1 (14.3)	6 (85.7)	>0.05
Solid tumors	12 (32.4)	8 (21.6)	17 (45.9)	
Total - n (%)	21 (23.9)	21 (23.9)	46 (52.3)	>0.05

ALL: Acute lymphoblastic leukemia, AML: Acute myelocytic leukemia, *Kruskal-Wallis H 7,419

Table 3. The distribution of microorganisms identified during the microbiologically proven infection episodes

Identified microorganisms	Bloodstream culture (peripheral) n (%)	Urinary tract culture n (%)
Staphylococcus epidermidis	12 (8.1)	
Streptococcus acidominimus	1 (0.7)	
Staphylococcus hominis	6 (4.0)	
Staphylococcus hemoliticus	1 (0.7)	
Staphylococcus aerus(mssa)	3 (2.0)	
Pantoea agglomerans	1 (0.7)	
Acinetobacter baumanii	1 (0.7)	
Serratia marcescens	1 (0.7)	
Stenotrophomonas maltophilia	1 (0.7)	
Klebsiella oxytoca	1 (0.7)	1 (0.7)
Klebsiella pneumonia	4 (2.7)	
Salmonella	1 (0.7)	
Pseudomonas aeruginosa	3 (2.0)	1 (0.7)
Escherichia coli		8 (5.4)
Citrobacter werkmanii		1 (0.7)
Enterobacter cloacae	3 (2.0)	
Candida parapsilosis	1 (0.7)	

episodes including febrile neutropenic (85.2%), and febrile non-neutropenic (14.8%) episodes were observed. According to the classification of febrile neutropenia; these episodes were categorized as FUO (44.9%), clinically defined (26%), and microbiologically proven (29.1%) infections.

Despite lack of statistically significant intergroup differences, during the follow-up period, patients with solid tumors had more frequently experienced infection-free periods when compared to those with hematologic malignancies This is not a surprising finding because infectious complications are among the major causes of morbidity and mortality in patients undergoing cancer therapy. Hematologic malignancies, in particular AML, have been more frequently associated with infectious complications compared to solid tumors[4,11-14]. Al-Tawfiq et al.[16] also detected febrile neutropenic episodes due to chemotherapy at indicated rates in cases with leukemia (80%) and solid tumors (10-50%)[15].

During our study, 76.2% of the patients had at least one febrile infectious episode. A cohort study of 101 pediatric patients aged 7-16 years, reported that 79% of the patients had infectious episodes at least once[16]. Among childhood cancers, the highest risk in terms of invasive infection was found in patients diagnosed with acute myeloid leukemia and relapsed ALL[5,17,18].

In our study, the median infectious episode rate was 3 at the AML patients. In support of our findings, a recent study has reported greater number of infectious episodes and prolonged antibiotherapy in AML patients compared to patients with other diagnoses[16].

Children with AML are particularly susceptible to the development of severe infections, due to the intense treatment and prolonged and profound neutropenia.

In our study, the longer hospitalization periods of AML patients compared to ALL patients also supported the findings of previous reports. Basu et al.,[19] investigated 12,446 children with cancer and detected comparatively longer hospitalization periods in patients with AML[20].

In our study, the average age of those who had no infectious episodes during follow-up was found to be significantly higher than those who had 2 and/or more infectious episodes. Inaba et al.,[21] conducted a research study on 409 pediatric patients, and found that older patients had suffered from lesser number of infectious episodes, as well[19].

Auletta et al.[15] investigated the infections developed in 155 pediatric cancer patients , and found that cases under 3 years of age had suffered more frequently from infectious episodes[14]. However, connection of infections with age in children receiving chemotherapy has not been fully confirmed[21,22]. One of the reasons for failure to prove the connection between development of infections and age of the children is that statistical significance of age in univariate analyzes could not be demonstrated in multivariate analyzes due to the presence of other confounding factors[23].

Some studies in the literature have indicated an increase in the frequency of mucositis in younger patients, possibly related to the increasing mitotic index[24,25]. Different chemotherapy protocols exert effects of varying intensity on bone marrow. In their study, Lyman et al.,[26] stated that some regimens were more myelotoxic[27]. Febrile neutropenic episodes were detected mostly during the consolidation (n=38; 29.9%), and induction (n=17; 13.3%) phases of chemotherapy in indicated number of ALL patients. In AML, febrile neutropenic episodes were most frequently observed during induction phase of chemotherapy (n=8; 6.2%). Yilmaz et al.,[28] examined 239 febrile neutropenic episodes in 82 pediatric patients with leukemia, and found that the most frequently, febrile neutropenic episodes occurred during the consolidation period[26].

Considering the classification of febrile neutropenia; in our study group, FUO was the most commonly seen clinical entity. Among febrile infectious episodes predominantly skin and respiratory tract infections were observed. Febrile neutropenic patients are susceptible to infections due to decreased neutrophil count and dysfunction and increased permeability as a result of altered skin barrier balance[28]. In support of our findings, lower respiratory tract, upper respiratory tract, soft tissue, and gastrointestinal tract infections can often be seen in febrile neutropenia[26].

The impact and rate of positive cultures in the diagnosis of neutropenic fever especially in the children were reported to be at a lower level[29]. According to the studies in the literature, growth of pathogenic microorganisms is detected in only 15% of the cultures taken and the culture positivity rate in our study was found to be higher than that cited in the literature. Daef et al.[30] found bacteremia in 25 (29.4%) of 85 febrile neutropenic attacks in 68 patients, and gram-positive growth was found in 15 (53.6%) attacks in the same study[31]. The rate of positive cultures might change depending on the sample collection methods, capacities of microbiology laboratories, and characteristics of the hospital's working conditions. In our study, the most common isolated microorganism was CoNS which is responsible for nearly half of the bloodstream infections. Recent studies have reported that CoNS and *Staphylococcus aureus* were isolated in nearly 50% of positive cultures[30,32]. The higher rate of Gram-positive bacteria identified during febrile neutropenic episodes was mainly due to presence of indwelling vascular catheters and multiple interventions performed[6].

This study was approved by the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (decision number: 2019/06-04; date: 11.04.2019).

Study Limitation

This study has several limitations. First, the malignancies in the study group were heterogenous especially regarding diagnoses, and includes both hematologic malignancies and solid tumors which might change the development of the infectious complications. Secondly, the treatment modalities change depending on the stage and the grade of the primary disease which also affects the nature of the infectious complications.

CONCLUSION

In conclusion, younger children with cancer are at higher risk of infectious complications compared to children of older ages. Children with hematologic malignancies are more likely to develop a neutropenic fever during the consolidation and induction periods. Regarding the high rate of FUO in our study, more attempts should be made to increase the rates of microbiological diagnosis in this patient population.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (decision number: 2019/06-04; date: 11.04.2019).

Informed Consent: Written consent was obtained from all patients.

Author Contributions

Surgical and Medical Practices: D.B., Concept: D.B., İ.Ç., E.B., Design: D.B., E.K., Data Collection or Processing: D.B., S.O.A., Analysis or Interpretation: D.B., N.T., Literature Search: D.B., T.H.K., Writing: D.B., Ö.Ö.Ş., B.D., İ.D.

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REFERENCES

1. Ammann RA, Tissing WJ, Phillips B. Rationalizing the approach to children with fever in neutropenia. Curr Opin Infect Dis. 2012;25(3):258-65. doi: 10.1097/QCO.0b013e328351d199.
2. McGregor LM, Metzger ML, Sanders R, Santana VM. Pediatric cancers in the new millennium: dramatic progress, new challenges. Oncology (Williston Park). 2007;21(7):809-20.
3. Klastersky J, Zinner SH, Calandra T, Gaya H, Glauser MP, Meunier F, et al. Empiric antimicrobial therapy for febrile granulocytopenic cancer patients: lessons from four EORTC trials. Eur J Cancer Clin Oncol. 1988;24Suppl1:S35-45.
4. El-Mahallawy H, Sidhom I, El-Din NH, Zamzam M, El-Lamie MM. Clinical and microbiologic determinants of serious bloodstream infections in Egyptian pediatric cancer patients: a one-year study. Int J Infect Dis. 2005;9(1):43-51. doi: 10.1016/j.ijid.2003.11.010.
5. Agyeman P, Aebi C, Hirt A, Niggli FK, Nadal D, Simon A, et al. Predicting bacteremia in children with cancer and fever in chemotherapy-induced neutropenia: results of the prospective multicenter SPOG 2003 FN study. Pediatr Infect Dis J. 2011;30(7):e114-9. doi: 10.1097/INF.0b013e318215a290.
6. Story-Roller E, Weinstein MP. Chlorhexidine versus Tincture of Iodine for Reduction of Blood Culture Contamination Rates: a Prospective Randomized Crossover Study. J Clin Microbiol. 2016;54(12):3007-9. doi: 10.1128/JCM.01457-16.
7. Campbell M, Castillo L, Riccheri C, Janic D, Jazbec J, Kaiserova E et al. A randomized trial of the I- BFMSG for the management of childhood non- b acute lymphoblastic leukemia, ALL IC-BFM 2009- Trial Steering Committee. 2009;1-191.
8. Creutzig U, van den Heuvel-Eibrink MM, Gibson B, Dworzak MN, Adachi S, de Bont E, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. Blood. 2012;18;120(16):3187-205. doi: 10.1182/blood-2012-03-362608.
9. Furtwängler R, Laux C, Graf N, Simon A. Impact of a modified Broviac maintenance care bundle on bloodstream infections in paediatric cancer patients. GMS Hyg Infect Control. 2015;16;10:Doc15. doi: 10.3205/dgkh000258.
10. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002;34(6):730-51. doi: 10.1086/339215.
11. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52(4):e56-93. doi: 10.1093/cid/cir073.
12. Feusner JH, Hastings CA. Infections in children with acute myelogenous leukemia. Concepts of management and prevention. J Pediatr Hematol Oncol. 1995;17(3):234-47. doi: 10.1097/00043426-199508000-00005.
13. Tobias JS, Wrigley PF, O'Grady F. Bacterial infection and acute myeloblastic leukaemia: an analysis of two hundred patients undergoing intensive remission induction therapy. Eur J Cancer (1965). 1978;14(4):383-91. doi: 10.1016/0014-2964(78)90209-8.
14. Madani TA. Clinical infections and bloodstream isolates associated with fever in patients undergoing chemotherapy for acute myeloid leukemia. Infection. 2000;28(6):367-73. doi: 10.1007/s150100070007.
15. Auletta JJ, O'Riordan MA, Nieder ML. Infections in children with cancer: a continued need for the comprehensive physical examination. J Pediatr Hematol Oncol. 1999;21(6):501-8.
16. Al-Tawfiq JA, Hinedi K, Khairallah H, Saadeh B, Abbasi S, Noureen M, et al. Epidemiology and source of infection in patients with febrile neutropenia: A ten-year longitudinal study. J Infect Public Health. 2019;12(3):364-6. doi: 10.1016/j.jiph.2018.12.006.
17. Af Sandeberg M, Johansson E, Wettergren L, Björk O, Hertting O, Nilsson A. Antibiotic use during infectious episodes in the first 6 months of anticancer treatment-A Swedish cohort study of children aged 7-16 years. Pediatr Blood Cancer. 2017;64(7). doi: 10.1002/pbc.26397.
18. Alexander SW, Wade KC, Hibberd PL, Parsons SK. Evaluation of risk prediction criteria for episodes of febrile neutropenia in children with cancer. J Pediatr Hematol Oncol. 2002;24(1):38-42. doi: 10.1097/00043426-200201000-00011.
19. Basu SK, Fernandez ID, Fisher SG, Asselin BL, Lyman GH. Length of stay and mortality associated with febrile neutropenia among children with cancer. J Clin Oncol. 2005;1;23(31):7958-66. doi:10.1200/JCO.2005.01.6378.
20. Boragina M, Patel H, Reiter S, Dougherty G. Management of febrile neutropenia in pediatric oncology patients: a Canadian survey. Pediatr Blood Cancer. 2007;48(5):521-6. doi: 10.1002/pbc.20810.
21. Inaba H, Pei D, Wolf J, Howard SC, Hayden RT, Go M, et al. Infection-related complications during treatment for childhood acute lymphoblastic leukemia. Ann Oncol. 2017;28(2):386-392. doi: 10.1093/annonc/mdw557.
22. Dodd MJ, Miaskowski C, Shiba GH, Dibble SL, Greenspan D, MacPhail L, Paul SM, Larson P. Risk factors for chemotherapy-induced oral mucositis: dental appliances, oral hygiene, previous oral lesions, and history of smoking. Cancer Invest. 1999;17(4):278-84. doi: 10.3109/07357909909040598.
23. McCarthy GM, Awde JD, Ghandi H, Vincent M, Kocha WI. Risk factors associated with mucositis in cancer patients receiving 5-fluorouracil. Oral Oncol. 1998;34(6):484-90. doi: 10.1016/s1368-8375(98)00068-2.

24. Hespanhol FL, Tinoco EM, Teixeira HG, Falabella ME, Assis NM. Manifestações bucais em pacientes submetidos à quimioterapia [Buccal manifestations in patients submitted to chemotherapy]. Cien Saude Colet. 2010;15 Suppl 1:1085-94. Portuguese. doi: 10.1590/s1413-81232010000700016.

25. Badr M, Hassan T, Sakr H, Karam N, Rahman DA, Shahbah D, et al. Chemotherapy-induced neutropenia among pediatric cancer patients in Egypt: Risks and consequences. Mol Clin Oncol. 2016;5(3):300-6. doi: 10.3892/mco.2016.957.

26. Lyman GH, Kuderer NM, Balducci L. Cost-benefit analysis of granulocyte colony-stimulating factor in the management of elderly cancer patients. Curr Opin Hematol. 2002;9(3):207-14. doi: 10.1097/00062752-200205000-00006.

27. Cheng KK, Lee V, Li CH, Goggins W, Thompson DR, Yuen HL, et al. Incidence and risk factors of oral mucositis in paediatric and adolescent patients undergoing chemotherapy. Oral Oncol. 2011;47(3):153-62. doi: 10.1016/j.oraloncology.2010.11.019.

28. Yilmaz S, Oren H, Demircioğlu F, Irken G. Assessment of febrile neutropenia episodes in children with acute leukemia treated with BFM protocols. Pediatr Hematol Oncol. 2008;25(3):195-204. doi: 10.1080/08880010801938231.

29. Lakshman R, Finn A. Neutrophil disorders and their management. J Clin Pathol. 2001;54(1):7-19. doi: 10.1136/jcp.54.1.7

30. Daef EA, Elsherbiny NM, Agban MN, Riad KF, Mohammed LF. Bloodstream Infections in Febrile Neutropenic Pediatric Cancer Patients: Microbiological and Sepsis Biomarkers Insight. Egypt J Immunol. 2018;25(2):21-34.

31. Luthander J, Bennet R, Giske CG, Nilsson A, Eriksson M. Age and risk factors influence the microbial aetiology of bloodstream infection in children. Acta Paediatr. 2013;102(2):182-6. doi: 10.1111/apa.12077.

32. Coullioud D, Van der Auwera P, Viot M, Lasset C. Prospective multicentric study of the etiology of 1051 bacteremic episodes in 782 cancer patients. CEMIC (French-Belgian Study Club of Infectious Diseases in Cancer). Support Care Cancer. 1993;1(1):34-46. doi: 10.1007/BF00326637.

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Original Article

Seven Cases of Severe Neutropenia: A Single-center Experience

Ağır Nötropenili Yedi Olgu: Tek Merkez Deneyimi

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ABSTRACT

Objective: Severe congenital neutropenia is a rarely encountered heterogeneous group of disorders characterized by myeloid maturation arrest in the bone marrow. The present study aimed to discuss clinical and laboratory findings, genetic mutations, therapeutic approaches and outcomes in these rarely seen seven cases followed up with the diagnosis of Kostmann syndrome in a single center so as to make a contribution to the literature.

Method: In this retrospective study, data of the seven cases followed up with the diagnosis of Kostmann syndrome were retrieved from the patient files. The diagnosis was established based on an absolute neutrophil count of <500/mm³ persisting for more than 3 months and presence of *HAX-1* gene mutations detected by positive molecular genetic analysis.

Results: All patients were born to consanguineous parents. Six of the seven cases had sibling history. All cases had homozygous HAX-1 mutation. Case 1 had motor-mental retardation and case 5 had urogenital system anomaly. Mortality or malignancy was not encountered in any of the cases despite the absence of prophylactic granulocyte-colony stimulating factor (G-CSF) therapy.

Conclusion: The diagnosis and differential diagnosis of congenital neutropenia must be considered in the patients presenting with neutropenia and recurrent infections. Monitoring of the cases with severe neutropenia like Kostmann syndrome carries extreme importance. Families should be educated in terms of early signs of infection and importance of regular patient monitoring for prophylactic G-CSF-free management of the disease.

Keywords: Congenital neutropenia, *HAX-1*, G-CSF therapy, mortality

ÖZ

Amaç: Ağır konjenital nötropeni, kemik iliğinde miyeloid olgunlaşmanın durması ile karakterize, nadir görülen, heterojen bir grup hastalıktır. Bu çalışmada tek merkezden takip edilen Kostmann sendromu için yedi olguda klinik ve laboratuvar bulguları, genetik mutasyonlar, tedavi yaklaşımları ve sonuçlarının tartışılması, nadir görülen bir hastalık olması ve nadir görülen bir hastalık olan yedi olgunun takip edilmesinin olağandışı olması nedeniyle literatüre katkı sağlanması amaçlandı ediliyor.

Yöntem: Bu retrospektif çalışmada Kostmann sendromu nedeniyle takip edilen yedi olgunun verileri hasta dosyalarından elde edildi. Tanı, 3 aydan uzun süredir mutlak nötrofil sayısının <500/mm³ olması ve *HAX-1* geninin moleküler genetik analizinin pozitif olmasıyla konuldu.

Bulgular: Olguların tümü akraba evliliği olan ebeveynlerden doğmuştu. Yedi olgunun altısında kardeş öyküsü vardı. Olguların tamamında homozigot HAX-1 mutasyonu vardı. Olgu 1'de motor zeka geriliği, olgu 5'te ise ürogenital sistem anomalisi vardı. Profilaktik granulocyte-colony stimulating factor (G-CSF) tedavisi uygulanmamasına rağmen hiçbir olguda mortalite veya maligniteye rastlanmadı.

Sonuç: Nötropeni ve tekrarlayan enfeksiyonlarla başvuran hastalarda konjenital nötropeni tanısı ve ayırıcı tanısı mutlaka göz önünde bulundurulmalıdır. Kostmann sendromu gibi ciddi nötropeni olgularının izlenmesi önemlidir. Aileler, enfeksiyonun erken belirtileri ve hastalığın profilaktik GCSF'siz tedavisi için düzenli hasta takibinin önemi açısından eğitilmelidir.

Anahtar kelimeler: Konjenital nötropeni, *HAX-1*, G-CSF tedavisi, mortalite

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INTRODUCTION

Severe congenital neutropenia (SCN) belongs to a rarely encountered heterogeneous group of disorders characterized by myeloid maturation arrest in the bone marrow affecting both neutrophil homeostasis and function[1]. An absolute neutrophil count (ANC) below 500/mm³ in peripheral blood circulation is considered severe neutropenia. The diagnosis of SCN is established in the presence of severe neutropenia lasting for more than 3 months together with myeloid maturation arrest in the bone marrow. Its prevalence is estimated to be nearly 1-2 to 10/1,000,000 with both genders being affected equally[2,3].

Congenital neutropenia was first defined in 1956 by Rolf Kostmann as "infantile genetic agranulocytosis". In 1975, the same author identified 10 more cases and thereafter the terms of SCN and Kostmann syndrome have been associated and showed up as a group of diseases. Dale et al.[4] firstly demonstrated mutations in the *ELA-2* gene in cyclic neutropenia cases in 1999 and then in SCN cases in 2000; thereby, these two diseases have been classified in the same group. So far, more than 20 gene mutations associated with neutropenia (including *G6PC3*, *GFI1*, *SBDS*, *JAGN1*, *SRP54*, and *DNAJC21* gene mutations) have been identified. Nevertheless, genetic defects remain unidentified in nearly 25% of patients[1].

The most frequent pathogenetic defects are autosomal dominant mutations in the *ELA2/ELANE* gene, which encodes the neutrophil elastase, and autosomal recessive mutations in the *HAX-1* (HS1-associated protein X-1) gene, the product of which contributes to the activation of the granulocyte-colony stimulating factor (G-CSF) signaling pathway[5]. *ELA2/ELANE* gene mutations also playsa role in myeloid differentiation, thus mutation of this gene enhances the risk of developing acute myeloid leukemia (AML)[6,7].

SCN presents particularly with recurrent skin, lung, and soft tissue infections caused mostly by *S. aureus, E. coli,* and *P. aureginosa* which can be seen from the first few months of life. Fifty percent of patients die of infections before the age of one year. In a study, rates of survival over 5 years was reported to be 30%[8]. The disease has been usually fatal with a mean survival of 13 years before the availability of colony-stimulating factors, but the mean survival has been remarkably prolonged along with the use of G-CSF therapy. Nevertheless, some patients (nearly 20%) can develop AML and myelodysplastic syndrome (MDS) after treatment with G-CSF[9,10]. It has been reported that G-CSF therapy can trigger the transformation of the underlying myeloid stem-cell defect into malignancy, or may increase the risk of malignancy by prolonging mean survival time[11]. Today, allogeneic bone marrow transplantation is the only curative therapy, which provides a favorable prognosis when a human leukocyte antigen (HLA)-matched donor can be found[3].

Establishment of a definite diagnosis of congenital neutropenia requires a detailed medical history, physical examination, family history, and realization of laboratory screening tests. These clinical and laboratory data can identify a viral infection, bone marrow malignancy, an iatrogenic cause, an immune deficiency, a metabolic disorder, an autoimmune disorder, or a congenital etiology leading to conduction of a more specific further investigation.

MATERIALS and METHODS

In this retrospective study, the data of seven cases followed between January 2014 and May 2021 with the diagnosis of Kostmann syndrome were retrieved from the patient files. The study was approved by the Mersin University Clinical Research Ethics Committee (approval number: 2022/715, date: 01.11.2022). The diagnosis was established based on an ANC of <500/mm³ persisting for more than 3 months and myeloid series maturation arrest in the bone marrow. In addition, molecular genetic analyses were requested from all patients for *HAX-1*, *ELANE*, *G6PC3*, and *CSF3R* gene mutations so as to make a diagnosis of congenital neutropenia. Information concerning demographic and clinical characteristics of the patients (age, gender, consanguinity, family history, presenting symptoms, age at symptom onset, and at diagnosis, follow-up period, clinical and laboratory findings, and treatments used) were recorded.

Before making the final diagnosis, drug-induced neutropenia, infection-related neutropenia, immune deficiency, metabolic disorder, and malignancies were ruled out for all patients. All patients received prophylactic antibiotic therapy (trimethoprim-sulfamethoxazole at a daily dose of 5 mg/kg). None of the patients received prophylactic G-CSF therapy; nevertheless, G-CSF was commenced at a daily dose of 5-10 µcg/kg in the presence of fever or infection.

Statistical Analysis

ANC was obtained as part of complete blood count, which was measured using Sysmex XN-1000™ Hematology Analyzer (Sysmex America, Inc., Illinois, USA). Molecular genetic analysis for *HAX-1* and *ELANE*

gene mutations was performed by polymerase chain reaction - based DNA line analysis.

RESULTS

Five male, and two patients were included in the study. The median age (91 months; range: 10-150 months) and the median age at diagnosis (40 months; range: 2-81 months) were as indicated. All patients were born to consanguineous parents. Six of the seven cases had sibling history (there were three pairs of siblings excluding case 7). In three of these six patients, Kostmann syndrome was suspected based on the fact that their siblings had Kostmann syndrome, and then the diagnosis was confirmed with genetic testing. In all of these three patients, the parents had refused to undergo prenatal diagnostic tests. Presenting symptoms included recurrent skin abscesses, gingivostomatitis, recurrent upper and/or lower respiratory tract infections, lymphadenitis, and recurrent urinary tract infections (Table 1). Motor-mental retardation was detected in case 1, and urogenital system anomalies including ambiguous genitalia, cryptorchidism, hypospadias and bifid scrotum were detected in case 5. Molecular genetic analysis revealed homozygous *HAX-1* mutation in all of the seven cases. Additionally, case 1 had homozygous KATNIP mutation (Table 1).

