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Overview

The Journal of Pediatric Academy is the official publication of the Kayseri Children Health Association. The Journal of Pediatric Academy is an international, peer-reviewed, open-access electronic and conventional published journal in the English language. The Journal of Pediatric Academy is publishing as 3 issues per year. Only for 2020, the Journal of Pediatric Academy will be published in July, September, December. After 2021 the Journal of Pediatric Academy will be published regularly as April, August, and December. The journal accepts original research articles, invited review articles, clinical reports, and case reports in all areas of pediatric research, which summarize recent developments about a particular subject based on standards of excellence and expertise.

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J. Pediatr. Acad. (JPA) was established in 2020 as open access and peer-reviewed journal that accepts articles in English. J. Pediatr. Acad. (JPA) is published 3 times a year. Articles submitted should not have been previously published or be currently under consideration for publication any place else and should report original unpublished research results. The journal does not expect any fees for publication. All articles are available on the website of the journal with membership.

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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

JPA publishes the types of articles briefly described below.

Editorial Comment:

Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with a high reputation in 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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Statistical analysis is usually necessary to support conclusions. Statistical analyses must be conducted by international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

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

Table 1
Limitations for each manuscript type

Manuscript Type	Word Limit	Abstract Word Limit	Reference Limit	Table Limit	Figure Limit
Editorial comment	1500	No abstract	15	2	5
Original Article	3500	300	50	6	6
Invited Review	5000	350	100	6	10
Case Report	1500	200	15	2	5
Image corner	500	No abstract	5	-	3
Letter to the Editor	1000	No abstract	5	1	1

References:

The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. Cite the references in the text in the order of appearance. 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 Tip 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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2. High lights must be added to the manuscript.
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Invited Review

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Common Viral Infections in Children after Kidney Transplantation

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Abstract

Viral infection is a common complication among pediatric kidney transplant recipients, causing significant morbidity and mortality. Sources of viral infection in pediatric transplant recipients include donor allografts, blood products, and latent virus reactivation. Major risks of viral infection include kidney donor-derived, nosocomial and community-acquired infections as well as the immunosuppressive status of recipients. Clinical presentations are variable, ranging from no symptoms to severe disease. Preventive strategies such as immunization and pretransplant-specific viral screening in both donors and recipients are performed before kidney transplantation to identify high-risk recipients. Posttransplant prophylactic strategies include universal prophylaxis and preemptive therapy. Universal antiviral prophylaxis is required for high-risk cytomegalovirus (CMV)-mismatch pediatric recipients. Preemptive therapy requires the administration of sensitive viral surveillance tests to detect subclinical viral infections to optimize individualized immunosuppressive drugs and initiate antiviral therapy. This review summarizes current knowledge regarding common viral infections in children after kidney transplantation, including CMV, BK polyomavirus, Epstein-Barr virus (EBV), and coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Keywords: Viral infection, post kidney transplantation, pediatrics

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Introduction

Posttransplant infection is a major cause of hospitalization among pediatric kidney transplant recipients.[1] Viral infection is a common opportunistic infection after kidney transplantation. The consequences of viral infection in transplant recipients include direct effects, such as invasive organ-specific disease, or indirect effects from immune processes, resulting in allograft rejection and opportunistic infections.[2,3] These effects are associated with significant morbidity and mortality in pediatric kidney transplant recipients. Risk of viral infection depends on the specific viral status of donors and recipients, complete or incomplete pretransplantation vaccination, types of immunosuppressive drugs and routine antiviral prophylaxis regimens.[3,4] Regular viral surveillance should be routinely performed for the early detection and early management.[5,6] Pediatric kidney transplant recipients who do not undergo regular viral surveillance are at risk of developing severe viral disease.[7]

Highlights

- The consequences of viral infection in transplant recipients include direct effects, such as invasive organ-specific disease, or indirect effects from immune processes, resulting in allograft rejection and opportunistic infections.
- Risk of viral infection depends on the specific viral status of donors and recipients, complete or incomplete pretransplantation vaccination, types of immunosuppressive drugs and routine antiviral prophylaxis regimens.
- The initial treatment for viral infection post kidney transplantation is reducing immunosuppressive therapy, but doing increases the risk of allograft rejection.

Several viral infections may occur post kidney transplantation. These infections may be caused by reactivation of latent viruses due to immunosuppression or transmission from a donor allograft or blood products; such viruses include cytomegalovirus (CMV), BK polyomavirus, Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus (HSV),varicella zoster virus (VZV), and human immunodeficiency virus (HIV) . Moreover, community-acquired infections such as respiratory syncytial virus (RSV), adenovirus, influenza and coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). may also occur. This review summarizes the current knowledge regarding common viral infections that occur after kidney transplantation in children, including CMV, BK polyomavirus, EBV, and SARS-CoV-2 infections.

Timetable of and general therapy for viral infection post kidney transplantation

The pattern of viral infection after kidney transplantation changes over time and depends on 2 major factors:[3,4] **1)** recipient exposure to kidney donor-derived, nosocomial and community-acquired infections; and **2)** the immunosuppressive status of the recipient.

Phase I: 1 month post kidney transplantation

Viral infection in the early post kidney transplantation period is uncommon and is generally associated with donor-derived viral infection, which can be caused by latent viruses in donor allografts or active donor-derived infection, such as HSV and HIV infections.[3,4] Children with previous HSV may have early reactivation within 2 months post transplantation.[2] In addition, respiratory viruses may be transmitted during hospitalization due to direct contact with medical personnel, infected patients, and infected families and visitors.[3]

Phase II: 1 to 6-12 months post kidney transplantation

Several reactivations of latent viruses, such as VZV, HBV, HCV, CMV, EBV, and BK polyomavirus usually occur during this period.[3,4,8] The median time to onset of VZV reactivation is approximately 9 months post kidney transplantation.[9] Children with chronic HBV infection are at risk for reactivation within the first 3 months after kidney transplantation.[2,8] Without antiviral prophylaxis, primary CMV and EBV infection or reactivation occurs 1-6 months after kidney transplantation, but with universal antiviral prophylaxis, the onset of these infections may differ.[3,10,11] Universal antiviral prophylaxis can prevent several common viral infections, including CMV, EBV, VZV and HSV infections, during the prophylaxis period, but these viruses may occur after the cessation of antiviral prophylaxis.[3,12] Most cases of polyomavirus-associated nephropathy (PVAN) occur in the 1st year post kidney transplantation.[2] In addition, community-acquired respiratory viruses such as influenza, parainfluenza, RSV, adenovirus and foodborne gastroenteritis due to rotavirus and norovirus are still common and occur at any time of exposure.[2,3]

Phase III: More than 6-12 months post kidney transplantation

Although the risk of late-onset infection decreases at more than 6-12 months post kidney transplantation due to immunosuppressive drug weaning, community-acquired viral infections, including respiratory viral infections and foodborne gastroenteritis, can still occur.[2,3] In addition, reactivation of latent viral infections can occur, especially during treatment for allograft rejection.[2]

General therapy

In general, the initial treatment for viral infection post kidney transplantation is reducing immunosuppressive therapy, but doing increases the risk of allograft rejection.[3] Furthermore, individualized antiviral therapy and diagnosis of other coinfections are still required based on specific viruses and the severity of viral infection.

