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The Journal of Pediatric Academy is the official publication of the Kayseri Child Health Association.

The Journal of Pediatric Academy which was established in 2020 is an international, unbiased double blinded peer-reviewed, open-access electronic and only-online published journal in the English language. The Journal of Pediatric Academy is published 4 times a year (March, June, September, December) and accepts original research articles, invited review articles, case reports and clinical images in all areas of pediatric research, which summarize recent developments about a particular subject based on standards of excellence and expertise.

The Journal of Pediatric Academy does not expect any fees for publication. All articles are available on the website of journal for all readers.

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

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Manuscript Types

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Editorial Comment:

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

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Letters To The Editor:

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

Table 1.
Limitations for each manuscript type

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

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Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including e-mail communications—in parentheses in the text.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

Journal Article:

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

Journal Article published in non-English Languages:

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

Book Chapter:

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

Entire Book:

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

Software:

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

Online Journals:

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

Database:

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

World Wide Web:

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

URL (Uniform Resource Locator)

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

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Case Report

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Analyse of Febrile Neutropenia Attacks in Children with Acute Lymphoblastic Leukemia

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Abstract

Febrile neutropenia (FN) is the most important cause of morbidity and mortality during treatment in childhood with acute lymphoblastic leukemia (ALL). The aim of this retrospective study was to assess clinical features, outcomes, treatment modalities, documented infection rates, and frequency of isolation of specific organisms from ALL patients treated by our Department of Pediatric Hematology and Oncology using Berlin-Frankfurt-Munich (BFM) protocols. In this study 132 children diagnosed with ALL and treated according to the ALL-BFM 2009 protocol at Kayseri City Hospital, Department of Pediatric Hematology and Oncology between July 2015 and May 2022 were enrolled and evaluated for episodes of FN during intensive chemotherapy. Treatment characteristics, the presence of relapse, duration of neutropenia, culture results, the choice and duration of antibiotics, and disease prognosis were retrospectively assessed using patient records. In 132 acute leukemia cases, 278 episodes of FN were observed aged 1.1 and 17.8 years (mean 7.1±4.9 years) in a male to female ratio of 1.5:1. Infection focus could be documented in 66 episodes (23.7%); pulmonary infections in 23 patients (34.8%), gastrointestinal tract infections in 20 patients (30.3%), in 10 patients urinary tract infections (15.1%), derma¬otological and soft tissue infections in 2 patients (3%). The causative infectious agent could be demonstrated in 92 (33%) episodes. The most common site of isolation was blood (86/92, 30.9%). While the most frequently identified bacterial infectious agents were Gram-positive bacteria (56 isolates, 20.1%), Gram-negative bacteria were identified in 28 isolates (n=10%). Fungal growth was detected in 6 (2.1%) patients and polymicrobial growth was detected in 3 (1.1%) patients. Of the 132 patients, 4 (3%) died due to infection 2 died during induction, and 2 died during reinduction phases. Centers should evaluate their results to identify changing epidemiological patterns and to treat FN early and efficiently.

Keywords: Acute lymphoblastic leukemia, children, febrile neutropenia

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Introduction

Febrile neutropenia (FN), observed at the time of diagnosis and during therapy, is a major cause of death and delay in treatment in patients with acute lymphoblastic leukemia (ALL).[1] Cytotoxic chemotherapy and cancer itself, which alter humoral and cellular immunity, are the most common and important risk factors for FN, particularly when neutropenia is expected to last longer than seven days. Intensive chemotherapy also predisposes to infection by destroying important protective anatomical barriers such as the oral cavity and gastrointestinal mucosa and may facilitate translocation of enteric pathogens into the bloodstream. Corticosteroids, commonly used for therapy, also have adverse effects on the host immune system, predisposing to infections. Central venous lines (CVLs) are used almost routinely, resulting in a risk of catheter-related blood flow and local infections at the CVL site.[1,2]

The management of FN with early and efficient therapy and advances in supportive care have significantly improved survival and outcomes from infectious complications. Cancer type is considered in the risk assessment for major infections in the decision rules proposed in guidelines. In some studies in the literature, the results may differ due to the heterogeneity of the groups, solid tumor or hematological cancer. In particular, patients with ALL who receive induction therapy are considered high-risk patients.[2-4]

The aim of this retrospective study was to assess clinical features, outcomes, treatment modalities, documented infection rates, and frequency of isolation of specific organisms from ALL patients treated by our Department of Pediatric Hematology and Oncology using Berlin-Frankfurt-Munich (BFM) protocols. Experience sharing is needed to accurately and early predict the risk of complications and death in patients at higher risk of serious complications. The results of this study may guide the appropriate initiation and duration of therapies for febrile neutropenic attacks.

Material and Method

In this study 132 children diagnosed with ALL and treated according to the ALL-BFM 2009 protocol at Kayseri City Hospital, Clinic of Pediatric Hematology and Oncology between July 2015 and May 2022 were enrolled and evaluated for episodes of FN during intensive chemotherapy. Treatment characteristics, the presence of relapse, duration of neutropenia, blood culture results, the selection and duration of antibiotics, and disease prognosis were retrospectively assessed using patient records.

Neutropenia is defined as an absolute neutrophil count (ANC) <500/mm^3 or an ANC expected to decrease to <500/mm^3 within the next 48 hours. Fever is defined as a single temperature of 38.3 °C or two temperature recordings greater than or equal to 38 °C recorded at least 4 h apart. Even if the patient is afebrile on admission, fever at home is considered important.[3,5] Conditions such as severe abdominal pain, severe mucositis, rectal abscesses, shock, catheter tunnel infections, diarrhea, localized pain, impaired consciousness, and hemodynamic abnormalities that are considered a febrile neutropenic episode, especially receiving glucocorticoids, may result in a lower/intermittent rise in temperature. The physical examinations of the patients were comprehensive and repeated at least daily. Complete blood count, electrolytes, creatinine and blood urea nitrogen, liver transaminases, total bilirubin, albumin, blood and urine cultures, C-reactive protein, and procalcitonin determined for the patients. Blood cultures were taken from the catheter only, we did not receive additional peripheral blood cultures. If there is abdominal pain and diarrhea, we get a stool adenovirus, rotavirus antigen test, with some cases *Clostridioides difficile* antigen and stool culture. Abdominal ultrasonography is required for typhlitis. Anaerobic blood culture is not available at our institution. The patients received trimethoprim-sulfamethoxazole orally 3 days/week for *Pneumocystis jiroveci* pneumonia prophylaxis. Other than that, no routine prophylactic antibiotics or antifungal drugs were administered. Broad-spectrum empirical antibiotics (cefepime, meropenem, piperacillin-tazobactam) were administered promptly (always within 30 minutes after arriving at hospital). Aminoglycosides (amikacin) were added to initial therapy for signs of fever with chills indicative of Gram-negative sepsis, increased acute phase reactants, early Gram-negative signs from blood culture, and septic shock. Glycopeptides (teicoplanin, vancomycin) were added if fever persisted for 48-72 (but always 24-48 hours) hours after the start of the initial antibiotics, catheter-associated infections, methicillin-resistant *Staphylococcus aureus*/penicillin-resistant pneumococcal colonization, growth of Gram-positive bacteria in culture, hypotension, cardiovascular disorder, and presence of severe mucositis. We used empiric antifungal therapy (liposomal amphotericin B, caspofungin) in children who had recurrent or persistent fever for 72-96 hours after initiation of empiric broad-spectrum antimicrobial therapy, no identified source of fever, and ANC not increasing. Diagnosis of invasive fungal infection (IFI) was based on the European Organization for Research and Treatment of Cancer and Mycoses Study Group criteria.[3,5-9] There is no sequel to the first episode. With respiratory signs and symptoms, we cannot obtain a molecular analysis of seasonal respiratory viruses such as influenza and respiratory syncytial viruses. Acyclovir was started in patients with any suspicion of herpes simplex or zoster, or symptoms of esophagitis. Molecular analysis of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was performed during the pandemic.

Statistical Analysis

All statistical analyzes were performed using IBM SPSS Statistics 22.0 (IBM Corp.). Descriptive data were presented as means or medians calculated according to whether the distribution was normal or not. This retrospective study was approved by the Ethics Committee of Kayseri City Hospital (decision no: 643, date: 02.06.2022) and was performed in accordance with the ethical standards of the Declaration of Helsinki.

Results

In 132 acute leukemia cases, 278 episodes of FN were observed aged 1.1 and 17.8 years (mean 7.1±4.9 years) in a male to female ratio of 1.5:1. FN attacks were observed in 31.2% (n=87) of patients during induction therapy, in 33% (n=92) intensification/consolidation, 28% (n=78) reinduction, and in 7.5% (n=21) at relapse therapy. Four patients completed their treatment without FN. This corresponds to an overall rate of 2.2 episodes per patient. Median ANC in FN episodes was 237/mm^3 (0-496/mm^3). The median duration of neutropenia was 6.3 days (range 1-19 days). Patient demographics and clinical characteristics are summarized in **Table 1**.

Highlights

- Infections are the leading cause of morbidity and mortality during treatment for childhood acute lymphoblastic leukemia.
- With persistent neutropenia, patients are at particular risk for serious infectious complications and worse outcomes.
- Treatment of febrile neutropenia with early and efficient therapy and advances in supportive care have significantly improved survival and outcomes in infectious complications.

Infection focus could be documented in 66 episodes (23.7%); pulmonary infections in 23 patients (34.8%), gastrointestinal tract infections in 20 patients (30.3%), in 10 patients urinary tract infections (15.1%), skin and soft tissue infection in 2 patients (3%). Two patients had acute appendicitis and 1 patient had 2 acute pancreatitis attacks. A revision was required in 10 patients (7.6%) due to the catheter infection. Septic shock developed in 20 patients, 16 of them secondary to Gram-negative bacteremia.

The causative infectious agent could be demonstrated in 92 (33%) episodes. The most common site of isolation was blood (86/92, 30.9%). While the most frequently identified bacterial infectious agents were Gram-positive bacteria (56 isolates, 20.1%), Gram-negative bacteria were identified in 28 isolates (n=10%). Fungal growth was detected in 6 (2.1%) patients and polymicrobial growth was detected in 3 (1.1%) patients (**Table 2**). Growths that did not correlate with clinical findings were considered contagious.

Initial empiric antimicrobial therapy (cefepime, meropenem or piperacillin/tazobactam) with a combination of amikacin was used in 172 (61.8%) of the episodes, and the average duration of use of amikacin was 7.4 days. Glycopeptides (teicoplanin, vancomycin) were mostly added agents to initial antimicrobial therapy 141 (50.7%) episodes. Antifungal therapy consisting of fluconazole, liposomal amphotericin B, caspofungin, and voriconazole was used in addition to therapy in 97 (34.8%) of the episodes. A single agent was used in 82 (29.4%) episodes and combination therapy was used in 15 (5.4%) patients for antifungal treatment. Six patients had proven fungal infections. The mean duration of antibiotic use was 6.7 days for cefepime, 10.3 days for meropenem, 7.4 days for amikasin, 7.9 days for teicoplanin, 9.6 days for vancomycin, vancomycin 9.6, liposomal amphotericin B 8.6, caspofungin 8.9,

Table 1.
Characteristics of acute lymphoblastic leukemia patients with febrile neutropenia

Characteristics	Value
Median age (range)	7.2 (min: 1.1-max: 17.8) years
Sex (male/female)	81 (61.3%)/51 (%38.6) patients
Race (Turk/ Syrian/other)	116 (87.8%)/14 (10.6%)/2 (1.5%) patients
The risk group (SR/MR/HR)	37 (28%)/84 (63.6%)/11 (8.3%) patients
Relaps	10 (7.6%) patients

SR; Standart risk, MR; Medium risk, HR; High risk

Table 2.
Isolated pathogens in episodes with proven infectious etiology

	Blood	Urine	Total
Gram-positive organisms	54 (19.4%)	2 (0.7%)	56 (20.1%)
Coagulase-negative staphylococci (hominis, haemolyticus, epidermidis)	40 (19.4%)	-	-
Micrococcus luteus	5 (1.8%)	1 (0.36%)	-
Streptococcus viridans	3 (1.1%)	-	-
Enterococcus faecalis	5 (1.8%)	1 (0.36%)	-
Gram-negative organisms	25 (8.9%)	3 (1.1%)	28 (10%)
Escherichia coli	5 (1.8%)	2 (0.7%)	7 (%)
Klebsiella spp. (pneumonia, oxytoca)	5 (1.8%)	1 (0.36%)	6 (2.1%)
Pseudomonas spp. (aeruginosa, stutzeri)	3 (1.1%)	-	-
Serratia marcescens	2 (0.7%)	-	-
Acinetobacter spp. (baumannii, ursingii, junii, lwoffii)	5 (1.8%)	-	5 (1.8%)
Enterobacter cloacae	3 (1.1%)	-	-
Stenotrophomonas maltophilia	2 (0.7%)	-	-
Fungal organisms	5 (1.8%)	1 (0.36%)	6 (2.1%)
Candida spp. (albicans, tropicalis, krusei, lusitaniae)	5 (1.8%)	1 (0.36%)	6 (2.1%)
Polymicrobial	3 (1.1%)	-	3 (1.1%)
	86 (30.9%)	6 (2.1%)	92 (%33)

voriconazole 8.6 days. Colistin, ciprofloxacin, linezolid and trimethoprim-sulfamethoxazole in treatment dose were rarely used in febrile neutropenic patients. Acyclovir was started in 12 (4.3%) and oseltamivir was added to treatment in 15 (5.4%) of episodes (**Table 3**). SARS-CoV-2 was detected in 20 patients and no death occurred due to SARS-CoV-2 during the pandemic.

Of the 132 patients, a total of 4 (3%) died due to infection, 2 in induction and 2 in reduction phases. All deaths were due to pneumonia; two of them bacterial and acute respiratory distress syndrome, two of them fungal with radiological and laboratory findings of aspergillus and pulmonary hemorrhage. Granulocyte-colony stimulating factor were used only in 15 (5.4%) episodes after high-risk treatment protocols.

Discussion

Infection is the most important cause of morbidity and mortality during treatment in childhood ALL, particularly in developing countries. Improving outcomes are associated with improved risk stratification and supportive care. Persistent neutropenia is considered to be at particular risk for serious infectious complications and poorer outcomes in patients with FN.[10-12]

Table 3.
Use rates of antibiotics

	n (%)
Gram-negative	278 (100%)
Cefepime	65 (23.3%)
Cefepime + amicasin	27 (9.7%)
Meropenem	34 (12.2%)
Meropenem + amicasin	142 (51%)
Piperacillin/tazobactam	7 (2.5%)
Piperacillin/tazobactam + amicasin	3 (1.07%)
Other additional Gram-negative	15 (5.4%)
Ciprofloxacin	13 (4.6%)
Colistin	2 (0.7%)
Gram-positive	141 (50.7%)
Teicoplanin	120 (43.1%)
Vancomycin	20 (7.2%)
Linezolid	1 (0.35%)
Antifungal	97 (34.8%)
Fluconazole	24 (8.6%)
Liposomal amphotericin B	26 (9.3%)
Caspofungine	32 (11.5%)
Liposomal amphotericin B + *voriconasole*	8 (2.9%)
Caspofungin + *voriconasole*	7 (2.5%)
Antiviral	27 (9.7%)
Oseltamivir	15 (5.4%)
Acyclovir	12 (4.3%)
Anaerobic	6 (2.1%)
Metronidazole	6 (2.1%)
Others	10 (3.6%)
Clarithromycin	10 (3.6%)
Pneumocystis jirovecii	6 (2.1%)
Trimethoprim/sulfamethoxazole	6 (2.1%)

In our study, the median duration of neutropenia was 6.3 days (3-19 days) and the median ANC in FN episodes was 237/mm^3 (0-496/mm^3). In a study evaluating ALL and acute myeloid leukemia patients from Turkey, neutropenia's duration in ALL patients was found 6.69±3.84 days mean ANC 312±267/mm^3.[13]

In this study, we reported 92 (33%) causative infectious agents in FN episodes. In previous studies, proven microbiological infection was reported in 30-40% of cases and the frequency of isolation of specific organism varies among institutions.[13-20] Some studies have shown an increasing frequency of Gram-positive bacterial isolates, probably with multifactorial causes. Increased use of long-term indwelling central venous systems, intensive chemotherapy causing more severe mucositis, longer duration of neutropenia, use of H2 antagonists, and use of prophylactic antibacterial agents (fluoroquinolone and cotrimoxazole) may be important considerations.[13-17] We use central venous catheter routinely. Our study documented the predominance (20.1% of 33%) of Gram-positive organisms.