Table 1. Baseline demographic characteristics of the cases

	Cases						
	#1	**#2**	**#3**	**#4**	**#5**	**#6**	**#7**
Age, months	39	135	10	78	91	150	121
Sex	Male	Male	Female	Male	Male	Male	Female
Parental consanguinity	+	+	+	+	+	+	+
Sibling history	+	+	+	+	+	+	-
Presenting symptom	None. Screened because his sibling had Kostmann syndrome	Fever	None. Screened because her sibling had Kostmann syndrome	URTI	Fever	Fever	Pneumonia
Age at diagnosis, months	3	2	2	52	53	81	40
Follow-up, months	36	133	8	26	38	69	81
Presence of an infection at diagnosis	+	+	-	+	+	-	+
G-CSF prophylaxis	-	-	-	-	-	-	-
Congenital anomalies	Motor mental retardation	-	-	-	Ambiguous genitalia Cryptorchidism Hypospadias Bifid scrotum	-	-
Molecular defects	**HAX-1** c.130_131insA Homozygous **KATNIP** c.4120C>T(p.Gln1374Ter) Homozygous	**HAX-1** , c.130_131insA Homozygous;	**HAX-1** c.130_131insA Homozygous	**HAX-1** c.130_131insA Homozygous	**HAX-1** c.130_131insA Homozygous	**HAX-1** c.130_131insA Homozygous	**HAX1** IVS1+1 G>A(G.267 G>A) Homozygous
Current survival status	Alive	Alive	Alive	Alive	Alive	Alive	Alive, lost to follow-up

G-CSF: Granulocyte-colony stimulating factor

Overall, the patients were hospitalized for median 11 (6-35) times over the median 38 (range 18-33)-month follow-up period. The most common cause of hospitalization was pneumonia (39.3%), followed by upper respiratory tract infection (19.6%) and prolonged diarrhea (15.4%). None of the patients developed sepsis or required intensive care (Table 2).

Mortality or malignancy was not encountered in the cases although none of them had received prophylactic G-CSF therapy.

DISCUSSION

SCN is a rare condition with underlying genetic mutations showing variabilities among ethnicities. For example, *HAX-1* mutation accounts for nearly 11% of SCN cases in Europe, whereas this mutation has not been detected in the USA so far, where ELANE mutation is frequent. On the other hand, G6PC3 mutation was detected in 25% of the cases in Israel[12]. In a study from Turkey, *HAX-1* mutation was detected in 36% of the patients[13]. All cases (100%) in the present study had homozygous *HAX-1* mutation.

HAX-1 protein, which is the main pathogenic factor in 15-20% of the cases with SCN, plays an important role in the maintenance of mitochondrial integrity. *HAX-1* deficiency results in impaired mitochondrial membrane potential leading to 2-3 times higher than normal spontaneous programmed cell death rates of neutrophils[14]. *HAX-1* protein is synthesized not only in the hematopoietic cells but also in the fibroblasts and neuronal cells, therefore neurological involvement at varying levels is likely to occur in people who carry this mutation[14,15]. This mutation should be considered when learning difficulty, developmental retardation, epilepsy, and neutropenia are seen in combination. Similar to the case presented by Patiroglu et al.[16], only one of our cases (case 1) had motor-mental retardation together with homozygous *HAX-1* mutation. As a striking fact that motor-mental retardation was not detected either in the sibling or in the remaining five cases despite the presence of homozygous *HAX-1* mutation. Motor-mental retardation in case 1 can be attributed to the presence of homozygous *HAX-1* mutation accompanied by homozygous KATNIP mutation, which in the literature has been associated with Joubert syndrome. So, it would be reasonable to start the mutation analysis starting with *HAX-1* gene and to continue with analyzing ELANE and *G6PC3* genes if *HAX-1* gene mutation was not detected. Since the percentage of consanguineous marriages is very high in Turkey, a sibling with negative result for genetic screening for *HAX-1* gene mutation should be screened also for the other rare genetic mutations to arrive at a more precise conclusion.

In the literature, urogenital anomalies and SCN have been usually associated with G6PC3 mutation[17]. Indeed, one of our cases (case 5) had urogenital system anomalies including ambiguous genitalia, cryptorchidism, hypospadias and bifid scrotum although he had homozygous *HAX-1* mutation alone. In this case, further genetic examinations may identify additional genetic mutations.

Results of demographic surveys indicate that consanguinity is responsible for 22% of SCN cases in general. Given the higher rate of consanguineous marriages in Turkey, we can hypothesize that the prevalence of SCN is high in our country[18]. In fact, in our series, all of the SCN cases were born to consanguineous parents and six of these seven cases had sibling history of SCN. As an important corollary, three of these six cases were suspected of having Kostmann syndrome based on the sibling history of the disease which was confirmed by diagnostic investigations.

Table 2. Number of hospitalizations due to neutropenic infections over follow-up period

Case	URTI	UTI	Pneumonia	Oral aphtha	Anal abscess	AGE	Total
#1	5	2	9	2	1	8	27
#2	5	3	12	8	-	7	35
#3	2	-	4	-	-	-	6
#4	3	-	6	-	-	2	11
#5	2	4	2	-	-	1	9
#6	3	-	8	-	-	-	11
#7	3	3	5	4	3	-	18
Total (n)	23	12	46	14	4	18	**117**

URTI: Upper respiratory tract infection, UTI: Urinary tract infection, AGE: Acute gastroenteritis

Intrinsic stem cell defect is the main cause of SCN. Indeed, some studies have reported that mononuclear cells of the patients with Kostmann syndrome normally synthesize and secrete G-CSF, indicating that G-CSF deficiency is not the underlying defect in this syndrome, while scarce number of studies have argued the opposite[7,8]. For example, Dong et al.[19] revealed the presence of a G-CSF receptor defect. In addition, a relationship was identified between the disease and *HLA B12* gene.

Today, G-CSF therapy accounts for the substantial proportion of SCN treatment modalities leading to an increase in survival rates up to 80% as well as an improvement in the patient's quality of life. However, sepsis-related mortality can be seen in approximately 10% of the patients on G-CSF therapy maintained for more than 10 years[20].

In a multicenter phase III study of 123 SCN patients, the patients were divided into G-CSF -treated and placebo groups In that study, G-CSF therapy was associated with a nearly 50% decrease in the incidence and duration of infectious complications. Again, protocols recommend prophylactic G-CSF therapy so as to maintain ANCs between 1000-1500/mm^3[3]. Contrary to the recommendations, prophylactic G-CSF therapy was not commenced in any of the patients in the present case series. G-CSF therapy was given only in the presence of infection at a daily dose of 5-10 IU/kg to increase the ANC above 1500/mm^3. Nevertheless, mortality was not observed in any of the patients throughout the follow-up period, and all of them are still alive.

Despite the fact that sepsis-related mortality rates decrease with regular G-SCF and appropriate antibiotherapy if infectious complications develop in the SCN patients, the risk of developing MDS or AML during a 10-year follow-up period is reported to be 20%. MDS/AML was reported in 16% of 374 patients registered in the Severe Chronic Neutropenia International Registry which was suggested to be a complication of underlying pathogenic mechanisms that became manifest during the prolonged patient survival rather than the direct effect of G-CSF therapy(11). However, the safety of long-term G-CSF therapy remains to be an important concern. In the present study, none of the patients developed AML or MDS during the median 38 (8-133)-month follow-up period.

CONCLUSION

The diagnosis and differential diagnosis of SCN must be taken into account and ruled out in the patients presenting with recurrent unexplained infection and concurrent neutropenia particularly in countries such as Turkey where consanguineous marriages are common. It should be kept in mind that neutropenia-related complications may have quite serious outcomes. Therefore, monitoring severe cases of neutropenia like Kostmann syndrome carries extreme importance. We believe that infection in SCN patients can be managed without resorting to prophylactic G-CSF therapy to minimize G-CSF-related side effects such as potential malignancies. It is critical to inform families about early predictive signs of infection and regular patient monitoring for prophylactic GCSF-free management of the disease.

Ethics

Ethics Committee Approval: The study was approved by the Mersin University Clinical Research Ethics Committee (approval number: 2022/715, date: 01.11.2022).

Informed Consent: Retrospective study.

Author Contributions

Surgical and Medical Practices: B.D.G., S.Ü., Concept: B.D.G., S.Ü., Design: B.D.G., S.Ü., Data Collection or Processing: B.D.G., H.K., Analysis or Interpretation: B.D.G., H.K., Literature Search: B.D.G., H.K., Writing: B.D.G.

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REFERENCES

1. Dale DC, Bolyard AA, Schwinzer BG, Pracht G, Bonilla MA, Boxer L, et al. The Severe Chronic Neutropenia International Registry: 10-Year Follow-up Report. Support Cancer Ther. 2006;3(4):220-31. doi: 10.3816/SCT.2006.n.020.
2. Donadieu J, Bellanné-Chantelot C. Genetics of severe congenital neutropenia as a gateway to personalized therapy. Hematology Am Soc Hematol Educ Program. 2022;2022(1):658-65. doi: 10.1182/hematology.2022000392.
3. Lebel A, Yacobovich J, Krasnov T, Koren A, Levin C, Kaplinsky C, et al. Genetic analysis and clinical picture of severe congenital neutropenia in Israel. Pediatr Blood Cancer. 2015;62(1):103-8. doi: 10.1002/pbc.25251.
4. Dale DC, Person RE, Bolyard AA, Aprikyan AG, Bos C, Bonilla MA, et al. Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. Blood. 2000;96(7):2317-22.
5. Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K. Severe congenital neutropenias. Nat Rev Dis Primers. 2017;3:17032.

6. Bernini JC. Diagnosis and management of chronic neutropenia during childhood. Pediatr Clin North Am. 1996;43(3):773-92. doi: 10.1016/s0031-3955(05)70432-6.

7. Koren A, Cohen H, Shneyour I, Shalev E. Prenatal diagnosis of congenital dysgranulopoietic neutropenia. Br J Haematol. 1994;88(1):207-8. doi: 10.1111/j.1365-2141.1994.tb05001.x.

8. Howard TH, Watts RG. Advances in pathophysiology, diagnosis, and treatment of neutrophil defects. Curr Opin Pediatr 1992;4:991-8.

9. Alizadeh Z, Fazlollahi MR, Houshmand M, Maddah M, Chavoshzadeh Z, Hamidieh AA, et al. Different pattern of gene mutations in Iranian patients with severe congenital neutropenia (including 2 new mutations). Iran J Allergy Asthma Immunol. 2013;12(1):86-92.

10. Boxer LA, Newburger PE. A molecular classification of congenital neutropenia syndromes. Pediatr Blood Cancer. 2007;49(5):609-14.

11. Carlsson G, Fasth A. Infantile genetic agranulocytosis, morbus Kostmann: presentation of six cases from the original "Kostmann family" and a review. Acta Paediatr. 2001;90(7):757-64. doi: 10.1111/j.1651-2227.2001.tb02801.x.

12. Welte K, Zeidler C, Dale DC. Severe congenital neutropenia. Semin Hematol. 2006;43(3):189-95. doi: 10.1053/j.seminhematol.2006.04.004.

13. Yılmaz Karapınar D, Patıroğlu T, Metin A, Çalışkan Ü, Celkan T, Yılmaz B, et al. Homozygous c.130-131 ins A (pW44X) mutation in the HAX1 gene as the most common cause of congenital neutropenia in Turkey: Report from the Turkish Severe Congenital Neutropenia Registry. Pediatr Blood Cancer. 2019;66(10):e27923. doi: 10.1002/pbc.27923.

14. Klein C, Grudzien M, Appaswamy G, Germeshausen M, Sandrock I, Schäffer AA, et al. HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease). Nat Genet. 2007;39(1):86-92. doi: 10.1038/ng1940.

15. Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: diagnosis, molecular bases and patient management. Orphanet J Rare Dis. 2011;6:26. doi: 10.1186/1750-1172-6-26.

16. Patiroglu T, Gungor HE, Triot A, Unal E. Severe congenital neutropenia in two siblings related to HAX1 mutation without neurodevelopmental disorders. Genet Couns. 2013;24(3):253-8.

17. Kiykim A, Baris S, Karakoc-Aydiner E, Ozen AO, Ogulur I, Bozkurt S, et al. G6PC3 Deficiency: Primary Immune Deficiency Beyond Just Neutropenia. J Pediatr Hematol Oncol. 2015;37(8):616-22. doi: 10.1097/MPH.0000000000000441.

18. Koc I. Prevalence and sociodemographic correlates of consanguineous marriages in Turkey. J Biosoc Sci. 2008;40(1):137-48. doi: 10.1017/S002193200700226X.

19. Dong F, Brynes RK, Tidow N, Welte K, Löwenberg B, Touw IP. Mutations in the gene for the granulocyte colony-stimulating-factor receptor in patients with acute myeloid leukemia preceded by severe congenital neutropenia. N Engl J Med. 1995;333(8):487-93. doi: 10.1056/NEJM199508243330804.

20. Rosenberg PS, Alter BP, Bolyard AA, Bonilla MA, Boxer LA, Cham B, et al. The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. Blood. 2006;107(12):4628-35. doi: 10.1182/blood-2005-11-4370.

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Original Article

Does Prebiotic Food Consumption Reduce Sleep Disorder Symptoms in Children With and Without Asthma? A Case-control Study

Prebiyotik Besin Tüketimi Astımlı ve Astımlı Olmayan Çocuklarda Uyku Bozukluğu Semptomlarını Azaltır mı? Olgu Kontrol Çalışması

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ABSTRACT

Objective: This study aims to evaluate the impact of prebiotic food consumption on sleep disturbance symptoms in children with and without asthma.

Method: This is a case-control study. Data were collected from 55 children with asthma and 70 children without asthma, aged 6 to 12 years. Data collection included the Sleep Disturbance Scale for Children (SDSC), Prebiotic Food Consumption Frequency Form, and Childhood Asthma Control Test. The asthma control level of children was determined by a pediatrician following the Global Initiative for Asthma's guidelines.

Results: The average age of children with asthma was 9.16±3.11, while for children without asthma, it was 9.39±3.24. No significant differences were found between children with and without asthma in daytime napping, nighttime awakening, SDSC score, and daily prebiotic food consumption ($p>0.05$). It was observed that children with asthma used more prebiotic-enriched products than children without asthma ($p<0.012$). There was no significant difference in asthma control level, SDSC score, and prebiotic food consumption between children with and without asthma ($p>0.05$). Furthermore, no significant relationship was found between the SDSC score and prebiotic food consumption in children with and without asthma ($p>0.05$).

Conclusion: Prebiotic food consumption's role in determining sleep disturbances and asthma control levels in children with asthma remains uncertain. Further research is needed on the use of prebiotics in children with asthma.

Keywords: Asthma, sleep disorders, prebiotic food consumption, children, case-control studies

ÖZ

Amaç: Astımlı ve astımı olmayan çocuklarda prebiyotik besin tüketim durumunun uyku bozuklukları semptomları üzerine etkilerinin değerlendirilmesi amaçlandı.

Yöntem: Bu çalışma bir olgu kontrol çalışmasıdır. Çalışmada 6-12 yaş arasında olan, astım grubunda 55, kontrol grubunda ise 70 çocuğa ait veriler elde edildi. Verilerin elde edilmesinde Çocuklar için Uyku Bozuklukları Ölçeği (ÇUBÖ), Prebiyotik Besin Tüketim Sıklığı Formu ve Çocukluk Çağı Astım Kontrol Testinden yararlanıldı. Uzman bir pediatri doktoru tarafından Küresel Astım Girişimi kılavuzu doğrultusunda çocukların astım kontrol düzeyi belirlendi.

Bulgular: Astım grubunda yer alan çocukların yaş ortalamasının 9,16±3,11, kontrol grubunda ise 9,39±3,24 olduğu saptandı. Astım ve kontrol grupları arasında gündüz uyuma ve gece uyanma durumu, ÇUBÖ puanı ve günlük prebiyotik besin tüketimi açısından farklılığın olmadığı belirlendi ($p>0,05$). Astım grubunda yer alan çocukların kontrol grubuna göre daha fazla prebiyotikle zenginleştirilmiş ürün kullandığı saptandı ($p<0,012$). Astım kontrol düzeyi ile ÇUBÖ puanı ve prebiyotik besin tüketimi açısından farklılığın olmadığı belirlendi ($p>0,05$). Hem astım hem de kontrol grubunda ÇUBÖ puanı ve prebiyotik besin tüketimi arasında anlamlı bir ilişkinin olmadığı tespit edildi ($p>0,05$).

Sonuç: Astımlı çocuklarda hem uyku bozuklukları hem de astım kontrol düzeyi üzerindeki etkisini belirlemede prebiyotik besin tüketiminin rolü belirsizdir. Astımlı çocuklarda prebiyotiklerin kullanımı ile ilgili daha fazla araştırmaya ihtiyaç duyulmaktadır.

Anahtar kelimeler: Astım, uyku bozuklukları, prebiyotik besin tüketimi, çocuk, olgu-kontrol çalışması

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INTRODUCTION

Asthma, one of the most common chronic respiratory diseases in childhood[1], is characterized by airway obstruction and chronic inflammation of the bronchial mucosa. Asthma symptoms include wheezing, difficulty breathing, and nocturnal cough attacks[2]. Asthma can lead to psychiatric issues in children[3] and adverse effects on cognitive functions and school performance[4]. Additionally, children with asthma often experience sleep disturbances, primarily worsening at night[5,6]. It has been observed that children who experience asthma symptoms more frequently tend to feel significantly more tired and sleepy during the day[6]. Furthermore, children with asthma and/or allergic rhinitis are more likely to suffer from sleep disturbances than healthy children[7,8], especially when asthma is not well controlled[8,9]. Inadequate sleep can exacerbate daytime asthma symptoms and decrease the overall quality of life for children with asthma[10].

Asthma control is paramount in improving the sleep quality of children with asthma, thereby enhancing their quality of life[8,9]. As an environmental factor, nutrition is reported to impact sleep quality. Specifically, prebiotic foods, known as indigestible carbohydrates that enhance the colonization of beneficial microorganisms in the gut, are believed to positively affect asthma symptoms and sleep quality through gut composition modulation[11]. Prebiotics offer several known health benefits and are thought to have a therapeutic effect on asthma parameters by reducing inflammation, particularly concerning asthma. Due to their beneficial effects on gut microbiota, prebiotics are considered to have a potential therapeutic role in asthma. A literature review revealed that prebiotics effectively suppress allergic and autoimmune responses, reduce allergic symptoms, and inhibit allergic airway responses in acute airway inflammation models[11-13].

Upon reviewing the relevant literature, it is evident that prebiotic food consumption could have an impact on sleep quality. The sleep quality of children with asthma is known to be influenced by asthma symptoms. In this context, the effect of prebiotic food consumption on the occurrence of sleep disturbance symptoms in children with asthma is contemplated. This study aims to assess the impact of prebiotic food consumption on sleep disturbance symptoms in children with and without asthma.

Research questions:

1. Is there a difference in sleep disturbance scale scores between children with and without asthma?

2. Is there a difference in prebiotic food consumption between children with and without asthma?

3. Is there a relationship between prebiotic food consumption and sleep disturbance symptoms in children without asthma?

4. Is there a relationship between prebiotic food consumption and sleep disturbance symptoms in children with asthma?

5. Is there a difference in asthma control levels and sleep disturbance scale scores in children with asthma?

6. Is there a difference in asthma control levels and prebiotic food consumption in children with asthma?

MATERIALS and METHODS

Design, Setting, Population, and Sample Size

The research, designed as a case-control study, was conducted at the Karabük Education and Research Hospital Children's Clinic with children aged 6-12 and their mothers. The study population consisted of children aged 6-12 diagnosed with asthma or who came for well-child follow-up at the Karabük Education and Research Hospital Children's Clinic during the study period, along with their mothers.

In the case group, the inclusion criteria for mothers were as follows: Being literate and providing written and verbal consent to participate in the research. For children, the criteria were as follows: being aged 6-12, having a diagnosis of asthma, and providing verbal consent to participate in the research.

In the control group, the inclusion criteria for mothers were as follows: being literate and providing written and verbal consent to participate in the research. For children, the criteria were as follows: being aged 6-12, not having a chronic illness, and providing verbal consent to participate in the research. The G*Power power analysis method determined that a minimum of 102 children, 51 in the asthma group and 51 in the control group, were required to achieve 80% power, a medium effect size (d=0.50), and a significance level of α=0.05. Considering potential data loss, the study was completed with 125 children, including 55 asthma patients and 70 controls.

Measures and Tools

The participant information form (PIF) consists of 21 questions generated by researchers in accordance with the literature, contains sociodemographic characteristics of parents and their children, height, and weight values, information about the children's asthma diagnosis, and sleep habits[1,4-10,14].

Sleep Disturbance Scale for Children (SDSC) developed by Bruni et al.[15] in 1996, the SDSC is a 5-point Likert-type scale (1: Never - 5: Always) that investigates sleep disorders in children aged 6-16 that have occurred within the last six months. The Turkish validity and reliability of the scale were established by Ağadayı et al.[16]. As a result, it was determined that the validity and reliability tests of the SDSC were at an acceptable level. The scale yields a minimum of 26 and a maximum of 130 points. Higher scores are interpreted in favor of sleep disorders[16].

The frequency form of prebiotic food consumption was developed by a dietitian who is also one of the researchers, and it aligns with the existing literature[11-13]. This form includes 25 foods exhibiting prebiotic properties, such as leeks, artichokes, Jerusalem, onions, and garlic. The form assesses how often and in what amounts children consume these foods with eight options: "every day", "5-6 days a week", "3-4 days a week", "1-2 days a week", "once every two weeks", "once a month", and "never". Responses regarding food consumption frequency were calculated through frequency calculations (daily food consumption frequency = quantity/day). The amounts of food and beverage consumed were multiplied by "1" for "every day," "0.7855" for "5-6 times a week," "0.498" for "3-4 times a week," "0.2145" for "1-2 times a week," "0.067" for "once every two weeks," and "0.033" for "once a month" to obtain daily average amounts.

The researchers, including a specialist pediatrician, assessed the asthma control status according to Levels of Asthma Control by Global Initiative for Asthma (GINA) criteria, which encompassed daily symptom frequency, nocturnal symptoms, bronchodilator use, degree of limitation in daily activities, and lung functions. Following evaluation, individuals were classified as having controlled, partly controlled, or uncontrolled asthma[17].

Childhood Asthma Control Test (C-ACT) was developed in 2007 by Liu et al.[18]. This scale aims to measure the levels of asthma control in children aged 4-11. The Turkish validity and reliability study of the scale was conducted by Sekerel et al.[19]. The scale consists of two parts. The first part includes four questions in a visual analog scale format with four pictorial options. These questions are posed to the child and are scored from 0 to 3. The remaining three questions are in a 6-point Likert-type format. The parent should complete this part. Scores on the scale can range from 0 to 27. A cutoff point of 19 is used for the scale, where a score of 19 or lower indicates that the child's asthma is not under control[18,19].

Procedures

Prior to the implementation of data collection forms, mothers were provided with verbal and written informed consent forms explaining the objective of the research, data confidentiality, and their right to withdraw from the study at any time. Mothers who provided consent were included in the research. In addition, the children who participated in the study provided verbal consent.

Mothers of healthy children included in the control group completed the PIF, SDSC, and the "Prebiotic Food Consumption Frequency Form".

Mothers of children with asthma in the case group completed the PIF, SDSC, "Prebiotic Food Consumption Frequency Form", and the second part of the C-ACT, the parental section. The first part of the C-ACT, the child section, was completed by children with asthma under parental and researcher supervision. Subsequently, the pediatrician within the research team determined the level of asthma control according to Levels of Asthma Control by GINA based on the child's examination findings. The assessments of asthma control levels made by parents and children were compared. The comparison revealed that assessments of asthma control levels by parents and children were consistent (Supplementary Table 1). The children's weight and height information, as well as body mass index (BMI9) [(kg)/height(m^2)] and z-scores, were calculated[20,21].