Cytomegalovirus (CMV)

CMV is a member of the betaherpesvirus family and is the most common viral infection and cause of morbidity and mortality in both adults and pediatric transplant recipients.[8]

Definitions

CMV in transplant recipients is classified into CMV infection or CMV disease. CMV infection is defined as CMV isolation or the detection of proteins (antigen, Ag) or nucleic acids in any body fluid or tissue specimen, such as plasma, whole blood, cerebrospinal fluid (CSF), bronchoalveolar lavage (BAL) fluid, urine or tissue, regardless of symptoms.[13,14] CMV disease is defined as CMV replication accompanied by symptoms.[14] CMV disease is classified further into either CMV syndrome or tissue-invasive CMV disease. CMV syndrome is defined as CMV infection with at least 2 of the following: (i) fever >38°C for at least 2 days; (ii) new or increased malaise or fatigue; (iii) a white blood cell count (WBC) <3,500 cells/cu.mm. on 2 separate measurements at least 24 hours apart if the initial WBC was >4,000 cells/cu.mm or a WBC decrease of >20% if the initial WBC was <4,000 cells/cu.mm.; (iv) atypical lymphocytes >5%; (v) thrombocytopenia with a platelet count <100,000 cell/cu.mm. if the initial platelet count was >115,000 cells/cu.mm. or a platelet count decrease of >20% if the initial platelet count was <115,000 cells/cu.mm.; or (vi) elevation of hepatic aminotransferase to 2 times the upper limit of normal.[14] Tissue-invasive CMV disease is associated with specific organ involvement, such as pneumonitis, colitis, hepatitis, retinitis, encephalitis, nephritis, myocarditis, or pancreatitis.[4,13]

Epidemiology and risk factors

The main risk factor for CMV deoxyribonucleic acid in blood (DNAemia) is the CMV serostatus of donors (D) and recipients (R). CMV recipient positivity (R+) is indicative of previous infection and immunity.[15,16] More children than adults are CMV naïve or CMV recipient negative (R-), which implies that they have no history of CMV exposure prior to kidney transplantation and do not have immunity. Therefore, CMV mismatched (donor-positive recipient-negative, D+R-) recipients have the highest risk for primary CMV infection, which is more severe than secondary CMV infection, post kidney transplantation.[4,15,17] Intermediate CMV risk is defined as CMV R+, which is associated with a substantial risk of secondary CMV infection due to either reactivation of latent CMV or superinfection (or reinfection).[14,16] Other risk factors include an intense immunosuppressive drug regimen, especially one that stimulates T cell-depleting antibodies.[3,16] A retrospective study in children demonstrated that children who received antithymocyte globulin for induction therapy developed CMV DNAemia within the first 3 months after cessation of universal antiviral prophylaxis compared with those who received anti-interleukin-2 (IL-2).[12]

Clinical manifestations

The clinical presentations of CMV infection and disease vary, ranging from no symptoms to fatal severe disease, and can be confused with those of other infections and allograft rejection.[18] The clinical presentation of CMV syndrome is nonspecific and includes symptoms such as fever, anorexia, myalgia, and arthralgia.[16] Laboratory results may show leukopenia and thrombocytopenia.[16] Children with tissue-invasive disease may present with organ-specific involvement, such as pneumonitis, colitis, hepatitis, retinitis, encephalitis, nephritis, myocarditis, or pancreatitis. The most common system affected by tissue-invasive CMV disease is the gastrointestinal system, which can result in vomiting, abdominal pain, diarrhea, and gastrointestinal hemorrhage.[10,19]

Furthermore, CMV has indirect effects, including an increased risk of allograft rejection and suppression of host immunity that predisposes patients to opportunistic infections such as EBV and human herpesvirus 6 (HHV-6) infections, fungal infections, and some bacterial infections.[2,4]

Diagnosis

Pretransplant testing

CMV IgG serology in both donors and recipients is recommended for the identification of recipients at high risk of CMV infection and can guide antiviral prophylaxis post kidney transplantation.[3,14] However, the passive transfer of CMV IgG from mothers to infants can produce false positive results in infants less than 1 year of age.[3]

Posttransplant testing

Quantitative CMV viral load: The diagnosis of CMV DNAemia is the presence of CMV DNA in whole blood or plasma.[4,16] Currently, quantitative nucleic acid amplification testing (QNAT) in whole blood or plasma for CMV viral load is the gold standard for the diagnosis and monitoring of CMV DNAemia, but the CMV viral load threshold is controversial.[14] A highly sensitive QNAT assay is suggested, which has a lower limit of quantification (LLOQ) <200 IU/ml.[14] However, a LLOQ <10 IU/ml is too sensitive and may detect latent CMV DNA, which is not clinically significant. In contrast, a LLOQ >1,000 IU/ml is too insensitive and is not recommended.[14] Antigenemia assays, such as pp65 and pp67 antigen detection, and semiquantitative fluorescence assays are no longer recommended.[2]

Tissue biopsy: CMV tissue-invasive disease generally requires tissue histopathology for a definitive diagnosis. The presence of CMV inclusion or immunostaining is the gold standard for the diagnosis of CMV tissue-invasive disease.[3] However, the presence of organ-specific symptoms combined with the detection of CMV DNAemia is adequate for the clinical diagnosis of CMV tissue-invasive disease.[16] In contrast, the absence of CMV DNAemia cannot exclude CMV disease in children who have organ-specific symptoms.[14,16] The CMV viral load during CMV infection of the gastrointestinal tract or central nervous system (CNS) is generally lower than that at other sites.[3] Tissue biopsy is still required in children who are treated with antiviral therapy and do not respond.

CMV serology: CMV seroconversion is defined as the presence of CMV IgG post kidney transplantation in CMV R- patients. The seroconversion rate in solid organ transplant patients is approximately 75% at 12 months post transplantation in patients receiving universal antiviral prophylaxis, and the detection of

CMV IgG at 6 months post kidney transplantation is associated with a decreased risk of late CMV disease at 6-12 months post transplantation.[20] However, CMV IgM and seroconversion of CMV IgG are not useful for the diagnosis of acute infection because of the delay in conversion.[3]

Treatment

According to the Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation, the recommendation for children is based mostly on adult data.[14] Ganciclovir is the primary antiviral agent to treat CMV disease by inhibiting CMV replication.[8] Valganciclovir is a prodrug of ganciclovir that is also used for the treatment of asymptomatic CMV DNAemia. However, initial treatment of severe CMV disease with intravenous ganciclovir in children is still recommended.[14] Once-weekly CMV surveillance is recommended to monitor response to antiviral therapy and discontinue therapy after CMV negativity by highly sensitive QNAT (LLOQ <200 IU/ml) 1 time or CMV negativity by non-highly sensitive QNAT (LLOQ >200 IU/ml) 2 consecutive times.[14] A recent study demonstrated that a CMV viral load <137 IU/ml, as measured by a test calibrated to the World Health Organization (WHO) standard, is predictive of clinical response to antiviral treatment.[21]

In addition to antiviral therapy, reduction in immunosuppressive therapy is an important adjunctive therapy if possible. Conversion to mTOR inhibitors may be useful to reduce the risk of recurrent CMV DNAemia, especially in patients at high risk of CMV infection.[14,22] There is no strong data supporting the use of CMV IgG and intravenous immune globulin (IVIG) in combination with antiviral therapy.[3,14]

Prevention

Currently, there are 3 strategies for CMV infection prevention in pediatric kidney transplant recipients: universal prophylaxis, preemptive therapy, and the sequential approach, depending on risk.[14] With universal prophylaxis, antiviral prophylaxis is provided to children at high risk of CMV infection, which is defined as CMV D+R- or receiving T cell-depleting antibodies, for 3-6 months post kidney transplantation.14 Although valganciclovir is widely used among adult kidney transplant recipients, pharmacokinetic data in pediatric patients are limited to only older children.[23-25] Furthermore, the risk of DNAemia is highest during the 3 months after antiviral prophylaxis cessation, so surveillance needs to be continued during this time period.[12,14]

For preemptive therapy, antiviral therapy is started when QNAT detects CMV before the development of CMV disease.[14] Unfortunately, the optimal CMV viral load threshold to initiate therapy is still controversial because of the variability in diagnostic tests. The sequential approach involves a short duration, typically 2-4 weeks, of antiviral prophylaxis, followed by regular CMV surveillance.[14] Children with intermediate CMV risk (R+) can receive universal prophylaxis, preemptive therapy or the sequential approach.[14] Weekly surveillance for CMV DNAemia for at least 3-4 months post transplantation is recommended.[20] Secondary antiviral prophylaxis might be advantageous in children with recurrent CMV DNAemia, but the proper duration is still unclear.[14] Although there are several studies on and developments in CMV vaccines, they are mostly in phase I and phase II trials.