Identifying clinical or laboratory predictors of Gram-negative infection in FN patients with cancer is critical for early treatment. Immediate empiric broad-spectrum antimicrobial therapy is important to improve survival when the risk of bacteremia is predicted based on clinical and laboratory findings.[21-23] In case of septic shock findings such as fever rising with shirts, abnormal vital signs, hypotension, tachycardia, broad pulse pressure, mental status changes and respiratory dysfunction, an emergency treatment approach is carried out. (Supportive care of patients, replacement and close monitoring of fluid and electrolytes). If abdominal distension and pulmonary edema are present, we aimed to lower the threshold for albumin infusion to reduce intracellular edema.[24,25] Corticosteroids were used if shock findings persisted. No mortality was observed in any of the 20 patients who developed septic shock.

We prefer our patients to have combination therapy, meropenem plus amikacin therapy for FN treatment with much earlier addition of glycopeptides and antifungal therapy. If clinical stability is stable and fever is under control, we prefer to stop amikacin early.

Increased rates of fungal infections include advances in diagnostic methods, use of intensive chemotherapy drugs and steroids, long-term neutropenia, and use of broad-spectrum antibiotics and venous catheters.[26,27] The prevalence of IFI in children with only ALL patients ranges from 9.7%, 12.5%, 23%, 24% and the mortality rates were 4.2%, 4.2%, 9.5%, 13.3%, respectively.[19,28-30] In this study the proven and probable IFI incidence was higher (34.6%) and mortality rate was lower (1.5%). This may be because we have a low threshold for suspecting a "possible" fungal infection. Clinical criteria, host factors, imaging studies, and galactomannan levels used for the classification. Bronchoalveolar lavage was not performed in any of the patients.

The rate of infection-related mortality in current ALL studies is reported as 2-4% in developed countries and higher rates (20%) in developing countries.[31] All-cause mortality was 10.6% (n=14) and infection-related mortality was 3% (n=4) in this study. Two out of

4 died from acute respiratory distress syndrome due to bacterial pneumonia, and 2 out of 4 died from pulmonary hemorrhage due to fungal infection. As a new pediatric hematology and oncology center, three deaths occurred in the first 2 years and one death in the last 5 years in a 7-year period. Ten patients died of relapsed or refractory disease.

The limitation of this study is that we did not analyze the association between acute phase reactants and clinical manifestations and the severity of FN attacks.

Conclusion

Pediatric patients with ALL are offered a higher level of supportive care to better monitor and manage infectious complications. Close monitoring of patients, early initiation of empiric broad-spectrum antifungal therapy, and modifications in chemotherapy dosage based on bone marrow reserve improve survival and overall outcome. In our study, we showed that FN can be less fatal in ALL patients. For early and efficient treatment of FN, centers should evaluate their results for recognizing changing epidemiological patterns. Improving future outcomes in childhood ALL is related to reducing infection-related mortality.

Today, the solution that makes us pay the lowest price, spend the least time and money is the solution that makes us pay the highest price tomorrow. Tomorrow comes sooner than we expected. Although the books are guides, good observation and understanding of each patient's dynamics, which can be different, can increase the chances of success.

Ethical Approval: This retrospective study was approved by the Ethics Committee of Kayseri City Hospital (decision no: 643, date: 02.06.2022) and was performed in accordance with the ethical standards of the Declaration of Helsinki.

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

Author Contributions: Karadoğan M: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Mutlu FT: Surgical and Medical Practices, Data Collection or Processing, Analysis or Interpretation, Writing.

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

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Evaluation of Families' Views on Disease Management by Applying Telemedicine During the COVID-19 Pandemic

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Abstract

The Coronavirus disease-2019 pandemic has led to the spread of telemedicine management of ketogenic diet therapy (KDT) in children with drug-resistant epilepsy (DRE). In this study, we evaluated the views and satisfaction of families about telemedicine and KDT management. Families of 25 children who underwent KDT for DRE were included in the 17-item questionnaire. Nearly half of the families had a primary education level. Most children with DRE were in the process of maintaining KDT. 88% of the families were applying KDT with telemedicine due to the pandemic. 60% of families found it difficult to start KDT via telemedicine, but 96% reported that reaching the KDT team via telemedicine was sufficient. The necessity of laboratory analyzes and evaluation of the results of the KDT team was evaluated as good in 72%, and their response when dietary changes or vitamin addition was required was evaluated as good in 68%. All families were satisfied with the management of the KDT team in emergencies. 60% of the family recommended others to follow the KDT with telemedicine at all times and 40% recommended them during the pandemic period. According to the results of our study, in selecting patients who will be started with telemedicine and KDT, it should be noted that the families have sufficient education levels. The use of the telemedicine method may be a good option in the presence of an experienced and trained team in KDT management.

Keywords: Telemedicine, ketogenic diet therapy, drug-resistant epilepsy, childhood, parent

Introduction

Drug-resistant epilepsy (DRE) is defined as the inability to control seizures despite the use of two antiseizure drugs as monotherapy or in combination at the maximum tolerated dose. Dietary therapy has a beneficial effect on patients with epilepsy, but the outcome is largely dependent on adherence to diet.[1] Ketogenic diet (KD) therapy (KDT) is a dietary therapy for people with the most common non-pharmacological DRE. The KD switches brain metabolism from glucose addiction to the use of ketone bodies. For treating epilepsy in children, four different KDTs are used: Classical KD, modified Atkins diet, medium chain triglyceride-KD and low glycemic index therapy.[2-4]

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Particularly during the Coronavirus disease-2019 (COVID-19) outbreak, it is important to assess child and/or family satisfaction with whether health systems meet the patient's needs. A survey-based study can be a useful tool to evaluate parental satisfaction. Surveys can have many advantages: family members can answer questions together, which can alleviate their fears. On the contrary, surveys are accepted more economically and faster than face-to-face interviews.[5]

Telemedicine involves the application of information and communication technology (ICT) in various healthcare domains, particularly when the geographical separation plays a pivotal role. From the initial recorded instance of a telephone-based consultation in 1879, remarkable advancements have occurred in leveraging telemedicine within child and adult neurology spheres.[6-9] Telemedicine is emerging as a feasible substitute for conventional medicine or as a supplementary approach to diminish and enhance disparities in healthcare access.[7]

In recent years, there has been significant progress in the advancement of novel telemedicine technologies, including smartphone applications. During the ongoing COVID-19 pandemic, e-health applications have been extensively used to reduce the risk of cross-contamination from close contact. Indeed, the adoption of e-health solutions has been crucial as we continue to provide information to patients and caregivers, while also trying to straighten the curve of rising COVID-19 cases.[10] During the COVID-19 pandemic, healthcare professionals sought to enhance the care of individuals with epilepsy through the utilization of telemedicine services.[11-13] Amidst the COVID-19 pandemic, the implementation of KDT for children with DRE through telemedicine has been practical and warmly welcomed by families and patients in Argentina[14] and the United States.[15] In Italy, although the use of e-health technologies and telecommunication and remote monitoring has increased recently, sufficient information for the long-term management of KDT is not readily available to patients and caregivers. Therefore, the free access of patients and caregivers to different e-health resources should play a key role in the dietary management of DRE. Specific guidelines and therapeutic approaches should be improved for patients following KDT, particularly in the acute medical setting.[16] A sudden change in eating habits (leakage) and constant monitoring of possible side effects are required during the administration of this particular treatment.[17] Numerous studies have been published regarding using telemedicine as the primary means for managing KDTs in patients with DRE.[18,19]

In this study, we determine the views and satisfaction of families of children with DRE regarding supervising KDT via telemedicine during the COVID-19 pandemic. Thus, awareness will be created for patients to be exposed to better practices during the pandemic.

Material and Method

Twenty-five families who wanted to participate were included in the study, among the families of children with DRE who underwent KDT, who were followed up by the pediatric neurology department of our hospital. KDT was initiated and followed by the KDT team in our hospital. As a pediatric neurologist in this team, A.Ü. and U.Y., Z.A. as a dietitian, S.B. was involved as a KD nurse. In this period, pediatric neurology fellows M.Y., İ.B.P. and Dr. P.K. have been found as pediatricians. They were asked to fill out a questionnaire consisting of 17 questions sent by phone or e-mail. Consent was obtained from the patient and/or their families while conducting the survey. The questions were about KDT management via telemedicine during the COVID-19 pandemic, so Ministry of Health approval was obtained. KD training was given by the dietician and KDT nurse in our hospital in the ward where the patient is inpatient and in outpatient clinics if the patient is followed up. In patient education, information about the disease is given and treatment options are discussed. It provides appropriate patient selection, and the necessary information about the KD is given to the family (for outpatients or inpatients). Evaluates patient/family readiness for a 2-month trial period of KDT; willing to life-type changes, evaluate support systems, monitor the patient's condition, monitor seizure activity, teach the signs/symptoms of ketone elevation/hypoglycemia, disease management plan, reducing side effects (constipation/diarrhea, kidney stones, etc.), define emergency seizure management information about emergency medicine, first aid for seizures, problems are discussed when to call the 112 emergency room/when to go to the emergency room.

This study is a descriptive cross-sectional survey. Ethical approval was obtained from the ethics committee of the University of Health Sciences Turkey, Dr. Behçet Uz Children's Training and Research Hospital with the number 2021/12-11, date: 08.07.2021. The questionnaire included questions about the sociodemographic characteristics of the families and their views and satisfaction with disease management by applying telemedicine for KDT during the COVID-19 pandemic.

Statistical Analysis

Categorical information will be analyzed through relative frequencies, whereas numerical data will be evaluated using either the median or mean, depending on their distribution characteristics (whether they follow a normal distribution or not). When comparing categorical factors, we will employ either Pearson's χ^2 test or Fisher's exact test. On the other hand, for numerical attributes, a comparison will be made using either the t-test or the nonparametric Mann-Whitney U test. We will consider a significance level of less than 0.05 as indicating statistical significance.

Results

The study included 23 (92%) mothers and 2 (8%) fathers who agreed to participate in the survey. The mean age was 33.7 years. Of the families, 12 (48%) had primary education, 6 (24%) had high school, 6 (24%) had a university, and 1 (4%) had a master degree (**Figure 1**). The income level of the families was medium in 22 (88%) and high in 3 (12%). The place of residence was determined as 13 (52%) families in the province

and 12 (48%) families outside the province. During the pandemic, 1 (4%) patient was in the pre-diet evaluation phase, 5 (20%) patients were in the initial phase, and 19 (76%) patients were in the maintenance phase. **Figure 2** shows the reasons for starting or continuing KDT via telemedicine. To the question of whether it would be easy to prepare food via video if the initiation of KDT was done with telemedicine; 1 (4%) answered as easy to understand, 9 (36%) difficult to understand, but I can do it via teleconsultation, 15 (60%) answered as very difficult to understand and we need face-to-face communication. To the question of learning how to control ketonemia/ketonuria with telemedicine, 1 (4%) answered as easy, 9 (36%) difficult but manageable by teleconsultation, 15 (60%) very difficult to understand and need to be done face-to-face. **Figure 3** shows the advantages of starting or continuing KDT with telemedicine.

Reaching the KDT team during the pandemic was evaluated by 24 (96%) as adequate and 1 (4%) as insufficient. **Figure 4** shows the necessity of laboratory data and the evaluation of the results by the KDT team through WhatsApp during the pandemic process. When the child had an emergency, 18 (72%) answered good and 7 (28%) answered excellent to the question of how you would evaluate the team's response to solving the problem. Twenty three (92%) stated that the KDT team provided family support groups via WhatsApp as beneficial, while 2 (8%) did not find it beneficial.

Figure 5 shows the answers given to the question of how you would evaluate the KDT team's response if changes in diet or adding vitamins are required during the pandemic according to laboratory results.

To the question of what is the probability of receiving a response via telemedicine when you need a change in recipes (for economic reasons or because of difficulty in accessing food), 22 families (88%) answered good and 3 families (12%) answered excellent.

Figure 6 shows how parents evaluated their communication with the KDT team during the pandemic. Fifteen (60%) parents recommended treatment with telemedicine only during the pandemic period, while 10 (40%) always recommended treatment with others.

Highlights

- Telemedicine remote monitoring of ketogenic diet therapy (KDT) in children with drug-resistant epilepsy is possible and is likely to be as safe and effective as conventional medicine.
- In the remote management of a non-pharmacological treatment such as KDT, the education level of the family should be considered in a patient selection.
- Telemedicine may be a good option for KDT management, as long as it is coordinated by a well-trained multidisciplinary ketogenic diet team.

Discussion

During the COVID-19 pandemic, the management of patients with epilepsy can be facilitated with telemedicine services. In our study, it was found that pediatric neurologists and families of children with epilepsy used the telemedicine method while maintaining KDT, and patient satisfaction was good in this regard.

In a survey conducted by Semprino et al.[14], they found that the management of children with DRE who received KDT was applicable via telemedicine and was accepted by the families. They reported

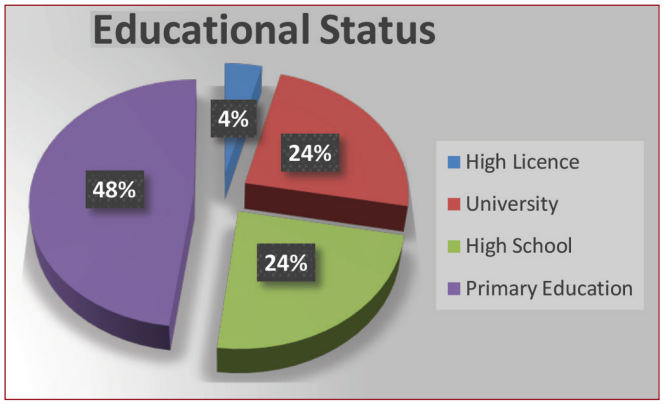

Figure 1. Educational status of parents who use ketogenic diet therapy.

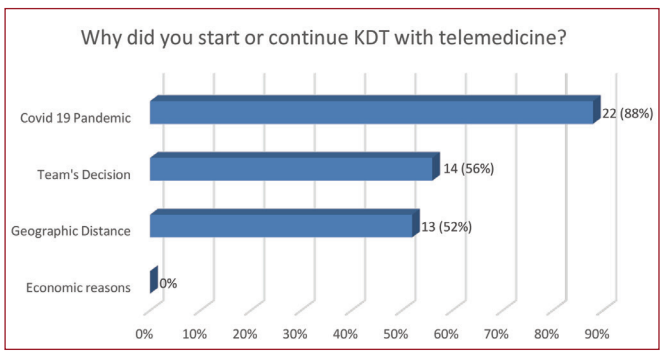

Figure 2. Reasons for starting or continuing ketogenic diet therapy with telemedicine.