Ethical Considerations

The research was conducted following ethical principles outlined in the Helsinki Declaration. Prior to the study, necessary approvals were obtained from the Karabük University Non-Interventional Clinical Research Ethics Committee (decision no: 2022/816, date: 20.01.2022). Subsequently, institutional approval was obtained from the hospital where the study was conducted (protocol no: E-34771223-774.99). Participants were provided with written informed consent explaining

the purpose of the research, data confidentiality, the voluntary nature of participation, and the right to withdraw from the survey at any time, which was presented on the first page of the questionnaire.

Statistical Analysis

Data analysis was performed using IBM SPSS 27.0 software. Descriptive variables were presented as number (n), percentage (%), mean (X), and standard deviation. Non-normally distributed data were described using median (M) and minimum-maximum values. Data normality was assessed through visual (histograms) and analytical (Kolmogorov-Smirnov) analysis. The chi-square test was employed to evaluate differences between categorical variables among groups.

Similarly, the independent t-test was used to assess differences between normally distributed continuous variables between the two groups. The Mann-Whitney U test was applied for non-normally distributed data. The One-Way ANOVA test was utilized to examine differences in continuous variables among more than two groups. All hypothesis tests were two-tailed, and p-values <0.05 were considered statistically significant.

RESULTS

The study determined that the average age of children in the asthma group was 9.16±3.11 years, while in the control group, it was 9.39±3.24 years. No significant differences were found when comparing the groups based on age, weight, height, and maternal age (p>0.05). While there was no significant difference in BMI values between the groups (p>0.05), the BMI z-scores in the asthma group were statistically significantly higher than those in the control group (p=0.029). Examination of maternal education levels revealed that 41.8% (n=23) of the asthma group and 42.9% (n=39) of the control group had attained a university-level education or higher. There were no statistically significant differences between the asthma and control groups in terms of maternal education level, socioeconomic status, daytime napping, and nighttime awakening (p>0.05) (Table 1).

When comparing the SDSC scores and daily prebiotic food consumption (total prebiotic food intake) between the asthma and control groups, no statistically significant differences were observed (p>0.05). However, it was found that the consumption of prebiotic-fortified products in the asthma group was statistically significantly higher than that in the control group (p=0.012) (Table 2).

Examination of the relationship between SDSC scores and daily prebiotic food consumption in both groups revealed no statistically significant differences (p>0.05) (Table 3).

When comparing asthma control levels with SDSC scores and daily prebiotic food consumption, no statistically significant differences were identified (p>0.05) (Table 4).

DISCUSSION

The initial findings of our study indicated that the SDSC scores of children with asthma were higher than those of children without asthma, albeit not significantly so. Similarly, there was no significant difference between the asthma and control groups regarding daytime napping and nighttime awakening frequency. In contrast to our findings, van Maanen et al.[6] reported that children with frequent asthma symptoms were more likely to experience daytime sleepiness/fatigue than children with seldom or no asthma symptoms. Urrutia-Pereira et al.[8] also found that children with asthma and/or allergic rhinitis exhibited more frequent sleep disturbances when compared to controls. Furthermore, no difference in asthma control levels and SDSC scores was observed in the current study. In the literature, several studies have shown that as the rate of asthma symptoms increases and asthma control worsens, sleep disturbances become more common. Suleyman et al.[14] reported decreased sleep duration and increased nocturnal awakenings in uncontrolled asthma.

Similarly, when children with well-controlled asthma or no asthma were compared to those with poorly controlled asthma, it was found that children with poorly controlled asthma had poorer sleep patterns, had more problems falling asleep, and had more sleep disruptions[22]. Despite the absence of differences in sleep disturbances between our groups, the asthma group had a higher SDSC score with a borderline p-value of 0.50. This inconsistency with the literature is thought to be due to the smaller sample size of our study. Further, the literature suggests the presence of numerous factors in children, such as urban factors, that can affect sleep outcomes alongside asthma symptoms[23]. It is assumed that unaccounted factors may have influenced the study's outcomes.

Our study showed no difference in prebiotic food consumption between the asthma and control groups. Moreover, no difference was observed between asthma control levels and prebiotic food consumption. Wawryk-

Table 1. Demographic and anthropometric characteristics of the children (n=125)			
	Asthma (n=55)	**Controls (n=70)**	
	Mean ± SD/Median (min-max)[a]	**Mean ± SD/Median (min-max)[a]**	**p-value**
Age (years)[c]	9.16±3.11	9.39±3.24	0.699
Body weight (kg)[d]	30.00 (17.0-100.0)	29.50 (19.0-95.0)	0.253
Body height (cm)[d]	132.00 (104.0-182.0)	129.50 (105.0-177.0)	0.560
BMI (kg/m²)[c]	19.91±4.83	18.57±4.12	0.098
BMI (z score)[d]	0.85 (-2.18-4.26)	0.30 (-5.57-3.41)	0.029[b]
Mother's age (years)[c]	37.11±5.18	37.89±5.12	0.405
	n (%)	**n (%)**	
Mother's Educational Status[e]			
Primary school	9 (16.4)	6 (8.6)	0.599
Middle school	8 (14.5)	12 (17.1)	
High school	15 (27.3)	122 (31.4)	
University or higher	23 (41.8)	30 (42.9)	
Socioeconomic status[e]			
Income less than expense	9 (16.4)	14 (20.0)	0.522
Income equals expense	39 (70.9)	43 (61.4)	
Income more than expenses	7 (12.7)	13 (18.6)	
Daytime sleep status[e]			
Yes	7 (12.7)	6 (8.6)	0.450
No	48 (87.3)	64 (91.4)	
Night waking condition[e]			
Yes	24 (43.6)	26 (37.1)	0.462
No	31 (56.4)	44 (62.9)	

[a]Mean ± standard deviation (SD) was used in parametric tests and median [minimum-maximum (min-max] was used in non-parametric tests. [b]p<0.05. [c]Student t-test used. [d]Mann-Whitney U test used. [e]The chi-square test used, min-max: Minimum-Maximum, BMI: Body mass index

Table 2. Comparison of asthma and control groups' total prebiotic food intake and SDSC score (n=125)			
	Asthma (n=55)	**Controls (n=70)**	
	Mean ± SD	**Mean ± SD**	**p-value[a]**
The SDSC total score	43.09±10.33	39.72±8.63	0.050
Total prebiotic food intake (g/day)	529.40±281.12	519.43±288.23	0.721
Prebiotic fortified products (g)[c]	4.61±7.44	2.83±6.75	0.012[b]

[a]The Independent t-test used. [b]p<0.05. [c]The use of prebiotic fortified products was also included in the total prebiotic consumption, SDSC: Sleep Disturbance Scale for Children, SD: Standard deviation

Gawda et al.[24] found that prebiotics and synbiotics effectively reduced asthma incidence in children in the first months after birth. Stokholm et al.[25] found that infants born via cesarean section had a greater risk of asthma in their sixth year of life, indicating that cesarean delivery impacted gut composition in the first year of life. Therefore, they emphasized the importance of the appropriate composition of gut bacteria in asthma prevention. Despite the absence of differences in prebiotic food consumption between groups in our study, it was determined that using prebiotic-enriched products was higher in children with asthma.

Furthermore, in our study, asthma and control groups exhibited homogeneity regarding socioeconomic status, maternal age, and education level. Thus, it is thought that this difference in the consumption of prebiotic-enriched products may be attributed to a higher inclination of mothers of children with asthma to resort to alternative methods due to the information they acquire during

frequent doctor visits and the presence of asthma symptoms, compared to the control group. In the literature, some studies support the reduction of asthma or recurrent wheezing risk with early prebiotic use[26] and suggest that it has no effect on upper respiratory tract infections[27]. The World Allergy Organisation's guidelines on prebiotics in allergy prevention recommend prebiotic supplementation only for infants not receiving breast milk and no prebiotic supplementation for breastfed infants. However, both recommendations are based on very low-certainty evidence[28]. Moreover, the relationship between prebiotic consumption and respiratory symptoms varies depending on the strain used and the duration of consumption[29]. In conclusion, there is limited evidence to recommend prebiotic use for preventing and managing asthma in children, and better-designed studies are needed[30].

Our study did not reveal a relationship between prebiotic food consumption frequency and SDSC scores in the asthma and control groups. It is assumed that this is due to the influence of various variables affecting gut microbiota, such as sleep patterns, the immune system, the endocrine system, stress/anxiety, and environmental factors. A literature review did not yield any studies investigating the relationship between prebiotic consumption and sleep disorders in children with asthma. In line with the present study, a meta-analysis study reported that probiotic or prebiotic interventions did not significantly improve sleep quality, indicating a need for more evidence[31]. In contrast to our study, recent years have seen increasing recognition of the critical role of bidirectional communication in the gut-brain axis in the etiology and pathogenesis of sleep disorders[32]. In a randomized controlled study involving healthy infants, infants fed with prebiotic-enriched formula had shorter episodes of crying/restlessness and longer sleep onset durations than the control group[33].

Further, the literature has also examined the effects of prebiotics on sleep through various animal experiments. A study conducted by Bozorgmehr et al.[34] in mice reported that supplementation of human milk oligosaccharides, a prebiotic, had the potential to protect against the development of asthma in later life. Other animal experiments have also shown positive effects of prebiotics on sleep quality[35,36]. However, well-structured randomized controlled trials are needed to understand better the relationship between prebiotic consumption and sleep disorders in children with asthma.

Practice Implications

Prebiotic food consumption's role in determining sleep disorders and asthma control levels in children with asthma remains unclear. The findings indicate the need for further research on the use of prebiotics in children with asthma. Positive interventions to improve sleep quality in children with asthma have been reported in the literature[1]. In this context, multidisciplinary teams should plan comprehensive interventions for children and parents to improve sleep quality and prevent sleep disorders in children with asthma.

Study Limitation

One of our study's strengths is that it is one of the first to investigate the relationship between sleep disorders

Table 3. The relationship between asthma and control groups' total prebiotic food intake and SDSC score (n=125)

		Asthma (n=55)		Controls (n=70)	
		SDSC	Total prebiotic food intake (g/day)	SDSC	Total prebiotic food intake (g/day)
SDSC	r	1		1	
	p				
Total prebiotic food intake (g/day)	r	-0.114	1	-0.162	1
	p	0.416		0.181	

r: Pearson's correlation coefficient, SDSC: Sleep Disturbance Scale for Children

Table 4. The association between total prebiotic food intake and SDSC score with the asthma control level (n=55)

	Levels of asthma control by GINA			
	Controlled	Partly controlled	Uncontrolled	p-value
The SDSC total score[a]	41.00±9.89	42.75±13.62	43.29±10.33	0.948
Total prebiotic food intake (g/day)[a]	545.72±144.73	596.75±354.59	507.84±281.12	0.639

[a]One-Way ANOVA, SDSC: Sleep Disturbance Scale for Children, GINA: Global Initiative for Asthma

and prebiotic food consumption in children with asthma. Furthermore, the assessment of asthma control levels by both the pediatrician and the mother and child enhances the reliability of our study.

Study Limitation

Our study has several limitations. Firstly, other factors that can influence sleep patterns (such as stress/anxiety, light, the endocrine system, etc.) could not be controlled due to the nature of the study. Additionally, the study was conducted only in children aged 6-12 years and at a single center. The generalisability of the relationship between prebiotic food consumption and sleep disorders in children with asthma and other age groups is limited.

CONCLUSION

Sleep disorder symptoms are frequently observed in children with asthma. In recent years, the effectiveness of prebiotic consumption in improving sleep quality in children has been acknowledged. The results of this study contribute to the understanding of the relationship between sleep disorder symptoms and prebiotic food consumption in children with and without asthma. Our study discovered no differences between the asthma and control groups regarding sleep disorder scale scores and prebiotic food consumption. However, the use of prebiotic-enriched products was found to be higher in the asthma group. It was also determined that sleep disorder scale scores and prebiotic food consumption did not differ with asthma control levels.

Ethics

Ethics Committee Approval: Prior to the study, necessary approvals were obtained from the Karabük University Non-Interventional Clinical Research Ethics Committee (decision no: 2022/816, date: 20.01.2022).

Informed Consent: Written consent was obtained from all patients.

Author Contributions

Concept: E.D., A.T., B.D., Design: Ö.Ö.Ş., B.D., Y.T., Data Collection or Processing: E.D., A.T., Y.T., Analysis or Interpretation: Ö.Ö.Ş., B.D., Y.T., Literature Search: Ö.Ö.Ş., E.D., A.T., B.D., Y.T., Writing: Ö.Ö.Ş., E.D., A.T., B.D., Y.T.

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REFERENCES

1. Sonney JT, Thompson HJ, Landis CA, Pike KC, Chen ML, Garrison MM, et al. Sleep intervention for children with asthma and their parents (SKIP Study): a novel web-based shared management pilot study. J Clin Sleep Med. 2020;16(6):925-36. doi: 10.5664/jcsm.8374.
2. Çalışkan ZI, Avcı Ö. Alerjik-İmmünolojik Hastalıklar ve Hemşirelik Bakımı In: Çavuşoğlu H, editor. Pediatri Hemşireliği Akıl Notları. Güneş Tıp Kitabevleri. 2018:241-59.
3. Türkoğlu S. Solunum sistemi hastalığı olan çocuk ve ergenlerde psikiyatrik bozukluk ve belirtiler. Genel Tip Derg. 2015;25(4):140-6.
4. Reynolds KC, Boergers J, Kopel SJ, Koinis-Mitchell D. Featured Article: Multiple Comorbid Conditions, Sleep Quality and Duration, and Academic Performance in Urban Children With Asthma. J Pediatr Psychol. 2018;43(9):943-54. doi: 10.1093/jpepsy/jsy027.
5. Jensen ME, Gibson PG, Collins CE, Hilton JM, Latham-Smith F, Wood LG. Increased sleep latency and reduced sleep duration in children with asthma. Sleep Breath. 2013;17(1):281-7. doi: 10.1007/s11325-012-0687-1.
6. van Maanen A, Wijga AH, Gehring U, Postma DS, Smit HA, Oort FJ, et al. Sleep in children with asthma: results of the PIAMA study. Eur Respir J. 2013;41(4):832-7. doi: 10.1183/09031936.00019412.
7. Brockmann PE, Bertrand P, Castro-Rodriguez JA. Influence of asthma on sleep disordered breathing in children: a systematic review. Sleep Med Rev. 2014;18(5):393-7. doi: 10.1016/j.smrv.2014.01.005.
8. Urrutia-Pereira M, Solé D, Chong Neto HJ, Acosta V, Cepeda AM, Álvarez-Castelló M, et al. Sleep disorders in Latin-American children with asthma and/or allergic rhinitis and normal controls. Allergol Immunopathol (Madr). 2017;45(2):145-51. doi: 10.1016/j.aller.2016.05.005 .
9. Koinis-Mitchell D, Kopel SJ, Boergers J, Ramos K, LeBourgeois M, McQuaid EL, et al. Asthma, allergic rhinitis, and sleep problems in urban children. J Clin Sleep Med. 2015;11(2):101-10. doi: 10.5664/jcsm.4450.
10. Meltzer LJ, Beebe DW, Jump S, Flewelling K, Sundstrom D, White M, et al. Impact of sleep opportunity on asthma outcomes in adolescents. Sleep Med. 2020;65:134-41. doi: 10.1016/j.sleep.2019.07.014.
11. Huang L, Guo J, Li W, Jiang M, Wang F, Kang J, et al. Probiotics, prebiotics, and synbiotics for the treatment of asthma: Protocol for a systematic review. Medicine (Baltimore). 2019;98(47):e17840. doi: 10.1097/MD.0000000000017840.
12. Ezendam J, de Klerk A, Gremmer ER, van Loveren H. Effects of Bifidobacterium animalis administered during lactation on allergic and autoimmune responses in rodents. Clin Exp Immunol. 2008;154(3):424-31. doi: 10.1111/j.1365-2249.2008.03788.x.
13. Nonaka Y, Izumo T, Izumi F, Maekawa T, Shibata H, Nakano A, et al. Antiallergic effects of Lactobacillus pentosus strain S-PT84 mediated by modulation of Th1/Th2 immunobalance and induction of IL-10 production. Int Arch Allergy Immunol. 2008;145(3):249-57. doi: 10.1159/000109294.
14. Suleyman A, Ozek Yucel E, Hizli Demirkale Z, Sipahi Cimen S, Ozdemir C, Tamay Z, et al. Feeding before bedtime in preschool children with asthma: does it affect upper respiratory symptoms and asthma control? J Ist Faculty Med. 2021;84(3):386-95. doi: 10.26650/iuitfd.2020.0031.

15. Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, et al. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Res. 1996;5(4):251-61. doi: 10.1111/j.1365-2869.1996.00251.x.

16. Ağadayı E, Çelik N, Başer DA. Çocuklar için uyku bozukluğu ölçeğinin türkçe geçerlik ve güvenirlik çalışması. Journal of Turkish Sleep Medicine. 2020;2:65-72. doi: 10.4274/jtsm.galenos.2020.98598

17. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31(1):143-78. doi: 10.1183/09031936.00138707.

18. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol. 2007;119(4):817-25. doi: 10.1016/j.jaci.2006.12.662.

19. Sekerel BE, Soyer OU, Keskin O, Uzuner N, Yazicioglu M, Kiliç M, et al. The reliability and validity of Turkish version of Childhood Asthma Control Test. Qual Life Res. 2012;21(4):685-90. doi: 10.1007/s11136-011-9970-z.

20. Neyzi O, Günöz H, Furman A, Bundak R, Gökçay G, Darendeliler F, et al. Türk çocuklarında vücut ağırlığı, boy uzunluğu, baş çevresi ve vücut kitle indeksi referans değerleri. Çocuk Sağlığı ve Hastalıkları Dergisi. 2008;51(1):1-14.

21. World Health Organization. BMI-for-age (5-19 years) 2022 [Available from: https://www.who.int/toolkits/growth-reference-data-for-5to19-years/indicators/bmi-for-age.

22. Meltzer LJ, Pugliese CE. Sleep in young children with asthma and their parents. J Child Health Care. 2017;21(3):301-11. doi: 10.1177/1367493517712064.

23. Martin SR, Boergers J, Kopel SJ, McQuaid EL, Seifer R, LeBourgeois M, et al. Sleep Hygiene and Sleep Outcomes in a Sample of Urban Children With and Without Asthma. J Pediatr Psychol. 2017;42(8):825-36. doi: 10.1093/jpepsy/jsx052.

24. Wawryk-Gawda E, Markut-Miotła E, Emeryk A. Postnatal probiotics administration does not prevent asthma in children, but using prebiotics or synbiotics may be the effective potential strategies to decrease the frequency of asthma in high-risk children - a meta-analysis of clinical trials. Allergol Immunopathol (Madr). 2021;49(4):4-14. doi: 10.15586/aei.v49i4.69.

25. Stokholm J, Thorsen J, Blaser MJ, Rasmussen MA, Hjelmsø M, Shah S, et al. Delivery mode and gut microbial changes correlate with an increased risk of childhood asthma. Sci Transl Med. 2020;12(569):eaax9929. doi: 10.1126/scitranslmed.aax9929.

26. Cuello-Garcia C, Fiocchi A, Pawankar R, Yepes-Nuñez JJ, Morgano GP, Zhang Y, et al. Prebiotics for the prevention of allergies: A systematic review and meta-analysis of randomized controlled trials. Clin Exp Allergy. 2017;47(11):1468-77. doi: 10.1111/cea.13042.

27. Leung TF, Ulfman LH, Chong MKC, Hon KL, Khouw I, Chan PKS, et al. A randomized controlled trial of different young child formulas on upper respiratory and gastrointestinal tract infections in Chinese toddlers. Pediatr Allergy Immunol. 2020;31(7):745-54. doi: 10.1111/pai.13276.

28. Cuello-Garcia CA, Fiocchi A, Pawankar R, Yepes-Nuñez JJ, Morgano GP, Zhang Y, et al. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Prebiotics. World Allergy Organ J. 2016;9:10. doi: 10.1186/s40413-016-0102-7.

29. Adjibade M, Davisse-Paturet C, Divaret-Chauveau A, Adel-Patient K, Raherison C, Dufourg MN, et al. Enrichment of Formula in Probiotics or Prebiotics and Risk of Infection and Allergic Diseases up to Age 5.5 Years in the Nationwide Etude Longitudinale Française depuis l'Enfance (ELFE) Cohort. J Nutr. 2022;152(4):1138-48. doi: 10.1093/jn/nxac013.

30. Meirlaen L, Levy EI, Vandenplas Y. Prevention and Management with Pro-, Pre and Synbiotics in Children with Asthma and Allergic Rhinitis: A Narrative Review. Nutrients. 2021;13(3):934. doi: 10.3390/nu13030934.

31. Gil-Hernández E, Ruiz-González C, Rodriguez-Arrastia M, Ropero-Padilla C, Rueda-Ruzafa L, Sánchez-Labraca N, et al. Effect of gut microbiota modulation on sleep: a systematic review and meta-analysis of clinical trials. Nutr Rev. 2023;81(12):1556-70. doi: 10.1093/nutrit/nuad027.

32. Wang Z, Wang Z, Lu T, Chen W, Yan W, Yuan K, et al. The microbiota-gut-brain axis in sleep disorders. Sleep Med Rev. 2022;65:101691. doi: 10.1016/j.smrv.2022.101691.

33. Colombo J, Carlson SE, Algarín C, Reyes S, Chichlowski M, Harris CL, et al. Developmental effects on sleep-wake patterns in infants receiving a cow's milk-based infant formula with an added prebiotic blend: a Randomized Controlled Trial. Pediatr Res. 2021;89(5):1222-31. doi: 10.1038/s41390-020-1044-x.

34. Bozorgmehr T, Boutin RCT, Woodward SE, Donald K, Chow JM, Buck RH, et al. Early Life Exposure to Human Milk Oligosaccharides Reduces Allergic Response in a Murine Asthma Model. J Immunol Res. 2023;2023:9603576. doi: 10.1155/2023/9603576.

35. Thompson RS, Roller R, Mika A, Greenwood BN, Knight R, Chichlowski M, et al. Dietary Prebiotics and Bioactive Milk Fractions Improve NREM Sleep, Enhance REM Sleep Rebound and Attenuate the Stress-Induced Decrease in Diurnal Temperature and Gut Microbial Alpha Diversity. Front Behav Neurosci. 2017;10:240. doi: 10.3389/fnbeh.2016.00240.

36. Thompson RS, Vargas F, Dorrestein PC, Chichlowski M, Berg BM, Fleshner M. Dietary prebiotics alter novel microbial dependent fecal metabolites that improve sleep. Sci Rep. 2020;10(1):3848. doi: 10.1038/s41598-020-60679-y.

Supplementary Table 1. Parent-child and doctor ratings of the asthma control levels in children (n=55)

		Levels of asthma control by GINA			
		Controlled	Partly controlled	Uncontrolled	p-value[a]
		C-ACT	C-ACT	C-ACT	
C-ACT	Controlled	1 (6.7)	2 (13.3)	12 (80.0)	0.526
	Uncontrolled	1 (2.5)	10 (25.0)	29 (72.5)	

[a]The chi-square test used, C-ACT: Childhood Asthma Control Test, GINA: Global Initiative for Asthma

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Original Article

Clinical Characteristics and Treatment Outcomes of Cases Diagnosed with Pediatric Optic Neuritis

Çocukluk Çağı Optik Nörit Tanılı Olguların Klinik Özellikleri ve Tedavi Sonuçları

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ABSTRACT

Objective: Optic neuritis (ON) is a condition that causes vision loss usually in one eye, often due to multiple sclerosis (MS). In this study, we aim to examine the clinical course, diagnostic tests, and treatment outcomes of patients presenting with acute or subacute ON.

Method: In this retrospective study, we examined the medical records of pediatric patients aged 3-18 years who were evaluated for acute ON in our neurology department between January 2015 and January 2021.