Polyomavirus

Polyomavirus is a small DNA virus. Primary infection in an immunocompetent host is subclinical or induces respiratory tract symptoms; subsequently, the virus becomes latent in renal tubular epithelial cells or the uroepithelium.[26,27] The two well-known human polyomaviruses are polyomavirus hominis type 1 or BK virus (BKV) and polyomavirus hominis type 2 or JC virus (JCV). The BK seropositivity rate in children less than 18 years of age is approximately 5-65% and in adults is more than 80%.[28-30] Immunocompetent children are usually asymptomatic, but polyomavirus can reactivate after kidney transplantation and initially induce no symptoms but subsequently lead to PVAN in up to 10% of patients and graft loss in approximately 10-100% of patients.[3,31,32]

Definition

Polyomavirus infection is defined as serological or virological evidence of polyomavirus exposure regardless of viral replication or latency.[31] Primary and secondary infections are detected in seronegative and seropositive individuals pre kidney transplantation, respectively. Polyomavirus disease is defined as evidence of polyomavirus in the tissue of the involved organ.[31]

Epidemiology and risk factors

The prevalence of PVAN ranges from 1.1 to 10.3%.[31] Most PVAN is caused by BKV, although there are a few case reports of PVAN due to JCV.[33-36] The major presentation of JCV is CNS disease with no renal involvement.[3] The main risk factors for BK viremia and PVAN are intense immunosuppressive regimens, especially regimens including high-dose tacrolimus, high-dose mycophenolate mofetil (MMF), T cell-depleting antibodies, and antirejection therapy.[2,26,31,37] Most PVAN occurs within the 1st year of kidney transplantation due to intense immunosuppressive drug use.[38,39] Retransplantation due to PVAN is also a risk factor for reinfection in a new allograft.[3]

Clinical manifestations

The majority of recipients with polyomavirus infection are asymptomatic.[2] Some children present with sterile pyuria, ureteral stenosis and hemorrhagic cystitis.[2,8,35,40] Children with ureteral stenosis may present with signs of urinary tract obstruction or elevated creatinine levels. In addition, an acute or gradual decline in renal function is usually a common presentation of PVAN.[2,8] Some children present with fever, but this is not the usual presentation and may mimic acute rejection or other infections.[8]

Diagnosis

Viral replication occurs in a usual sequence. After BKV reactivation, the virus initially replicates in renal tubular cells, leading to tubular damage and resulting in viruria. Subsequently, BKV enters peritubular capillaries, resulting in BK viremia, at a median of 4 weeks later. Finally, PVAN developed at a median of 4 weeks later.[26]

Urine cytology: Decoy cells include infected tubular and ureteral epithelial cells that can be observed on urine cytology and serve as a marker of high levels of urine BK DNA. Although urine decoy cells are used in screening for PVAN, the sensitivity, specificity, and positive predictive value (PPV) are only 66.7%, 88.6%, and 11.7%, respectively.[41]

Quantitative BK viral load in urine: The detection of a low BK viral load in urine commonly occurs in immunocompetent hosts without clinical consequences.[42] However, a post-kidney transplantation urine BK viral load of >107 copies/ml is increasingly predictive of PVAN, although it is not highly specific.[3,36] In addition, some patients with BK viruria do not develop BK viremia, and the detection of BK viruria is not cost efficient in a clinical setting.[43]

Quantitative BK viral load in plasma: A BK viral load >10,000 copies/ml detected by polymerase chain reaction (PCR) quantification has a good PPV and 93% specificity for PVAN.[26,44,45]

Allograft biopsy: Allograft biopsy should be performed when the BK viral load in plasma is >10,000 copies/ml with or without elevated creatinine because of its high association with PVAN.[3,26] Histopathological findings include interstitial inflammation in early infection that progresses to tubular atrophy and interstitial fibrosis.[46,47] In addition, allograft rejection may coexist with PVAN.[48-50] The definitive diagnosis of PVAN includes the presence of viral inclusion bodies, the detection of simian virus 40 (SV40) on staining or in situ hybridization for BK virus genetic sequences, but the lesions of PVAN are usually focal and easily missed.[3,26,46,47] Presumptive PVAN is defined as the presence of a BK viral load >10,000 copies/ml with no evidence of polyomavirus in allograft tissue.[26]

Treatment

Since there is no specific antiviral therapy for polyomavirus infection, the mainstay of treatment is a reduction in immunosuppression when there is evidence of viral replication, especially when the BK viral load is higher than 10,000 copies/ml.[2,26,51] The goal of immunosuppressive drug reduction is to restore immunity against polyomavirus, but this increases the risk of acute rejection, which is associated with poor renal outcomes.[52] There is currently no consensus protocol for immunosuppressive reduction. According to recent guidelines,[26,51] a common practice is to half or withdraw the antimetabolite drug (azathioprine or MMF) and to reduce the calcineurin inhibitor target level. In addition, switching from the antimetabolite drug to leflunomide is also commonly used. Leflunomide has both immunosuppressive and antiviral activities.[53,54] To date, there are limited data on the use of fluoroquinolones and IVIG for treating PVAN.[3,26] Treatment for cooccurring PVAN and acute rejection remains unclear.[55]

Prevention

Currently, there is no single standard strategy to prevent BK reactivation.[26] BK viral load monitoring and early identification of BK viremia allow early intervention to prevent progression to PVAN. According to recent guidelines, QNAT to detect the BK viral load in plasma is the main screening method and should be performed monthly for the first 3-6 months and then every 3 months for the first year post kidney transplantation, when there is an unexplained elevation in the creatinine level, and after treatment for acute rejection.[26,31]

Epstein-Barr virus (EBV)

EBV is in the gammaherpesvirus family.[8] Most children in developing countries are infected with primary EBV before 5 years of age.[56,57] In contrast, EBV infection in developed countries occurs in late adolescence or adulthood.[56,57] After primary infection in an immunocompetent host, EBV remains latent in lymphocytes and reactivates due to immunosuppression after kidney transplantation.[8] However, the majority of symptomatic EBV infections post kidney transplantation are due to EBV-mismatched recipients (EBV D+R-).[8,57] EBV is detected in more than 90% of patients with early posttransplant lymphoproliferative disorders (PTLDs) after kidney transplantation and is an uncommon but fatal complication.[2,3,57,58] The role of EBV in late PTLDs is uncertain.

Epidemiology and risk factors

Primary EBV infection usually occurs within the 1st year post kidney transplantation.[3] The majority of EBV-naïve (EBV R-) patients are pediatric patients, so they are at risk of developing primary infection and subsequently early PTLDs than adults.[57] The major risk factor for EBV infection is intense immunosuppression, especially in patients receiving T cell-depleting antibodies and OKT3.[2,8] A persistently high level of EBV DNAemia post kidney transplantation may indicate a risk of PTLD.[3,59]

PTLD is more common in children (up to 20%) than adults (less than 1%) post kidney transplantation and can present with a bimodal pattern of onset in the first year post transplant; it can also present late, at 5-10 years post transplantation.[3,60-62] Risk factors for early PTLD (<12 months) include primary EBV infection, young recipient age, and polyclonal antilymphocyte antibody use.[57,62-65] In contrast, risk factors for late PTLD (>12 months) include duration of immunosuppression and older recipient age.[57,62-65]

Clinical features

Children with EBV DNAemia are usually asymptomatic. The clinical manifestation of EBV disease (non-PTLD) includes infectious mononucleosis, including fever, exudative tonsillitis, lymphadenopathy, hepatosplenomegaly and atypical lymphocytosis.[2,57] Some children present with organ-specific symptoms such as hepatitis, pneumonitis, pancreatitis, meningitis,

leukopenia, or thrombocytopenia.[2,57] However, some of these clinical manifestations are similar to those associated with PTLDs. Patients with graft dysfunction as well as EBV DNAemia should be evaluated for PTLDs and graft rejection.[3]

PTLDs can affect either allografts or other organs; the clinical presentation is based on organ involvement and can include abdominal pain or mass, gastrointestinal bleeding, obstruction, perforation, hepatic or pancreatic dysfunction, headache, other CNS disease, allograft dysfunction, or pulmonary nodules or infiltration.[2,3] In addition, some children present with nonspecific symptoms, including unexplained fever and weight loss.[3] The definitive diagnosis of PTLDs requires tissue biopsy.[8]

Diagnosis

Pretransplant testing

EBV serology: Screening by EBV serology in both donors and recipients is recommended for the prediction of EBV DNAemia risk.[57] Antiviral capsid antigen (VCA) IgG and anti-Epstein-Barr virus nuclear antigen (EBNA) IgG are recommended for screening tests. However, the passive transfer of EBV IgG from mother to child can produce a false positive in infants less than 1 year of age.[57]

Posttransplant testing

Quantitative EBV viral load: According to a recent recommendation,[51,57] QNAT for EBV should be performed in children at high risk of primary EBV infection and PTLD development, including in EBV-mismatched children (EBV D+, R-) once in the first week after transplant, at least monthly for the first 3-6 months, and then every 3 months for the first year post transplant, and after treatment for acute rejection. Quantitative EBV viral load using assays calibrated to the WHO standard for EBV DNA is recommended.[57] There is currently no consensus on the exact threshold level to start treatment. There is no evidence that surveillance is beneficial in patients who are EBV R+.[57]