KDT; Ketogenic diet therapy

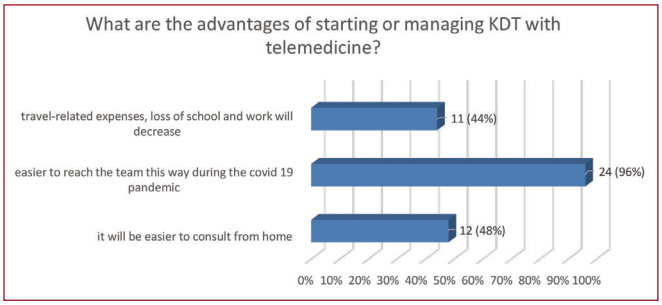

Figure 3. Advantages of initiating or managing ketogenic diet therapy with telemedicine.

KDT; Ketogenic diet therapy

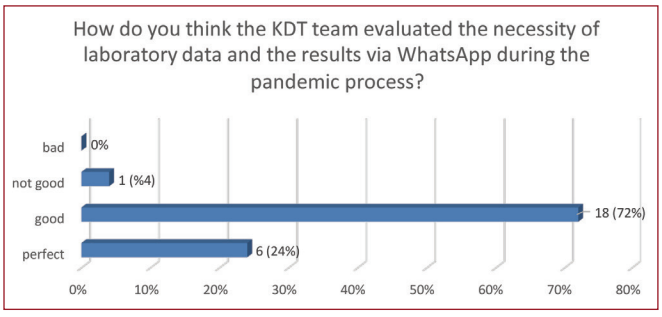

Figure 4. Evaluation of the necessity of laboratory data and results by the ketogenic diet therapy team through WhatsApp during the pandemic process.

KDT; Ketogenic diet therapy

that during the pandemic, they were more likely to continue KDT with telemedicine and the team could be easily reached from the convenience of their home. In contrast to our investigation, the majority of families expressed a preference for telemedicine adoption in all circumstances, irrespective of the COVID-19 pandemic. None of the families indicated any opposition to telemedicine interventions. In our study, the fact that most families preferred the telemedicine application during the pandemic and that they preferred face-to-face education outside the pandemic made us think that it may be related to socio-cultural situations. Similar to our study, ninety percent of the participants reported positive outcomes from a social support network (the WhatsApp family support group) administered by the KDT team.

In an Italian study, they evaluated the feasibility, patient acceptability, and satisfaction of family caregivers using different web materials, including smartphone apps, websites, and videos, for the management of KDT. Specifically, they conducted an analysis designed specifically for children with DRE and aimed to compare the beneficial effects of paper-based and web-based information materials on KDT. The use of e-health applications in the daily management of the KD is a promising tool, especially valuable in attempting to start or maintain a diet during the ongoing COVID-19 pandemic.[20]

Recently Kossoff et al.[15] shared their successful outcomes in implementing and maintaining KDT using telemedicine for both children and adults at the Johns Hopkins KDT center during the COVID-19 pandemic.

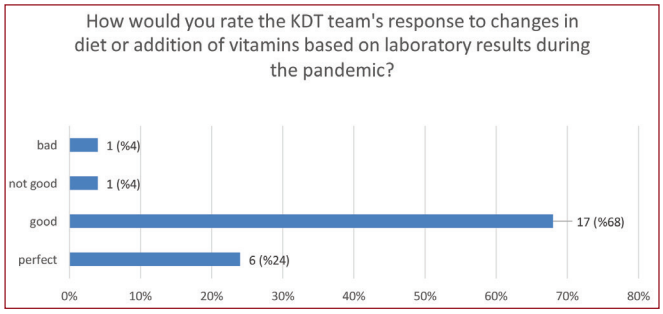

Figure 5. Changes in diet or adding vitamins according to laboratory results of the ketogenic diet therapy team during the pandemic.

KDT; Ketogenic diet therapy

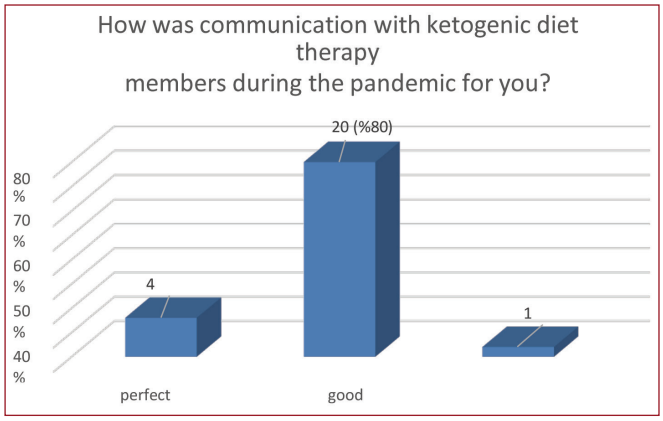

Figure 6. Changes in diet or adding vitamins according to laboratory results of the ketogenic diet therapy team during the pandemic.

KDT; Ketogenic diet therapy

The study employed various online platforms such as Zoom, Polycom, or Doximity to communicate with families and patients through phone calls and e-mail. The authors provided recommendations on effectively managing KDT during the pandemic. Initial virtual visits lasted between 60 and 120 min, with additional time allocated to educate patients and caregivers about telemedicine services before the actual visit. Depending on the clinic's requirements and the patient's needs, dietitians attended the televisit, followed by a separate phone call or responses to questions via the secure messaging system in the electronic medical record. The workflow was further improved by including a medical assistant who engaged with patients and families before the visit, guiding them on how to connect to the telemedicine session 15 min before it began. During 8 h, they could virtually see 8 children. Parents received an email a week ahead of their appointment, requesting them to install Zoom™ on their devices with cameras and providing necessary information in advance, such as final height and weight, updated medication list, completed forms (including the ketogenic formula), and a list of questions to ask. Each appointment involved discussions with both the neurologist and dietitian, starting with a 20-minute interaction with the parents, followed by a 10-minute video-observed physical examination, and concluding with 15 min of follow-up, including planning diet and medical changes, ordering medication, and interpreting lab tests if needed. The majority of families expressed satisfaction with the experience and appreciated the convenience of avoiding hospital travel and potential exposure to COVID-19. Despite the 2018 KDT consensus guideline for pediatrics recommending that classical KD be initiated in the hospital, 80% of the panelists considered it optional and a reasonable approach during the pandemic, according to 92% of them.[21]

In our study, a significant portion of the parents (60%) stated that if the initiation of KDT was done via telemedicine, it would be difficult to prepare food and learn ketonemia/ketonuria control via video, and they would prefer f ace-to-face learning. Considering that 48% of the parents were primary school graduates, it was thought that this might be due to the low educational level of the families. The educationalstatus of the families should also be considered when selecting patients who will start KDT with telemedicine.

Ferraris et al.[19] conducted a long-term remote study on classical KDT via e-mail in 34 children with DRE or glucose transporter type 1 deficiency syndrome, reporting that this approach was effective and feasible. In our study, based on laboratory results, most parents (92%) rated the response of the KDT team as good/excellent when dietary changes or vitamin additions were required during the pandemic. ICT plays a crucial role in sharing information, building consensus and coordinating between different teams, particularly for training and consulting through telemonitoring.[20] The rapid spread of the epidemic has shifted the healthcare landscape toward prioritizing care for COVID-19 patients, leading to the transformation of healthcare facilities

into potential sources of transmission. Consequently, new doctor-patient relationship models have emerged. To optimize the access, remote management and monitoring of KDTs, KDT teams should actively promote the use of information and communication technologies. In our study, most of the parents (96%) stated that monitoring via telemedicine was advantageous because they could reach the KDT team more easily.

During the COVID-19 pandemic, there was a pressing need to employ WhatsApp and prioritize the advancement of telemedicine. This entailed ensuring connectivity, cyber, and legal security and educating healthcare professionals and patients about the proper utilization of ICT. Moreover, confidentiality, fair remuneration, and the establishment of a robust ethical framework was also crucial elements that required urgent attention.

In the context of the COVID-19 pandemic, using WhatsApp has provided constant contact and tight control of families as a fast, easy and free communication tool for monitoring patients with DRE using KDT, so that these difficult patients who receive complex treatment do not lose their follow-up. In our research, parents rated the requirement for laboratory data and the assessment of the KDT team's results via WhatsApp during the pandemic as highly satisfactory, with 96% indicating a good/excellent evaluation.

Similar to a previous study, our survey showed high satisfaction with telemedicine and KDT management among patients' families.[21] However, the study has several limitations, while a significant proportion of parents reported satisfaction with questions about maintaining KDT, suggesting that starting KDT via telemedicine may be a better option for parents with higher levels of education. On the other hand, the research was carried out in a developing country, in an area where resources are limited, by using widely used and cost-free communication tools such as e-mail, WhatsApp, and Survey Monkey Survey Forms.

The all-inclusive telemedicine management of KDT has facilitated convenient access to each team member for medical and dietary guidance throughout the COVID-19 pandemic. The majority of families expressed their endorsement of telemedicine adoption in any circumstance, with less regard for the pandemic. Previous literature also recommends the use of telemedicine not only in emergencies but also in daily practice.[14,22]

Conclusion

Telemedicine's remote monitoring of KDTs in patients with DRE is feasible and potentially just as secure and efficient as conventional medical practices. According to the results of our study, starting KDT via telemedicine may only be more appropriate for families with a sufficient level of education. Therefore, this issue should be considered in the selection of patients who will be starting telemedicine and KDT. Telemedicine could be a viable alternative, given that it is overseen by a proficient, diverse team in the remote administration of a nondrug therapy like KDT.

Ethical Approval: Ethical approval was obtained from the ethics committee of the University of Health Sciences Turkey, Dr. Behçet Uz Children's Training and Research Hospital with the number 2021/12-11, date: 08.07.2021.

Informed Consent: Consent was obtained from the patient and/or their families while conducting the survey.

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Bloodstream Infections by Extended-spectrum β-lactamase-producing *Klebsiella* Species in Children

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Abstract

Infections caused by resistant Gram-negative bacteria are a serious public health problem, with *Klebsiella* spp. being the most common cause and increasing over the years. There is a striking increase in antibiotic resistance worldwide. The aim of this study was to retrospectively evaluate the characteristics and treatment of bloodstream infections (BSIs) caused by *Klebsiella* spp. and to identify possible risk factors for extended-spectrum β-lactamase (ESBL) resistance in our hospital between August 2019 and March 2023. Of 250 *Klebsiella* isolates, 112 (44.8%) were ESBL producers and 138 (55.2%) were ESBL nonproducers. Catheter-related BSIs (CRBSIs) accounted for 49.6% of infections and were more common in the ESBL nonproducer group. Most of the *Klebsiella* spp. were K. pneumoniae (233/250). Most of the infections were healthcare-associated infections (85.6%). Most patients had an underlying disease, the most common underlying disease in the ESBL-producing group was neurometabolic disease (26.8%), whereas in the ESBL-non-producing group it was malignancy (35.5%). The median age of the ESBL-producing group was 14 months and was younger (p=0.01). Previous antibiotic use in the last 30 days, especially aminoglycosides (p<0.006), β-lactam-β-lactamase inhibitor combinations (p<0.001) and cephalosporins (p<0.001), increased ESBL-resistant infection. Use of β-lactam-β-lactamase inhibitor combinations in the last 30 days increased the risk of ESBL resistance by approximately 7.4 times, and cephalosporins increased the risk by 5 times. In the ESBL-producing group, the median duration of treatment was longer at 14 days (p=0.01), and carbapenems were most commonly used (p<0.001). Thrombocytopenia (p=0.003), elevated C-reactive protein (p<0.001), CRBSI (p=0.009), presence of central venous catheter (p=0.03), urinary catheter (p<0.001), mechanical ventilation (p<0.001), intensive care admission (p=0.005), previous use of carbapenems, aminoglycosides, fluoroquinolones in the last 30 days (p=0.003, p=0.001, p=0.006, respectively) and colistin treatment (p<0.001) increased the risk of mortality. The 28-day mortality rate was 11.6%. Appropriate use of narrow-spectrum antibiotics and reduction of invasive procedures is important in reducing ESBL resistance and BSI-related mortality.

Keywords: Extended spectrum β-lactamase, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, children

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Introduction

Infections caused by resistant Gram-negative microorganisms are a serious public health problem due to the lack of treatment options, insufficient clinical data and high mortality, especially in children.[1] There is a striking increase in antibiotic resistance worldwide. Bacterial resistance patterns change over time and across geographic regions. Extended-spectrum β-lactamase (ESBL) is class A β-lactamases, a rapidly evolving group of β-lactamases with ability to hydrolyze and cause resistance to the oxy-imino cephalosporins (cefotaxime, ceftazidim, ceftriaxone, cefuroxime, and cefepime) and monobactams (aztreonam).[2] The emergence of ESBL-producing bacteria occurred in the 1980s; nosocomial infections due to ESBL-producing *K. pneumoniae* strains have increased since the 1990s, while community-acquired infections caused by ESBL-producing bacteria have increased since 2000.[3] ESBL-producing *Klebsiella spp.* are the predominant cause of childhood infections and pose significant challenges such as development of adverse outcomes, treatment failure due to multidrug resistance, high morbidity and mortality.[2,4]

Klebsiella spp. is a common and severe pathogen of bloodstream infections (BSIs) due to Gram-negative bacilli.[5-10] *K. pneumoniae* is an important cause of human infections among all *Klebsiella* species, followed by *K. oxytoca, K. ozaenae,* and *K. rhinoscleromatis*.[2] Infections due to ESBL-producing *Klebsiella* tend to have higher mortality rates and longer hospital stays after infection compared to children with BSI due to non-ESBL-producing isolates.[6,11] Although it has been studied in many studies for adults, it is still a serious concern for children on few pediatric studies.

The aim of this study was to determine the characteristics, risk factors, and outcomes of BSIs caused by *Klebsiella spp.* in a tertiary care pediatric hospital, to assess risk factors for BSI caused by ESBL-producing *Klebsiella* in children, and to compare them with ESBL-non-producing *Klebsiella*.

Material and Method

In our study, blood cultures sent between August 2019 and March 2023 in Ankara City Hospital with a capacity of 610 beds were retrospectively analyzed. The results of blood cultures and catheter cultures collected from children aged 1 month to 18 years in the pediatric intensive care unit (PICU), pediatric surgical service and intensive care unit, pediatric burn unit, bone marrow transplant unit, palliative intensive care unit and pediatric services of our hospital were scanned from the registry systems.

Ethics Committee Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Ethics Committee of Ankara City Hospital Ethic Commitee (decision no: E2-23-4168, date: 26.05.2023).

The Study Group

In blood cultures and catheter cultures, *Klebsiella spp.* (*K. pneumoniae, K. oxytoca*) culture results, culture antibiograms, and patient files were analyzed using computer recording systems. Demographic characteristics (age, gender), hospital inpatient service, underlying disease, mechanical ventilation, presence of central venous catheter, presence of urinary catheter, feeding with percutaneous endoscopic gastrostomy, treatment received, presence of neutropenic fever, and antimicrobial exposure (during the previous 30 days were: carbapenems, fluoroquinolones, glycopeptides, cephalosporins, aminoglycosides, colistin, β-lactam-β-lactamase inhibitor combinations and exposure to combined antimicrobials) were assessed. Duration of treatment, time to culture negativity, type of infection [BSI, catheter-related BSI (CRBSI)], mortality in the last 28 days, leukocyte count, neutrophil count, lymphocyte count, platelet count, C-reactive protein (CRP) level, and culture antibiogram results were recorded. If a patient had more than one episode of *Klebsiella* infection, only the first episode was included to avoid misinterpretation in the risk factor analysis. Results of polymicrobial cultures were not included. Because some patients died before culture negativity was confirmed and the treatment period was completed, treatment periods and time to first culture negativity were not included in the evaluation of these patients.

Culture antibiograms of patients with *Klebsiella spp*. in blood and catheter cultures were examined. Carbapenem-resistant, both carbapenem-resistant and ESBL-resistant *Klebsiella* species were excluded from the study to avoid confounding risk factors and mortality outcomes. ESBL-producing *Klebsiella* and ESBL-non-producing culture results were included in the study.