Results: Our study population of 18 participants consisted of female (55.6%), and male (44.4%) patients with an overall mean age of 13.8±2.3 years at admission. During the follow-up period, patients received the diagnosis of isolated ON (n=10), MS (n=7), and acute disseminated encephalomyelitis (n=1). The most common complaints at initial presentations were blurred vision and visual loss. ON was unilateral in 83.7% and bilateral in 16.7% of the patients. Color vision was initially impaired in 11 of 18 patients. Cranial magnetic resonance imaging (MRI), orbital MRI and spinal MRI revealed demyelinating lesions at different rates.

Conclusion: It is crucial to consider ON as one of the potential causes of vision loss in patients. The possibility of other demyelinating diseases, including MS, which can be present or may develop in patients with ON either during the initial presentation or follow-up should be kept in mind.

Keywords: Optic neuritis, demyelinating diseases, vision loss, children

ÖZ

Amaç: Optik nörit (ON) genellikle akut ve subaküt monooküler görme kaybına neden olan demiyelinizan bir hastalıktır. Yüksek oranda multiple skleroz (MS) ile ilişkilendirilmiştir. Bu çalışmada akut veya subaküt ON ile başvuran hastalardaki klinik seyir, yardımcı tanı testleri ve tedavi uygulamaları sonuçlarını değerlendirmeyi amaçladık.

Yöntem: Bu çalışmada Ocak 2015-Ocak 2021 yılları arasında akut ON ile çocuk nöroloji bölümünde değerlendirilen 3-18 yaş arası ON hastaların tıbbi kayıtları retrospektif olarak incelendi.

Bulgular: Çalışmamıza 18 hasta dahil edildi. Hastaların %55,6'sı kız, %44,4'ü erkekti. ON'nin ilk başlangıç yaşı ortalama 13,8±2,3 yıldı. Takip sürecinde hastalardan 10'u (%56) izole ON, 7'si (%39) MS, 1 hasta akut dissemine ensefalomiyelit (%5) tanısı aldı. Hastalarımızda ilk başvuruda en sık görülen şikayetler bulanık görme ve görme kaybıydı. ON hastaların %83,7'sinde (16 hasta) unilateral ve %16,7'sinde bilateral (2 hasta) idi. Görme alanı muayenesi yapılan 11 hastanın 10'un da başlangıçta görme alanı etkilenmişti. İncelenen 18 hastanın 11'inde başlangıçta renkli görmede bozulma mevcuttu.

Sonuç: Çalışmamız neticesinde görme kaybı bulguları ile gelen hastalarda ON'nin ayırıcı tanılarda düşünülmesi gerektiği, bununla birlikte ON'li hastalarda ilk başvuru sırasında veya izlemlerde MS başta olmak üzere diğer demiyelinizan hastalıkların olabileceği veya gelişebileceği akılda tutulmalıdır.

Anahtar kelimeler: Optik nörit, demiyelinizan hastalıklar, görme kaybı, çocuk

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INTRODUCTION

Optic neuritis (ON) is a condition that develops due to an inflammatory process involving the optic nerve. ON is among the most common causes of acute and subacute vision loss and can be characterized by many ophthalmic symptoms[1,2]. The main features of ON can be listed as decreased visual acuity, visual field defects, dyschromatopsia (abnormal color vision, especially red color desaturation)[3]. Since ON may be seen in many disease states, as a critically important issue, specific causes of ON should be identified at admission to prevent development of relapses and complications. An initial clinical history and detailed examination are required to narrow the list of differential diagnosis and make a diagnostic evaluation[4,5]. Although ON is often considered an isolated pathology or a part of another disease, imaging exams, and laboratory tests still play a significant role in confirming its diagnosis[6]. During follow-up, clinical progression, as well as changes in laboratory variables, can sometimes lead to a revision of the initial diagnosis of ON. Utilizing diagnostic tools is essential to aid in making the differential diagnosis of ON.

ON accounts for approximately 25% of acute demyelinating syndromes in children, with an annual incidence of 1-5 per 100,000 cases[1,7]. ON is a medical condition that is commonly observed as an isolated idiopathic form in children. However, it may also be associated with acute or subacute demyelinating syndromes of the central nervous system, such as acute disseminated encephalomyelitis (ADEM), myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD), multiple sclerosis (MS) and neuromyelitis optica (NMO). It has been observed that some patients initially diagnosed with isolated ON may eventually receive the final diagnosis of MS[8,9]. However, there is not enough data available about pediatric ON in our country. Therefore, in this study, we have retrospectively evaluated pediatric patients with the diagnosis of acute ON. We examined the demographic characteristics, diagnoses, clinical findings, laboratory and imaging results, responses to treatment, and clinical follow-up of these patients to evaluate the clinical features of ON in pediatric patients and to emphasize the significance of follow-up and treatment.

MATERIALS and METHODS

A cohort study was conducted at the Pediatric Neurology Clinic of Manisa Celal Bayar University Faculty of Medicine. The study analyzed the data of all patients aged between 3 to 18 years who were admitted to the pediatric neurology service with suspected acute or subacute ON between January 2015 and January 2021. The data were collected from electronic medical records available in a computerized database. The analysis only included cases that were diagnosed with ON by neuro-ophthalmologists. The cases were identified by the symptoms such as pain with eye movements and/or loss of vision lasting for a maximum of two weeks. Other diagnostic indicators included decreased color vision, abnormal visual field, relative afferent pupillary defect (RAPD), and optic disc swelling. ON affecting both eyes at the time of registration or developed within one month after admission was considered bilateral ON.

The study population consisted of patients who had received the diagnosis of ON and evaluated by a neuro-ophthalmologist. Participants with incomplete information regarding the diagnosis of ON, pathologies of the other eye that affected visual acuity, or any signs of a previously experienced ON were excluded from the study. The patient's demographic data, clinical characteristics, treatment history, and discharge diagnosis were recorded upon admission.

Any recurrent ON or new neurological conditions emerged during follow-up were documented. ON was interpreted as isolated ON or a condition associated with other demyelinating diseases. The diagnosis of idiopathic ON was made according to the current diagnostic methodologies used at the time of admission and during the follow-up period after excluding all other possible etiologies for ON.

ON that occurs at least four weeks after the initial event associated with or without the presence of oligoclonal band (OCB) in the cerebrospinal fluid (CSF) samples of patients with normal cranial magnetic resonance imaging (MRI) findings but experienced at least two novel episodes is termed as recurrent ON[10,11]. The diagnoses were made based on the current diagnostic criteria. MS-associated ON was defined according to the 2017 revision of the McDonald diagnostic criteria for MS[12]. The follow-up period was described as the time interval extending from the patients' admission date to their last visit or the time elapsed during data collection.

All patients underwent initial examination by an experienced ophthalmologist, with periodic follow-up appointments for patients under treatment. Furthermore, study participants underwent cranial and orbital MRI scans, which were evaluated for signs of ON,

location of the lesions and post-gadolinium contrast enhancement.

All patients received a comprehensive evaluation, including a complete blood count, serological analyses for the identification of infectious agents, and biochemical and immunological blood tests. In children who underwent lumbar puncture, biochemical and microbiological test results of CSF samples, the presence of OCB (if any) and calculated immunoglobulin G index were recorded. If Neuromyelitis Optica Spectrum Disorder (NMOSD) or MOGAD was suspected, AQP4 and anti-MOG levels were measured in peripheral blood serum during diagnostic process or follow-up.

This study was approved by the institutional Ethics Review Board of Manisa Celal Bayar University (approval number: 386, date: 23.01.2023).

Statistical Analysis

The study analysed both quantitative and categorical data. The quantitative data was analysed using IBM SPSS Statistics 20 software program and presented as mean ± standard deviation or median and range. Categorical data was presented as frequencies and percentages. The level of statistical significance was set at $p<0.05$.

RESULTS

A total of 18 patients diagnosed with ON were examined. Of them, 55.6% were girls and 44.4% were boys. None of them had a family history of ON or any demyelinating diseases. The average age at the first onset of ON was 13.8±2.3 (range 7-18) years. The follow-up period of the patients ranged from 7 days to 42 months. During the follow-up period, the patients received the diagnosis of isolated ON (n=10; 56%), MS (n=7; 39%), and ADEM (n=1; 5%) (Table 1).

The most common complaints in our patients at first admission were vision problems such as blurred vision, vision loss, and pain at eye movements. In addition, patients complained of numbness in the hand (n=1), and headache (n=5). In our study, ON was unilateral in 16 (83.7%) and bilateral in 2 (16.7%) patients) (Table 2). The initial visual examination was conducted on all of the study patients, and 16 patients underwent visual acuity testing. The tests revealed visual acuity of less than 0.5 in 8 patients after correction. Additionally, visual field examinations were performed in 11 patients and in 10 of them the visual field was affected at baseline. Visual field examinations were maintained during follow-up period in only two patients. Their visual fields improved in the sixth and twelfth months, respectively. However, 10 patients did not receive a follow-up visual field examination. Baseline visual field examinations of 11 out of 18 patients revealed the presence of an impaired color vision.

In the neurological examination of our patients, in addition to eye findings, the patients had dysmetria (n=5), sensory loss (n=1), limited vision, (n=1) and abnormal pupillary reflexes (n=1). Our study found that 11 out of 14 patients who underwent visual evoked potential tests had prolonged central motor conduction times. In addition, we performed orbital MRI and cranial MRI on 16 patients, out of which optic nerve involvement was detected in 9 (56.2%) patients) who underwent orbital MRI. Lesions were found in 50% (n=8) of patients who underwent cranial MRI. Spinal MRI detected demyelinating lesions in 7, and spinal cord lesions in 3 patients at presentation (Table 3). Analysis of the sera of 14 patients to diagnose NMOS or to detect anti-MOG, AQP4 and anti-MOG antibodies yielded negative results. Elevated OCB type 2 and type 3 proteins were observed in 4 out of 6 patients who underwent CSF examination.

In our study, we administered pulse methylprednisolone therapy to all patients as an attack treatment at daily doses of 20-30 mg/kg for 3-5 days. Oral steroid maintenance therapy was given to 8 patients for 4-6 weeks. While we achieved a complete clinical response in all patients, ON recurred, as expected, in 2 patients who were initially diagnosed with MS. During clinical follow-up, visual symptoms improved within three days to one month (average ten days). Among the patients who returned for their follow-up visits, complete recovery was detected in the third month in 10, and partial recovery in the sixth month in 3 patients. The remaining five patients with isolated ON did not come for control. When we reached them by phone, they had not reported any complaints.

DISCUSSION

Although pediatric ON typically causes reversible vision loss that usually occurs within hours to days,

Table 1. Distribution of patients with optic neuritis according to disease groups

Disease group	Number (%)
Patients with Isolated optic neuritis	10 (50)
Patients with MS	7 (39)
Patients with ADEM	1 (5)
Total	18 (100)

MS: Multiple sclerosis, ADEM: Acute disseminated encephalomyelitis

it can lead to development of severe vision loss in some patients[1,13]. A study conducted on the risk of MS development among patients with isolated ON observed that children with bilateral ON had a lower risk of developing MS[14]. Recurrent ON is commonly associated with autoimmune or demyelinating diseases such as MS or NMOSD[15]. ON is more common in women, with a female to male ratio of approximately 2:1 in postpubertal children, similar to adults. However, it is seen at equal incidence rates in prepubertal girls and boys[16-18]. Due to the small number of patients in our study, pre- or postpubertal periods could not be evaluated separately, and the male-female ratio was 10/8. The average age at onset of pediatric ON varies between 9 to 11 years of age in the literature[19,20]. Age range of our study population varied between 7 and 18 years, with an average age of 13.8 years Children under 10 years of age are more likely to develop infectious optic neuropathies or isolated ON, while those older than ten years are more likely to develop MS[21]. In adult patients, ON typically presents as retrobulbar neuritis, while papillitis is more frequently observed in children. In our study, 83.3% of the patients had retrobulbar neuritis, there were no abnormalities on fundoscopic examination at first admission, but color vision deficiency with/without RAPD was observed.

Pain with eye movement is a common symptom in pediatric cases, with reported prevalence rates ranging from 33% to 77%[22]. Headache is also frequently reported. One study reported its prevalence as 53% in children[23] which may be due to children's difficulty in distinguishing between pain behind the eyes and a headache. In our study, all patients in our ON cohort had vision loss at their initial visit, while 61.1% of them reported pain with eye movement, consistent with previous research. According to the study by Wilejto et al.,[23] 58% of cases of ON were unilateral and 42% of them were bilateral. Another study reported that bilateral involvement was more common. However, we found that approximately 83% of our cases had unilateral ON[24-26]. Various studies reported that visual acuity of children with ON recovers better compared to adult patients[24-26]. All the patients initially experienced reduced vision. Eight (50%) out of 16 patients evaluated for visual acuity had severe visual acuity of less than 0.5. However, during the follow-up period, the visual acuity of all patients, including those with MS, improved either fully or almost completely. We can interpret this high recovery rate in association with the low recurrence rates detected in our cases with isolated ON, scarce number of attacks of ON experienced by our cases with MS and failure to diagnose NMOS or

Table 2. Sociodemographic and clinical characteristics of pediatric patients diagnosed with optic neuritis

	n=18 (%)
Gender	
Female	10 (55.6)
Male	8 (44.4)
Age at onset (year)	13.8±2.35 (7-18)
Follow-up, months, mean ± SD (range)	11.2±12.12 (1-42)
Relative afferent pupillary defect	
Present	15 (83.3)
Absent	3 (16.7)
Painful eye movements	
Present	11 (61.1)
Absent	7 (38.9)
Unilateral/bilateral	15 (83.3)/3 (16.7)
Visual evoked potential	
Normal	3 (21.4)
Abnormal	11 (78.6)
Oligoclonal bands in cerebrospinal fluid samples	
Present	4 (57.1)
Absent	3 (42.9)
MOG IgG serum	
Positive	0 (0)
Negative	14 (100)
AQP4-IgG serum	
Positive	0 (0)
Negative	14 (100)
Relapse	
Yes	3 (37.5)
No	5 (62.5)

SD: Standard deviation, IgG: Immunoglobulin G, MOG: Myelin oligodendrocyte glycoprotein, AQP4: Aquaporin-4

Table 3. Presence of demyelinating lesions detected by various neuroimaging techniques in pediatric patients with optic neuritis

Neuroimaging techniques	Number (%)
Orbital MRI	
Present	9 (56.3)
Absent	7 (43.8)
Cranial MRI	
Present	8 (50)
Absent	5 (31.3)
Spinal MRI	
Present	3 (20)
Absent	12 (80)

MRI: Magnetic resonance imaging

anti-MOG-related diseases. Studies have found that ON has been reported as the presenting symptom in 25% of MS patients[27,28]. Also, it has been observed that 13-50% of children who experienced their first attacks of ON are diagnosed with MS during follow-up[21,29,30]. Furthermore, it has been reported that 38% of patients who presented with isolated ON were diagnosed with MS[13].

A multicentre study conducted in our country found that cranial MRI abnormalities increased the risk of development of MS in female patients with unilateral ON older than 10 years[31]. In our study, 5 of 7 MS patients received the diagnosis of MS during their first attack of ON. One patient was diagnosed with MS six months after the first attack of ON, and the other patient 14 months later. As a result, in our study, 38.9% of the patients who applied to the ON clinic received the final diagnosis of MS in compatible with the relevant literature data.

It has been reported that an OCB can be detected in neuroinflammatory conditions such as MS, paraneoplastic syndromes, NMO spectrum disorders, and infections such as herpesvirus encephalitis[32]. We revealed the presence of OCB type 2 in CSF samples of 6 out of 7 patients diagnosed with MS. It is important to monitor patients presenting to ON clinic with manifestations of the first attack of ON, as MS may be observed during follow-up of these patients.

According to Chang and Pineles[13] steroid treatment is usually effective in patients who develop MS, but it does not prevent its recurrence. For the treatment of acute ON, use of pulse steroids at daily doses of 20-30 mg/kg for 3-5 days is recommended, and oral steroids should be taken for 4-6 weeks as a maintenance therapy. All patients in our cohort received pulse methylprednisolone treatment to relieve their attacks, and 8 more patients received oral steroid maintenance therapy. In our series, all five MS patients experienced a complete response, and only two of them had a relapse during follow-up.

Study Limitations

This study has several important limitations. Firstly, the limited number of patients evaluated in a retrospectively designed study performed in a single centre a prevents generalisation of our findings. However, the fact that our study was conducted at a single centre increased the availability of healthy and homogenous data. Furthermore, in several cases, visual field examinations were not conducted after discharge, which restricted our ability to provide comments on this issue. Prospectively designed studies with a larger number of patients diagnosed with ON and longer follow-up periods will provide valuable information about the course of the disease and the final diagnosis.

CONCLUSION

It is crucial to consider ON as a possible diagnosis for pediatric patients who experience symptoms such as vision loss, pain with eye movements, and blurred vision. Medical professionals should closely monitor these patients. The initial appearance of ON can be an isolated event or a sign of a demyelinating disorder linked with MS, NMOS, or anti-MOG. It is crucial to understand that even if these disorders were not detected during the first diagnosis of ON, they could still be identified during follow-up.

Ethics

Ethics Committee Approval: This study was approved by the institutional Ethics Review Board of Manisa Celal Bayar University (approval number: 386, date: 23.01.2023).

Informed Consent: Retrospective study.

Author Contributions

Concept: S.A.O., M.P., Design: S.A.O., Ç.Ç.K., Data Collection or Processing: S.A.O., Analysis or Interpretation: S.A.O., Ç.Ç.K., A.K.A., M.P., Literature Search: S.A.O., H.K., Writing: S.A.O., Ç.Ç.K., H.K.

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REFERENCES

1. Banwell B, Kennedy J, Sadovnick D, Arnold DL, Magalhaes S, Wambera K, et al. Incidence of acquired demyelination of the CNS in Canadian children. Neurology. 2009;72(3):232-9. doi: 10.1212/01.wnl.0000339482.84392.bd.
2. Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL. Bradley's neurology in clinical practice e-book. Elsevier Health Sciences. (2015).
3. Yeh EA, Graves JS, Benson LA, Wassmer E, Waldman A. Pediatric optic neuritis. Neurology. 2016;87(9 Suppl 2):S53-8. doi: 10.1212/WNL.0000000000002822.
4. Gaier ED, Boudreault K, Rizzo JF 3rd, Falardeau J, Cestari DM. Atypical Optic Neuritis. Curr Neurol Neurosci Rep. 2015;15(12):76. doi: 10.1007/s11910-015-0598-1.
5. Weerasinghe D, Lueck C. Mimics and chameleons of optic neuritis. Pract Neurol. 2016;16(2):96-110. doi: 10.1136/practneurol-2015-001254.

6. Biousse V, Newman N J. Diagnosis and clinical features of common optic neuropathies. The Lancet. Neurology. 2016;15(13):1355-67. doi: 10.1016/S1474-4422(16)30237-X.
7. Pérez-Cambrodí RJ, Gómez-Hurtado Cubillana A, Merino-Suárez ML, Piñero-Llorens DP, Laria-Ochaita C. Optic neuritis in pediatric population: a review in current tendencies of diagnosis and management. J Optom. 2014;7(3):125-30. doi: 10.1016/j.optom.2013.12.008.
8. Bojić L, Ivanisević M, Sinićić A, Lesin M, Rogosić V, Mandić Z, et al. The incidence of optic neuritis in Split-Dalmatia county, Croatia. Coll Antropol. 2004;28(1):343-7.
9. El-Dairi MA, Ghasia F, Bhatti MT. Pediatric optic neuritis. Int Ophthalmol Clin. 2012;52(3):29-49, xii. doi: 10.1097/IIO.0b013e318259dec6.
10. Borchert M, Liu GT, Pineles S, Waldman AT. Pediatric Optic Neuritis: What Is New. J Neuroophthalmol. 2017;37 (Suppl 1):S14-S22. doi: 10.1097/WNO.0000000000000551.
11. Arzani M, Sahraian MA, Rezaei H, Moghadasi AN. Recurrent isolated optic neuritis: A study on 22 patients. Iran J Neurol. 2017;16(3):130-5.
12. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-73. doi: 10.1016/S1474-4422(17)30470-2.
13. Chang MY, Pineles SL. Pediatric Optic Neuritis. Semin Pediatr Neurol. 2017;24(2):122-8. doi: 10.1016/j.spen.2017.04.004.
14. Du Y, Li JJ, Zhang YJ, Li K, He JF. Risk factors for idiopathic optic neuritis recurrence. PLoS One. 2014;9(9):e108580. doi: 10.1371/journal.pone.0108580.
15. Kurne A, Karabudak R, Yalcin-Cakmakli G, Gursoy-Ozdemir Y, Aydin P, Ilksen-Colpak A, et al. Recurrent optic neuritis: clues from a long-term follow up study of recurrent and bilateral optic neuritis patients. Eye Brain. 2010;2:15-20. doi: 10.2147/eb.s8888.
16. Absoud M, Cummins C, Desai N, Gika A, McSweeney N, Munot P, et al. Childhood optic neuritis clinical features and outcome. Arch Dis Child. 2011;96(9):860-2. doi: 10.1136/adc.2009.175422.
17. Boomer JA, Siatkowski RM. Optic neuritis in adults and children. Semin Ophthalmol. 2003;18(4):174-80. doi: 10.1080/08820530390895172.
18. Morales DS, Siatkowski RM, Howard CW, Warman R. Optic neuritis in children. J Pediatr Ophthalmol Strabismus. 2000;37(5):254-9.
19. Lana-Peixoto MA, Andrade GC. The clinical profile of childhood optic neuritis. Arq Neuropsiquiatr. 2001;59(2-B):311-7. doi: 10.1590/s0004-282x2001000300001.
20. Cakmakli G, Kurne A, Güven A, Serdaroğlu A, Topaloğlu H, Teber S, et al. Childhood optic neuritis: the pediatric neurologist's perspective. Eur J Paediatr Neurol. 2009;13(5):452-7. doi: 10.1016/j.ejpn.2008.09.003.
21. The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. Optic Neuritis Study Group. Arch Ophthalmol. 1991;109(12):1673-8. doi: 10.1001/archopht.1991.01080120057025.
22. Alper G, Wang L. Demyelinating optic neuritis in children. J Child Neurol. 2009;24(1):45-8. doi: 10.1177/0883073808321052.
23. Wilejto M, Shroff M, Buncic JR, Kennedy J, Goia C, Banwell B. The clinical features, MRI findings, and outcome of optic neuritis in children. Neurology. 2006;67(2):258-62. doi: 10.1212/01.wnl.0000224757.69746.fb.
24. Morales DS, Siatkowski RM, Howard CW, Warman R. Optic neuritis in children. J Pediatr Ophthalmol Strabismus. 2000;37(5):254-9.
25. Cassidy L, Taylor D. Pediatric optic neuritis. J AAPOS. 1999;3(2):68-9. doi: 10.1016/s1091-8531(99)70072-8.
26. Sun MH, Wang HS, Chen KJ, Su WW, Hsueh PY, Lin KK, Kao LY. Clinical characteristics of optic neuritis in Taiwanese children. Eye (Lond). 2011;25(11):1457-64. doi: 10.1038/eye.2011.196.
27. Pau D, Al Zubidi N, Yalamanchili S, Plant GT, Lee AG. Optic neuritis. Eye (Lond). 2011;25(7):833-42. doi: 10.1038/eye.2011.81.
28. Hintzen RQ, Dale RC, Neuteboom RF, Mar S, Banwell B. Pediatric acquired CNS demyelinating syndromes: Features associated with multiple sclerosis. Neurology. 2016;87(9 Suppl 2):S67-73. doi: 10.1212/WNL.0000000000002881.
29. Heussinger N, Kontopantelis E, Gburek-Augustat J, Jenke A, Vollrath G, Korinthenberg R, et al. for GRACE-MS (German-speaking Research Alliance for ChildrEn with Multiple Sclerosis). Oligoclonal bands predict multiple sclerosis in children with optic neuritis. Ann Neurol. 2015;77(6):1076-82. doi: 10.1002/ana.24409.
30. Optic Neuritis Study Group. The 5-year risk of MS after optic neuritis. Experience of the optic neuritis treatment trial. Neurology. 1997;49(5):1404-13. doi: 10.1212/wnl.49.5.1404.
31. Direk MÇ, Besen Ş, Öncel İ, Günbey C, Özdoğan O, Orgun LT, et al. Optic neuritis in Turkish children and adolescents: A multicenter retrospective study. Mult Scler Relat Disord. 2024;81:105149. doi: 10.1016/j.msard.2023.105149.
32. Juryńczyk M, Craner M, Palace J. Overlapping CNS inflammatory diseases: differentiating features of NMO and MS. J Neurol Neurosurg Psychiatry. 2015;86(1):20-5. doi: 10.1136/jnnp-2014-308984.