Tissue biopsy: EBV can be detected in specific organ involvement. In some settings, tissue biopsy is required to diagnose EBV disease and PTLDs, as defined by the WHO.[66]

EBV serology: Anti-VCA and anti-EBNA IgM are used to diagnose primary infection in immunocompetent hosts, but the response in immunocompromised hosts, including posttransplant hosts, is delayed.[3,56,57] Therefore, EBV serology is not useful for the diagnosis of early EBV infection, and the detection of EBV DNAemia according to EBV viral load is preferable.[2] In addition, children who are EBV-naïve pre transplantation should undergo EBV IgG detection annually to determine their risk of developing primary EBV infection.[57]

Treatment

A reduction in immunosuppressive drugs is recommended when there is evidence of increasing EBV viral load, EBV disease or PTLDs, but this increases the risk of allograft rejection.[3,51] A persistently high EBV viral load should be reevaluated for PTLDs.[3,67] Cessation of immunosuppressive drugs might be necessary in some cases of PTLDs.[51] To date, there are no conclusive data on the role of antiviral therapy in PTLDs.

Prevention

Although a universal antiviral prophylaxis strategy in high-risk EBV children (EBV D+R-) is used in some transplant centers, there are no sufficient data to support the routine use of prophylaxis to prevent either primary EBV infection or PTLDs.[3,68-70] A recent meta-analysis[71] did not demonstrate a benefit of antiviral prophylaxis in reducing the incidence of PTLDs. Therefore, the use of universal prophylaxis in EBV mismatches is not recommended.[57] EBV viral load surveillance and preemptive therapy are recommended in EBV-mismatched patients.[57,61,62,72] Initial preemptive therapy involves a reduction in immunosuppressive drugs.[73] The role of antiviral therapy, IVIG, or conversion to an mTOR inhibitor or rituximab is uncertain.[57,73] Research and development of EBV vaccines are ongoing; there are currently no EBV vaccine options available.[74-76]

Coronavirus-19 (COVID-19)

The number of kidney transplantation procedures has decreased during the COVID-19 pandemic.[77] COVID-19 is caused by SARs-CoV-2 infection. The overall deceased donor transplantation rates during the COVID-19 outbreak in France and the USA were 90.6% and 51.1%, respectively.[77] A recent study demonstrated that patients who were waitlisted for kidney transplantation had an increased risk of hospitalization and mortality.[78] The first concern regarding kidney transplantation are the immunosuppressive status of recipients and the risk for COVID-19. The second concern is that there might be inadequate equipment, medical personnel, and intensive care unit resources post kidney transplantation. The third concern is the risk of potential transmission of COVID-19 from a kidney donor to a recipient. Almost all studies on COVID-19 among transplant recipients have been conducted in adults.

Clinical features

The most common presentations are similar to those in nontransplant patients and include fever, cough, dyspnea, and diarrhea.[79-81] In addition, lymphopenia is common in transplant recipients.[80,81] However, transplant recipients have more rapid clinical progression and higher mortality than nontransplant patients.[80,81] Thirty-day mortality was approximately 20-23% in hospitalized adult recipients.[81,82]

The criteria for testing for COVID-19 in kidney transplant recipients are similar to those in nontransplant patients.[83] Routine screening of asymptomatic kidney transplant recipients is not recommended.

Diagnosis

All donors and recipients are recommended to undergo COVID-19 screening to prevent donor-derived infection and adjust the immunosuppressive drug regimen. Reverse-transcriptase polymerase chain reaction (RT-PCR) assays of respiratory tract specimens should be

used for screening.[84,85] This assay has high sensitivity, with detection ranging from 100 to 1,000 copies, and high specificity.[84] Antigen tests of nasopharyngeal swabs are generally less sensitive than RT-PCR but have a shorter turnaround time.[86]

Treatment

General management in kidney transplant recipients is similar to that in nontransplant patients.[87] The general approach is to reduce immunosuppressive drugs in patients with moderate to severe infection, but the optimal strategy is not well defined.[79,81,87,88] Many observational studies suggest decreasing or withdrawing antimetabolite drugs such as mycophenolate mofetil and azathioprine.[79-81,88]

Several COVID-19 drugs have potential drug-drug interactions with immunosuppressive drugs, including tacrolimus, cyclosporine, mycophenolate mofetil, everolimus, and sirolimus, so therapeutic drug monitoring (TDM) is recommended.[89]

Conclusion

Viral infection is still a common opportunistic infection in children post kidney transplantation and must be considered in the differential diagnosis. Appropriate pretransplant screening and posttransplant surveillance may help with early diagnosis. In addition, appropriate antiviral prophylaxis and early management have improved patient and allograft outcomes.

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Long-Term Follow-Up of Adolescent and Adult Patients with Cystic Fibrosis: A Single Center's Experience

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Abstract

Cystic fibrosis (CF) is a chronic disease with autosomal recessive inheritance, chlorine duct defect, and multisystemic involvement. In this study, we evaluated the problems of our adolescent and adult patients with CF who were followed up in our unit to determine their problems at the regional level, to better observe their treatments, and to offer solutions for complications that occurred during their follow-up. Sixty-five patients with CF (50 adolescents and 15 adults) who consulted our clinic between September 2008 and November 2020 were included in this study, and their retrospective data were reviewed and saved. The mean age of the patients was 17.2±6.21 years, and the mean age at diagnosis was 7.1 years. Nearly three-quarters (73.8%) of the patients were adolescents, 26.2% were adults. Their mean body mass index (BMI) was 18.81±4.06 kg/m2. The mean FEV_1 was 82.94±25.22% in the adolescent group and 64.47 ±28.47% in the adult group. Pseudo-Bartter syndrome was the most common clinical presentation in adolescents (44%) and productive cough 28.6% was most common in adults. The rate of bronchiectasis was 73.6% in the adults and 29.2% in the adolescents. CF-related diabetes was seen in 33.3% of the adults and 8.3% of the adolescents. Gastroesophageal reflux disease was present in 25.5% of the adolescents, but it was not seen in the adults. Mortality was 20.0% in the adult group and 4.1% in the adolescents. There was no significant difference between the groups regarding BMI, chronic pseudomonas colonization, and pulmonary exacerbation. In both groups, the most common allele (21.8%) was delf508. We saw that the disease complications were less in the adolescent group. We thought that early diagnosis and treatment were related to this condition.

Keywords: Cystic fibrosis, adults, adolescents

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Introduction

Cystic fibrosis has an autosomal recessive inheritance model with an incidence varying between populations, and it is common in Caucasians.[1] A protein called cystic fibrosis transmembrane conductance regulator (CFTR) is synthesized from the CF gene.[2,3] Structural and functional disorder in the CFTR protein leads to the disruption of the ion transport in the epithelial cell plasma membrane of the organs such as lungs, pancreas, liver, intestines, sweat glands, and epididymis.[4]

Highlights

- Cystic fibrosis is more mortal in the late diagnosed adult patient group
- Early diagnosis and treatment increases life expectancy by reducing disease complications.
- As in childhood, the adult patient group should also be followed up with a multidisciplinary approach.

According to the reports of the Cystic Fibrosis Foundation Patient Registry (CFFPR), the total number of patients diagnosed as having CF in 2018 was 30,770. Some 54.6% of these patients were adults. The number of adult patients has increased in recent years, but pediatric patient numbers have remained stable. Similarly, it was found that among the total population of 293,028,000 in the United States of America, there were 23,347 patients with CF, with a prevalence of 0.797/10,000, and its frequency was 1/3000.[5] According to the 2017 results for the Central Anatolia Region of Turkey, the frequency was 2.9/10,000 (1/3400 live births).[6]

The most involved organ in CF is the lungs, but clinical findings vary according to the patient's age, genetic mutation, involved systems, and disease severity.[7] Many factors determine the amount of lung damage in CF. It is known that the pulmonary disease of individuals with severe mutations progresses rapidly, and the respiratory problems individuals with slight mutations are at a light level.[8] However, the mutation type is not effective alone in determining lung damage. Apart from the type of mutation, female sex, pancreatic failure, growth retardation, poor environmental conditions (encountering microorganisms, exposure to cigarette smoke, incompliance with treatment at a young age), not being able to bring diabetes under control, and mutations in other regulator genes that affect the anti-inflammatory and antioxidant systems are other factors that causing rapid disruptions of pulmonary functions.[9]

Although life expectancy was very low in CF in previous years, it has increased as a result of the early recognition of the disease through the inclusion of CF in newborn screening programs, developments in treatment, developed respiratory physiotherapy methods, the increase in the foundation of CF follow-up centers, and improvements in disease consciousness by informing patients and their families. It has also become a multidisciplinary topic involving endocrinology, gynecology, urology, general surgery, and especially chest diseases, regarding the follow-up and treatment of patients other than children. In our country, Turkey, CF was included in the screening program in 2015.[10]

In our study, we aimed to retrospectively examine adolescent patients followed up in our Pediatric Chest Diseases unit and adult patients with CF.