Definitions

The definition of nosocomial infections was made according to the surveillance diagnostic criteria determined by the Centers for Disease Control and Prevention (CDC) in the United States.[12]

A laboratory-confirmed BSI was defined according to the followings: a) the patient has a recognized pathogen identified from one or more blood specimens by a culture or non-culture based microbiological testing method which is performed for purposes of clinical diagnosis or treatment, and b) organism (s) identified in blood which is not related to an infection at another site.[13]

A definitive diagnosis of CRBSI requires that the same organism is isolated from at least 1 peripheral blood culture and from a culture of the catheter tip, or that two concurrent positive blood cultures obtained from the catheter hub and peripheral vein meet the CRBSI criteria.[13]

Microbiological Methods

Samples were inoculated on routine 5% sheep blood agar and MacConkey agar. After 16-24 hours of incubation at 37 °C, the growing isolates were identified with VITEK® MS (bioMérieux, France). Antimicrobial susceptibility profiles of the isolates of *Klebsiella spp* were determined by VITEK® 2 Compact (bioMérieux

Vitek, Hazelwood, MO, ABD) and interpreted based on the Clinical and Laboratory Standards Institute Criteria for other non-Enterobacteriaceae. Antibiotic susceptibility tests were performed in accordance with the European Committee on Antimicrobial Susceptibility Testing Enterobacterales guidelines.[14]

Statistical Analysis

All statistical analyzes were conducted using the Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc). The data of the patients were collected retrospectively from hospital records. The distribution of data was tested using the Kolmogorov-Smirnov test. Categorical variables were presented as numbers and percentages. Continuous data are presented as medians. The medians of parameters were compared using the Mann-Whitney U test. Chi-square test was used in comparison of categorical variables between independent groups. Multivariate logistic regression analysis was used to determine the effect of risk factors on carbapenem resistance and mortality. The results of the regression analysis were given as odds ratio (OR) and 95% confidence interval (CI). P<0.05 was considered statistically significant.

Highlights

- *Klebsiella* is the most common Gram-negative pathogen causing healthcare-associated infections, and resistance rates are increasing every year.
- Neurometabolic diseases, previous use of aminoglycosides, β-lactam-β-lactamase inhibitor combinations and cephalosporins in last 30 days has been associated with bloodstream infection (BSI) by extended-spectrum β-lactamase-producing *Klebsiella* spp.
- Catheter-associated BSIs, indewelling devices, intensive care unit patients, history of carbapenem, aminoglycoside and fluoroquinolone use, treatment with colistin, thrombocytopenia and elevated C-reactive protein are associated with mortality in *Klebsiella* spp. BSIs.

Results

A total of 250 pediatric patients with *Klebsiella spp.* isolates in BSIs were included in the study (**Figure 1**). One hundred thirty-eight isolates (55.2%) were ESBL nonproducers and 112 (44.8%) were ESBL producers. CRBSIs were 49.6% of the whole infections. While CRBSI was more common in the ESBL-non-producing group (52.9%), BSI was more common in the ESBL-producing group (54.5%). Most of the *Klebsiella spp.* were *K. pneumoniae* (233/250), while most of the *K.oxytoca* were ESBL nonproducers (13/17). Eighty-five patients (34%) had febrile neutropenia, and the majority were in the ESBL-non-producing group (53/85) (**Table 1**). The infection was hospital-acquired or healthcare-associated in 214 (85.6%) children and community-associated in 36 (14.4%) children.

Underlying medical conditions/ diseases were not significantly different between two groups. ESBL-producing group displayed 26 (23.2%) malignancy, 30 (26.8%) neurometabolic diseases, 8 (7.1%) immunsupressed states, 14 (12.5%) cardiovascular diseases, 6 (5.4%) bronchopulmonary diseases, 13 (11.6%) surgical conditions and ten (9%) patients had not any underlying diseases. ESBL-non-producing group displayed 49 (35.5%) malignancy, 32 (23.2%) neurometabolic diseases, 11 (8%) immunsuppressed states, 12 (8.7%) cardiovascular diseases, 3 (2.2%) bronchopulmonary diseases, 16 (11.6%) surgical conditions and 2 (1.4%) patients had not any underlying diseases. There was no underlying disease in 9% of the ESBL-producing group, 1.4% in the ESBL-non-producing group. Approximately one-third (35.7%) of the ESBL-producing group were hospitalized in the intensive care unit (**Table 1**).

Median age of patients was 14 months in the ESBL-producing group, and patients with ESBL-producing isolates were younger than ESBL-non-producers

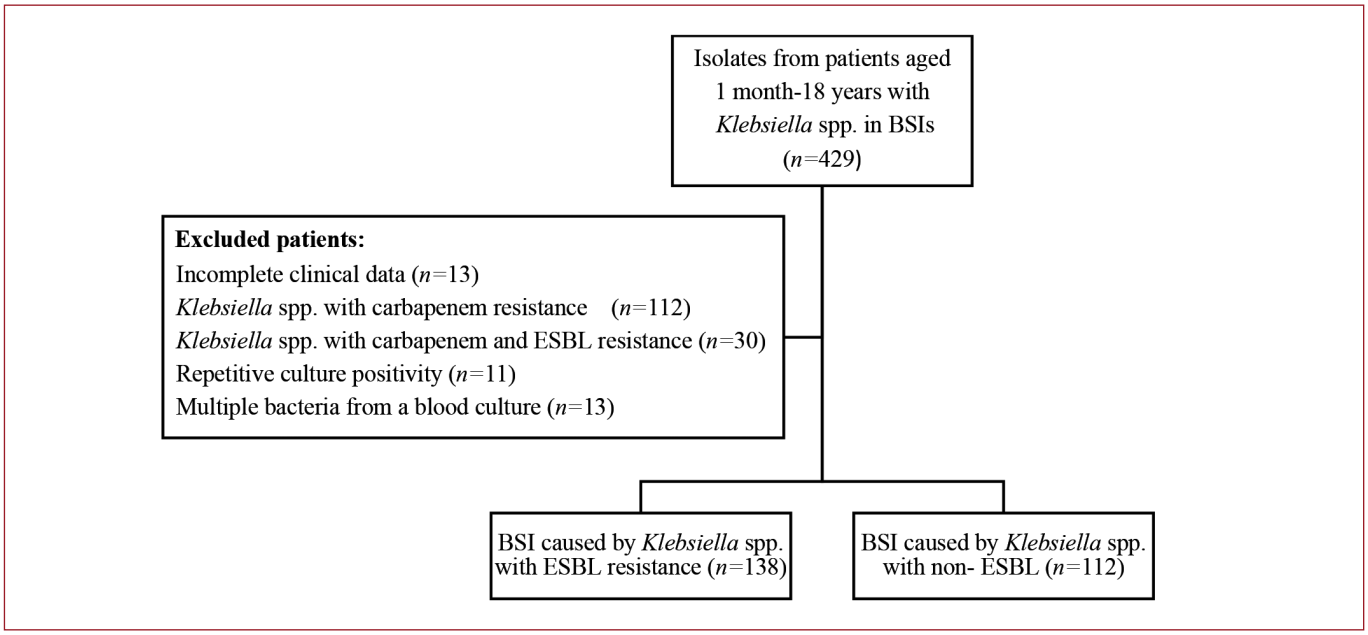

Figure 1. Flowchart of the selection process

ESBL; Extended spectrum beta-lactamase, BSI; Bloodstream infection

Table 1.
Demographics and clinical characteristics, treatment, and outcome of patients

	ESBL (-) n=138	ESBL (+) n=112	p
Age (months), median (min-max)	24 (1-214)	14 (1-224)	**0.01**
Gender, female/male	52/86	57/55	**0.03**
Underlying disease, n (%)	-	-	0.37
Malignancy	49 (35.5)	26 (23.2)	-
Immunosuppressed situations	11 (8)	8 (7.1)	-
Neurologic/metabolic disorders	32 (23.2)	30 (26.8)	-
Cardiovascular diseases	12 (8.7)	14 (12.5)	-
Bronchopulmonary diseases	3 (2.2)	6 (5.4)	-
Surgical conditions (e.g. burn, abdominal surgery)	16 (11.6)	13 (11.6)	-
Other	13 (9.4)	5 (4.5)	-
None	2 (1.4)	10 (9)	-
The type of infection	-	-	0.24
Bloodstream infection	65 (47.1)	61 (54.5)	-
Catheter-related bloodstream infection	73 (52.9)	51 (45.5)	-
Wards, n (%) of patients	-	-	0.56
Pediatric intensive care unit	37 (26.8)	40 (35.7)	-
Hematology oncology department	38 (27.5)	28 (25)	-
Pediatric surgery unit	13 (9.4)	10 (8.9)	-
Paediatrics department	37 (26.8)	29 (25.9)	-
Pediatric burn unit	5 (3.6)	2 (1.8)	-
Pediatric bone marrow transplantation unit	8 (5.8)	3 (2.7)	-
Medical devices present at the onset of infection, n (%) of patients			
Central venous catheter	96 (50.5)	66 (51.1)	0.08
Mechanical ventilation	12 (6.12)	14 (10.8)	0.32
Percutaneous endoscopic gastrostomy	9 (4.59)	6 (4.6)	0.7
Urinary catheter	20 (10.2)	11 (8.5)	0.26
Neutropenic fever	53 (38.4)	32 (28.5)	0.1
The history of antibiotic use in the last 30 days, n (%)			
Yes	18 (13)	63 (56.2)	**<0.001**
Use of combined antibiotics	5 (3.6)	10 (8.9)	0.07
Carbapenems	7 (5)	12 (10.7)	0.09
Aminoglycosides	2 (1.45)	10 (8.9)	**0.006**
β-lactam- β-lactamase inhibitor combinations	5 (3.6)	21 (18.7)	**<0.001**
Cephalosporins	6 (4.34)	28 (25)	**<0.001**
Glycopeptides	4 (2.9)	3 (2.6)	0.91
Fluoroquinolones	0	1 (0.89)	0.26
Colistin	1 (0.7)	1 (0.89)	0.88
Initial culture negativity (day), median (min-max)	2 (1-7)	2 (1-10)	0.08
Microorganism	-	-	0.06
Klebsiella pneumoniae	125 (90.6)	108 (96.4)	-
Klebsiella oxytoca	13 (9.4)	4 (3.6)	-
Initial leukocyte counts (mm^3), median (min-max)	7840 (10-23400)	11820 (40-59090)	0.09
Initial neutrophil counts (mm^3), median (min-max)	5430 (0-40190)	6720 (10-50490)	0.39
Initial lymphocyte counts (mm^3), median (min-max)	1210 (0-8980)	2180 (40-10580)	**0.03**
Initial thrombocyte counts ($x10^9/L$), median (min-max)	210 (2-800)	222 (6-1006)	0.28
CRP levels (mg/L), median (min-max)	68 (0-460)	74 (0-424)	<0.95
The duration of treatment (day), median (min-max)	12 (3-26)	14 (3-32)	**0.01**
Antibiotics used in treatment			
Carbapenems	72 (52.1)	84 (75)	**<0.001**
Aminoglycosides	48 (34.8)	44 (39.2)	0.46
Cephalosporins	22 (15.9)	12 (10.7)	0.23
Fluoroquinolones	6 (4.3)	2 (1.7)	0.25
Colistin	10 (7.2)	11 (9.8)	0.46
β-lactam- β-lactamase inhibitor combinations	32 (23.1)	11 (9.8)	**0.005**

Min-max; Minimum-maximum, CRP; C-reactive protein, ESBL; Extended spectrum beta-lactamase

(p=0.01). Most patients in the ESBL-non-producing group were males (86/138), and there was a significant difference between the groups in terms of gender (p=0.03). We performed analysis on the relationship of previous antibiotic usage before the identification of BSI. Use of antimicrobial treatment during the last 30 days was significantly different between ESBL-producing and ESBL-non-producing groups, 63/112, and 18/138, respectively (p<0.001). In the ESBL-producing group, 49 patients had not received any antibiotic treatment in the last 30 days. When analysis of antibiotic regimens was considered, previous aminoglycoside, β-lactam-β-lactamase inhibitor combinations, and cephalosporin use were higher in patients with ESBL-producing isolates than in those with ESBL-non-producing isolates (p=0.006, p<0.001, p<0.001, respectively) (**Table 1**).

Logistic regression analysis showed a significant correlation between ESBL resistance and two variables: β-lactam- β-lactamase inhibitor combinations exposure during the last 30 days (OR 7.425; CI 1.229-44.849; p=0.02) and cephalosporin exposure during the last 30 days (OR 5.063; CI 1.062-24.136; p=0.04). According to this result, the use of β-lactam- β-lactamase inhibitor combinations in the last 30 days increased the risk approximately 7.4 times, and the use of cephalosporins increased the risk 5 times for ESBL resistance (**Table 2**).

Although the lymphocyte count was lower in the ESBL-non-producing group (p=0.03), there was no significant difference between the two groups in neutrophil, leukocyte, platelet counts and CRP levels.

The duration of treatment was statistically significantly higher in the ESBL-producing group (p=0.01). In the treatment, carbapenem (p<0.001) was used more frequently in the ESBL-producing group, while β-lactam-β-lactamase inhibitor combinations were used more frequently in the ESBL-non-producing group (p=0.005).

The 28-day mortality rate was 11.6%. While the mortality rate in the ESBL-producing group was 12.5% (14/112), it was 10.8% (15/138) in the ESBL-non-producing group, and there was no significant statistical difference. The comparison of demographic, clinical characteristics and laboratory findings of patients according to the mortality group (MG) in **Table 3**. The platelet counts were statistically significantly lower in the MG group (p=0.003) and the CRP value was found to be higher in MG (p<0.001). CRBSI had a higher mortality rate than BSI (72.4%) (p=0.009). A central venous catheter was in 64.8% of all patients, and mortality was higher in these patients (p=0.03). Also, mechanical ventilation and presence of a urinary catheter were statistically significantly higher in MG (p<0.001, p<0.001, respectively). Mortality was more common in patients in intensive care (p=0.005). While mortality rates were higher in patients with neurometabolic disease (27.6%) and cardiovascular disease (27.6%), the difference was not statistically significant (p=0.055). While underlying immunosuppressed conditions and malignancy did not increase mortality, the presence of neutropenic fever did not increase mortality either (p=0.19). Mortality was higher in those who used carbapenem (p=0.03), aminoglycoside (p=0.01) and fluoroquinolone (p=0.006) in the last 30 days. In terms of antibiotic used in treatment, a statistically significant lower usage of cephalosporin was observed in MG (p=0.02), while colistin was statistically higher in MG (p<0.001). In MG, ESBL resistance was observed in 14/29 patients (p=0.68). In the multivariate logistic regression analysis between clinical variables and mortality, thrombocyte count (OR, 0.984: 95% CI, 0.973-0.995; p=0.005) was found to be an independent predictor of mortality (**Table 4**).