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Original Article

Prevalence and Risk Factors of Iron Deficiency Anemia in Children with Atopic Dermatitis

Atopik Dermatitli Çocuklarda Demir Eksikliği Anemisi Sıklığı ve Risk Faktörleri

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ABSTRACT

Objective: Refraining from intake of allergic foods, chronic inflammation and immunosuppressive drug use are factors associated with anemia in atopic dermatitis (AD). In this study, we aimed to investigate the frequency of iron deficiency anemia (IDA) and comorbid risk factors affecting this frequency in children with AD.

Method: The medical records of 100 children aged 0-6 years with AD (patient group) and 100 healthy children of the same age group without AD (control group) were treated in Sivas Numune State Hospital from May 2019 to October 2019 were retrospectively analyzed.

Results: In our study, the frequency of AD in children with AD (15%) was significantly higher than in healthy children (5%) (p<0.001). Early-onset AD, increased SCORAD severity index scores, concomitant food sensitivities, especially multiple food sensitivities, asthma, skin infection, breastfeeding for more than 6 months and presence of multiple atopic conditions were associated with a higher frequency of AD in children with AD. However, hay fever, family history of atopy, exposure to cigarette smoke, large family size, consanguinity and parental socioeconomic status were not significantly associated with a higher prevalence of AD in children with AD.

Conclusion: The prevalence of AD was significantly higher in children with AD compared to healthy children. Therefore, improving clinicians' self awareness of screening and monitoring for AD in children with AD is essential to minimize the burden of AD disease. More comprehensive further studies are needed to investigate the link between IDA and AD and relevant influencing factors

Keywords: Atopic dermatitis, anemia, iron deficiency, children, risk factors

ÖZ

Amaç: Alerjik gıdalardan kaçınma, kronik enflamasyon ve immünsüpresif ilaç kullanımı atopik dermatitte (AD) anemi ile ilişkili faktörlerdir. Bu çalışmada AD'li çocuklarda demir eksikliği anemisi (DEA) sıklığını ve bu sıklığa etki eden komorbid risk faktörlerini araştırmayı amaçladık.

Yöntem: Mayıs 2019'dan Ekim 2019'a kadar Sivas Numune Devlet Hastanesi'nde 0-6 yaş arası AD'li 100 çocuk (hasta grubu) ve aynı yaş grubunda AD'si olmayan 100 sağlıklı çocuğun (kontrol grubu) tıbbi kayıtları geriye dönük olarak analiz edildi.

Bulgular: Çalışmamızda AD'li çocuklarda DEA sıklığı (%15), sağlıklı çocuklara (%5) göre anlamlı olarak yüksekti (p<0,001). AD'nin erken başlangıcı, artmış SCORAD şiddeti, eşlik eden gıda duyarlılığı, özellikle çoklu gıda duyarlılığı, astım, deri enfeksiyonu, 6 aydan uzun süre emzirme ve çoklu atopik hastalık tanısı, AD'li çocuklarda daha yüksek DEA sıklığı ile ilişkilendirildi. Oysa saman nezlesi, ailede atopi öyküsü, sigara dumanına maruz kalma, geniş aile büyüklüğü, akrabalık ve ebeveynlerin sosyoekonomik düzeyi, AD'li çocuklarda daha yüksek DEA sıklığı ile anlamlı bir şekilde bağlantılı değildi.

Sonuç: AD'li çocuklarda DEA prevalansı sağlıklı çocuklara göre anlamlı olarak yüksek bulundu. Bu nedenle, AD'li çocuklarda DEA için tarama ve izleme konusunda klinisyen farkındalığının artırılması, AD hastalık yükünün en aza indirilmesi için esastır. Gelecekte bu ilişkiyi ve etkileyen faktörleri araştırmak için daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Atopik dermatit, anemi, demir eksikliği, çocuklar, risk faktörleri

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INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin conditions with increasing incidence rates in childhood. AD worsens the quality of life for both the parent and child due to allergic (food allergy, asthma, allergic rhinitis etc) and non-allergic comorbidities such as skin infections, mental health disorders, and obesity. It may be possible to improve patient outcomes and lessen the costs and burdens related to these conditions by better understanding these non-allergic comorbidities[1,2]. However, there is very little information about the links between AD and non-allergic conditions.

Iron deficiency anemia (IDA) is the most typical cause of childhood anemia and estimated to affect 20% to 25% of all preschool children worldwide, and up to 45% of children under the age of five in Turkey[3,4]. As a result, IDA is a common and important health issue affecting children under the age of five, particularly in our country.

The relationship between allergic conditions and anemia has attracted more attention in recent years. and surprisingly a strong association between anemia and allergic diseases has been detected in patients even after making adjustments for patient's confounding factors such as sex, prematurity, and obesity[5-9]. Epidemiological studies in the US[5] and Korea[6-10] have shown that children with atopic conditions, including AD,[9] wheezing, and allergic rhinitis/conjunctivitis, are up to 8 times more likely to be anemic than those without allergies. Chronic inflammation and the use of immunosuppressive drugs, in addition to food restriction, were identified as contributing factors to increased risk of anemia. Furthermore, epidemiological studies have shown a link between allergy and low iron status, suggesting that immune activation under iron-deficient conditions results in the expansion of Th2-cells rather than Th1 cells, so as to pave the way for allergic sensitization[9,11]. Therefore, we carried out a comparative case-control study among young children aged 0-6 years, to evaluate the incidence of IDA in children with and without AD in Sivas.

MATERIALS and METHODS

This case-control study included 200 pediatric patients aged 0-6 years who applied to Sivas Numune Hospital between May 1 and October 1, 2019. Our patient population included 100 children diagnosed with AD, and the control group consisted of 100 healthy children without any allergic disease. Power analysis was performed and the number of 100 cases each for the control and study groups was found to be sufficient. Retrospective analysis of the medical records, anamneses, and the results of physical exams of all pediatric patients was performed. Age, gender, socioeconomic status, personal and family histories of allergic diseases, and environmental risk factors like smoking exposure and large family sizes (more than five people living in one household) were noted. Results of the skin prick and serum-specific IgE tests were analyzed for the detection of individual sensitization patterns. The accompanying non-allergic (obesity, skin infections, etc.) and allergic (allergic rhinitis, asthma, food allergies, etc.) comorbid diseases were noted. The patients were grouped according to their age during the survey as follows: 0-2 years (infant) and 3-5 years (preschooler). The frequencies of IDA and risk factors associated with AD were analyzed and compared between the patient and the control groups.

Definition and classification of AD: The diagnostic criteria for AD proposed by Hanifin and Rajka[12] were used. Severity of AD was categorized as mild to moderate, and severe using the SCORAD (SCOring AD) index[13].

Definition and classification of IDA: Laboratory tests for hemoglobin, mean corpuscular volume, ferritin, red cell distribution width, and transferrin saturation were performed using venous blood samples. The World Health Organization guidelines were used to define and categorize IDA[14]. In IDA, erythrocyte counts, hemoglobin, hematocrit, mean erythrocyte volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, serum ferritin and iron levels decrease, while red blood cell distribution width, and levels of free erythrocyte protoporphyrin and serum soluble transferrin receptor increase[14].

Exclusion criteria: We did not include children with C-reactive protein levels above 5 mg/dL so as to eliminate active inflammation or bacterial infection in our study. Patients with congenital anomalies, syndromic patients with metabolic and genetic disorders, premature babies born at ≤35 weeks of gestation, low birth weight (LBW) babies, cases with obesity, parasitic infections, history of intensive care unit and/or hospital stay due to a recent serious infection, immunosuppressive therapy, hereditary or acquired disorders affecting hemoglobin synthesis, malnutrition, infants breastfed for less than 4 months, patients with neuromotor retardation, and other comorbid chronic diseases (kidney, cyanotic heart and lung diseases, cancer, immunodeficiency, and chronic

bowel diseases) were excluded from the study. A birth weight of <2.5 kg was considered to be LBW. Patients who had recently received iron therapy and blood transfusions as well as those who did not regularly take medications for iron prophylaxis, and those born from anemic mother were also excluded.

Statistical Analysis

The statistical analyses were performed by using IBM SPSS 22.0 statistical software package (SPSS, Inc., Chicago, IL, USA). A descriptive analysis was performed to examine the demographic features of the study population. The mean, median, standard deviation, or percentile (%) results were used to define variables including sex, age, presence of atopic diseases, use of inhalant allergens, etc. The Kruskal-Wallis or Pearson chi-square test -whichever is appropriate- was used to compare patient groups. The p-value <0.05 was regarded as the level of statistical significance. Power analysis was performed to determine the sample size.

RESULTS

Population Characteristics

The study population consisted mainly of female infants in the patient (n=104; 52%), and the control (n=96; 48%) groups with female/male ratios of 53/47, and 51/49, respectively. Median ages of the patient, and the control groups were 2.94, and 3.01 years, respectively. Children under the age of two made up the majority of cases in both the patient (62% of them) and the control (61%) groups. Any statistically significant difference was not noted between both groups in terms of demographic characteristics including gender, age, and age range at the time of study, socioeconomic status of the families, breastfeeding more than 6 months, family size, exposure to smoke and consanguinity. However, a significantly higher frequency of familial atopy was observed in the patient group (Table 1).

Comorbidities of Children with Atopic Dermatitis

According to the SCORAD scoring of severity of AD, our patients had severe (n=42; 42%), moderate (n=30; 30%), and mild (n=28; 28%) AD. The most frequent allergic comorbidities in all patients with AD were food allergy (26%), allergic rhinitis (15%), followed by asthma (7%), and urticaria (5%). Sleep disturbance (31%), IDA (15%), skin infections (5%), and immunodeficiency (2%) were the most prevalent non-allergic comorbidities (Figure 1).

Association Between Iron Deficiency Anemia and Atopic Dermatitis

The frequency of IDA was statistically higher in the group of patients with AD (15%) compared to those without (5%) (p<0.001) (Figure 2). Mean serum hemoglobin levels in the patient and control groups were 10.9 g/dL vs. 12.5 g/dL between the ages of 0-2, and 12.3 g/dL vs 13.2 g/dL between the ages of 3-5 years, respectively. In both the patient and the control groups, the frequency of IDA in children aged 0-2 years was noticeably higher than that in children aged 3-5 years. When all of the study population was considered, the mean serum hemoglobin values of the patient, and the control groups were 11.4 g/dL, and 12.8 g/dL, respectively (Table 2).

Table 1. Demographic characteristics of the study participants with (patient group) and without (control group) atopic dermatitis

Characteristics of patients	Patient group (n=100)	Control group (n=100)	p-value
Gender, female, n (%)	53 (53%)	51 (51%)	0.345
Median age during the study (year)	2.94	3.01	0.212
Age groups, n (%) 0-2 years 3-5 years	 62 (62%) 38 (38%)	 61 (61%) 39 (39%)	0.724
Low economic level, n (%)	32 (32%)	23 (23%)	0.855
Large family size, n (%),	38 (38%)	39 (39%)	0,895
Breastfeeding >6 month, n (%)	60 (60%)	64 (64%)	0.785
Exposure to smoke, n (%)	22 (22%)	32 (32%)	0.146
Family history of atopy, n (%)	49 (49%)	21 (21%)	0.025
Consanguinity, n (%)	13 (13%)	9 (9%)	0.456

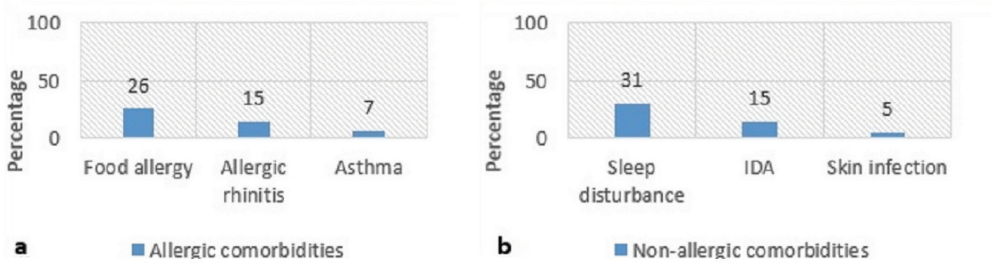

Figure 1. The three most common comorbidities of children with atopic dermatitis: a) allergic comorbidities, b) non allergic comorbidities

Iron Deficiency Anemia in Children with Atopic Dermatitis and Risk Factors

We also analysed the risk factors that may be related to the frequency of IDA in the children with AD. Gender, socioeconomic status, personal or family history of atopy, consanguinity, and large family size were not significant risk factors associated with the frequency of IDA in children with AD (the patient group) (Table 3). However, the frequency of IDA was found to be associated with the age of onset of symptoms before 2 years (early-onset AD), history of atopy except AD, having an increased SCORAD score, skin infections and breastfeeding more than 6 months (Table 3). While the median ages at the onset of AD in patients with and without IDA were 12, and 39.5 months respectively (Table 3).

There was no significant difference in terms of concomitant aeroallergen sensitization patterns between patients with AD and IDA (20.0%) and those without IDA (14.1%) (p=0.454). IDA, on the other hand, was strongly associated with food sensitization (53.3%, p=0.034) or multiple food allergen sensitization (26.7%, p=0.024). AD with and without IDA were compared in terms of concomitant allergic diseases (except AD). Patients with concomitant allergic diseases (80.0%, p<0.001), particularly asthmatics (26.7%, p<0.001) had significantly higher IDA rates. Although the patients with allergic rhinitis (20.0%) were more likely to have IDA when compared to patients without (14.1%), the correlation was not statistically significant (p=0.254). The frequency of IDA in patients with AD significantly increased with the increased number of accompanying atopic diseases (p=0.028) (Figure 3). Patients with one, and more than one atopic disease had IDA at frequencies of 26.7% and 53.3%, respectively (Figure 3).

DISCUSSION

Previous epidemiological studies have shown that people with allergic diseases are more likely to develop anemia[5-8,10,11]. In our study, children with AD had a statistically significantly higher risk of IDA compared to healthy children even after making adjustments for patient's confunding factors such as sex, prematurity, and obesity[5-8]. Our findings have shown that higher frequency of IDA in children with AD was found to be associated with non-allergic and allergic comorbid

Table 2. Distribution of Hb and IDA by age groups

Age groups	Hb g/dL (mean) ± SD	Hb g/dL min-max	Study participants with IDA n (%)
0-2 years			
Patient group	10.9±1.05	6.8-15	12 (19.3%)
Control group	12.5±1.04	7.7-17	4 (6.6%)
3-5 years			
Patient group	12.3±1.14	6.9-17	3 (7.9%)
Control group	13.2±1.02	7-18	1 (2.6%)
Total			
Patient group	11.4±1.08	6.8-17	15 (15%)
Control group	12.8±1.03	7.7-18	5 (5%)

IDA: Iron deficiency anemia, Hb: Hemoglobin, SD: Standard deviation, min-max: Minimum-maximum

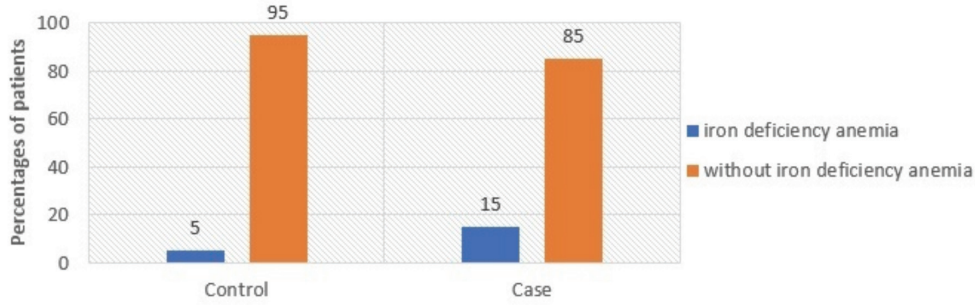

Figure 2. Distribution of iron deficiency anemia in children in the patient and control groups

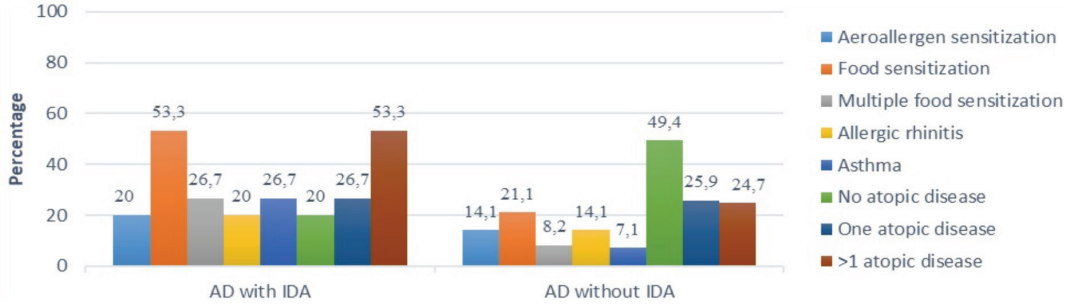

Figure 3. Association between allergic comorbidities and IDA in children with atopic dermatitis

IDA: Iron deficiency anemia

Table 3. The risk factors associated with IDA in the patients with AD

Risk factors (patient group)	AD with IDA (n=15, 100%)	AD without IDA (n=85, 100%)	p-value
Female, n (%)	8 (53.3)	45 (52.9)	0.384
Age at onset of AD, median, month (25-75 percentil)	12 (2-41)	39.5 (13.7-72)	
Early- onset AD (<2 years)	12 (80.0)	40 (47.4)	0.024
Low economic level (household income)	8 (53.3)	48 (57.6)	0.392
Education level	8 (53.3)	47 (55.3)	0.495
Large family size	5 (33.3%)	33 (38.8%)	0.358
History of atopy (except AD)	12 (80.0)	43 (50.6)	0.028
Family history of atopy	7 (46.6)	42 (49.4)	0.457
Consanguinity	6 (40.0)	28 (32.9)	0.212
Severe AD	12 (80.0)	30 (35.3)	<0.001
Skin infection	10 (66.6)	21 (24.7)	<0.001
Breastfeeding >6 months	12 (80.0)	48 (57.6)	0.036

IDA: Iron deficiency anemia, AD: Atopic dermatitis

diseases such as skin infections, asthma, food allergies with multiple food sensitization patterns, a relatively higher SCORAD score, early onset (<2 years) AD and breastfeeding for more than six months. Furthermore, we have observed that frequency of IDA increases significantly in children with AD who received diagnoses of multiple atopic diseases (allergic rhinitis, asthma, and dertmatitis etc.) as stated in previous studies[5-8]. Since AD and IDA are two of the most common medical problems affecting children under the age of five, particularly in developing countries, our findings may contribute to better understanding of the connection between these two disorders in the pediatric population of Turkey.

The underlying mechanism of AD is multidimensional and includes intricate interactions among genetic disorders, epidermal barrier deficiencies, altered immune responses, and microbiome changes. Throughout its natural course, the disease exhibits a high degree of heterogeneity, and individual trajectories are unpredictable, with a wide range of comorbid allergic and non-allergic health disorders[15-17]. IDA, on the other hand, is prevalent in both industrialized and developing nations, affecting up to 45% of children under the age of five in Turkey[4,18-20].

Despite growing interest in the relationship between anemia and atopic diseases in recent years, limited number of publications are available on this issue[5-10]. Children with atopic diseases, including AD, food allergies, allergic rhinitis, asthma are more likely to develop IDA, according to studies conducted in Japan by Yang et al.,[6] in South Korea by Rhew et al.[7,8] and in Qatar by Bener et al.[21] In line with these pediatric studies, the above-mentioned South Korean study group found a similar link between atopic diseases and IDA in the general population[7]. Furthermore, When Chang et al.[10] compared the prevalence of anemia in children with controlled asthma, they discovered that patients with uncontrolled asthma were more likely to experience anemia. The results of the present study are consistent with previously published data, revealing that IDA is more common in children with AD than in healthy children without any comorbid allergic diseases. In a 2014 study performed in Sivas, the incidence rates of IDA were 8.1%, and 3.4% in children aged 1-3 and 4-6 years, respectively[20]. According to the results of our study, the frequencies of IDA in the healthy group, and the group with AD were 6.6% vs. 19.3%, and 2.6% vs. 7.9% in the age groups of 0-2, and 3-5 years, respectively. Overall, the prevalence of IDA was statistically significantly higher in patients with AD (15%) than in control subjects without AD (5%). In line with earlier studies, our findings have also indicated that children who had more than one atopic disease had an increased frequency of IDA[5-7].

It is unclear exactly how allergic diseases increase the risk of IDA. As previously suggested in previous studies, chronic inflammation present in AD may be responsible for the increased risk of IDA in patients with allergic diseases[5-7]. Inflammatory mediators have been shown to prevent differentiation of erythrocyte, shorten half-life of erythroid cells, and suppress the response of erythropoietin to anemia leading to the development of anemia of inflammation (AI)[22]. Proinflammatory factors like ferroportin, IL-1, IL-6, and TNF-like cytokines are released as a result of the inflammatory nature of atopic diseases. These cytokines stimulate the production of hepcidin in liver, which in turn inhibits duodenal absorption, and release of iron. Ferroportin also inhibits the release of iron. Anemia is consequently caused as a result of a decrease in the iron availability required by erythroid progenitor cells[22]. Notably, both Drury et al.'s[5] and our study found that allergic rhinitis was not associated with anemia, whereas children with AD, asthma, and food allergies were more likely to develop IDA. Rhew et al.'s [7] research also showed the presence of a weaker but still statistically significant correlation between allergic rhinitis and anemia than that between other atopic diseases including asthma and AD. These findings suggest that there may be variations in the severity of inflammation in allergic diseases and systemic inflammation may exert varying effects on different atopic disease states. The increasing frequency of anemia, along with the number of allergic diseases and multiple food sensitivities, supports our theory that the inflammatory state of allergic diseases is linked to an increased risk of anemia. Additionally, the higher frequency of IDA in our study was also linked to the presence of early-onset AD, skin infection, and higher SCORAD index scores. These factors may have exacerbated the inflammatory effects of AD on outcomes and comorbidities. Skin infections that disrupt the skin barrier by lowering inflammatory threshold to haptens and irritants and activation of the innate immune system, which includes the production of inflammatory cytokines and chemokines[23]. Increased SCORAD index scores signifying severe AD were linked to increased levels of inflammatory cytokins such as IL-10, 1L-17, 1L-23[24]. As a result, the increased frequency of IDA in children with allergic comorbidities like asthma and food allergies, as well as skin infections and higher SCORAD scores and early-onset AD may be explained by the fact that these conditions enhance the impact of systemic inflammation in children with AD.

The use of systemic immunosuppressive drugs, malnutrition, obesity, and unbalanced food diet are the most frequently reported additional factors that may cause the IDA in children with AD[5,8]. Immunosuppressive medications like methotrexate, cyclosporine, or steroids were utilized as a treatment for patients with moderate to severe atopic disease. These medications may lead to hematologic disorders, anemia, or bleeding[25]. In our study, by excluding these confounding factors from our analysis, we have aimed to disregard obesity, and use of immunosuppressant drugs that can lead to anemia. In addition, children with food allergies who avoid suspected food products may suffer from a variety of nutrient deficiencies. According to studies that investigated nutritional consequences in food-allergic children, children with milk, soy, and wheat allergies were more likely to have insufficient intakes of zinc, vitamin B6 and iron[26]. In addition, the immune system may become activated due to a lack of micronutrients like iron, zinc, selenium, folate, and vitamins A, D, and C. This activation has the potential to exacerbate the situation, leading to anemia and chronic inflammation[27]. Additionally, some studies have indicated that allergies may, at a molecular level, result in iron deficiency[11]. In accordance with these studies, in our study, IDA was more frequently observed in children with AD who had food allergies, especially multiple food allergies. Therefore, nutritional interventions, such as patient or family education and developing a balanced diet, should be carefully planned to prevent unnecessary dietary restrictions.