Material and Method

Necmettin Erbakan Üniversity,Meram Faculty of Medicine Ethics Committee was obtained for this study (Date:18.09.2020, Decision No:2020/2815).

In accordance with the definition of the American Academy of Pediatrics (AAP), we grouped our patients as adolescents between the ages of 10-18 years and adults as those aged over 18 years.[11] This study included 50 adolescents and 15 adult patients with CF, who had presented to our clinic between September 2008 and November 2020. The outpatient clinic records of the last one year were examined.

These files were reviewed retrospectively, and information within the period between the time of diagnosis and the last follow-up was recorded. When CF was first suspected, all patients were diagnosed using the quantitative sweat chloride test in addition to clinical findings, and mutation examinations were performed for all patients. The patients were monitored in 3-month routine follow-ups, and the patients' clinical characteristics, examination findings, laboratory examinations, mutation analysis results, ultrasound results, sputum culture results, respiratory function tests, treatments, and complications that emerged during follow-up were recorded in their files at each appointment.

Statistical Analysis

The SPSS 2022 software package was used in the evaluation of numerical data. Student's t-test was used when numerical data were normally distributed, and the Mann-Whitney U test was used when they were not distributed normally. The Chi-square test was used for the evaluation of categorical data. $P<0.05$ was considered statistically significant.

Results

A total of 258 patients with CF were being monitored in our clinic. Sixty-five patients - 50 adolescents and 15 adults - were included in the study. This group accounted for 25.1% of the total patient number (6.5% were adults, and 18.6% were adolescents). Of the patients included in the study, 26.2% were adults, and 73.8% were adolescents, 44.6% (n=29) were male and 55.4% (n=36) were female. A family relation was present among 6.9% of the total number of patients (brothers/cousins). The mean age of our patients was 17.2±6.21(range, 10.5-43) years, and the mean age at diagnosis was 7.05 ±8.93 years (median: 2.5 years; range,1 month - 40 years). Five (7.6%) patients died. Eight (12.3%) patients did not attend their follow-ups regularly. **Table 1** shows the epidemiological and clinical characteristics of the patients.

The most common symptom at presentation was pseudo-Bartter syndrome (PBS) at a rate of 30%, which was followed by the medical history of the sibling at a rate of 15%, and then frequent pneumonia and growth and developmental delay. Diagnostic symptom and findings of the patients were shown in **Figure 1**.

Table 1.
The epidemiological and clinical characteristics of CF patients

RESULTS	Total	Adolescent	Adult	p
Number	65	50 (73.8%)	15 (26.2%)	
Sex F/M	55.3% / 44.7%	42.1% / 47.9%	60% / 40%	
Mean age	7.05±8.93 (1 month-40 years	4.18±4.87	16.28±12.41	0.001
Median age	2.5	0.84	15	
Last age Min: Max: Mean:	 10 years, 3 months 43 years 14.9 years	 10.25 months 17 years 13.3±2.11 years	 18 43 24.96±6.78	
Clinical presentation	PSB: 24.5% Growth retardation: 11.8% Relative: 10.9%	PSB: 44% Relative: 14.9% Growth retardation: 8.5%	Productive cough: 28.6% Relative: 21.4% Infertility: 21.4%	0.004
Mean FEV1	82.94±25.22	88.71±21.33	64.47±28.47	0.001
Mean BMI	18.81±4.06	F:17.85±4.48 M:18.45±3.17	F:22.29±3.03 M:19.03±4.87	>0.05
Pseudomonas colonization	39.3% (n=24)	36.2% (n=17)	50% (n=7)	>0.05
MRSA	14.5% (n=9)	14.9% (n=7)	13.3% (n=2)	>0.05
pulmonary exacerbation (last year)	24.5% (n=16)	22.9% (n=11)	33.3% (n=5)	>0.05
Asthma	37.1% (n=23)	38.5% (n=18)	33.3% (n=5)	>0.05
GERD	19.7% (n=12)	25.5% (n=12)	0	0.004
CFRD	14.3% (n=9)	8.3% (n=4)	33.3% (n=5)	0.017
Sinusitis	36.8% (n=23)	39.6% (n=19)	26.7% (n=4)	>0.05
Polyp	20.6% (n=13)	20.8% (n=10)	20.0% (n=3)	>0.05
Polypectomy	7.9% (n=5)	8.3% (n=4)	6.6% (n=1)	>0.05
Pancreatitis	15.3% (n=10)	14.5% (n=7)	20.0% (n=3)	>0.05
Z score	-1.0±1.38	-0.98±1.27	-1.07±1.73	>0.05
Bronchiectasis	39.7% (n=25)	29.2% (n=14)	73.6% (n=11)	0.035
Mortality	7.6% (n=5)	4.1% (n=2)	20.0% (n=3)	0.004
Mutations	Delf508: 23.1% N1303K: 8.7% G85E: 7.1%	Delf508: 23% G85E: 8.7% N1303K: 5.4%	Delf508: 16.6% N1303K: 16.6% D1152H	0.05

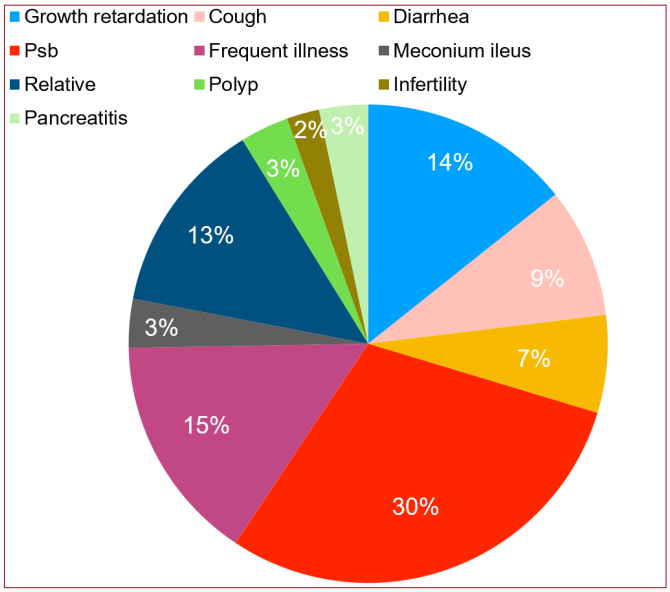

Figure 1. Symptoms and clinical findings of CF patients at the admission

The most common allele was delf508 with 23.1%, followed by N1303K with 8.9%. In 13.8% (n=9) patients, the delf508 mutation was found to be homozygous. In 10.7% (n=7) patients, this mutation was identified in a single allele of the patients. The mutation analysis of the patients are shown in **Table 2**.

Table 2.
The mutation alleles of the patients

Allele gene	Patients n (%)
Delf508	26 (23.1%)
N1303K	10 (8.9%)
G85E	8 (7.1%)
D1152H	6 (5.3%)
I1051V	4 (3.5%)
c.3849+5G>A	4 (3.5%)
R334W	4 (3.5%)
delTA	3 (2.6%)
G542X	3 (2.6%)

R785X, L568F, F1052V, 2694T/G, 4521G/A, and L732X were seen in only 2 alleles and 125G<C, 2789+56>A, E217G, D110H, R170H, 1248+1G>A, G576A, R668C, S1455X,1234VI, 2183delAA, I1295, E831X were seen in only 1 allele.

The last percentiles of patients were as follows: heights and body weights of 26% (n=13) patients were below the 3rd percentile. Five (7.6%) of our patients were diagnosed as having allergic bronchopulmonary aspergillosis (ABPA). Two patients who developed ABPA were among the patients who died.