Table 2.
Multivariate analysis for ESBL resistance

	OR	95% CI	p
Initial lymphocyte counts	1	1-1	0.76
Antibiotic exposure during the last 30 days			
Yes	1.748	0.432-7.069	0.43
β-lactam- β-lactamase inhibitor combinations	7.425	1.229-44.849	**0.02**
Aminoglycosides	2.832	0.379-21.187	0.31
Cephalosporins	5.063	1.062-24.136	**0.04**

OR; Odds ratio, CI; Confidence interval, ESBL; Extended spectrum beta-lactamase

Discussion

BSIs caused by ESBL-resistant *Klebsiella spp.* are a growing public health concern worldwide with significant morbidity and mortality in children.[15,16] It is important to know the etiologic and demographic characteristics, predisposing factors, and possible antibiotic susceptibility in children because of the high mortality rates, prolonged hospital stays, and limited treatment strategies. Statistics vary widely from continent to continent, from center to center, and over the years. According to the 2020 report of the Central Asian and European Surveillance of Antimicrobial Resistance study, which also includes our country, ESBL resistance in *K. pneumoniae* strains in our country, which was 59% in 2013, gradually increased until 2019 and became 73%.[8] This resistance rate was 89% in Russia in 2020.[17] In the present study, we observed 44.8% ESBL production in *Klebsiella spp.*, causing BSI. In the study by Park et al.[16], ESBL resistance in children with *K. pneumoniae* bacteremia was 35.7% (30/84). In a previous study conducted in our country, ESBL resistance in BSIs due to *K. pneumoniae* in children was 62%.[6] Unlike these studies, our study also included *K. pneumoniae* and *K. oxytoca*, and most of the *K. oxytoca* isolates did not produce ESBL. In addition, the lower ESBL resistance in *Klebsiella* species in our study may be related to the implementation of a strict antimicrobial stewardship program to reduce excessive antibiotic prescribing in hospitalized patients and the fact that only BSIs were evaluated in the study.

In some studies, almost all patients had underlying disease,[16,18,19] while in some studies, patients had underlying diseases, although at lower rates, more in ESBL-producing patients.[6,20] In our study, patients without underlying diseases were more common in the ESBL producing group. It should be considered that children without underlying disease may also have ESBL-resistant BSIs, and empirical treatment should be initiated accordingly, especially in severe patients.

Table 3.
Demographics, clinical characteristics and laboratory findings characteristics of patients according to mortality

	Survival (n=221)	Death (n=29)	p
Age (months) (median)	16 (1-224)	12 (2-212)	0.78
Gender, F/M	96/125	13/16	0.88
Leukocyte counts (mm^3) Median (min-max)	9334 (10-59090)	14530 (40-41480)	0.17
Neutrophil counts (mm^3), Median (min-max)	6280 (0-50490)	10970 (0-38600)	0.09
Lymphocyte counts (mm^3) Median (min-max)	2080 (0-10580)	1540 (0-9080)	0.18
Thrombocyte counts ($x10^9$/L), Median (min-max)	220 (6-1006)	105 (2-602)	**0.003**
CRP (mg/L), median (min-max)	71 (0-438)	131 (0-460)	**<0.001**
Underlying disease	-	-	0.055
Malignancy	68 (30.8)	7 (24.1)	-
Immunosuppressed situations	17 (7.7)	2 (6.9)	-
Neurologic/metabolic disorders	54 (24.4)	8 (27.6)	-
Cardiovascular diseases	18 (8.1)	8 (27.6)	-
Bronchopulmonary diseases	9 (4.1)	0	-
Surgical conditions (e.g. burn, abdominal surgery)	27 (12.2)	2 (6.9)	-
Other	28 (12.7)	2 (6.9)	-
The type of infection	-	-	**0.009**
Bloodstream infection	118 (53.4)	8 (27.6)	-
Catheter-related bloodstream infection	103 (46.6)	21 (72.4)	-
Wards, n (%) of patients	-	-	**0.005**
Pediatric intensive care unit	59 (26.7)	18 (62.1)	-
Hematology oncology department	62 (27.1)	4 (13.8)	-
Pediatric surgery unit	23 (10.4)	0	-
Paediatrics department	61 (27.6)	5 (17.2)	-
Pediatric burn unit	6 (2.7)	1 (3.4)	-
Pediatric bone marrow transplantation unit	10 (4.5)	1 (3.4)	-
Microorganism	-	-	0.12
Klebsiella pneumonia	204 (92.3)	29 (100)	-
Klebsiella oxytoca	17 (7.7)	0	-
Medical devices present at the onset of infection, n (%) of patients			
Central venous catheter	138 (62.4)	24 (82.7)	**0.03**
Mechanical ventilation	1 (0.4)	25 (86.2)	**<0.001**
Percutaneous endoscopic gastrostomy	14 (6.3)	1 (3.4)	0.53
Urinary catheter	21 (9.5)	10 (34.4)	**<0.001**
Neutropenic fever	72 (32.5)	13 (44.8)	0.19
The history of antibiotic use in the last 30 days, n (%)			
Yes	69 (31.2)	12 (41.3)	0.27
Use of combined antibiotics	11 (5)	4 (13.7)	0.06
Carbapenems	14 (6.3)	5 (17.2)	**0.03**
Aminoglycosides	8 (3.6)	4 (13.8)	**0.01**
β-lactam- β-lactamase inhibitor combinations	23 (10)	3 (10.3)	0.99
Cephalosporins	32 (14.4)	2 (6.9)	0.26
Glycopeptides	5 (2.2)	2 (6.9)	0.15
Fluoroquinolones	0	1 (3.4)	**0.006**
Colistin	1 (0.4)	1 (3.4)	0.08
Antibiotics used in treatment			
Carbapenems	138 (62.4)	18 (62)	0.96
Aminoglycosides	86 (38.9)	6 (20.6)	0.056
Cephalosporins	34 (15.3)	0	**0.02**
Fluoroquinolones	8 (3.6)	0	0.29
Colistin	13 (5.8)	8 (27.5)	**<0.001**
β-lactam- β-lactamase inhibitor combinations	40 (18)	3 (10.3)	0.29
ESBL resistance	98 (44.3)	14 (48.2)	0.68

CRP; C-reactive protein, ESBL; Extended spectrum beta-lactamase, Min-max; Minimum-maximum, F/M: Female/male

In studies, malignancy patients were more common in *Klebsiella* BSIs and especially in the ESBL-producing group.[16,20] In the present study, the most common underlying disease was malignancy in all patients and in the ESBL-non-producing group, while neurometabolic disease was more common in the ESBL-producing patient group, similar to a study conducted in our country.[6] In an adult study in which data from 33 hospitals from 12 countries were analyzed, ESBL-producer *K.pneumoniae* BSIs were mostly detected in patients with neurometabolic and cardiovascular diseases.[21] In our study, mortality was also higher in patients with neurometabolic and cardiovascular diseases. All these results show that apart from malignancy patients, patients with neurometabolic and cardiovascular diseases should be cautioned in terms of resistance and high probability of mortality.

In addition, febrile neutropenia was more common in the ESBL non-producing group in our study. It was thought that the reason for this was that most of the patients with malignancy were in the ESBL nonproducing group.

Similar to studies in our country and other countries, younger patients were at a significantly higher risk of BSI with ESBL-producing *Klebsiella spp.* The median age of the ESBL-producing group was 14 months.[6,22]

In our study, the overall mortality rate in BSIs due to *Klebsiella spp.* was 11.6%, and although analysis did not reveal statistical significance, 28 day mortality was relatively higher in patients with ESBL-producing isolates (12.5%). While mortality rates in most adult studies (23.9-47.9%) are higher than in studies including children (17-26.6%), these rates vary by years, countries, and centers.[6,16,18,21,23-27] This mortality was lower compared with other studies. Even though our hospital is a tertiary care hospital where serious patients are referred, it may be associated with low mortality, early initiation of effective treatment due to a good surveillance network, higher proportion of patients without underlying disease, fewer patients with malignancy, and febrile neutropenia than other studies. According to the results of the CDC National and State Healthcare-Associated Infections Progress Report, there was a 7% increase in central line-associated BSIs during the Coronavirus disease-2019 (COVID-19) pandemic.[28,29] In our study, which included the duration of the COVID-19 pandemic, about half of the patients had CRBSI. In this study, although ESBL resistance was lower in catheter-associated BSIs, the mortality rate was higher during the pandemic period. This finding may be related to the density of healthcare services and deficiencies in routine healthcare services such as catheter care. There is also a need to discontinue catheter use early in catheter infections, especially with resistant organisms, and to understand the importance of catheter care.

Table 4.
Multivariate analysis for mortality

	OR	95% CI	p
Thrombocyte counts	0.984	0.973-0.995	**0.005**
CRP	0.996	0.986-1.006	0.42
The type of infection	0.245	0.007-9.101	0.44
Clinic of pediatric surgery unit	0.384	0.038-3.926	0.42
The presence of central venous catheter	2.617	0.050-135.689	0.63
The presence of urinary catheter	2.081	0.207-20.885	0.53
Colistin used in treatment	9.334	0.173-504.986	0.27

OR; Odds ratio, CI; Confidence interval, CRP; C-reactive protein

We found a significant association between BSIs with ESBL-producing *Klebsiella spp.* and previous antibiotic use, especially aminoglycosides, β-lactam-β-lactamase inhibitor combinations, and cephalosporins. Among previously used antibiotics, cephalosporin and β-lactam-β-lactamase inhibitor combinations have been associated with a significantly increased risk of BSIs in ESBL-producing isolates. The association between previous antibiotic use and ESBL-producing *Klebsiella* infections in children is supported by some studies. The body of work supporting an association between previous antibiotic use and infection with ESBL-producing *Klebsiella spp.* in children is not as extensive as in adults, but it is growing and much of it focuses on urinary tract infections and prophylaxis.[6,20,30-34] Supporting the results of our study, previous studies have shown that prior use of cephalosporins and aminoglycosides is associated with ESBL-resistant infections in children with BSIs caused by *Klebsiella*.[6,20,26,27,34] This study also showed that use of β-lactam-β-lactamase inhibitor combinations in the previous 30 days is also a risk for ESBL-producing *Klebsiella* BSIs. Zerr et al.[34] showing that use of β-lactam-β-lactamase inhibitor combinations in the last 30 days increases ESBL resistance in *Klebsiella* infections is similar to our data. Our study differs in that the number of patients was higher and only BSIs were included. In addition, aminoglycoside use was higher in the MG in our study, as were carbapenems and fluoroquinolones.

While there are studies showing that the presence of urinary and central venous catheters, mechanical ventilation, and PICU hospitalization are more common in ESBL-resistant infections, in contrast to these findings, these were found to be associated with mortality in our study.[6,20,26] Short-term use or, if possible, not using indwelling catheters is important to control infection and reduce mortality.

In our study, the duration of treatment was longer in the ESBL-producing group and the use of carbaphem in treatment was significantly higher. Identifying and correcting the factors that increase ESBL resistance may help shorten treatment duration and prevent unnecessary carbaphem use.

In addition, our results showed that mortality was lower in those using cephalosporins and higher in those using colistin. The use of β-lactam-β-lactamase inhibitor combinations in the treatment of the ESBL-non-producing group was more frequent in our study. The use of narrow-spectrum antibiotics as much as possible is important to reduce antibiotic resistance rates and mortality.

This study had several limitations. First, due to the retrospective design, data were obtained from clinical reports, so some incomplete data were inevitable. According to the literature, the number of patients in our study was high compared with single-center studies. However, this was a single-center study. Multicenter studies can help clarify demographic and epidemiologic characteristics and avoid statistical limitations. The data also lack genotyping and molecular analysis, which, if available, would be very valuable in demonstrating.

Conclusion

Klebsiella spp. is one of the major causes of health care-associated BSI infections in pediatric patients. We found that younger age, neurometabolic disease, prior use of antibiotics, especially aminoglycosides, β-lactam-β-lactamase inhibitor combinations, and cephalosporins in the last 30 days, and being in an intensive care unit were strongly associated with the development of BSI with ESBL-producing *Klebsiella spp.* Mortality was higher in patients with CRBSI, presence of central venous and urinary catheters, mechanical ventilation, intensive care unit patients, history of carbapenem, aminoglycoside, and fluoroquinolone use in the previous 30 days, treatment with colistin, thrombocytopenia, and elevated CRP. It is clear that some of these factors may be preventable. These results suggest that the appropriate choice of antimicrobial agents, less invasive procedures may reduce the incidence of BSIs caused by *Klebsiella spp*., especially ESBL-producing *Klebsiella* in children. The use of narrow-spectrum antibiotics and as few antibiotics as possible is important to reduce ESBL resistance and mortality.

Ethical Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Ethics Committee of Ankara City Hospital Ethic Commitee (decision no: E2-23-4168, date: 26.05.2023).

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

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Breast Refusal and Maternal and Perinatal Risk Factors in the Newborn Period From a Single Center in Şanlıurfa

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Abstract

The many benefits of breastfeeding for both the mother and infant are well known. Therefore, the conditions that influence breastfeeding are important. Therefore, we investigated the frequency of breast refusal in the newborn period and the associated maternal perinatal risk factors at an Şan Med Hospital in Şanlıurfa. A total of 407 mother-infant pairs fulfilling the study's inclusion criteria were enrolled. The percentage of breast refusal in infants was higher in young maternal and paternal age (<25 years), being the first child, and active or passive smoking exposure of the mother during pregnancy. The percentage of breast rejection was lower when the baby started to be breastfed within the first hour of birth. The percentages of infants experiencing breast rejection were found to be significantly higher in the absence of skin-to-skin contact following delivery and in the presence of prelactal feeding at the first 3 days than in their counterparts. The rate of breast rejection was found to be higher in infants fed with mixed or formula compared with infants fed only breast milk during the last 24 h. Multiple logistic regression analysis determined that the risk of breast rejection was higher in maternal smoking/exposure during pregnancy [adjusted odds ratio (aOR): 3.19, 95% confidence interval (CI): 1.01-10.06] and delayed initiation of breastfeeding after the first hour (aOR: 3.45, 95% CI: 1.09-11.0). Being in a smoke-free environment for pregnant women should be supported by an indoor smoking ban, and early initiation of breastfeeding in the first hour after birth should be encouraged.

Keywords: Breast refusal, breastfeeding, newborn

Introduction

An infant suddenly developing an unwillingness to suckle the breast, turning his or her head away when the breast is presented, crying and screaming at the breast, or giving up the breast after a short duration of feeding is accepted as breast rejection.[1]

The rejection of the breast may arise from either the mother or the infant. Some ailments of the infant, such as thrush, pharyngitis, clavicle fracture or diseases of the mother, the smell of perfume, or lack of knowledge and experience, can cause breast rejection.[1] A mother's breast problems will also negatively affect the success of breastfeeding. Using a

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bottle or pacifier may cause nipple confusion, resulting in breast rejection.[2] Rejection of the breast by infants can negatively affect breastfeeding and hinder many of the benefits of breastfeeding for the mother-infant pair.[3-6] There are limited studies on this topic both in Turkey[7-12] and in the world.[2,13] To increase breastfeeding rates, it is necessary to examine the frequency and related factors of the non-sucking status of babies.

In this study, we aimed to examine the frequency of breast rejection in the first month after birth and the maternal and perinatal risk factors in infants in Şanlıurfa Şan Med Hospital.

Materials and Methods

Infants and their mothers who gave birth in the Şanlurfa Şan Med Hospital between June 2017 and September 2017 and who visited the Pediatric Health and Diseases Outpatient Clinic 7-15 days after birth constituted the study population.

Inclusion criteria: (a) voluntary mothers (b) newborns aged 7-15 days.

Exclusion criteria: (a) infants hospitalized in the first week of life because of any health problems such as respiratory distress syndrome, meconium aspiration syndrome, pneumonia, transient tachypnea of the newborn, neurological diseases, and asphyxia or cleft palate, (b) diseases requiring hospitalization of the mother and/or affecting the continuity of breastfeeding.

A study form was administered face-to-face to all voluntary mothers addressing maternal and paternal age, educational status, health problems during pregnancy, exposure to cigarette smoke, birth order, gestational duration, birth weight, mode of delivery, health problems of the infant, mother-infant skin-to-skin contact in the first hour after delivery, initiation of breastfeeding within the first hour, prelacteal feeding status, feeding type at the visit (exclusive breastfeeding, mixed feeding, and only formula feeding), and breast refusal.