After six months of life, breast milk is no longer sufficient to meet nutritional needs for energy and micronutrients (iron and zinc) because, five months after birth, the amount of nutrients in breast milk, including minerals, proteins, and vitamins, begins to decline. As a consequence, after four to six months of age, food intake should be initiated in combination with breastfeeding. Moreover, consuming a severely restricted range of meals or avoiding allergenic foods that are typically high in micronutrients can significantly decrease the micronutrient content of breast milk[28]. In accordance with the findings of these studies, breastfeeding for more than 6 months was linked to a greater frequency of IDA in children with AD in our study. Therefore, physicians should offer comprehensive dietary counseling to mothers breastfeeding their children with AD.

Study Limitations

There are a number of limitations concerning our study. We have not directly evaluated AI because of its similarities to IDA. Second, the use of a small sample size and lack of a large dataset drawn from national healthcare assertions prevented us from comprehensively determining the relationship between atopic disease and IDA. The amount of iron present in the foods consumed by patients can not be evaluated and analysed statistically. A strength of this study is that this is one of the first studies conducted on Turkish children regarding this topic and many confounding factors (obesity, LBW, prematurity, breastfeeding less than four months, etc.) that can influence the frequency of IDA were excluded in our study.

CONCLUSION

In our study, children with AD had a statistically significantly increased risk of IDA compared to healthy children. The presence of non-allergic and allergic comorbid diseases like skin infections, asthma, and food allergies with multiple food sensitization patterns as well as having increased SCORAD scores indicating a severe form of AD and breastfeeding for more than 6 months were found to be associated with higher frequency of IDA in children with AD. Consequently, we emphasized the importance of increasing clinicians' awareness and knowledge of IDA screening in children with AD in order to reduce disease burden, due to the elevated risk of adverse effects of IDA on development, growth, and quality of life.

Ethics

Ethics Committee Approval: The Ethics Committee of Cumhuriyet University in Sivas, Turkey, approved this study (approval number: 2019-10/36, date: 09.10.2019).

Informed Consent: All participants provided informed consent.

Author Contributions

Surgical and Medical Practices: M.S., Concept: M.S., Design: M.S., Data Collection or Processing: M.S., E.G.K., Analysis or Interpretation: M.S., E.G.K., Literature Search: M.S., E.G.K., Writing: M.S.

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REFERENCES

1. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood:

ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733-43. doi: 10.1016/S0140-6736(06)69283-0.

2. Paller A, Jaworski JC, Simpson EL, Boguniewicz M, Russell JJ, Block JK, et al. Major Comorbidities of Atopic Dermatitis: Beyond Allergic Disorders. Am J Clin Dermatol. 2018;19(6):821-38. doi: 10.1007/s40257-018-0383-4.
3. Gedfie S, Getawa S, Melku M. Prevalence and Associated Factors of Iron Deficiency and Iron Deficiency Anemia Among Under-5 Children: A Systematic Review and Meta-Analysis. Glob Pediatr Health. 2022;9:2333794X221110860. doi: 10.1177/2333794X221110860.
4. Yıldız İ. Iron deficiency anemia. Turk Arch Ped. 2009;44:14-8.
5. Drury KE, Schaeffer M, Silverberg JI. Association Between Atopic Disease and Anemia in US Children. JAMA Pediatr. 2016;170(1):29-34. d10.1001/jamapediatrics.2015.3065.
6. Yang L, Sato M, Saito-Abe M, Miyaji Y, Shimada M, Sato C, et al. Allergic Disorders and Risk of Anemia in Japanese Children: Findings from the Japan Environment and Children's Study. Nutrients. 2022;14(20):4335. d10.3390/nu14204335.
7. Rhew K, Brown JD, Oh JM. Atopic Disease and Anemia in Korean Patients: Cross-Sectional Study with Propensity Score Analysis. Int J Environ Res Public Health. 2020;17(6):1978. doi: 10.3390/ijerph17061978.
8. Rhew K, Choi J, Kim K, Choi KH, Lee SH, Park HW. Increased Risk of Anemia in Patients with Asthma. Clin Epidemiol. 2023;15:31-8. doi: 10.2147/CLEP.S394717.
9. Oh SY, Chung J, Kim MK, Kwon SO, Cho BH. Antioxidant nutrient intakes and corresponding biomarkers associated with the risk of atopic dermatitis in young children. Eur J Clin Nutr. 2010;64(3):245-52. doi: 10.1038/ejcn.2009.148.
10. Chang JE, Lee HM, Kim J, Rhew K. Prevalence of Anemia in Pediatric Patients According to Asthma Control: Propensity Score Analysis. J Asthma Allergy. 2021;14:743-51. doi: 10.2147/JAA.S318641.
11. Roth-Walter F, Pacios LF, Bianchini R, Jensen-Jarolim E. Linking iron-deficiency with allergy: role of molecular allergens and the microbiome. Metallomics. 2017;9(12):1676-92. doi: 10.1039/c7mt00241f.
12. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980;92:44–7.
13. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186(1):23-31. doi: 10.1159/000247298.
14. DeMaeyer EM, Dallman P, Gurney JM, Hallberg L, Sood SK, Srikantia SG, et al . Iron Deficiency Anaemia Assessment, Prevention, and Control A Guide for Programme Managers. World Health Organization; Geneva, Switzerland: 1989.
15. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet. 2020;396(10247):345-60. doi: 10.1016/S0140-6736(20)31286-1.
16. Silverberg JI. Comorbidities and the impact of atopic dermatitis. Ann Allergy Asthma Immunol. 2019;123(2):144-51. doi: 10.1016/j.anai.2019.04.020.
17. Laughter MR, Maymone MBC, Mashayekhi S, Arents BWM, Karimkhani C, Langan SM, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990-2017. Br J Dermatol. 2021;184(2):304-9. doi: 10.1111/bjd.19580.
18. Allali S, Brousse V, Sacri AS, Chalumeau M, de Montalembert M. Anemia in children: prevalence, causes, diagnostic work-up, and long-term consequences. Expert Rev Hematol. 2017;10(11):1023-8. doi: 10.1080/17474086.2017.1354696.
19. Özdemir N. Iron deficiency anemia from diagnosis to treatment in children. Turk Pediatri Ars. 2015;50(1):11-9. doi: 10.5152/tpa.2015.2337.
20. Karagün BŞ, Korkmaz Ö, Gürsu AH, Cevit Ö, Solmaz S, Bayram B, ve ark. Sivas İlinde Hastaneye Başvuran 1-15 Yaş Grubu Çocuklar Arasında Anemi Prevalansı. Güncel Pediatri. 2014;12(2):67-72. doi: 10.4274/jcp.55264.
21. Bener A, Ehlayel MS, Hamid Q. The impact of anemia and hemoglobin level as a risk factor for asthma and allergic diseases. Indian J Allergy Asthma Immunol. 2015;29:72-8. doi: 10.4103/0972-6691.178271.
22. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood. 2019;133(1):40-50. doi: 10.1182/blood-2018-06-856500.
23. Tsakok T, Woolf R, Smith CH, Weidinger S, Flohr C. Atopic dermatitis: the skin barrier and beyond. Br J Dermatol. 2019;180(3):464-74. doi: 10.1111/bjd.16934.
24. Celakovská J, Bukač J. The severity of atopic dermatitis evaluated with the SCORAD index and the occurrence of bronchial asthma and rhinitis, and the duration of atopic dermatitis. Allergy Rhinol (Providence). 2016;7(1):8-13. doi: 10.2500/ar.2016.7.0144.
25. Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014;4(5):e004587. doi: 10.1136/bmjopen-2013-004587.
26. Nowak S, Wang H, Schmidt B, Jarvinen KM. Vitamin D and iron status in children with food allergy. Ann Allergy Asthma Immunol. 2021;127(1):57-63. doi: 10.1016/j.anai.2021.02.027.
27. Peroni DG, Hufnagl K, Comberiati P, Roth-Walter F. Lack of iron, zinc, and vitamins as a contributor to the etiology of atopic diseases. Front Nutr. 2023;9:1032481. doi: 10.3389/fnut.2022.1032481.
28. Han Y, Lee Y, Park H, Park S, Song K. Nutrient intakes of infants with atopic dermatitis and relationship with feeding type. Nutr Res Pract. 2015;9(1):57-62. doi: 10.4162/nrp.2015.9.1.57.

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Original Article

Clinical and Laboratory Features of Culture-positive Neonatal Sepsis: A 5-year Single-center Experience at Tertiary Neonatal Intensive Care Unit in Turkey

Kültür Pozitif Neonatal Sepsisin Klinik ve Laboratuvar Özellikleri: Türkiye'de Üçüncü Düzey Bir Yenidoğan Yoğun Bakım Ünitesindeki 5 Yıllık Deneyim

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ABSTRACT

Objective: Neonatal sepsis is an important cause of neonatal mortality and morbidity, especially in low birth-weight premature babies. This study aimed to examine the clinical and laboratory features of cases with culture-positive neonatal sepsis.

Method: Medical records of 233 newborn infants with culture-positive sepsis among 4241 hospitalized patients between January 2013 and December 2017 were reviewed. Demographic and clinical data of these patients were retrospectively recorded.

Results: The majority of patients was extremely and moderately preterm infants (39.1% vs. 11.6%). These patients had a history of invasive mechanical ventilation (74.2%) or central catheterization (26.9%). The mostly isolated pathogens (56.2%) were Gram-negative bacteria, especially *Klebsiella pneumoniae* in 67 (28.8%) cases. Post-hoc test showed a statistically significant difference in the incidence rates of leukopenia between patients infected with Gram-positive, Gram-negative bacteria and fungi (12.3%, 16.8% and 17.2%, respectively) (p=0.021). Patients who developed leukopenia (n=36, 15.5%) had a higher mortality rate compared to those with leukocytosis (n=50, 21.5%) (72.2% vs. 50%, p<0.001). The duration of total parenteral nutrition was found to be a significant risk factor in terms of mortality (p=0.015).

Conclusion: Prolonged parenteral nutrition is an important risk factor for mortality in low-birth weight newborns and those with sepsis. It is noteworthy that the mortality rate is higher in newborns with sepsis who developed leukopenia and neutropenia.

Keywords: Newborn, microorganism, risk factors, sepsis, prognosis

ÖZ

Amaç: Neonatal sepsis yenidoğanda, özellikle de düşük doğum ağırlıklı prematüre bebeklerde önemli bir mortalite ve morbidite nedenidir. Bu çalışmada kültür pozitif neonatal sepsisli hastaların klinik ve laboratuvar özelliklerinin araştırılması amaçlandı.

Yöntem: Ocak 2013 ile Aralık 2017 tarihleri arasında hastanemizde yatan 4241 hasta arasında kültür pozitif sepsis tanısı alan 233 yenidoğan bebeğin tıbbi kayıtları incelendi. Bu hastaların demografik ve klinik verileri geriye dönük olarak kaydedildi.

Bulgular: Hastaların çoğunluğunu ileri derecede ve orta derecede prematüre bebekler oluşturmaktaydı (%39,1 vs. %11,6). Bunların %74,2'sinde invaziv mekanik ventilasyon, %26,9'unda santral kateterizasyon öyküsü vardı. En çok izole edilen patojenler (%56,2) Gram-negatif bakteriler, özellikle *Klebsiella pneumoniae* (n=67, %28,8) idi. Post-hoc analizi Gram-pozitif ve Gram-negatif bakteriler ile mantarlar arasında lökopeni yönünden istatistiksel olarak anlamlı bir fark olduğunu (sırasıyla %12,3, %16,8 ve %17,2) gösterdi (p=0,021). Lökopeni gelişen hastalarda (n=36, %15,5) ölüm oranı, lökositoz gelişen hastalara (n=50, %21,5) göre daha yüksekti (%72,2 vs. %50, p<0,001). Total parenteral beslenme süresinin mortalite açısından anlamlı risk faktörü olduğu belirlendi (p=0,015).

Sonuç: Uzun süreli parenteral beslenme, düşük doğum ağırlıklı ve septik yenidoğanlarda mortalite açısından önemli bir risk faktörüdür. Lökopeni ve nötropeni gelişen septik yenidoğanlarda ölüm oranının daha yüksek olması dikkat çekicidir.

Anahtar kelimeler: Yenidoğan, mikroorganizma, risk faktörleri, sepsis, prognoz

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INTRODUCTION

Neonatal sepsis is a clinical syndrome characterized by systemic symptoms and signs of infection in the first month of life, whether or not a specific microorganism was isolated in blood culture[1]. It has incidence rates ranging from 15/1000 to 49-170/1000, especially in very-low- birth-weight infants (VLBW) (<1500 g). Although perinatal and neonatal care has been improved thanks to recent medical and technological advances, many challenges still remain in the diagnosis and management of neonatal infections. Diagnosis of neonatal sepsis is difficult in some cases, particularly in preterm infants, because of the prevalence of sepsis-like non-infectious conditions and the lack of optimal diagnostic tests. These conditions will cause unnecessary use of both broad-spectrum antibiotics and prolonged treatment with empirical antibiotics which is associated with adverse outcomes and increase in antimicrobial resistance rates[2,3].

Neonatal sepsis is one of the leading causes of neonatal mortality and an important public health problem, especially in developing countries. According to the estimates made by the World Health Organization for 195 countries, neonatal bacterial infections cause the death of approximately 680,000 newborns, which corresponds nearly one quarter of all neonatal deaths[4]. Given the higher incidence and mortality rates of neonatal sepsis, especially in preterm infants, and its long-term consequences on growth and development, efforts to reduce infection rates in this vulnerable population appear to be one of the most important interventions in neonatal care. Therefore, in order to draw attention to the importance of neonatal sepsis, this retrospective study was conducted to examine the incidence, risk factors, clinical and laboratory features of culture-positive cases with neonatal sepsis that were referred to a tertiary neonatal intensive care unit (NICU) over four years, and the effects of clinical and laboratory parameters as well as the given treatments on mortality and morbidity.

MATERIALS and METHODS

Before starting the study, study approval was obtained from the Ethics Committee of Fırat University (decision no: 03, date: 19.01.2016). Among 241 newborns hospitalized in the Medical Faculty Hospital NICU of Fırat University between January 1, 2013 and December 31, 2017, 233, infants diagnosed with culture-positive sepsis were included in the study. Demographic data (gestational age, birth weight, gender, mode of delivery, Apgar scores), invasive procedures (tube thoracostomies, peripheral insertion of central venous catheters, umbilical catheterization and mechanical ventilation), and surgical procedures performed, length of hospitalization, duration of parenteral nutrition, laboratory test results [complete blood count, C-reactive protein, cerebrospinal fluid (CSF) analyzes, if any], reports of diagnostic imaging modalities (echocardiography, transfontanelle and abdominal ultrasonography, and cranial magnetic resonance imaging), complications and patient outcomes were evaluated retrospectively.

Patients with suspected sepsis were evaluated according to the "Töllner sepsis scoring system". Accordingly, <5 points were evaluated as "no suspected sepsis", 5-10 points as "suspected sepsis" and ≥10 points as "probable sepsis"[5]. Among the cases with "probable sepsis", the patients were considered to have "clinical sepsis" and "culture-positive sepsis" if a causative agent could not, and could be isolated in their blood cultures, respectively[6]. Isolation of coagulase-negative streptococci (CoNS) was accepted as contamination, except in cases of clinical sepsis characterized by symptoms of hyperthermia, hypothermia, apnea, or bradycardia and also excluding patients whose two or multiple blood cultures obtained during the same study period demonstrated growth of CoNS on separate occasions or patients with an intravascular line whose at least one blood culture revealed the presence of CoNS despite appropriate antibiotherapy, as well[7] .

According to the onset time of neonatal sepsis, early-onset neonatal sepsis (EOS) was defined as sepsis occurring at ≤72 h of life and late-onset sepsis (LOS) was defined as sepsis occurring 72 h after birth. In accordance with our treatment protocol of our unit, until the antibiogram results were obtained, empirical antibiotherapy was started with ampicillin + amikacin (or gentamicin) for patients with suspected EOS, while vancomycin + amikacin (or ceftazidime) was used as initial antibiotherapy for cases with suspected LOS[8].

Preterm birth refers to all deliveries occurring before $37^{0/7}$ gestational weeks; and extremely preterm (<28 weeks), very preterm ($28^{+0/7}$ -$31^{+6/7}$ weeks), moderately preterm ($32^{+0/7}$-$33^{+6/7}$ weeks), and late preterm births ($34^{+0/7}$-$36^{+6/7}$ weeks) are classified as preterm births. Term births refer to deliveries occurred between $37^{+0/7}$-$42^{+0/7}$ gestational weeks, and post-term births refer to any delivery occurring after $42^{+0/7}$ gestational weeks. According to the weight of a baby at birth, birth weights <1000 g was defined as extremely low birth-weight

(ELBW), 1000-1500 g as very low birth-weight (VLBW), 1500-2500 as low birth-weight (LBW), and >2500 g as normal birth-weight (NBW)[9,10].

Hemoglobin (Hb) levels lower than the normal range for birth weight and postnatal age were defined as "anemia"[11]. Platelet counts <150.000/mm^3, and >450.000/mm^3 were defined as thrombocytopenia "and thrombocytosis, respectively[12]. White blood cell (WBC) counts of 6.000-30.000/mm^3 in the first 24 hours of life and 5.000-20.000/mm^3 in the postnatal >3 days were considered to be within normal range[13]. Neutropenia was defined as an absolute neutrophil count (ANC) below 1.5×10^9/L (1500/mm^3)[14].

Bronchopulmonary dysplasia was defined as the condition where the oxygen requirement still continues at the postconceptional 36th week or during discharge in babies with a gestational age of <32 weeks, and between the postnatal 28-56th days in babies with a >32-week gestational age or at discharge[15]. Patients with suspected necrotizing enterocolitis were evaluated according to the Modified Bell staging[16]. In addition, patients were screened for retinopathy of prematurity at appropriate postconceptional weeks[17].

Prelabor rupture of the membranes (PROM) refers to rupture of the fetal membranes prior to the onset of regular uterine contractions. It may occur at term (≥37^{+0} gestational weeks) or preterm (<37^{+0} gestational weeks) (preterm PROM)[18].

Complete blood count analysis was performed with the ADVIA 2120i analyzer (Siemens AG, Erlangen, Germany). Approximately 0.5-1 mL of venous blood sample was inoculated into pediatric BACTEC culture media which was placed in the oven of the BACTEC 9240 hemoculture device (Becton Dickinson, USA). The samples were checked for bacterial growth every day. Antibiotic susceptibility tests were performed for the isolated microorganisms. The culture media kept in an oven for at least 7 days without any growth of pathogenic microorganism was considered to be culture negative. Micro-C-reactive protein (CRP) measurements were made using the QuikRead go® instant diagnostic system (Orion, Finland) installed in our unit.

Statistical Analysis

For data analysis, the 22.0 version of the SPSS for Windows; statistical software program was used. Data were shown as mean ± standard deviation for normally distributed data, and median (maximum and minimum) values for non-normally distributed continuous variables, while nominal variables were expressed as numbers (n), and percentages (%). Student's t-test was used to compare mean, and Mann-Whitney U test to compare median values, while for the comparison of percentage values chi-square test was employed. Non-parametric multiple comparison tests included in one-way analysis of variance (ANOVA) were used to determine the conditions that caused the difference between groups. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 4241 patients were hospitalized in the NICU of our hospital during the study period. Accordingly, the prevalence of blood culture-positive neonatal sepsis was calculated as 5.5 percent. The majority of the patients (67.8%) were low birth-weight babies. The mean birth-weight was 1999.72±905.41 g (range, 550 g-4200 g). According to the gestational age, the majority of the patients were extremely/very preterm and moderately preterm infants (39.1% vs. 11.6%). The mean gestational age of the patients was 33.13±4.67 weeks (range, 24-42 weeks).

The median 5th minute Apgar score was 8 in 171 patients whose data could be obtained from their medical records. There was no significant difference between EOS and LOS cases in terms of median Apgar scores. Respiratory distress syndrome (RDS) was present in 19 (22%) cases with EOS and 47 (31.9%) cases with LOS. The mean duration of total parenteral nutrition (TPN) was 15.3±14.63 days (range, 0-85 days). Cardiac pathology was detected on echocardiography in 76 (32.6%) patients. Main cardiac defects were patent ductus arteriosus (PDA) (n=51, 67.1%), ventricular septal defect (n=14, 18.4%), atrial septal defect (n=7, 9.2%) and atrioventricular septal defect (n=4, 5.3%). Medical PDA closure treatment was applied to 21 (41.2%) of those patients diagnosed with PDA. Demographic and clinical characteristics of the patients are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the patients

Gender	**n (%)**
Male	125 (53.6)
Female	108 (46.4)
Type of birth	**n (%)**
Cesarean section	172 (73.8)
NSVY	61 (26.2)
Gestational age	**n (%)**
Extremely/very preterm babies	91 (39.1)
Moderately preterm babies	27 (11.6)
Late preterm babies	39 (16.7)

Table 1. Continued	
Gestational age	**n (%)**
Early term babies	9 (3.9)
Full-term babies	66 (28.3)
Post-term babies	1 (0.4)
Birth weight	**n (%)**
Normal birth-weight babies	75 (32.2)
Low birth-weight babies	73 (31.3)
Very- low- birth-weight babies	50 (21.5)
Extremely low- birth-weight babies	35 (15)
Onset time of neonatal sepsis	**n (%)**
Early-onset neonatal sepsis	86 (36.9)
PROM	20/86 (23.3)
Late-onset neonatal sepsis	147 (63.1)
Respiratory distress syndrome	**n (%)**
Yes	66 (28.3)
Mechanical ventilation	**n (%)**
Invasive	173 (74.2)
Non-invasive	21 (9.1)
Thoracic tube insertion	**n (%)**
Yes	15 (6.4)
Surgical operation	**n (%)**
Yes	15 (6.4)
Central catheterization	**n (%)**
Yes	58 (24.9)
TPN	**n (%)**
Yes	211 (90.6)
Lumbar puncture	**n (%)**
Yes	27 (11.6)
Meningitis	6/27 (22.2)
Complications	**n (%)**
Hydrocephalus	17 (7.3)
ARF	12 (5.2)
Cholestasis	11 (4.7)
PVL	9 (3.9)
GMH	8 (3.4)
NEC	8 (3.4)
BPD	7 (3)
Outcomes	**n (%)**
Survival without sequelae	107 (45.9)
Death	102 (43.8)
Survival with sequelae	24 (10.3)

NSVY: Normal spontaneous vaginal delivery, PROM: Prelabor rupture of the membranes[18], ARF: Acute renal failure, PVL: Periventricular leukomalacia, GMH: Germinal matrix hemorrhage, BPD: Bronchopulmonary dysplasia, NEC: Necrotizing enterocolitis

The most common pathogens in blood culture were Gram-negative bacteria (n=131, 56.2%), Gram-positive bacteria (n=73, 31.3%), and fungi (n=29, 12.4%). The most common pathogens in both EOS and LOS cases were Gram-negative bacteria (61.6% vs. 53.1%). There was no statistically significant difference between the cases with EOS and LOS in terms of distribution of causative pathogens including Gram-positive bacteria and fungal strains (p=0.453). The most common pathogens in blood cultures of patients diagnosed with neonatal sepsis was *K. pneumoniae* (n=67, 28.8%). Causative pathogens isolated from blood cultures of the septic patients are given in Table 2. Of the patients with accompanying meningitis, 2 (33.3%) had EOS and 4 (66.6%) had LOS. There was no statistically significant difference between the cases with EOS and LOS in terms of accompanying meningitis (p=0.458). The most commonly isolated pathogen in CSF culture media was *K. pneumoniae* (50%). Similarly, *K. pneumoniae* was isolated most frequently (30%) in urine cultures, (30%), and 10 (4.3%) patients with positive urine cultures were considered to have urosepsis.