Throat and sputum cultures were taken in the regular follow-up of our patients.The mean age of the first microorganisms growing in throat and sputum cultures is 10.8 years.

Pseudomonas aeruginosa was the first microorganism that detected in 29.2% (n=19) patients, *Staphylococcus aureus* was first to detected in 18% (n=12) patients. Chronic pseudomonas colonization was seen in 39.3% (n=24) patients and 14.5% (n=4) of the patients with Methicillin-resistant *Staphylococcus aureus* (MRSA). No nontuberculous mycobacteria detected was observed in any patients. The patient who had *Burkholderia cepacia* also died. Nine (14.3%) patients were diagnosed as having CFRD, and they received insulin treatment. Two patients who developed diabetes were among the patients who died. The glycated hemoglobin (HbA1c) values of 15.2% (n=10) of patients were 6 years and over.

Osteopenia was observed in 60% (n=39) of patients, and osteoporosis in two patients who could be evaluated with bone densitometry over the last 5 years.

Twenty-five (35%) patients regularly performed airway cleaning. The treatments used by patients are shown in **Table 3**.

Table 3.
The treatments prescribed to the patients

Treatment	Patient number	Patient percentage (%)
Pancreatic lipase	51	78.8
Dornase alfa	49	75.4
Inhaler antibiotic	8	11.7
Inhaler mannitol	25	39
Ursodeoxycholic acid	24	21.1
Inhaler Ventolin	38	57.6
Inhaler corticosteroid	22	34.6
Azithromycin	4	5.7
Oral corticosteroid	22	34.6
Hypertonic saline	16	25

One (1.7%) patient who had oxygen support was also waiting for lung transplantation. One patient who had non-invasive mechanic ventilation support died.

One (1.5%) patient underwent lung transplantation, and two (3%) patients are waiting to undergo lung transplantation.

Eighteen (27.6%) patients are using enteral products in addition to their diets. Two patients underwent gastrostomy.

In the last 1 year, 25.4% (n=16) of our patients received IV antibiotics for lung exacerbations. In terms of the gastrointestinal system (GIS) complications of the disease, 4.6% (n=3) patients developed cirrhosis, and three underwent liver transplantation.

Fifteen percent of the patients had vitamin A deficiency, 16.6% had vitamin E deficiency, and 64.6% had vitamin D deficiency.

Considering the socioeconomic level of our patients, 40% (n=6) adult patients worked full time. Nineteen (29.2%) patients are receiving primary education, and 34.6% (n=18) patients are studying in high school. Three (5.2%) patients are at university. Eight patients are married, and three have children. We have three patients who are receiving treatment for infertility.

Discussion

CF is the most common disease with an autosomal recessive inheritance pattern in Caucasians, together with a carrier frequency of approximately 1/25 and a live birth incidence of 1/2000-3500.[11,12] The risk of developing the disease increases in countries such as Turkey, where consanguineous marriage is common. According to the data of the 2008 Turkey Demographic and Health Research, consanguineous marriage had an extremely high rate, 24.1%,[8] its frequency in the Central Anatolia Region was found as 2.9/10,000 in the study of Hangul et al.[6]

In light of the current information about CF, early diagnosis, new treatment methods, increase in families' awareness about the disease, and treatment adherence prolongs the lives of patients with CF, worldwide. Therefore, with the increase in the number of appropriate centers where adult patients with CF can be monitored, the number of children with CF has remained stable in the United Kingdom over the years, but the number of patients with CF in adult clinics is increasing. This increase is also predicted to continue in this way in all countries in the coming years.[1]

According to the CFFPR, the adult group increased from 29.4% to 54.6% when 1988 and 2019 were compared, and in the 2018 patient data report of the European Cystic Fibrosis Society (ECFS), 51.2% of patients were reported to be adults. According to the national cystic fibrosis registry system in Turkey (UKKS), the oldest patient was aged 41 years, and the adult patient group constituted only 4.6% of the total group. In our study, on the other hand, the adult group accounted for 6.5% of the entire group. It is still observed to be low when compared with Europe and America. According to the CFFPR, the adolescent group formed 25% of all patients. The reason for the higher number of patients in the adolescent age group than in the adult group was that pediatric chest diseases cover a period of 12 years, and every diagnosed patient had reached an adolescent age within this period, whereas the other group was included in the follow-up with late diagnosis.

The most common clinical presentation was PSB in the adolescent group and bronchiectasis in the adult group. There was a significant difference between the groups in terms of bronchiectasis and PSB (p=0.035, p=0.004, respectively).

According to the CFFPR, the median survival age was 26 years in 1988; however, the median survival age was 47.4 (range, 44.2-50.3) years in 2019. These data have shown that CF is now a disease monitored in childhood, and lifespans can also be prolonged with meticulous monitoring and treatment in adulthood.

It is important to provide nutrition and growth at an optimal level in the follow-up of individuals with CF

because nutritional status is directly related to respiratory functions and lifespan.[12] In patients with low BMI, FEV_1 drops, and a low FEV_1 leads to frequent hospitalization, and frequently sickness causes a further drop in BMI.[6,13] According to the CFFPR, the targeted BMI for children with CF should be ≥50 percentile in older children and adolescents. In line with this report, when adult BMI values are above 22 kg/m² in women and 23 kg/m² in men, FEV_1% rises above 60, and the increase in FEV_1 continues the same way as in increased BMI values.[14,15] Considering the ECFS 2018 data, BMI was reported as 20.7-21.7 kg/m² for the 18-38 years' age range, and 23 kg/m² for those aged 38 years and over. In our study, there was a similarity with the results of Europe in both sexes. Malnutrition was observed in 20% (n=14) of patients in total. This showed that we need to be more careful about the nutrition of malnourished patients and monitor them closely for vitamin support and weight. Improvements in the nutrition of patients will provide better lung functions and thus increase the survival of our patients.

Annual changes in FEV_1 are followed for patients with CF. Improving FEV_1 and preventing its decrease are the main objectives of treatment methods developed for protecting the lungs and keeping them healthy in CF. According to the CFFPR, the FEV_1 rate has been reported as 88% for age 18 years and 69% for age 30 years. For the ECFS, mean FEV_1 is 92% for the adolescent group, whereas it is 69% in adults.[16] According to the cystic fibrosis patient registry in Turkey (UKKS) the estimated mean FEV_1 is 86%.[17] In our patients, the mean FEV_1 value was found as 82.94±25.22%. There was a significant difference between the groups (p=0.001). Due to the low FEV_1 in the adult group, the need for lung transplantation has a higher rate in this group. In seven patients, FEV_1 was found to be below 40%. Regular and effective cleaning of the airway, detection and treatment of lung inflammation, and chest physiotherapy are factors that slow down the FEV_1 decrease in our patients. In our study, 25% of our patients cleaned their airway. We thought that our patients did not perform their respiratory tract physiotherapy regularly. We associated this result with the lack of awareness of our patients because there were no respiratory tract physiotherapists in our clinics.

Frequent infections in CF, colonizations, and lung inflammation are significant causes of lung damage. Infections that cause this damage are *Haemophilus influenzae* and *Staphylococcus aureus* in young ages, and *Pseudomonas aeruginosa* is observed as age increases. The rarer ones are bacteria with multiple antibiotic resistance such as *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and *A. xylosoxidans*. According to the CFFPR, culture positivity was obtained in 45.3% of patients for *Pseudomonas aeruginosa*, and chronic pseudomonas colonization was seen in 28.3%; MRSA by 25%, *Stenotrophomonas maltophilia* by 12%, and *Burkholderia cepacia* by 3%. According to the ECFS, the average incidence of chronic pseudomonas infection was 30% in total, 24.4% in the adolescent group, and 48% in the adult group. In the UKKS, chronic pseudomonas infection was reported as 20.9%, chronic *Staphylococcus aureus* as 25.2%, and *Burkholderia cepacia* as 1.2%. In our patients, similar results to the CFFPR and ECFS were obtained in terms of chronic pseudomonas reproduction, and there was no significant difference between the groups (p>0.05). MRSA colonization reproduction was found at a lower rate. No nontuberculous mycobacteria reproduction was observed in the patients. This was associated with clinical polymorphism and the low yield of bacteriologic tests in tuberculosis. In CFFPR, the first pseudomonas infection age was 5 years, whereas it was 2 years in our patients. It was 9 for *Stenotrophomonas maltophilia*, and 43 in our patient group. For MRSA, it was 11, which was similar to our patient group.