Prelacteal feeding is the administration of any substances other than breast milk to newborn babies during the first 3 days after birth.[1]

There is no standardized definition of breast rejection. In this study, breast rejection was defined as unwillingness of the infant to suckle the breast that lasted longer than 2 days and continued for at least 3 breastfeeding sessions in a day.

Sample Size Determination

Refusal/unwillingness to breastfeed in infants has been reported in several 2-24%.[2,7-13] Therefore, 374 mother-infant pairs are needed for a problem with an effect size of 15% with an alpha of 0.05 and a power of 90% (G*Power 3.1.9.4). The study was planned to reach 448 mother-infant couples, with the expectation that the frequency of non-compliance with the inclusion criteria would be 20%.

Statistical Analysis

Data were analyzed with SPSS v.22 Program and are presented as mean, standard deviation (SD), or percentages.

The percentages of breast rejection according to parent-infant characteristics were analyzed using the chi-square test.

Multiple logistic regression analysis revealed an association between breast refusal and paternal and perinatal characteristics. The characteristics with p-value <0.20 in univariate analysis were taken as covariances. Skin-to-skin contact and early initiation of breastfeeding were highly correlated, and to prevent collinsarity, early initiation of breastfeeding was included in the analysis. “Feeding type of infant during the last 24 h” variable was not included in the model as it would be a result of the breast rejection. The adjusted odds ratio (aOR) and 95% confidence intervals (CI) were calculated by logistic regression analysis. A value of $p<0.05$ was considered significant.

Ethical Approval

The mothers were first informed about the study, and a written consent form was obtained from all participants. The study protocol was approved by Hacettepe University’s Non-Interventional Research Ethics Committee (decision no: GO 17/515-22, date: 13.06.2017).

Results

During the study period, 463 mothers wanted to participate in the study. Of these, 56 were excluded from the study because their babies had health problems. A total of 407 mother-infant pairs fulfilling the study’s inclusion criteria were enrolled.

The mean maternal age was 27.4 (SD: 5.4; range: 16-45) years and the mean paternal age 31.5 (SD: 5.6; range: 20-57) years. The median number of children was 2 (range: 1-9). The mean gestational duration was 38.5 (SD: 1.3; range: 35-41) weeks. The mean birth weight was 3.2 (SD: 0.4; range: 1.9-4.5) kg.

Overall, 42 mothers (10.3%) reported smoking during the pregnancy period. Of them, 36 mothers also had environmental smoke exposure. Environmental smoke exposure without maternal smoking was in 41.0%. While the median exposure number of cigarets per day is 20 (range: 1-50) in mothers with environmental exposure, the median number of smoked cigarets is 5 (range: 1-40) in mothers who smoke. Therefore, both smoke exposure and smoking mothers were grouped according to the presence and absence of exposure.

In the study, breast refusal was 4.9% (n=20) (**Table 1**). The percentages of infants experiencing breast rejection were found to be significantly higher in young maternal and paternal age (<25 years), first child, absence of skin-to-skin contact after delivery, delayed initiation of breastfeeding after the first hour of birth, and presence of prelactal feeding than in their counterparts (**Table 1**). Breast rejection was detected in 7.7% of babies having mothers who had environmental exposure or smoked cigarets whereas it was 2.0% in those who had no exposure to smoke, which was statistically significant (p=0.009). In addition, maternal education level, paternal education level, having health problems in pregnancy, type of birth, gestational duration, birth weight, and

gender were also evaluated. The relationship between these criteria and breast rejection was examined, but it was not statistically significant (**Table 1**).

On admission, 98.3% of the newborns aged 7-15 days were being breastfed, seven infants were not breastfed during the last 24 h. However, only 58.2% of newborns were exclusively breastfed. Mixed or formula-fed infants had 8.8% breast refusal and exclusively breastfed infants 2.1% (p=0.002, **Table 1**).

When maternal age (yr), paternal age (yr), birth order (≥2 vs 1), smoking/smoke exposure during pregnancy (presence vs absence), gestational duration (≥37 vs <37 weeks), delayed initiation of breastfeeding (presence vs absence), and prelacteal feeding (presence vs absence) were taken into analysis, multiple logistic regression analysis showed that the maternal active or passive smoke during pregnancy and delayed initiation of breastfeeding had a higher risk for breast refusal at the newborn period (aOR: 3.19, 95% CI: 1.01-10.06 and aOR: 3.45, 95% CI: 1.09-11.0; respectively, **Table 2**).

Highlights

- The mother's exposure to cigarette smoke during pregnancy should be avoided.
- The baby should be brought to the mother's breast within the first hour after birth.
- To encourage and increase breastfeeding, diverse methods should be tried.

Discussion

In this study, we found that the rate of breast rejection was 4.9% in the first 15 days after childbirth. Yesildal et al.[8], in their survey conducted in Düzce in 2006, reported that 1.9% of 158 infants admitted to the hospital did not breastfeed. Ünalan et al.[9] reported the frequency of unwillingness to breastfeed as 2.0% in 358 infants aged 0-12 months in a primary health care institution in Istanbul in 2006. Yılmazbaş et al.[10] found that 5.4% of 205 babies in Istanbul in 2013

Table 1.
Effects of maternal and infant characteristics on the frequency of breast rejection in healthy infants

		Whole population		Baby experience breast rejection		p
		n	%*	n	%**	
Maternal age	<25 years	125	30.7	11	8.8	**0.023**
	≥25 years	282	69.3	9	3.2	-
Paternal age	<25 years	31	7.6	4	12.9	**0.032**
	≥25 years	376	92.4	16	4.3	-
Maternal education level	≤ Primary school	173	42.5	6	3.5	0.246
	≥ Secondary school	234	57.5	14	6.0	-
Paternal education level	≤ Primary school	84	20.6	4	4.8	0.942
	≥ Secondary school	323	79.4	16	5.0	-
Health problems during pregnancy	Absence	333	81.8	16	4.8	0.829
	Presence	74	18.2	4	5.4	-
Maternal active or passive smoking	Absence	198	48.6	4	2.0	**0.009**
	Presence	209	51.4	16	7.7	-
Birth order	1	148	36.4	13	8.8	**0.006**
	≥2	259	63.6	7	2.7	-
The type of birth	Normal delivery	121	29.7	4	3.3	0.329
	Caesarean delivery	286	70.3	16	5.6	-
Gestational duration	<37 weeks	37	9.1	4	10.8	0.082
	≥37 week	370	90.9	16	4.3	-
Birth weight	<2500 g	22	5.4	0	0.0	0.273
	≥2500 g	385	94.6	20	5.2	-
Gender	Boy	202	49.6	11	5.4	0.622
	Girl	205	50.4	9	4.4	-
Skin-to-skin contact after delivery	Absence	148	36.4	15	10.1	**<0.001**
	Presence	259	63.6	5	1.9	-
Early initiation of breastfeeding within the first hour after birth	Absence	157	38.6	15	9.6	**0.001**
	Presence	250	61.4	5	2.0	-
Prelacteal feed during the first three days	Absence	269	66.1	8	3.0	0.011
	Presence	138	33.9	12	8.7	-
Feeding type during the last 24 h	Exclusive breastfed	237	58.2	5	2.1	0.002
	Mixed or only formula	170	41.8	15	8.8	-
Total		407	100	20	4.9	-

*Percentage of columns, **Row percentage

Table 2.
Factors associated with breast rejection in healthy infants by multiple logistic regression analysis

	aOR	95% CI	p
Maternal age, years	0.98	0.85-1.13	0.819
Paternal age, years	0.94	0.81-1.14	0.419
Birth order, ≥2 vs 1	0.43	0.14-1.27	0.126
Maternal active or passive smoke during pregnancy: presence versus absence	3.19	1.01-10.06	**0.048**
Gestational duration, ≥37 vs <37 week	0.54	0.15-1.88	0.329
Delayed initiation of breastfeeding: presence vs. absence	3.45	1.09-11.0	**0.036**
Prelacteal feeding: presence vs absence	1.51	0.53-4.30	0.438

aOR; Adjusted odds ratio, CI; Confidence interval

stopped breastfeeding in the first 6 months. Çatak et al.[11] reported that 8.7% of 1080 infants aged 0-18 months followed in the 2009-2010 primary healthcare institution in Burdur did not want the breast. However, Çıtak Bilgin et al.[12] found that 23.8% of the mothers who applied to a lactation outpatient clinic experienced a rejection of the breast. In a study by Nayyeri et al.[13] in Iran, the frequency of breast rejection among 6-month-old infants was 24%. Karaçam and Sağlık[7] reported that 24.5% of mothers had breastfeeded problems in a systematic review. The lack of a standard definition for breast rejection in the studies, the difference in the centers studied, and the difference in the infant age ranges make comparison difficult.

We determined that a delay in bringing the infant to the mother's breast after the first hour and exposure to cigaret smoke increased the risk of breast rejection. In previous studies, the negative effects of cigaret smoke and late initiation of breastfeeding on the success and duration of breastfeeding were similarly shown.[2-6] Ekström et al.[14] stated that exposure to cigaret smoke negatively affected the success of breastfeeding and its duration. Demirci and Bogen[15] showed that early breastfeeding after birth increased the success of breastfeeding. It is thought that problems with breastfeeding can be resolved with education programs, raising awareness, and training for parents. Many mothers reported breastfeeding problems related to stop breastfeeding early. These problems can be avoided with appropriate support. In Egypt, 46 infants who were restless at the breast were examined, and it was reported that 13 of them used a pacifier, and half of them had stopped suckling in the follow-up period. Furthermore, five mothers smoked and four infants stopped suckling completely in those cases.[2] In a study by Amaral et al.[16] In a study that included 1377 mothers in Brazil, unexplained breast rejection was observed in 40% of infants with reduced and interrupted breastfeeding.

The exact pathogenesis of breast rejection in infants of smoking mothers who do not use bottles or pacifiers is unknown. Memiş and Yalçın[17] showed that active and passive smoke exposure increased the levels of some mycotoxins in breast milk. In their study, it was observed that nipple problems such as cracking increased significantly in mothers who were exposed to some of these mycotoxins at high levels, and breastfeeding problems were experienced as a result. Further studies are required in this regard.

In our study, we found that breast rejection was more common among infants of parents under the age of 25. Similarly, Scott et al.[18] studied 587 nursing mothers in Roudbari et al.[19] studied 450 nursing mothers in Iran, and both groups concluded that maternal age was positively associated with breastfeeding duration. Ekström et al.[14] showed that high maternal age had a positive effect on breastfeeding duration in their study, which included 488 cases of primiparous (n=194) and multiparous (n=294) mothers in Sweden. In our study, we found higher rates of breast rejection among infants born as the mother's first child. Demirci and Bogen[15] reported similar findings. This is thought to be due to inexperience. Our finding that supports this situation is that in multiple regression analysis, the significance of the effect on breast rejection of the mother being younger than 25 years old and the infant being first in birth order was lost, supporting the previously described results.

In a study by Yngve and Sjöström[20] among mothers in Europe, it was reported that the mother's education and a family structure supporting breastfeeding increased breastfeeding success and reduced the rate of breast rejection. Xiang et al.[21] surveyed 2300 Australian mothers who were working in paid employment in the 13 months before birth by telephone and found that managerial, professional, and self-employed mothers were more likely to breastfeed. Nayyeri et al.[13] obtained the opposite results. They found that working mothers and those with academic careers were more likely to experience a breast rejection. In our study, no relationship was found between the education level of the mother and breast rejection.

In cases of breast rejection, the parents, and especially the mothers, should be encouraged to continue breastfeeding, training should be provided, and opportunities for breastfeeding should be increased, especially for working mothers. Efforts to continue to breastfeed should be pursued for infants who reject the breast, such as using spoons or droppers as necessary and not using bottles. Education should be given to mothers and those who will support them in terms of correct breastfeeding methods. Rates of motherhood at young ages should be reduced, mothers should be given self-confidence, frequent breastfeeding should be recommended, and skin contact should be offered outside breastfeeding times.[1,7,22,23]

Strengths and Limitations of the Study

The main limitation of our study is that it was cross-sectional; therefore, cause-and-effect relationships cannot be established. Our second limitation is that the study was based on mothers' statements. Furthermore, our study evaluated only the first 15 days after birth, and more studies are needed to explore this situation up to the age of 2 years. In our study, only perinatal factors were considered. Because all infants receiving formula used feeding bottles, three-nipple confusion could not be examined in the study.

The major strength of our study is that it is the first comprehensive study on breast rejection in China. However, the results cannot be generalized to the country as they were collected from only one hospital. In this study, the diagnosis of breast rejection was made with the given definition by the same experienced healthcare personnel who received breastfeeding counseling. This definition makes it possible to compare future studies.

Conclusion

In conclusion, to reduce the occurrence of breast rejection by infants, skin contact with the mother's breast should be initiated within 1 h after birth at the latest and smoking should be avoided during pregnancy. Structural, social, and environmental factors that prevent breastfeeding should be investigated and solutions should be produced. The efforts should be made to eliminate factors that cause breast rejection, and deficiencies in current policies on breastfeeding should be identified and addressed.

Ethics Committee Approval: The study protocol was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (decision no: GO 17/515-22, date: 13.06.2017).

Informed Consent: The mothers were first informed about the study and then signed written consent forms.

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Management of Foreign Body Aspiration in Children: Insights From 664 Cases in the Operating Room

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Abstract

Tracheal or bronchial foreign body aspiration is an important emergency o childhood requiring bronchoscopy under general anesthesia. In this retrospective study, bronchoscopy were performed for foreign body aspiration; anesthesia methods, risks, and postoperative complications were evaluated. Children who underwent bronchoscopy with suspicion of a foreign body in the pediatric surgery operating room between January 2010 and December 2021 were included in the study. Six hundred and sixty four children were evaluated. General anesthesia was applied to all bronchoscopy. Demographic characteristics of the patients, type of foreign body, localization of foreign body, distribution of foreign body according to age groups, complications related to anesthesia and surgical process, length of stay in the postoperative intensive care unit, and duration of hospital stay were evaluated. The patients who aspirated foreign bodies most frequently were children aged 1-3 years (73.6%). During bronchoscopy, organic matter (seeds, hazelnuts, peanuts, chickpeas) was the most frequently removed foreign body in children (559 patients). It was observed that foreign bodies were mostly located in the right main bronchus at a rate of 52.4%, the left main bronchus at 28%. The most common anesthesia-related complications were desaturation in 400 patients, hypercarbia in 200 patients, bronchospasm in 108 patients, and respiratory arrest in 2 patients. Many problems may be encountered in foreign body inhalation, and bronchoscopy of these patients should be performed by an experienced anesthesiologist and surgeon at the right time and in the safest way in terms of anesthesia and surgery.

Keywords: Anaesthesia, foreign body aspiration, rigid bronchoscopy

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Introduction

Foreign body aspiration in infants and children is an emergency surgical procedure that can be fatal.[1] Anamnesis of the family or the patient, rapid diagnosis, and bronchoscopy are lifesaving. Bronchoscopy is the gold standard for the diagnosis and treatment of foreign bodies. Flexible bronchoscopy successfully removes foreign bodies in the subsegments; however, because it requires sedation, cooperation might be challenging in children.[2,3] Rigid bronchoscopy is performed in the operating room under general anesthesia. Oxygenation and ventilation problems may occur due to joint use of the airway with the anesthesiologist and the clinician performing bronchoscopy.[4,5] Different ventilation methods (controlled and spontaneous ventilation) can be applied according to the experience of the anesthesiologists and hospital protocols.[6] The disadvantage of spontaneous ventilation is that the foreign body can be displaced by airway reflexes (cough, laryngospasm, or bronchospasm).[5] Adequate depth of anesthesia for a rigid bronchoscope can be achieved using muscle relaxants.[7] Positive pressure ventilation reduces atelectasis and increases oxygenation.[4]

Foreign body aspirations are a serious health problem that can lead to fatal outcomes in childhood. According to the literature, although most deaths occur before admission to the hospital, anesthesia management and bronchoscopy procedures are also important causes of mortality and morbidity. However, there is still no consensus on the optimal anesthesia technique in the literature. In this article, we wanted to update and share our anesthesia methods for rigid bronchoscopy in foreign body aspiration, which is an important problem in childhood.