The mean total WBC count of the patients was 12.350±9.067/mm^3 (range, 600-57.790/mm^3). Gram-positive bacteria (12.3%), Gram-negative bacteria (16.8%) and fungi (17.2%) caused leukopenia in respective percentages of patients, and the post-hoc test revealed the presence of a statistically significant difference between them (p=0.021). Twenty-six (72.2%) out of 36

Table 2. Causative pathogens isolated from blood cultures		
Pathogens causing infection	**n**	**%**
Klebsiella pneumoniae	67	28.8
Acinetobacter baumannii	32	13.7
CoNS	31	13.3
Staphylococcus haemolyticus	24	10.3
Escherichia coli	18	7.7
Candida parapsilosis	16	6.9
Candida albicans	13	5.6
Serratia marcescens	11	4.7
Streptococcus pneumoniae	11	4.7
MRSA	5	2.1
Stenotrophomonas maltophilia	3	1.3
Pseudomonas aeruginosa	1	0.4
Proteus mirabilis	1	0.4
Total	233	100

CoNS: Coagulase-negative staphylococci, MRSA: Methicillin-resistant *S. aureus*

(15.5%) patients with leukopenia, and half of the patients with leukocytosis (n=50, 21.5%) died, with a statistically significant difference between groups regarding mortality rates (p=0.001).

The mean ANC was 5.620±6.758/mm^3 (range, 90-48.270/mm^3). Gram-positive bacteria (17.8%), Gram-negative bacteria (19.1%), and fungi (24.1%) caused neutropenia in indicated percentages of patients, without any statistically significant difference between them (p=0.762). *Stenotrophomonas maltophilia* was the leading (100%) cause of neutropenia among all pathogens. Twenty-five (60%) out of 45 (19.3%) patients with neutropenia died (p=0.024). Accordingly, 70.6% of the infants who died due to sepsis developed neutropenia (p=0.003).

The mean platelet count of the patients was 132.000±195.676/mm^3 (range, 6000-1.190.000 mm^3). Gram-positive (42.5%), Gram-negative bacteria (58%), and fungal agents (65.5%) caused thrombocytopenia in indicated percentages of patients without any statistically significant difference between them in this respect (p=0.094). Most frequently, fungal agents (65.5%) caused neonatal sepsis, and among them the leading pathogen was *Candida parapsilosis* in 87.5% of the cases. However, *Serratia marcescens* (90.9%) was the leading cause of thrombocytopenia among all pathogens. Accordingly, a statistically significant difference was detected between *Serratia marcescens* and other pathogens in this regard (p=0.01). The mean platelet counts of patients with sepsis due to *Serratia marcescens* was 56.860/mm^3. In addition, among Gram-positive bacteria, most frequently thrombocytopenia was found in cases infected with *Streptococcus pneumoniae* (50%).

The mean Hb value of the septic newborn was 11.4±3.35 g/dL (range, 5.4-22 g/dL), while in 188 (80.7%) patients priorly CRP-positivity was detected.

The mean age at diagnosis of sepsis was 17.24±16.4 days (range, 0-85 days). Most of the patients (n=210, 90.1%) had used antibiotherapy before the development of sepsis and while 23 (9.9%) patients had not. The mean duration of antibiotherapy during sepsis attack was 22.5±12.5 days (range, 1-65 days). The mean total hospital stay was 39.3±32.1 days. Any statistically significant difference was not detected between patients infected with Gram-positive, Gram-negative bacteria and fungi in terms of length of hospital stay (110.53, 118.06 and 128.48 days, respectively), (p=0.461).

Mortality rates among ELBW (n=24; 68.6%) VLBW (n=27; 54%), LBW (n=22; 30.1%), and NBW (n=29; 38.6%) infants were also estimated. Post-hoc tests showed a statistically significant difference between birth weights and mortality rates. Mortality rates were significantly higher in patients with ELBW and VLBW infants than in LBW and NBW infants (p=0.02).

Mortality rates according to gestational ages were 58.2% (n=53) in extremely/very preterm, 25.9% (n=7) in moderately preterm, 38.5% (n=15) in late preterm, 22.2% (n=2) in early term and 37.3% (n=25) in term infants. The impact of gestational age on mortality rates was not statistically significant (p=0.062). Similarly, there was no statistically significant difference in mortality rates between patients with and without RDS (p=0.32). In addition, average mortality rate was statistically significantly higher (n=13, 61.9%) in patients who underwent medical PDA closure (p=0.036).

The mortality rate was statistically significantly higher (70%) in patients who had central venous catheter (p=0.01). The total duration of TPN in patients who died due to sepsis (n=102) was 16.48±15.7 days (range, 0-85 days), while it was 14.38±13.7 days (range, 0-65) in survivors (n=131) (p=0.015).

Sixty (45.8%) patients with Gram-negative, 24 (32.9%) patients with Gram-positive, and 18 (62.1%) patients with fungal sepsis died (p=0.094). However, among pathogenic agents, *Candida parapsilosis* was associated with the highest mortality rate (68.8%). Congenital anomalies were detected in 25 (24.5%) of the deceased patients.

Cranial MR images obtained in 173 (74.2%) patients, were unremarkable only in 129 (74.6%) cases, while pathological findings were reported for the remaining 44 cases (Table 1). Since the data related to the hearing test results could not be found in the medical records, it was not possible to conclude how many patients developed hearing loss in total. Unfortunately, the hearing test (audiogram) results of all patients could not be obtained.

DISCUSSION

Neonatal sepsis continues to be an important cause of mortality and morbidity among newborn infants. High incidence rates ranging from 1-5/1000 to 49-170/1000 have been reported, especially among LBW infants[3]. Getabelew et al.[19] reported a very high prevalence (77.9%) of "probable sepsis" in Ethiopia. In Taiwan, which is a developing country, its prevalence was reported as 3-9.3% in previous years[20,21]. Hacımustafaoğlu et al.[22]

reported the prevalence of culture-positive nosocomial sepsis as 12% in Turkey. As can be seen, prevalence rates between countries, and NICUs are highly variable according to the development level of the countries. We speculate that the low prevalence rate of neonatal sepsis (5.5%) in our study is a result of good compliance of our patients with infection control measures.

Inverse relationships existed between gestational age, birth weight, mortality and morbidity. As the gestational age and birth weight decrease, the incidence of neonatal sepsis increases inversely. In their study, Harris and Goldman[23] reported the incidence rates of neonatal sepsis in VLBW (15-20%), and ELBW (40%) infants as indicated. Seo et al.[24] indicated the incidence rates of neonatal sepsis as 0.6% in full-term and 16.6% in premature babies born before 28th gestational week. Similarly, approximately two-thirds of the cases included in our study consisted of LBW, VLBW and ELBW infants. Likewise, approximately two-thirds of our cases were preterm infants. Among these, especially preterm VLBW and ELBW babies constituted the highest risk group. These infants are at risk for healthcare-associated infections due to their innate immunodeficiency, exposure to highly invasive procedures and prolonged hospitalizations[1,21,22,24].

EOS is a community-acquired infection transmitted mainly from the mother, while LOS mostly refers to healthcare-associated infections. In a study investigating the epidemiology of neonatal sepsis during the last 10 years in the UK, the prevalence rates of EOS and LOS were found to be 24% and 76%, respectively[25]. Getabelew et al.[19] reported that 65% of their cases in Ethiopia were EOS and 35% of them were LOS. In consistent with the results of the above-mentioned study performed in the UK, infants with EOS, and LOS comprised of 40%, and 60% of our study population, respectively.

Patients hospitalized in the NICU frequently undergo invasive procedures. Central venous catheterization, mechanical ventilation, TPN, and time to start first enteral feeding are independent risk factors for LOS in VLBW infants. In addition, other invasive procedures such as thoracic tube insertion and surgical interventions increase the risk of infection[26,27]. Kung et al.[28] reported that 78% of their cases with neonatal sepsis had undergone tracheal intubation and invasive mechanical ventilation. In addition, thoracic tube insertion, and surgical operations had been performed in approximately 6%, and 15 % of their cases, respectively.

In the study of Osman et al.[29] the most frequently isolated microorganism was CoNS (17.5%), followed by *S. aureus* (12.5%) and *K. pneumoniae* (10%). According to a study by Kara et al.[30] from Eastern Turkey, the mainly isolated pathogenic agents in neonatal sepsis were ConNS (46.1%), *K. pneumoniae* (21.2%), *E. coli* (9.6%), and *A. baumannii* (3.8%). In their study, de Benedetti et al.[31] reported commonly seen pathogens of neonatal sepsis as *K. pneumoniae* (47.5%), *P. aeroginosa* (20%), *E. coli* (10%) and *C. albicans* (10%). Similarly, in our study, approximately 1/3 of the isolated pathogens of neonatal sepsis were *K. pneumoniae*, followed by *A. baumannii* (13.7%) and CoNS (13.3%). Fungal infections were mainly caused by *C. parapsilosis* (6.9%) and *C. albicans* (5.6%). The high prevalence of *K. pneumoniae* in our study may be due to its colonization in the environment and *klebsiella pneumoniae* outbreaks seen in certain periods of time. The fact that CoNS was not the leading pathogen in our study may be due to the acceptance of some isolated pathogens as contaminants. CoNS is a commensal microorganism of the skin, and therefore its isolation in blood culture may reflect contamination if blood samples are obtained appropriately.

Abnormal WBC counts were observed in only 2/3 of the patients at the onset of neonatal sepsis, and in some series, this rate increased to 80-90%[32,33]. Wu et al.[21] reported leukocytosis or leukopenia in 27% of their cases with neonatal sepsis. In our study, leukopenia, and leukocytosis were detected in 15.5%, and 21.5% of the cases, respectively. Although the most common cause of leukopenia was fungal infections, it was determined that the specific agent was mostly streptococci. In the bone marrow, both leukopenia and thrombocytopenia can occur due to cessation of maturation and insufficient bone marrow supply of progenitors[34]. Hornik et al.[33] reported a high odds ratio (5.38%) and specificity rate (73.7%) together with a sensitivity rate (0.3-54.5%) for leukopenia in neonatal sepsis. These data show that WBC count has an important place in the diagnosis of sepsis, but it will not be sufficient diagnostic criterion on its own.

In addition to leukocytosis or leukopenia, low ANC and high I/T neutrophil ratios help to diagnose sepsis. Hornik et al.[33] reported high odds ratios (6.84-7.97), high specificity (99.9% and >99.8%), and low sensitivity rates (0.3-54.5%) for low ANS and high I/T neutrophil ratios. In the present study, there was a statistically insignificant difference between Gram-positive and Gram-negative bacteria and fungi in terms of causing neutropenia. Similar to cases with leukopenia, the most common

pathogens causing neutropenia were fungal strains and *S.maltophilia* was isolated in all cases of neutropenia (100%).

Thrombocytopenia is a non-specific finding that occurs late in neonatal sepsis. In a study by Lim et al.[35] in which they investigated the prevalence of neonatal sepsis and the distribution of pathogens in VLBW infants, they found thrombocytopenia at a rate of 50% in EOS and 47.3% in LOS; however, thrombocytopenia -though not statistically significant- was observed more frequently in fungal sepsis. Arif et al.[36] showed that thrombocytopenia was more severe in Gram-negative septicemia than in Gram-positive septicemia. In our study, although fungi, Gram-negative and Gram-positive microorganisms were causative pathogens in cases with thrombocytopenia without any statistically significant difference among them in terms of incidence rates. Among all pathogens, *S. marcessens* was the leading cause of thrombocytopenia in neonatal sepsis.

Long-term hospitalization of LBW premature babies in the NICU increases the risk of neonatal sepsis. In a study conducted in Spain, the average LOS of patients with nosocomial infections in the NICU was reported to be 30 days[37]. Hacımustafaoğlu et al.[22] reported that the mean length of stay in the NICU of patients diagnosed with nosocomial infection was 67 days. The mean duration of hospitalization of our patients was 39.3±32.1 days. Although the longest hospital stay was in sepsis caused by fungi followed by Gram-negative and Gram-positive bacteria, any statistical difference was not found among them in terms of LOS.

Parenteral nutrition is an important risk factor for the development of nosocomial infections. Sohn et al.[38] and Kawagoe et al.[39] reported that TPN increased the risk of neonatal sepsis by 5.7, and 4 times, respectively. In our study, a significant relationship was found between the duration of TPN and the development of sepsis, which is consistent with the literature. In addition, mortality rates were higher in patients with central catheters and on long-term TPN.

The mortality rates of neonatal sepsis generally range from 10-50%[40,41]. As a result of the 6-year analysis by Wu et al.[21], the mortality rates of EOS and LOS were 10% and 7%, while Martius et al.[42] a mortality rate of 10.5% for neonatal sepsis. Şahin and Şahin[43], reported that 7 (29%) of their 24 patients with neonatal sepsis died. However, the high mortality rate of 44% in our patients may be due to the inclusion of only culture-proven sepsis cases in this study and the fact that only cases with poor clinical condition were referred to our reference center hospital. In addition, multi-drug resistance may explain our high mortality rate compared to previous years.

Mortality and morbidity rates in LBW preterm infants are inversely proportional to gestational age and birth-weight[44]. About half of our patients were ELBW infants, and 60% of these infants died.

We have revealed statistically significant effect of birth-weight on mortality. Mortality rates in Gram-negative septicemia and fungal infections are higher compared to Gram-positive septicemia[45]. Similarly, sepsis caused by fungi, Gram-negative bacteria and Gram-positive bacteria, respectively, although not statistically significant, had the worst prognosis among our cases. In addition, patients with leukopenia and neutropenia had a worse prognosis compared to patients with leukocytosis.

Study Limitations

Limitations of our study were i) the prevalence of neonatal sepsis could not be estimated precisely because cases with clinical sepsis were not included in the study; ii) Some data concerning CRP levels, Apgar scores and blood gas analyzes of some patients could not be obtained from their medical records; iii) the prevalence of cases with meningitis could not be determined due to extremely low rates of lumbar puncture which could not be performed at an optimal frequency probably because of the hemodynamic instability of the patients and/or the severity of the prematurity not allowing the procedure; iv) since micro-CRP, one of the infection markers, is studied in our unit, patients are not routinely asked for PCT examination; v) Results of interleukin-6 assay were not available because this test is not routinely performed in our hospital.

CONCLUSION

In conclusion, neonatal sepsis is an important health problem of the newborn infants, which causes prolonged hospitalization, mortality and morbidity. The prevalence of culture-positive neonatal sepsis in NICU is 5.5%. Preterm birth and LBW are crucial risk factors for neonatal sepsis and mortality. *K. pneumoniae* is one of the leading pathogens causing neonatal sepsis. However, *C. parapsilosis* is the pathogen with the highest mortality in neonatal sepsis. Fungal strains and Gram-negative bacteria cause leukopenia more frequently. However, *S. marcescens* is the most common pathogen causing thrombocytopenia. Mortality rate is higher in septic neonates who develop leukopenia and neutropenia. Prolonged parenteral nutrition increases the risk of sepsis and mortality.

Ethics

Ethics Committee Approval: Study approval was obtained from the Ethics Committee of Fırat University (decision no: 03, date: 19.01.2016).

Informed Consent: Retrospective study.

Author Contributions

Surgical and Medical Practices: M.A., I.Ö., S.B., N.H., E.T., Concept: M.A., I.Ö., E.T., Design: M.A., I.Ö., E.T., Data Collection or Processing: M.A., I.Ö., A.O., Analysis or Interpretation: M.A., I.Ö., A.O., S.B., N.H., Literature Search: M.A., I.Ö., A.O., S.B., N.H., Writing: M.A., I.Ö., A.O., N.H.

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REFERENCES

1. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390(10104):1770-80. doi: 10.1016/S0140-6736(17)31002-4.
2. Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr. 2015;61(1):1-13. doi: 10.1093/tropej/fmu079.
3. Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. Virulence. 2014;5(1):170-8. doi: 10.4161/viru.26906.
4. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet. 2016;388(10063):3027-35. doi: 10.1016/S0140-6736(16)31593-8.
5. Töllner U. Early diagnosis of septicemia in the newborn. Clinical studies and sepsis score. Eur J Pediatr. 1982;138:331-7. doi: 10.1007/BF00442511.
6. Aydin M, Barut S, Akbulut HH, Ucar S, Orman A. Application of flow cytometry in the early diagnosis of neonatal sepsis. Ann Clin Lab Sci. 2017;47:184-90.
7. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16(3):128-40. doi: 10.1016/0196-6553(88)90053-3.
8. Satar M, Arısoy AE, Çelik İH. Turkish Neonatal Society guideline on neonatal infections-diagnosis and treatment. Turk Pediatri Ars. 2018;53(Suppl 1):S88-100. doi: 10.5152/TurkPediatriArs.2018.01809
9. Quinn JA, Munoz FM, Gonik B, Frau L, Cutland C, Mallett-Moore T, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine. 2016;34(49):6047-56. doi: 10.1016/j.vaccine.2016.03.045.
10. Hamilton BE, Martin JA, Osterman MJ. Births: Provisional Data for 2021. National Center for Health Statistics. National Vital Statistics System, Vital Statistics Rapid Release Program, no 20. Hyattsville, MD. National Center for Health Statistics. 2022.
11. Henry E, Christensen RD. Reference Intervals in Neonatal Hematology. Clin Perinatol. 2015;42(3):483-97. doi: 10.1016/j.clp.2015.04.005.
12. Patel RM, Josephson C. Neonatal and pediatric platelet transfusions: current concepts and controversies. Curr Opin Hematol. 2019;26(6):466-72. doi: 10.1097/MOH.0000000000000542.
13. Schelonka RL, Yoder BA, desJardins SE, Hall RB, Butler J. Peripheral leukocyte count and leukocyte indexes in healthy newborn term infants. J Pediatr. 1994;125(4):603-6. doi: 10.1016/s0022-3476(94)70018-4.
14. Newburger PE, Dale DC. Evaluation and management of patients with isolated neutropenia. Semin Hematol. 2013;50(3):198-206. doi: 10.1053/j.seminhematol.2013.06.010.
15. Hwang JS, Rehan VK. Recent Advances in Bronchopulmonary Dysplasia: Pathophysiology, Prevention, and Treatment. Lung. 2018;196(2):129-38. doi: 10.1007/s00408-018-0084-z.
16 Battersby C, Santhalingam T, Costeloe K, Modi N. Incidence of neonatal necrotising enterocolitis in high-income countries: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2018;103(2):F182-9. doi: 10.1136/archdischild-2017-313880.
17. Bancalari M A, Schade R. Retinopatía del prematuro: Actualización en detección y tratamiento [Retinopathy of the premature: Update in screening and treatment]. Rev Chil Pediatr. 2020;91(1):122-30. doi: 10.32641/rchped.v91i1.1079.
18. Hannah ME, Ohlsson A, Farine D, Hewson SA, Hodnett ED, Myhr TL, et al. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. TERMPROM Study Group. N Engl J Med. 1996;334(16):1005-10. doi: 10.1056/NEJM199604183341601.
19. Getabelew A, Aman M, Fantaye E, Yeheyis T. Prevalence of Neonatal Sepsis and Associated Factors among Neonates in Neonatal Intensive Care Unit at Selected Governmental Hospitals in Shashemene Town, Oromia Regional State, Ethiopia, 2017. Int J Pediatr. 2018;2018:7801272. doi: 10.1155/2018/7801272.
20. Jiang JH, Chiu NC, Huang FY, Kao HA, Hsu CH, Hung HY, et al. Neonatal sepsis in the neonatal intensive care unit: characteristics of early versus late onset. J Microbiol Immunol Infect. 2004;37(5):301-6.
21. Wu JH, Chen CY, Tsao PN, Hsieh WS, Chou HC. Neonatal sepsis: a 6-year analysis in a neonatal care unit in Taiwan. Pediatr Neonatol. 2009;50(3):88-95. doi: 10.1016/S1875-9572(09)60042-5.
22. Hacımustafaoğlu M, Çelebi S, Köksal N, Kavurt S, Özkan H, Çetinkaya M, et al. Nosocomial infections in neonatology clinic and neonatal intensive care unit. Turk Arch Ped. 2011;46:293-8. doi: 10.4274/jcp.36025.
23. Harris JS, Goldman DA. Infections acquired in the nursery; epidemiyoloji and control. In: Remington JS, Klein JO (Eds). Infectious Diseases of the Fetus and Newborn Infant. Philadelphia: WB Saunders 2001:1371-418.
24. Seo K, McGregor JA, French JI. Preterm birth is associated with increased risk of maternal and neonatal infection. Obstet Gynecol. 1992;79(1):75-80.
25. Cailes B, Kortsalioudaki C, Buttery J, Pattnayak S, Greenough A, Matthes J, et al. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. Arch Dis Child Fetal Neonatal Ed. 2018;103(6):F547-53. doi: 10.1136/archdischild-2017-313203.
26. Sundaralingam A, Bedawi EO, Harriss EK, Munavvar M, Rahman NM. The frequency, risk factors, and management of complications from pleural procedures. Chest. 2022;161:1407-25. doi: 10.1016/j.chest.2021.11.031.
27. García H, Torres-Gutiérrez J, Peregrino-Bejarano L, Cruz-Castañeda MA. Factores de riesgo asociados a infección nosocomial (IN) en

una Unidad de Cuidados Intensivos Neonatales (UCIN) de tercer nivel. Gac Med Mex. 2015;151:711-9.

28. Kung YH, Hsieh YF, Weng YH, Lien RI, Luo J, Wang Y, et al. Risk factors of late-onset neonatal sepsis in Taiwan: A matched case-control study. J Microbiol Immunol Infect. 2016;49(3):430-5. doi: 10.1016/j.jmii.2013.10.001.
29. Osman AS, Awadallah MG, Tabl HAEM, Abed NT, Goudah ESS. Presepsin as a novel diagnostic marker in neonatal septicemia. Egypt J Med Microbiol. 2015;24:21-6.
30. Kara H, Ertuğrul S, Gündoğuş N, Akpolat N, Özmen Ö. [An evaluation of patients with culture-proven sepsis in a neonatal intensive care unit]. Dicle Medical Journal. 2015;42:355-60. doi: 10.5798/diclemedj.0921.2015.03.0589.
31. de Benedetti F, Auriti C, D'Urbano LE, Ronchetti MP, Ravà L, Tozzi A, et al. Low serum levels of mannose binding lectin are a risk factor for neonatal sepsis. Pediatr Res. 2007;61:325-8. doi: 10.1203/pdr.0b013e318030d12f.
32. Benuck I, David RJ. Sensitivity of published neutrophil indexes in identifying newborn infants with sepsis. J Pediatr. 1983;103:961-3. doi: 10.1016/s0022-3476(83)80731-8.
33. Hornik CP, Benjamin DK, Becker KC, Benjamin DK Jr, Li J, Clark RH, et al. Use of the complete blood cell count in early-onset neonatal sepsis. Pediatr Infect Dis J. 2012;31:799-802. doi: 10.1097/INF.0b013e318256905c.
34. Belok SH, Bosch NA, Klings ES, Walkey AJ. Evaluation of leukopenia during sepsis as a marker of sepsis-defining organ dysfunction. PLoS One. 2021;16:e0252206. doi: 10.1371/journal.pone.0252206.
35. Lim WH, Lien R, Huang YC, Chiang MC, Fu RH, Chu SM, et al. Prevalence and pathogen distribution of neonatal sepsis among very-low-birth-weight infants. Pediatr Neonatol. 2012;53:228-34. doi: 10.1016/j.pedneo.2012.06.003.
36. Arif SH, Ahmad I, Ali SM, Khan HM. Thrombocytopenia and bacterial sepsis in neonates. Indian J Hematol Blood Transfus. 2012;28:147-51. doi: 10.1007/s12288-011-0118-7.
37. Mireya UA, Martí PO, Xavier KV, Cristina LO, Miguel MM, Magda CM. Nosocomial infections in paediatric and neonatal intensive care units. J Infect. 2007;54:212-20. doi: 10.1016/j.jinf.2006.03.023.
38. Sohn AH, Garrett DO, Sinkowitz-Cochran RL, Grohskopf LA, Levine GL, Stover BH, et al. Pediatric Prevention Network. Prevalence of nosocomial infections in neonatal intensive care unit patients: Results from the first national point-prevalence survey. J Pediatr. 2001;139:821-7. doi: 10.1067/mpd.2001.119442.
39. Kawagoe JY, Segre CA, Pereira CR, Cardoso MF, Silva CV, Fukushima JT. Risk factors for nosocomial infections in critically ill newborns: a 5-year prospective cohort study. Am J Infect Control. 2001;29:109-14. doi: 10.1067/mic.2001.114162.
40. Stoll BJ, Hansen NI, Higgins RD, Fanaroff AA, Duara S, Goldberg R, et al. National Institute of Child Health and Human Development. Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002-2003. Pediatr Infect Dis J. 2005;24(7):635-9. doi: 10.1097/01.inf.0000168749.82105.64.
41. Makhoul IR, Sujov P, Smolkin T, Lusky A, Reichman B; Israel Neonatal Network. Pathogen-specific early mortality in very low birth-weight infants with late-onset sepsis: a national survey. Clin Infect Dis. 2005;40:218-24. doi: 10.1086/426444.
42. Martius JA, Roos T, Gora B, Oehler MK, Schrod L, Papadopoulos T, et al. Risk factors associated with early-onset sepsis in premature infants. Eur J Obstet Gynecol Reprod Biol. 1999;85:151-8. doi: 10.1016/s0301-2115(99)00018-4.
43. Şahin Y, Şahin DA. [The role of interleukin-6 and C-reactive protein in the early diagnosis of neonatal sepsis]. Turk Pediatr Arş. 2004;39:171-7. doi: 10.1016/s0301-2115(99)00018-4.
44. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110(2 Pt 1):285-91. doi: 10.1542/peds.110.2.285.
45. Steinbach WJ, Roilides E, Berman D, Hoffman JA, Groll AH, Bin-Hussain I, et al. Results from a prospective, international, epidemiologic study of invasive candidiasis in children and neonates. Pediatr Infect Dis J. 2012;31(12):1252-7. doi: 10.1097/INF.0b013e3182737427.