In patients with CF, pulmonary exacerbation is characterized by newly developed respiratory system symptoms and physical examination findings. It is important to identify and treat exacerbations because they affect mortality. In the CFFPR data, pulmonary exacerbation was observed in 42% of adults and 22% of adolescents. In the UKKS, pulmonary exacerbation was observed as 19.2% in patients below the age of 12 years and above 29.2% in patients older than 12 years. In our study, there was no significant difference between the groups (p>0.05). The lower rates compared with Europe are thought to be related to the patients not being aware of their symptoms at presentation.

ABPA is seen in 1-15% of cases and may cause lung findings to become more severe.[9] Our results were similar to the literature.

Recurrent sinusitis, pansinusitis, and nasal polyps are common complications in adolescents.[18] In the CFFPR data, nasal polyps accounted for 10.4%, and 1.4% of them underwent surgery. The Incidence of sinusitis is reported as 21% in adolescents and 56% in adults. In the UKKS, sinusitis was reported at a rate of 9.4%. In our study, we observed a higher value and there was no significant difference between the groups (p>0.05). We thought that the higher incidence of sinusitis and polyps in our patients was associated with sinusitis and polyp development resulting from insufficient irrigation of the sinus.

Hemoptysis and pneumothorax, which are complications seen in adult patients, are usually common in patients who have severe pulmonary disease, have FEV_1 values below 40%, and who develop chronic colonization.[19] In the CFFPR data, pneumothorax requiring chest drain was found as 0.2% and hemoptysis as 3%. In the UKKS, pneumothorax was found as 0.1%, and hemoptysis as 0.5%. In our patient group, when compared with Europe and Turkey, the pneumothorax rate was similar. Our patient with recurrent pneumothorax had an FEV_1 value of 30 and chronic pseudomonas colonization. This patient underwent lung transplantation. Hemoptysis was found as 9.2% in our patient group, higher than the European and Turkish means. This was observed in pulmonary exacerbation periods and thought to be related to the severity of bronchiectasis. In our study, bronchiectasis was found as 66.6% in the adult patient group, which was substantially higher than that of the adolescent group. This situation could be associated with early diagnosis, early initiation of treatment, and treatment and family compliance in the adolescent group.

According to the CFFPR data, asthma was found as 28% in the adolescent group, and 35% in the adult group. We found similar results in our patients. There was no significant difference between the groups(p>0.05).

The most common causes of mortality and morbidity in CF are respiratory system inflammation and infection. The second cause of mortality is transplantation complications, and thirdly, CF-related liver disease.[19] According to the CFFPR, the incidence of cirrhotic liver disease is 3.3%, and for the UKKS, the incidence of chronic liver disease is 7.9%. In our patient group, the incidence of cirrhosis was similar. Three of our patients underwent transplantation, and one patient died in the acute period of the transplantation. Two patients are clinically stable. These results suggest that liver involvement in CF is not uncommon, and we have two patients awaiting transplantation.

Other gastrointestinal complications observed in adolescence and adulthood are reported, according to the CFFPR: distal intestinal obstructive syndrome (DIOS) (2.3%), fibrosing colonopathy <0.1%, and gastroesophageal reflux (GER) (36%). For the UKKS, GER was 4%. In our patients, gastrointestinal complications were similar to the literature. However, there was a significant difference of GER in the adolescent and adult groups (p=0.004). It was thought that GER might be related to verbal questioning in the adult group.

Children with a chronic disease such as CF are at risk for osteoporosis and osteopenia due to factors such as disease and treatment-related factors, risky nutrition, and reduced physical activity. The risk increases as the severity of lung disease and malnutrition increase.[15,16] According to the CFFPR data, osteopenia was found by 10%, and osteoporosis by 3%. For UKKS, the incidence of osteoporosis is 2.4%. In our patient group, osteopenia was lower and osteoporosis was similar to the bone mineral density measurements of the last 5 years. In these patients, it is important to perform BMI measurements and to provide vitamin support.

CFRD is now a more common condition due to the increase in the survival of patients with CF. CFRD significantly increases mortality in patients with CF. Although the risk of diabetes in the first 10 years is the same with children without the disease, the risk increases in adolescents and adults.[7,19] According to CFFPR data, the incidence of CFRD is 31% in adults and 5% in adolescents. In our patients, similar results were found with the literature and there was a significant difference between the adolescent and adult groups (p=0.017).

According to the CFFPR, the total number of patients who had lung transplantation in 2018 was 253, only one of our patients underwent transplantation. One of our patients is still waiting to undergo transplantation, and two patients have transplantation requests pending.

In our country, because the patients' weights are less, especially in childhood and adolescence, clinical experience is limited when it comes to lung transplantation for adolescent patients; one patient (0.6%) who is waiting for transplantation continuously needs oxygen support. This is rate is 10.8% in the CFFPR.

In our country, patients with irregular follow-up or discontinuation of follow-up constitute a significant problem in chronic patient monitoring. According to CFFPR, the rate of patients with irregular follow-up was 2.9%. This was high (12.3%) in our study. We thought this was related to families being bored with the process and not perceiving the importance of the disease.

There are about 2000 mutations identified related to the disease in genetic tests today. The most common mutation in the disease is delta F508.[1,2] The frequency of this mutation in the chromosome alleles of patients with CF in Northern Europe and North America is 70-80%. According to the CFFPR, homozygous delta F508 mutations were identified in 40% of patients, heterozygous mutations were seen in 41%, and other mutations in 19% of patients. In the UKKS delta F508 was the most frequent mutation with 28%, followed by N1303K at 4.9%. In our study, we found a similar result. There was no significant difference between the groups (p>0.05). This was thought to be associated with the difference in the genetic distribution compared with Northern Europe and America because our country is located on migratory routes.

Nutrition and growth at an optimal level is a significant part of the treatment of patients with CF.[13,14] The pancreas is an important organ in CF, and pancreatic insufficiency (PI) is encountered in around 85-90% of patients with CF. If PI is not diagnosed and treated on time, growth-developmental delay, malnutrition, short height, vitamin and mineral deficiencies will be unavoidable. Pancreatic enzyme replacement therapy (PERT) is supported for treating impaired fat absorption due to pancreatic insufficiency.[8,9] According to CFFPR, the use of pancreatic enzyme therapy was 84.9%. In the ECFS data, the rate was 83%. In the UKKS, it was 87.4%. In our patients, it was 78.8%. These results suggest that awareness on the use of PERT is the same as in Europe and America.

Respiratory system involvement is the most important cause of morbidity and mortality in CF, and clearance of sputum constitutes one of the most important points of treatment.[7] According to the CFFPR, 91.4% of patients used dornase alfa, 73.4% hypertonic saline, 64.2% azithromycin, and inhaled antibiotics was 15%. In the ECFS, the use of hypertonic saline was 54%, and inhaled antibiotics was 44%. In UKKS, 86.7% of patients used dornase alfa, 8% hypertonic saline, and 6.3% azithromycin. In our study, 75.4% of patients used dornase alfa, 11.7% inhaled antibiotics, 57.6% inhaled beta-agonist, 25% hypertonic saline, and 5.4% azithromycin. This suggests that our patients are conscious and compliant about the use of dornase alfa and hypertonic saline, but not about the use of azithromycin.

According the ECFS, mortality was 1.3%. In our study, the median age of mortality was 23.1 in the adult group, where the youngest age was 20 years and the oldest 28 years. In adolescents, the median age of mortality was 13.5 years. In our study, mortality was 7.6% in all patients, whereas it was 20% in the adult group. There was a significant difference between the groups(p=0.004). This was thought to be associated with the late diagnosis in the adult patient group and the progression of the disease.

According to the CFFPR, 53% of adults with CF have full-time or part-time jobs, 30.9% are university graduates, and 30% were still studying at university. In our study, 40.2% of the adult patient group had full-time jobs, 6.1% were university graduates, and 4.6% were still studying at university. The lower rate of working patients compared with European countries can be explained by the observation of a higher female patient rate. Besides, the lower rate of education was thought to be related to the fact that families did not send their children to school for protection because they became sick frequently.

The number of pregnancies reported to the CFFPR between 2008 and 2018 was 280, we had two pregnant patients. We thought this could be related to the lower number of adult patients than the overall number of patients, and the lower number of married female patients in our study.