Materials and Methods

In this retrospective study, 664 pediatric patients aged 0-18 years who came to our hospital with a diagnosis of a foreign body and underwent rigid bronchoscopy were evaluated in terms of age, gender, type of foreign body, localization, and complications observed during and after the procedure. After obtaining study permission from the Erciyes University Clinical Research Ethics Committee (decision no: 2022/381, date: 11.05.2022), the data obtained by scanning the files over the electronic information systems in our hospital were evaluated.

Patients who had a history of cardiopulmonary arrest before bronchoscopy and whose files were missing any datum planned to be evaluated were not included in the study. Demographic characteristics of the patients, type of foreign body, localization of foreign body, distribution of foreign body according to age groups, complications related to anesthesia and surgical process, length of stay in the postoperative intensive care unit, and duration of hospital stay were evaluated.

In the presence of findings such as acute asphyxia, radiopaque foreign body presence, unilateral decreased respiratory sound, mediastinal shift, or emphysema in patients who came to our clinic with foreign body aspiration, the procedure was performed under general anesthesia without premedication because rigid bronchoscopy was indicated. General anesthesia was administered without premedication in patients admitted to our clinic with tracheal bronchial foreign body aspiration. Before the intervention, electrocardiograph, oxygen saturation, and non-invasive blood pressure were monitored. Anesthesia induction was performed with propofol 2-3 mg/kg intravenous (IV) in the presence of 100% oxygen or with 4-5% sevoflurane if there was no vascular access. Rocuronium 0.6-1.2 mg/kg IV was administered to prevent the airway reflex in the patient. Intraoperative ventilation was continued manually with 4-6 lt /min 100% oxygen by attaching the breathing circuit to the ventilation section of the rigid bronchoscope. In the maintenance of anesthesia, 2% sevoflurane-100% oxygen and remifentanil were provided with 0.1-02 μg kg^{-1} min^{-1} or with longer-acting fentanyl (1 μg kg^{-1}). Manual ventilation was intermittently interrupted in coordination with the bronchoscopist and apnea periods and oxygen insufflation were performed. The trachea and main bronchi were re-checked for possible complications after the foreign body was removed with forceps. When the procedure was completed, anesthetic drugs were discontinued and muscle relaxants were antagonized. The patient's spontaneous respiration was supported with 100% oxygen until it reached a sufficient level. Patients with respiratory distress received 1 mg/kg lidocaine or 1 mg/kg methylprednisolone. Patients with respiratory distress, despite medical treatment, were treated in the intensive care unit by endotracheal intubation. At the end of the procedure, patients without respiratory distress were transferred to the recovery unit, and patients with an Aldrete recovery score[8] of ≥9 were sent to their rooms in the thoracic surgery ward.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) v.26.0 (IBM Corp. Armonk, NY, USA) package program was used for the statistical analysis of the study. Compliance of numerical data with normal distribution was evaluated using the Shapiro-Wilk test in each group. Those who did not show a normal distribution were evaluated using the Mann-Whitney U test, and categorical data were evaluated using the chi-square exact test. The homogeneity of variances was evaluated using Levene's test.

Numerical variables are given as mean standard deviation, and categorical variables are given as frequency (percentage). Relationships between categorical variables were evaluated by chi-square analysis, and $p<0.05$ was accepted as sufficient for statistical significance in testing two-way hypotheses.

Results

Between January 2010 and December 2021, 664 patients underwent rigid bronchoscopy with the suspicion of foreign body aspiration in the thoracic surgery operating room of Erciyes University Medical Faculty. The mean age of the patients was two years. Of these, 415 (62.5%) were male and 249 (37.5%) were female. Foreign bodies were detected in 612 (92.1%) of 664 patients (**Table 1**). The average procedure duration was 52 minutes.

The patients who most frequently aspirated foreign bodies were children aged 1-3 years (73.6%) (**Table 2**). Among these, the number of children in the 1-year age group was high (55.9%). The distribution of foreign body type by the age group is given in **Table 3**. In the distribution of gender by the age group, the number of males was significantly higher than that of females ($p<0.05$). During bronchoscopy, organic matter (seeds, hazelnuts, peanuts, chickpeas) was the most frequently removed foreign body in children (559 patients). In contrast, inorganic substances such as toys and pencils were found more frequently in children over school age. Pin aspiration was among the aspirated inorganic materials, especially in female patients who wore headscarves.

It was observed that foreign bodies were mostly located in the right main bronchus at a rate of 52.4%, the left main bronchus at 28%, and the trachea at 7.8% It was observed that it was in both lungs with a rate of 3.4% and outside the respiratory system with a rate of 0.6% (**Table 4**). Foreign body aspiration was outside the respiratory tract in 4 patients. One was located in the esophagus, one in the epiglottis, one in the mouth, and one in the vocal cords.

Of the 664 patients who underwent bronchoscopy, 605 did not require intensive care (91.1%). Of the patients staying in the intensive care unit, 13 remained in the intensive care unit for more than one week (**Table 1**).

The most common anesthesia-related complications were desaturation (SpO_2< 95%) in 400 (60.2%) patients, hypercarbia in 200 (30.1%) patients, bronchospasm in 108 (16.2%) patients, and respiratory arrest in 2 patients (0.4%). There were 4 (0.6%) pneumothorax, three bleeding (0.5%), one pneumomediastinum (0.2%), and 3 (0.5%) open surgery requirements. Complications related to the rigid bronchoscopy procedure were also observed. Because of the development of cardiac arrest during the procedure, one patient was resuscitated by cardiopulmonary resuscitation, but the patient died after 24 h during intensive care follow-up (**Table 5**).

Highlights

- Foreign body aspiration in infants and children is an emergency surgical procedure that can be fatal.
- Bronchoscopy is the gold standard for the diagnosis and treatment of foreign bodies.
- Rigid bronchoscopy is performed in the operating room under general anesthesia oxygenation and ventilation problems may occur due to joint use of the airway with the anesthesiologist and the clinician performing bronchoscopy.

Discussion

In this retrospective study, we evaluated 664 patients who met the study criteria perioperatively and underwent rigid bronchoscopy due to suspicion of foreign body aspiration in Erciyes University Hospitals between 2010-2021.

Foreign body aspiration is especially common in boys under the age of 3.[2] In this age group, curiosity about the objects in the environment, taking the objects to their mouth to recognize the object, and talking and laughing when there is an object in the mouth due to the anatomically underdeveloped larynx and epiglottis cause aspiration.[9] Aspirated foreign bodies may differ from country to country. Paksu et al.[10] reported that under the age of 3 years, organic body aspiration was higher, and for those above the age of 3 years, inorganic body aspiration was higher. In our study, although the inorganic body aspiration was not statistically

Table 1.
Demographic datas

Age (years) (mean ± SD)	2.09±3.01
Gender, n (%)	
Female	249 (37.5)
Male	415 (62.5)
Foreign body detected, n (%)	
Yes	612 (92.1)
No	52 (7.9)
Duration of bronchoscopy (minutes)	52±2.9
Hospital stay (days) (med, min-max)	2.31 (0-39)
Need for ıntensive care n (%)	
Yes	59 (8.9)
No	605 (91.1)

SD; Standard deviation, Min-max; Minimum-maximum
Parameters are presented as mean ± standard deviation or n (%)

Table 2.
Gender distribution by age groups

	Female	Male	Total	p
0-1 years	38 (5.8)	50 (7.5)	88 (13.3)	-
1-3 years	170 (25.6)	319 (48)	489 (73.6)	-
4-6 years	13 (1.9)	23 (3.4)	36 (5.3)	-
7-10 years	13 (1.9)	9 (1.4)	22 (3.3)	-
10-18 years	15 (2.2)	14 (2.3)	29 (4.5)	-
Total	249 (37.4)	415 (62.6)	664 (100)	0.046

Parameters are presented as n (%), p<0.05, significant difference

Table 3.
Distribution of foreign body type by age groups

	Organic n (%)	Inorganic n (%)	p
0-1 years	66 (11.8)	7 (13.1)	-
1-3 years	445 (79.6)	18 (34)	-
4-6 years	26 (4.7)	8 (15.1)	-
7-10 years	8 (1.4)	10 (18.9)	-
10-18 years	14 (2.5)	10 (18.9)	-
Total	559 (100)	53 (100)	0.001

Parameters are presented as n (%), p<0.05, significant difference

Table 4.
Foreign body localization

	n (%)
Right bronchial tree	348 (52.4)
Left bronchial tree	186 (28)
Trachea	52 (7.8)
Double lung	22 (3.4)
Outside the respiratory tract	4 (0.6)

Parameters are presented as n (%)

Table 5.
Peri-interventional complications

	n (%)
Complications related to anesthesia	
Desaturation	400 (60.2)
Hypercarbia	200 (30.1)
Laryngospasm	108 (16.2)
Arrest	2 (0.4)
Complications related to bronchoscopy	
Pneumothorax	4 (0.6)
Bleeding	3 (0.5)
Pneumomediastinum	1 (0.2)
Transition to open surgery	3 (0.5)
Cardiac arrest	1 (0.2)

Parameters are presented as n (%)

significantly higher in school-age children aged 7-10 years, the number was higher. However, organic body aspiration was statistically high in children under 3 years of age.

Bronchoscopy is the gold standard for diagnosing and treating foreign body aspiration.[11] The mortality rate in bronchoscopy has been reported to be 0.42%.[12] Factors affecting mortality can be described as hypoxia developing before or after bronchoscopy, age of the child, type of foreign body, inflammation, duration of inflammation, and complications that may develop during anesthesia and the procedure.[13] Therefore, it would be ideal to perform rigid bronchoscopy when the foreign body aspiration is suspected. Flexible bronchoscopy are preferred for small-diameter foreign bodies.[14-16]

The time of bronchoscopy may also affect mortality and morbidity. In patients whose fasting period has not expired but who have respiratory distress, aspiration forms the basis of complications that may develop. When patients are respiratoryly stable, it is ideal to perform bronchoscopy in daytime conditions where experienced anesthesiologists and surgeons are present in the most suitable conditions regarding anesthesia and the procedure.[17] In our clinic, if the patient does not have respiratory distress and the foreign body is located in an area that does not cause a problem, we aim to wait for the appropriate time to remove the foreign body to reduce the complications that may develop.

In patients presenting with suspected foreign body aspiration, clinical findings differ according to the location of the foreign body.[18] While cough is the most common reason for admission, wheezing and respiratory distress are the following findings.[2] The most common hospital admission symptoms in our study were cough, wheezing with sudden onset, cyanosis, and vomiting. The literature recommends bronchoscopy in suspected foreign body aspiration cases.[19] Şahin et al.[2] reported the rate of negative bronchoscopy as 24.6% in 28 cases. Pan et al.[20] reduced this rate from 18% to 4% because they performed fiberoptic bronchoscopy before rigid bronchoscopy. It is stated in studies that the rate of negative bronchoscopy varies between 14% and 22.3%. Negative bronchoscopy was found in 52 (7.9%) of 664 patients in our study. Our negative bronchoscopy rate is quite low compared with the literature. The reason for this result is that the diagnosis is established by flexible bronchoscopy performed under sedation in children who were clinically stable and whose diagnosis could not be supported by chest X-ray or tomography. However, routine fiberoptic bronchoscopy was not performed before rigid bronchoscopy.

There is no definite consensus regarding the premedication to be administered to patients who will undergo rigid bronchoscopy.[21,22] Midazolam may increase respiratory distress because of its sedative and respiratory depressant effects. It is not easy to share the airway with a surgeon during bronchoscopy. Therefore, general anesthesia would be a good choice for foreign body aspirations. Some studies have stated that spontaneous breathing and propofol-remifentanil anesthesia might delay cough, apnea, body movement, and awakening during the removal of the foreign body.[4] We used the short-acting rocuronium as a muscle relaxant to reduce the complications arising from manipulations during the removal of the foreign body with the combination of propofol-fentanyl or remifentanil. Rocuronium is an agent that acts more rapidly in children, and its effect ends quickly.[4]

Corticosteroids are recommended before or during bronchoscopy to reduce inflammation and subglottic edema in the airway.[18] However, there is no consensus on the timing of corticosteroid administration Li et al.[22] administered methylprednisolone as a prophylactic agent before induction. Apa et al.[19] initiated steroid treatment before bronchoscopy and administered steroid infusion for 24 h. Zhang et al.[23] suggested intraoperative methylprednisolone or dexamethasone treatment. In our clinic, a 1 mg/kg dose of methylprednisolone is administered intraoperatively, and laryngospasm and bronchospasm that might develop are prevented.

Because the right main bronchus is wider, shorter, and more vertical than the left main bronchus, the incidence of foreign bodies in the right bronchial system is more common. However, according to the literature, the incidence of foreign bodies is equal in the right and left bronchi because the bronchi protrude from the trachea at an equal angle in early childhood.[20] Cohen et al.[14] reported that foreign body aspiration is most common in the left main bronchus. In our clinic, contrary to the literature, foreign bodies were observed in the right and left bronchial systems at a rate of 52.4% and 28%, respectively.

Complications due to anesthesia or the procedure that may result in mortality may develop during bronchoscopy.[2] Studies reported that the most common complication due to anesthesia was laryngospasm.[24] Laryngospasm might be caused by preoperative respiratory distress, degree of airway obstruction, depth of anaesthesia and stress-related factors.[25] Qiu et al.[4] reported the rate of laryngospasm development as 0.6% in their study consisting of 2886 patients under ten years of age, but this rate was 16.2% in our study. Although propofol and muscle relaxants were used for anesthesia it was thought that the reason for this finding might be mucosal damage during the removal of the foreign body

and the long duration of the procedures. In 3 patients, the foreign body could not be removed by bronchoscopy, and thoracotomy was performed.

The mortality rate due to rigid bronchoscopy was 0.42%. In our clinic, two patients had an arrest after desaturation due to the foreign body's complete obstruction of the trachea during the procedure, which was reversed with resuscitation. However, one patient had sudden cardiac arrest due to bronchial rupture during the procedure and died within 24 h in the intensive care unit after resuscitation. The duration of hospital stay may vary according to the economic conditions and hospital policies in the literature. In the study of Qiu et al.[4], the average hospital stay was two days, whereas it was 2.3 days in our study.

Conclusion

Foreign body aspiration is a severe condition that can be fatal to childhood. Although it can be seen in all age groups, it is more common under the age of 3 years. Both rigid bronchoscopy and anesthesia management for diagnosis and treatment require experience. Over time, developments in anesthesia and bronchoscopy have contributed positively to the management of foreign body aspiration. There is no clear consensus on the ideal anesthesia management and premedidication among various anesthesia techniques. As long as the hemodynamics of the patients are stable, it is recommended to perform bronchoscopy under elective conditions. In patients scheduled for bronchoscopy with suspected foreign body aspiration, the anesthesiologist and the team that will perform the bronchoscopy should be in close cooperation. This cooperation and teamwork should be considered the most important factor affecting the success of the process.

Although our study is retrospective, applying the anesthesia protocol accepted in our clinic in the anesthesia management of all patients increases the reliability of our results. However, we believe that prospective studies with more extensive patient series are required.

Ethical Approval: After obtaining study permission from the Erciyes University Clinical Research Ethics Committee (decision no: 2022/381, date: 11.05.2022), the data obtained by scanning the files over the electronic information systems in our hospital were evaluated.