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Case Report

A New Potential Threat for Nosocomial Infections: *Cupriavidus metallidurans* as a Cause of Bacteremia in Children

Nozokomiyal Enfeksiyonlarda Yeni Bir Olası Tehdit: Çocuklarda Bakteriyemi Sebebi Olarak Cupriavidus metallidurans

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ABSTRACT

Hospital infections associated with uncommon pathogens usually originated from environmental sources and are challenging for microbiologists and clinicians because of the difficulties in the differentiation of colonization vs infection. Increasing reports of bacteremia caused by environmental pathogens point out their importance in hospital infections. The increasing number of case reports of bacteremia due to *Cupriavidus* spp., impose to consider these unusual microorganisms which are aerobic Gram-negative rods that live in soil and water. In this report, we present two cases of bacteremia in which *Cupriavidus metallidurans* were isolated from blood cultures and discuss the roles of the isolates in hospital infection.

Keywords: *Cupriavidus metallidurans*, bacteremia, opportunistic premise plumbing pathogens, hospital infection

ÖZ

Enfeksiyon etkeni olarak sık rastlanmayan ancak klinik örneklerde çevresel kökenli mikroorganizmaların soyutlandığı hastane enfeksiyonlarında, saptanan mikroorganizmanın kolonizasyon mu yoksa enfeksiyon etkeni mi olduğu konusundaki ayrımın güçlüğü hem mikrobiyologlar hem de klinisyenler yönünden başa çıkılması zor bir durum yaratır. Bakteriyemi olgularında çevresel kökenli mikroorganizmalara ilişkin artan bildirimler bu etkenlerin hastane enfeksiyonlarındaki önemini ortaya koymaktadır. Giderek daha çok sayıda Bakteriyemi olgusunda *Cupriavidus* türlerinin soyutlanması, su ve toprakta bulunan bu Gram-negatif çomakların hastane enfeksiyonları yönünden dikkate alınması gerektiğini düşündürmektedir. Bu çalışmada iki olguda kan kültürlerinden soyutlanan *Cupriavidus metallidurans* kökenlerinin özellikleri ve hastane enfeksiyonundaki rolleri ele alınmaktadır.

Anahtar kelimeler: *Cupriavidus metallidurans*, bakteremi, yapı tesisat sistemi fırsatçı patojenleri, hastane enfeksiyonu

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INTRODUCTION

Hospital-acquired infections can be related to several factors associated with health care services in which the water system can be an important one of them. Increasing reports of outbreaks associated with hospital water environments impose to consider the unusual microorganisms isolated from the patients and the hospital environment[1]. *Cupriavidus* bacteria that are aerobic Gram-negative rods that live in soil and water. Even though invasive infections are uncommon in healthy people, case reports suggest that they could be significant in immunocompromised patients. Various cases of significant infections caused by different species of the genera have been recorded in the literature to date[2-6]. Besides reporting cases with *Cupriavidus metallidurans* isolated from blood culture samples

in two children, it was also intended to emphasize the importance of the assessment of the environmental bacterial isolates from blood in determining whether the isolate is a contaminant or a real pathogen.

CASE REPORTS

Case 1

The first case was a 3-year-old girl with graft-versus-host disease following her second allogeneic hematopoietic stem cell transplantation for acute lymphoblastic leukemia. She was transferred to the pediatric intensive care unit (PICU) because of septic shock symptoms and intubated due to increasing work of breathing and increased requirement for inotropes. On the third day of the PICU hospitalization, due to persistent hyperlactatemia, compromised renal functions, and decreased urine output, continuous venovenous hemodiafiltration was started. Due to refractory septic shock and respiratory insufficiency, the patient developed acute respiratory distress syndrome and died on the fifth day of his PICU stay. While no growth was found in the urine sample, *C. metallidurans* was isolated in blood culture. While the isolate grew initially under antimicrobial therapy with various antibiotics such as meropenem, amikacin, and voriconazole, no growth was identified in both blood cultures acquired from the venous catheter and recurrent peripheral blood cultures after the catheter was replaced.

Case 2

The second case was a previously healthy 11-year-old boy who had been diagnosed with coronavirus disease-2019 pneumonia. He was admitted to the hospital and given favipiravir and ceftriaxone therapy. *C. metallidurans* was isolated from a blood culture obtained after hospital admission. Because the patient was asymptomatic and the ceftriaxone treatment has not resulted in a recurrence of fever, the medication was not changed and the patient was continued in the same manner. On the fourth day of treatment, there was no growth in repetitive blood culture. On the seventh day of stay, the patient was discharged with full recovery, and isolation of the bacteria was recognized as contamination.

The blood samples were inoculated into the aerobic blood culture bottles and incubated by using an automated blood culture system (BD BACTEC FX, Becton Dickinson Company, USA) Gram-negative rods from the small, greyish colonies that grew on subcultures were identified as *Cupriavidus pauculus* with VITEK-2 compact system (bioMerieux, France) Consequently, both strains were identified as *Cupriavidus metallidurans* by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics GmbH, Leipzig, Germany).

Antimicrobial sensitivity testing was initially performed using the VITEK®2 Compact automated ID/AST System (bioMerieux, France), and interpreted using the EUCAST *Pseudomona*s breakpoints. In addition, broth microdilution assays were used to determine the minimal inhibitory concentrations (MICs) of the isolates using Sensititre™ Gram-negative DKMGN Plates (Thermo Fisher Scientific, Cleveland, USA) according to the manufacturer's instructions. Clinical and Laboratory Standards Institute 2021 breakpoints for additional non-enterobacterales[7] were used to interpret the antibiotics' MICs (Table 1).

DISCUSSION

Because of its resistance to heavy metals, ability to mediate the extracellular manufacture of antimicrobial nanoparticles, and vast genetic diversity derived from a large, mobile gene pool and megaplasmids, *C. metallidurans* has sparked attention in various sectors of microbiology. Endogenous megaplasmids are thought to have resistance qualities that help them survive even in harsh environments like space[8,9].

Langevin et al.[6] reported the first report of human infection caused by *C. metallidurans* that resulted in nosocomial septicemia in 2011. In 2015, four examples of the species were recorded in Italy, following the initial report[10]. All published cases of *C. metallidurans* infections had bloodstream infections and were most likely nosocomial in origin, just as in the first case.

In both cases, the bacterial growth was determined in the initial blood cultures. However, in the first case, the patient's clinical picture supported an infection, while in the second case, the clinical picture strongly suggested the contamination. Growth in a blood culture bottle does not always indicate the presence of a real pathogen, and distinguishing a contaminant from a bacteremia-causing agent might be difficult[11]. The earlier case reports' superiority is the isolation of germs from several blood culture bottles, which is improbable in our pediatric cases since blood culture sets including a single bottle were employed.

Although the initial growths were questioned due to the lack of growth in repetitive blood cultures or concomitant cultures from other body sites, the unusual

Table 1. Antimicrobial susceptibility testing of *Cupriavidus metallidurans* isolates

	***C. metallidurans* Strain 1**				***C. metallidurans* Strain 2**			
	VITEK®2		**Sensititre™**		**VITEK®2**		**Sensititre™**	
Antibiotics	**MIC_{50}**	**AST Result**	**MIC_{50}**	**AST Result**	**MIC_{50}**	**AST Result**	**MIC_{50}**	**AST Result**
Amikacin	≥64	R	≥32	R	≥64	R	≥32	R
Amoxicillin/clavulonic acid	N/A	-	4/2	N/A	N/A	-	4/2	N/A
Aztreonam	16	I	>32	R	16	I	>32	R
Cefotaxime	N/A	-	2	S	N/A		2	S
Cefepime	2	I	N/A	-	1	I	N/A	-
Ceftazidime	8	I	16	I	8	I	16	I
Ceftazidime/avibactam	N/A	-	8/4	N/A	N/A	-	8/4	-
Ceftolozane/tazobactam	N/A	-	16/4	N/A	N/A	-	16/4	-
Ciprofloksasin	0,25	I	0,5	S	0,25	I	0,25	S
Colistin	≥16	R	>8	N/A	≥16	R	>8	N/A
Ertapenem	N/A	-	2	N/A	N/A	-	2	N/A
Gentamicin	≥16	R	>8	R	≥16	R	>8	R
Imipenem	≤0,25	I	1	S	≤0,25	I	0.5	S
Levofloksasin	0,5	S	N/A	-	0,5	I	N/A	-
Meropenem	1	S	0.5	S	0,5	S	1	S
Netilmicin	≤32	R	N/A	-	≥32	R	N/A	-
Piperacillin/tazobactam	≤4	I	2/4	S	≤4	I	2/4	S
Tigecyline	N/A	-	1	N/A	-	N/A	0,5	N/A
Tobramycine	≥16	R	>8	R	≥16	R	>8	R
Trimethoprim/sulphamethoxazole	N/A	-	2/38	S	N/A	N/A	2/38	S

MIC: Minimal inhibitory concentration, AST: Antimicrobial susceptibility testing, R: Resistance, S: Sensitive, I: Intermediate, N/A: Not applicable

growth of *Cupriavidus* species from blood cultures in our facility and isolation from the blood cultures of first patient with hospitalization history led us to believe these strains could be responsible for bacteremia. During the febrile episode, blood cultures were collected in both patients, and the first case had possible risk factors such as a central venous catheter and hospitalization in PICU. Because of the absence of risk factors for nosocomial infection such as prolonged hospital stay or invasive medical procedures and having no growth in repetitive blood cultures, the strain isolated from the second case was evaluated as a contaminant.

As it was stated that environmental microorganisms can be associated with hospital infections[12], the isolation of the rare environmental bacteria in the same period from two children's blood samples promoted us to consider that the isolates might be potential nosocomial agents colonized or contaminated from environmental sources. However, the isolation of *C. metallidurans* was limited in two cases and the second case had no evidence of nosocomial infection.

Environmental pathogens associated with water in healthcare settings which are also called as opportunistic premise plumbing pathogens (OPPPs) inhabit and grow in water systems. Nosocomial transmission of these pathogens may become with direct contact or indirectly by use of contaminated water for personal or medical purposes. Besides being highly tolerant to chlorine and chloramine, *C. metallidurans* can also maintain and spread antibiotic resistance in potable water systems. Contamination of water systems might be originated either from retrograde seeding of water from contaminated outlets or low-level seeding of the microorganisms from the incoming supplying system[4,13,14].

Despite routine water supply monitoring as part of hospital infection control surveillance, no pathogen was found in water analysis performed at the public health laboratory. This could be due to the lack of the OPPPs' intended analysis. Routine water analysis is most likely to detect only a few pathogens, and no specific analysis for OPPPs has been performed. *Cupriavidus* spp., isolation

from clinical specimens should trigger a warning, and particular testing for uncommon waterborne infections should be performed[15].

Following these occurrences, no other indication of hospital infection linked to the *Cupriavidus* genus was found in our facility. Unfortunately, sequencing for phylogenetic analysis was not possible, but MALDI-TOF MS analysis, which has been shown to be superior in terms of diagnostic accuracy and reproducibility, was used to rule out phenotypic tests misidentification[16].

The discovery of a matching database in MALDI-TOF MS and an identical antimicrobial susceptibility profile led to the hypothesis that the two strains originated from the same source, raising awareness of nosocomial infections caused by OPPPs such as *Cupriavidus* spp. However, while evaluating isolations due to rare microorganisms such as *C. metallidurans,* not only the isolated organism, but also the other factors such as the patients findings, co-morbidities and risk factors should be taken to account to differentiate the colonization and infection.

Furthermore, OPPPs should be considered as potential threats for nosocomial infections, and surveillance of these pathogens in hospital water systems must be implemented in the hospital infection control procedures.

Ethics

Informed Consent: Informed consent is not required.

Author Contributions

Surgical and Medical Practices: U.K., M.G., Ö.A.Ö., A.A.K., G.G.Ö., Concept: F.Y.A, Design: F.Y.A, H.A., Data Collection or Processing: F.Y.A, U.K., A.A.K., Analysis or Interpretation: F.Y.A, H.A., Literature Search: F.Y.A, U.K., Writing: F.Y.A, H.A.

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REFERENCES

1. Kizny Gordon AE, Mathers AJ, Cheong EYL, Gottlieb T, Kotay S, Walker AS, et al. The Hospital Water Environment as a Reservoir for Carbapenem-Resistant Organisms Causing Hospital-Acquired Infections-A Systematic Review of the Literature. Clin Infect Dis. 2017;64(10):1435-44. doi: 10.1093/cid/cix132.
2. Massip C, Coullaud-Gamel M, Gaudru C, Amoureux L, Doleans-Jordheim A, Hery-Arnaud G, et al. In vitro activity of 20 antibiotics against Cupriavidus clinical strains. J Antimicrob Chemother. 2020;75(6):1654-8. doi: 10.1093/jac/dkaa066.
3. Yahya R, Mushannen A. Cupriavidus pauculus as an emerging pathogen: a mini-review of reported incidents associated with its infection. EC Pulmonology and Respiratory Medicine. 2019;8:633-8.
4. Kweon OJ, Lim YK, Kim HR, Kim TH, Ha SM, Lee MK. Isolation of a novel species in the genus Cupriavidus from a patient with sepsis using whole genome sequencing. PLoS One. 2020;15(5):e0232850. doi: 10.1371/journal.pone.0232850.
5. Kobayashi T, Nakamura I, Fujita H, Tsukimori A, Sato A, Fukushima S, et al. First case report of infection due to Cupriavidus gilardii in a patient without immunodeficiency: a case report. BMC Infect Dis. 2016;16:493. doi: 10.1186/s12879-016-1838-y.
6. Langevin S, Vincelette J, Bekal S, Gaudreau C. First case of invasive human infection caused by Cupriavidus metallidurans. J Clin Microbiol. 2011;49(2):744-5. doi:10.1128/JCM.01947-10.
7. Clinical and Laboratory Standards Institute (CLSI) 2021. Performance standards for antimicrobial susceptibility testing, 31st ed. CLSI standard M100. Clinical and Laboratory Standards Institute, Wayne, PA.
8. Van Houdt R, Provoost A, Van Assche A, Leys N, Lievens B, Mijnendonckx K, et al. Cupriavidus metallidurans strains with different mobilomes and from distinct environments have comparable phenomes. Genes. 2018;9(10):507.
9. Mijnendonckx K, Provoost A, Ott CM, Venkateswaran K, Mahillon J, Leys N, et al. Characterization of the survival ability of Cupriavidus metallidurans and Ralstonia pickettii from space-related environments. Microb Ecol. 2013;65(2):347-60. doi: 10.1007/s00248-012-0139-2.
10. D'Inzeo T, Santangelo R, Fiori B, De Angelis G, Conte V, Giaquinto A, et al. Catheter-related bacteremia by Cupriavidus metallidurans. Diagn Microbiol Infec Dis. 2015;81(1):9-12. 10.1016/j.diagmicrobio.2014.09.015.
11. Dargère S, Cormier H, Verdon R. Contaminants in blood cultures: importance, implications, interpretation and prevention. Clin Microbiol Infect. 2018;24(9):964-9. doi: 10.1016/j.cmi.2018.03.030.
12. Suleyman G, Alangaden G, Bardossy AC. The Role of Environmental Contamination in the Transmission of Nosocomial Pathogens and Healthcare-Associated Infections. Curr Infect Dis Rep. 2018;20(6):12. doi: 10.1007/s11908-018-0620-2.
13. Zhang M, Chen S, Gnegy M, Ye C, Lin W, Lin H, et al. Environmental strains potentially contribute to the proliferation and maintenance of antibiotic resistance in drinking water: A case study of Cupriavidus metallidurans. Sci Total Environ. 2018;643:819-26. doi: 10.1016/j.scitotenv.2018.06.013.
14. Inkster T, Peters C, Wafer T, Holloway D, Makin T. Investigation and control of an outbreak due to a contaminated hospital water system, identified following a rare case of Cupriavidus pauculus bacteraemia. J Hosp Infect. 2021;111:53-64. doi: 10.1016/j.jhin.2021.02.001.
15. Inkster T, Wilson G, Black J, Mallon J, Connor M, Weinbren M. Cupriavidus spp. and other waterborne organisms in healthcare water systems across the UK. J Hosp Infect. 2022;123:80-6. doi: 10.1016/j.jhin.2022.02.003.
16. Urwyler SK, Glaubitz J. Advantage of MALDI-TOF-MS over biochemical-based phenotyping for microbial identification illustrated on industrial applications. Letters in Applied Microbiology. Lett Appl Microbiol. 2016;62(2):130-7. doi: 10.1111/lam.12526.

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Letter to the Editor

Children's Rights in the Turkish Healthcare System

Türkiye Sağlık Sisteminde Çocuk Hakları

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Dear Editor,

I am writing to draw attention to an issue that I believe is of paramount importance in the field of healthcare - the level of knowledge among physicians regarding children's rights.

In recent years, significant strides have been made globally to raise awareness and the level of understanding of children's rights[1]. Various initiatives, campaigns, and international agreements have underscored the importance of safeguarding the rights of every child[2]. However, when it comes to the medical profession, particularly the knowledge physicians possess about children's rights, there remains room for improvement[3].

Physicians play a crucial role in the health and well-being of children. Their expertise is instrumental in diagnosing and treating illnesses, but as an issue of equal importance they possess a comprehensive understanding of the rights that children are entitled to under various international conventions, such as the United Nations Convention on the Rights of the Child[4].

Despite the progress made in pediatric healthcare, it has become evident that there is a need for a more focused approach to ensuring that physicians are well-versed in the principles, specific, and unique characteristics of children's rights. This knowledge is not only essential for the ethical practice of medicine but also for the overall well-being of young patients[5].

One of the key aspects that demand attention is informed consent. Children, like any other individuals, have the right to be involved in decision-making processes about their own healthcare[6]. Physicians need to be adept at communicating effectively with their younger patients, explaining procedures in age-appropriate language, and seeking assent whenever possible. This approach not only respects the child's autonomy but also fosters a trusting relationship between the physician, the child, and their parents or guardians[7].

Moreover, understanding the right to privacy is of vital importance in pediatric healthcare. Physicians must be cognizant of the importance of confidentiality and be skilled in navigating situations where the child's privacy might conflict with the need to involve parents or guardians in their healthcare decisions. Striking a

balance between the child's right to privacy and the responsibility to keep parents informed is a delicate yet crucial aspect of pediatric practice[8].

Education is a cornerstone of improving the level of knowledge among physicians regarding children's rights. Comprehensive training on pediatric rights should be incorporated in the curriculum of medical schools and ongoing professional development programs. This strategy should not only cover the legal aspects but also delve into the ethical considerations, cultural sensitivities, and practical implications of respecting children's rights in a clinical setting[9].

Beyond the academic realm, healthcare institutions should actively promote a culture that values and prioritizes children's rights which can be achieved through the development of policies and protocols that explicitly address the rights of pediatric patients. Regular training sessions, case discussions, and awareness campaigns can further reinforce these principles among healthcare professionals[10].

In addition to issues such as informed consent and privacy, physicians must be well-informed about issues such as the right to benefit from health care services, protection from exploitation, and access to education. Children, regardless of their background, deserve equal opportunities to thrive, and physicians can play a crucial role in advocating and ensuring that these rights are upheld[11].

Furthermore, cultural competency is of paramount importance. Physicians often work with diverse patient populations, each with its unique cultural norms and values. Understanding how these cultural factors may influence a child's rights and healthcare decisions is imperative for providing patient-centered healthcare services.

I would like to emphasize that this call for improved awareness does imply a strong dedication to ethical principles on the part of physicians, and recognizes the dynamic nature of healthcare and the constant evolution of our understanding of what constitutes optimal care, especially for vulnerable populations such as children.

As a society, we have a collective responsibility to ensure that every child receives healthcare that is not only medically sound but also respectful of their inherent human rights. By addressing this issue head-on, we have contributed to a healthcare system that prioritizes the well-being of its youngest members.

In conclusion, I urge your medical journal to shine a spotlight on the importance of enhancing physicians' knowledge about children's rights. By fostering a dialogue on this crucial topic, we can catalyse positive changes in medical education, healthcare policies, and ultimately, improve the quality of healthcare provided to our children.

Thank you for considering this matter, and I look forward to seeing the continued impact of your publication in promoting awareness and positive change in the realm of pediatric healthcare.

Ethics

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REFERENCES

1. Peterson-Badali M, Ruck MD. Studying Children's Perspectives on Self-Determination and Nurturance Rights: Issues and Challenges. J Soc Issues. 2008;64(4):749-69. doi: 10.1111/j.1540-4560.2008.00587.x.
2. Livingstone S, Bulger M. A Global Research Agenda for Children's Rights in the Digital Age. J Child Media. 2014;8(4):317-35. doi: 10.1080/17482798.2014.961496.
3. Streuli JC, Michel M, Vayena E. Children's rights in pediatrics. Eur J Pediatr. 2011;170(1):9-14. doi: 10.1007/s00431-010-1205-8.
4. Waterston T, Goldhagen J. Why children's rights are central to international child health. Arch Dis Child. 2007;92(2):176-80. doi: 10.1136/adc.2006.098228.
5. Reynaert D, Bouverne-De Bie M, Vandevelde S. A Review of Children's Rights Literature Since the Adoption of the United Nations Convention on the Rights of the Child. Childhood. 2009;16(4):518-34. doi: 10.1177/0907568209344270.
6. Davies A, Randall D. Perceptions of Children's Participation in Their Healthcare: A Critical Review. Issues Compr Pediatr Nurs. 2015;38(3):202-21. doi: 10.3109/01460862.2015.1063740.
7. Lowden J, Msc BA, Rscn R, Diphv R. Children's rights: a decade of dispute. J Adv Nurs. 2002;37(1):100-7. doi: 10.1046/j.1365-2648.2002.02049.x.
8. Beidler SM, Dickey SB. Children's Competence to Participate in Healthcare Decisions. In: JONA's Healthcare Law, Ethics and Regulation [Internet]. 2021 [cited 2024 Jan 30]. p. 80-7. Available from: journals.lww.com/jonalaw/Fulltext/2001/09000/Children_s_Competence_to_Participate_in_Healthcare.4.aspx
9. Correia N, Camilo C, Aguiar C, Amaro F. Children's right to participate in early childhood education settings: A systematic review. Child Youth Serv Rev. 2019;100:76-88. doi: 10.1016/j.childyouth.2019.02.031.
10. Chapman AR, Brunelli L, Forman L, Kaempf J. Promoting children's rights to health and well-being in the United States. Lancet Reg Health Am. 2023;25:100577. doi: 10.1016/j.lana.2023.100577.
11. Kilkelly U. Operationalising children's rights: Lessons from research. J Child Serv. 2006;1(4):35-46. doi: 10.1108/17466660200600030.