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

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Case Report

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A Patient Diagnosed with Li-Campeau Syndrome and Biotinidase Deficiency

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Abstract

Biotinidase (BTD) enzyme deficiency is a congenital metabolic disorder with autosomal recessive inheritance. Main symptoms in its deficiency are nervous system and skin manifestations. A 15-month-old patient who was diagnosed with Li-Campeau syndrome, was also diagnosed with BTD deficiency and his clinic rapidly improved with biotin treatment. With the awareness of different clinical presentations of BTD deficiency, patients presenting with clinical symptoms raising the suspicion of this disorder must be evaluated for enzyme activity and genetic analysis must be planned. It is of great importance to keep in mind the possibility of this rare but treatable neurometabolic disorder, even in countries with neonatal screening programme and include it in differential diagnoses in order to prevent irreversible symptoms.

Keywords: Biotinidase deficiency, partial, clinical findings, treatment

Introduction

Biotinidase (BTD) deficiency is an autosomal recessive metabolic disorder presenting with neurocutaneous manifestations for which mutations in *BTD* gene are responsible. BTD is an enzyme required for the formation of biotin through a cascade of reactions called biotin turnover and it is involved in biotin recycling in the body. In BTD deficiency, the body is unable to recycle vitamin biotin, resulting in a decrease in biotin levels in the body. The disorder can present with a variety of clinical manifestations including alopecia, dermatitis, ataxia, convulsions, hypotonia, growth retardation, and hearing loss. Patients are grouped as having either profound (residual activity <10% of mean activity) or partial (residual activity <10-30% of mean activity) deficiency depending on the plasma enzyme activity.[1-3] The incidence rate is 1 in 60.000 people. Turkey is one of the countries with the highest incidence rates.[3-5] Thus, the newborns are screened as part of the National Neonatal Screening Program since October 2008.[4] The screening program aims to diagnose the condition in the early period and instigate early therapy before the development of irreversible symptoms such as permanent hearing loss, optic atrophy and global growth retardation in the long term.[6] Our patient who had dysmorphic facial features, neurodevelopmental delay, hypotonia, seizures, cardiac system abnormalities was diagnosed with

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Li-Campeau syndrome (LICAS), a neurodevelopmental disorder characterized by global developmental delay, impaired intellectual development, variable abnormalities of cardiac and genital system, hypotonia, seizures and dysmorphic features.[7] The patient, who had skin findings in addition to neurological findings, was also evaluated in terms of BTD deficiency. The current report presents a case of LICAS who was diagnosed with BTD deficiency. The patient's guardian provided informed consent for publishing this study.

Case Report

A 15-month-old male patient presented to pediatric neurology outpatient clinic due to hypotonia, growth retardation, feeding problems, vomiting and diarrhea. The patient had been diagnosed with growth retardation during intrauterine period and been delivered by Cesarean section at 38 weeks of gestation and with a birth weight of 2010 gr. He had been intubated due to respiratory distress immediately after birth. The patient was born as the third child to a 31-year-old healthy mother and her first cousin, 32-year-old healthy father. He had two siblings one of whom was healthy and the other was on follow-up with the diagnosis of autism. The patient did not have a family history of chronic disease. In his medical history, he had suffered from respiratory and feeding problems since birth, had sucking and swallowing dysfunctions as well as growth retardation and developmental delay. A percutaneous endoscopic gastrostomy (PEG) tube had been inserted at seven months due to sustained feeding problems. The patient had frequent hospitalizations due to respiratory and gastrointestinal tract infections. Antiepileptic drug had been initiated at six months due to focal onset motor seizures with impaired awareness that were controlled by the given therapy. Electoencephalography (EEG) was normal. The patient had a recurrent seizure one year after, during a period of infection for which the dose of antiepileptic drug had been increased. The patient did not have any seizures thereafter and was on a therapy with levetiracetam at 30 mg/kg/day.

The vital signs were stable on physical examination. The body weight was 6.4 kg (<3rd percentile), the height was 78 cm (<3rd percentile) and the head circumference was 43 cm (<3rd percentile). The patient was aware of his surroundings, had social smile and was able to use a few words. On physical examination, the patient was found to have epicantal fold, downslanting palpebral fissures, ptosis, hypertelorism, low set ears, prominent forehead, thick but weak eyebrows, hypertrichosis and long fingers (**Figure 1a, b**). The skin was dry and the hair was weak. The patient had head control, was able to sit with support for a short period and had trunk hypotonia (**Figure 1a, b**). Muscle tone was increased bilaterally in the lower extremities and he had brisk deep tendon reflexes. He had bilateral cortical thumbs. Hearing and visual examination revealed normal findings. Cardiac examination revealed secundum atrial septal defect and patent ductus arteriosus. The patient did not have oral intake due to lack of sucking-chewing-swallowing functions and was fed with a PEG tube.

From laboratory tests, hematological parameters, serum electrolytes, thyroid function tests, vitamin B12, liver and kidney function tests, arterial blood gas analysis, serum ammonia, plasma and urine amino acid results were within normal ranges. Urine organic acids were normal. Cranial magnetic resonance imaging revealed no abnormal findings. An examination of the *UBR7* gene revealed a homozygous frameshift mutation (ENST00000013070.6)(c.1192_1193 del) and as a result, the patient was diagnosed with LICAS. Even after a neonatal screening turned out to be negative, BTD activity was also studied during metabolic testing, since the patient had skin and some neurological findings that were inconsistent with the diagnosis. Suprisingly, the enzyme activity was found to be 23% (normal if >30%), suggesting partial (10-30%) BTD deficiency. The patient was placed on biotin therapy at a daily dose of 5 mg/day based on clinical findings, and further genetic analysis was foreplanned. The patient showed rapid improvements in his clinical condition during the follow-up visit at two weeks. The patient was able to sit without support, turn and stand up with support for a short period; spasticity decreased; the patient was able to take liquid oral food and showed increased awareness of his surroundings. Vomiting and diarrhea have also improved. Improvements in drinking and swallowing functions were also noted at one-month control examination. The patient was able to stand up for a longer period and showed an

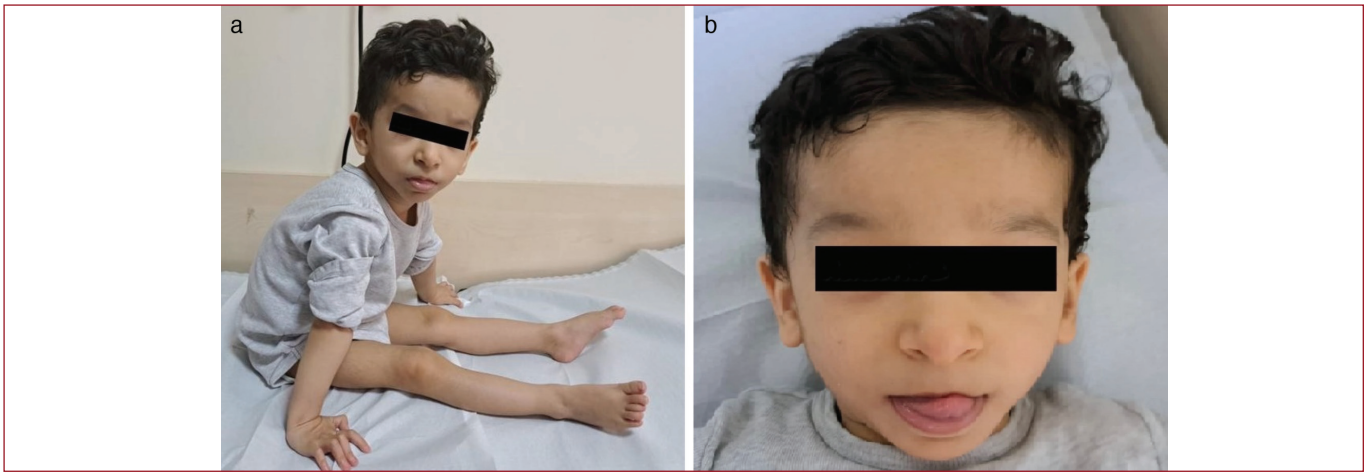

Figure 1. Characteristic features of the patient; **a)** Clinical features (hypotonia, long fingers, prominent forehead, hypertrichosis), **b)** Dysmorphic facial features (epicantal fold, ptosis, low set ears, hypertelorism).

increased awareness of his surroundings along with an improvement in his speech. Genetic analyses performed to support the diagnosis revealed heterozygous missense variation (ENST00000437172.1) c.1336G>C (p.D446H) and heterozygous missense variation (ENST00000437172.1) c.974A>G (p.H325R) in the *BTD* gene, classified as pathogenic and likely pathogenic, respectively. In molecular genetic analysis of the mother and the father, it was found that the c.1336G>C variant was originated from the father and the c.974A>G variant was originated from the mother, and these two variants were compound heterozygous in the probant.

Because patients with BTD deficiency present with a variety of clinical symptoms and rarely with the symptoms of autism, BTD enzyme activity was also evaluated in the 9-year-old older sister who had symptoms of autism. BTD enzyme activity of the sister was found to be 32% (normal if >30%). The sister was placed on biotin therapy at a daily dose of 5 mg/day due to levels close to the lower limits of normal. Laboratory tests and cranial imaging study revealed no pathological findings. Genetic analysis did not reveal any mutations in *BTD* gene, and thus ruled out BTD deficiency.

The patient was put on biotin therapy at a daly dose of 5 mg/day and a month later the dose was increased to 10 mg/day due to lack of complete clinical response. Despite the improvements with biotin therapy initially, there were no further clinical improvements with the increase in the daily dose and his neuromotor development was still not up to the normal range. The patient continues to attend outpatient visits and is back on 5 mg/day biotin therapy as well as rehabilitation and mental health support programmes.

Our patient, who was followed up with the diagnosis of LICAS syndrome, was also diagnosed with BTD deficiency. To the best of our knowledge, the presence of the two diseases in the same patient was not reported in the literature.

Discussion

BTD deficiency is common and the incidence rates in Turkey are known to be higher than the world's average due to frequent consanguineous marriages.[4] The gene responsible for BTD synthesis is located in the 3p25 region with more than 240 genetic alterations associated with the disorder.[3] The mutations that cause enzyme deficiency include "missense", "nonsense", single or multiple nucleotide deletion or insertion, and "cryptic splice site" mutations. Genotype-phenotype relationship is not clear in BTD deficiency. Deletion/insertion and "nonsense" mutations result in the absence of enzyme activity, while "missense" mutations may not cause complete absence of the enzyme activity. In cases of deficiency, carboxylases requiring biotin for their activity stop functioning.[2] Development of symptoms is inevitable in patients with profound enzyme deficiency, while patients with partial deficiency present with milder symptoms. Clinical symptoms occur generally in the first 3-6 months. The patients may present with a wide variety of clinical symptoms and complaints with an acute or chronic clinical course. In cases of attacks, patients often present with feeding and respiratory problems, alopecia, skin rash, seizures, hypotonia and ataxia. Feeding problems, vomiting and retching are observed in bulbar involvement and respiratory problems include apnea, stridor and hyperventilation. Developmental delay, conjunctivitis, fungal infections, recurrent upper respiratory tract infections and lung infections, optic atrophy and visual problems, and hearing loss are other clinical presentations.[2-4] Laboratory tests can show metabolic acidosis, ketosis, increase in organic acids and hyperammoniemia. Diagnosis is based on measurement of serum BTD activity and molecular genetic studies. The enzyme activity must be evaluated with repeated measurements for precise classification of the disorder and deliver appropriate therapy because BTD enzyme activity shows physiological variations during the day.[1,2,4] The patient's sister who was diagnosed with autism at the age of two had an enzyme activity of 32%, but the results of molecular genetic analysis did not support those findings and as a result of that, BTD deficiency was ruled out.

The affected patients respond dramatically to biotin therapy. Even though early biotin therapy can prevent development of symptoms, neurological damage in symptomatic patients may not always be reversible. Therefore, it is of great importance to establish early diagnosis and start early therapy to prevent the sequels in the central nervous system. As in the reported patient, the clinicians must be vigilant about the possibility of BTD deficiency in patients presenting with skin findings, hypotonia, vomiting and respiratory symptoms even if neonatal screening tests turn out to be negative, and early therapy must be initiated before the development of permanent complications.[2,4] Clinical symptoms develop over time in untreated patients and BTD enzyme deficiency may not be considered by the clinician in the countries implementing neonatal screening programs, as the symptoms are not specific and can be associated with other etiologies. So we evaluated patient it in terms of BTD deficiency. Although dysmorphic features such as prominent forehead, hypertelorism, low-set ears, epicanthal folds, ptosis, long fingers, hypertichosis; gastrointestinal dysmotility, developmental delay, hypotonia, seizure and congenital cardiac defects were typically associated with LICAS, skin and hair findings were inconsistent with the diagnosis. The coexistence of neurological and cutaneous findings led us to the differential diagnosis of BTD deficiency.

Neonatal screening programs using a fluorometric method have reported a sensitivity of 100% and a specificity of 97%, while a sensitivity of 90.5% and a specificity of 93.7% has been reported for spectrophotometric method. The percentage of patients found to have normal enzyme activity using spectrophotometric method, but still have this condition was reported as 9.5%, which is a significant rate.[8] The diagnosis is challenging in patients presenting with atypical and mild clinical symptoms. It is crucial to consider the diagnosis in those presenting with atypical symptoms. The symptoms in BTD deficiency are not solely dependent on the enzyme activity, but also affected by other factors such as exogenous biotin intake and biotin requirement in metabolic pathways.

The symptoms in patients with partial BTD deficiency can be milder than those with profound deficiency; however, symptoms may still be present such as skin rash, alopecia, ataxia, hypotonia and developmental delay. Most symptoms disappear with biotin therapy. Clinical symptoms such as hypotonia, seizures and skin rash can occur in partial enzyme deficiency, but keto-or lactic acidosis and organic aciduria may not be observed due to preserved carboxylase enzyme activity. Organic acidemia is observed in relation to the dysfunction of carboxylation enzymes in patients with profound BTD deficiency.[2,4,6,9] Seizure is a frequent symptom in patients with BTD deficiency, even it may be a presentng symptom. Impairment in the function of biotin-dependent carboxylases causes accumulation of neurotoxic and epileptogenic metabolites.[4] Seizures are usually generalized tonic-clonic, but there have also been described some patients with myoclonic seizures, focal seizures and infantile spasms. EEGs can be normal or mostly abnormal with burst attenuation pattern or epileptiform discharges. Cranial imaging studies show no pathological findings in the majority of patients with symptomatic BTD deficiency, but cerebral/cerebellar atrophy, cerebral edema, calcification in basal ganglia, ventriculomegaly and a decrease in the volume of white matter are the most common findings in those with pathological findings based on imaging studies.[4,10]

Biotin therapy is delivered at a dose of 5 mg/day in patients with partial enzyme deficiency and the dose may be increased to 10 mg/day in the absence of complete clinical response. The compliance of the patient to therapy is as important as the diagnosis. Patients placed on therapy during the presymtomatic period and receiving life-long therapy are known to have good prognosis. The symptoms may disappear, or become less severe or at least remain stable in patients who are put on a therapy in the symptomatic period.[2,4,6,11]

Conclusion

More than one disease can be seen in a patient. Therefore, patients may present with the symptoms of both diseases. BTD deficiency is quite common in our society and therefore, children with dermatological and neurological manifestations among its wide variety of symptoms must be evaluated for it. Analysis of the enzyme activity and genetic tests are recommended, even in patients with a negative test result as a part of the neonatal screening program, if the clinical symptoms suggest enzyme deficiency. Clinical symptoms recover rapidly with early therapy and the outcomes are satisfactory in those receiving regular life-long therapy.

Author Contributions: Arslan M: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Özbaş H: Design, Data Collection or Processing, Analysis or Interpretation, Literature Search.; Karakoç Ş: Design, Data Collection or Processing, Literature Search.; Karataş RM: Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search.

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