Conclusion

With early diagnosis and treatment, lifespans of patients with CF are prolonged, and they can reach adulthood. Multidisciplinary follow-up together with other departments, especially the department of adult chest diseases after the age of 18 years, will affect the life qualities of patients.

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Does Dietary Treatment Cause Obesity in Phenylketonuria? Comparison of Obesity Ratios of Patients Receiving Dietary Treatment and Tetrahydrobiopterin Treatment

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Abstract

Phenylketonuria is treated either with tetrahydrobiopterin (BH4) or with a phenylalanine-restricted diet. Patients in the diet group may tend to consume carbohydrate-rich foods which have a risk for obesity. In this study, the prevalence of obesity+overweight among phenylketonuria patients either treated with phenylalanine-restricted diet or with BH4 were compared.Patients with phenylketonuria were divided into two groups on dietary treatment and BH4 treatment. Body mass index (BMI), BMI-percentile, and z-score values of patients were calculated and classified as underweight, normal-weight, overweight, and obese according to their nutritional status. The annual mean phenylalanine level of each patient is also evaluated. The study was done retrospectively.A total of 130 patients was included. 77 were receiving diet (female (n,%):37, 48.1%; male (n,%):40, 51.9%) and 53 were receiving BH4 (female (n,%):33, 62.3%; male (n,%):20, 37.7%) respectively. According to BMI-z-score, the sum of the ratio of obesity+overweight was found to be 35.1% in the diet group, 16.9% in the BH4 group. Ratio was significantly higher in diet group (p=0.02). When obesity+overweight ratios were examined in terms of female/male distribution, no significant difference was found. Considering the correlation of obesity+overweight ratios with age in two groups, the median age of the patients with normal weight+underweight in the BH4 group were found as 46-months, and the median age of obese+overweight patients was 137-months (p=0.001). For the same situation, there was no significant difference in the dietary treatment group (p=0.92). Mean annual phenylalanine levels were significantly higher in obese+overweight patients (p=0.047) in the BH4 treatment group but this difference was not significant in the diet group (p=0.051).Patients on the phenylalanine-restricted diet have a risk of obesity or overweight. Therefore, attention should be paid not only to the phenylalanine levels of these patients but also to their weight control and dietary content.

Keywords: Phenylketonuria, diet, tetrahydrobiopterin, obesity, overweight

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Introduction

Phenylketonuria (PKU) is an inherited metabolic disorder that is caused by the deficiency of phenylalanine hydroxylase enzyme.[1] Due to phenylalanine hydroxylase enzyme deficiency, conversion of phenylalanine (Phe) to tyrosine is affected completely or partially, and the accumulated phenylalanine in untreated cases causes irreversible brain damage.[1] Phenylketonuria (PKU) is the most common inherited disorder of amino acid metabolism in Turkey.[1,2] In the treatment of the disease, if patients are tetrahydrobiopterin (BH4) responsive, BH4 treatment is started and if unresponsive, patients are treated with a phenylalanine restricted diet.[3,4]

Highlights

- PKU patients on dietary treatment may tend to be overweight or obese more than the normal population.
- Therefore attention should be paid not only to the phenylalanine levels of these patients but also to their weight control and dietary content.

Dietary treatment aims to keep the blood phenylalanine levels within the target values by applying a diet containing low phenylalanine which means low natural protein.[5-7] Patients on dietary treatment tend to eat carbohydrate-rich foods and this situation creates a risk for obesity.[5-7] Various studies are arguing that the prevalence of obesity in PKU patients are equal or increased to the general population of the related country.[5-8]

In this study, we aimed to compare the obesity ratios of our PKU patients receiving BH4 treatment and dietary treatment. We also compared the obesity ratios of our PKU patients with the overall obesity ratios in Turkish children.

Material and Method

Ethics committee approval was taken from local ethic committee (Decision No: 2021/470). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We included patients diagnosed with PKU, who were followed up at Erciyes University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Nutrition and Metabolism, and divided them into two groups according to their treatments, dietary treatment or BH4 treatment. Patients <19 years of age were collected. Our patients are from the city of Kayseri and the neighboring cities of Kayseri which reflects the population of, Central Anatolia Region, in Turkey. The PKU diagnosis was made by either measuring blood phe levels or both phe levels and genetic testing. BH4 responsiveness was defined as a 30% reductions of phe levels at the time of the 24th hour after 20 mg/kg/dose of BH4 administration. Patients receiving both BH4 and dietary treatment were excluded from the study. PKU patients without any treatment, with severe neurological problems, and patients who have additional diseases, were also excluded. Anthropometric measurements were done by using a Densi® branded digital weighing scale and stadiometer. Height of children under two years of age and those who are unable to stand stably enough were measured in the supine position on a measuring board. The weight and height of the patients were recorded routinely in their files in our clinic. The weight measurements were done with light clothes and the height measurements were done without shoes. Anthropometric calculations of the body mass index (BMI) (kg/m²), BMI percentile (%), and z-score values were evaluated retrospectively from the files of patients by using the age and gender-specific charts of the World Health Organisation (WHO).[8]

The overweight classification was as follows: for patients <5 years: BMI z score ≥2 and <3 SD, for patients 5-18 years; BMI z score ≥1 and <2 SD.[8] Obesity classification was for patients <5 years: BMI z score ≥3 and for patients 5-18 years: BMI z score ≥2 SD.[8] Percentages of overweight+obesity and obesity were calculated respectively from BMI z scores and compared with the overall obesity prevalence of children in Turkey. Underweight status was defined as BMI z score < -3 SD.[9] Annual mean phenylalanine levels were evaluated from the blood phenylalanine amino acid measurements (mg/dl) with the high-performance liquid chromatography (HPLC) analysis. The mean value of at least three measurements was calculated.

Statistical analysis was done with SPSS 15.0. Descriptive criteria are presented as mean, median, and percentage distribution. The compliance of the data to normal distribution was checked with the Kolmogorov-Smirnov test. To determine the mean differences between the groups, student t-test was used when parametric conditions were met, Mann Whitney U test in cases where they could not be met, and Pearson Chi-square to compare the differences between percentages were used when necessary, and also Fisher's exact test was used. Pearson Correlation Analysis was used to evaluate the correlation. For the significance level, p <0.05 was taken.

Results

A total of 130 patients were included to the study. There were 77 patients (female (n,%): 37, 48.1%; male (n,%): 40, 51.9%) receiving dietary treatment and 53 patients (female (n, %): 33, 62.3%; male (n,%): 20, 37.7%) receiving BH4 treatment.

The distribution of nutritional status of the patients in the dietary treatment group and BH4 treatment group according to BMI z-score is given in table 1 below.

According to the BMI z-score, the ratio of obesity and overweight was found to be significantly higher in the dietary treatment group and it is shown in **Figure 1** (dietary treatment group 35.1%, BH4 treatment group 16.9%, p: 0.02).

When obesity and overweight ratios were examined in terms of female / male distribution, no significant difference was found in both groups (p=0.33 in the group receiving dietary treatment and p=0.49 in the BH4 treatment group).

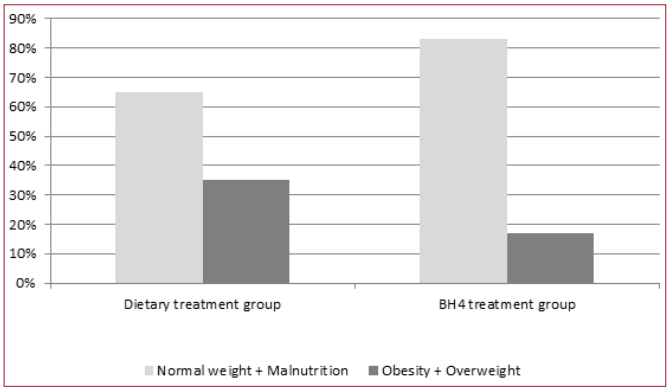

Figure 1. Percentage distribution of obesity + overweight status among the patient groups receiving dietary treatment and BH4 treatment

When the median age of the group receiving dietary treatment and the group receiving BH4 treatment was compared with the Mann-Whitney U test, the median age of the group receiving BH4 drug was found to be significantly lower (p=0.002) (**Table 1**).

Table 1.
Number of patients, demographic features and analysis of nutritional status according to treatment groups

	Dietary treatment group	BH4 treatment group	P value
Gender			
Male (n,%)	40 (51.9)	20 (37.7)	
Female (n,%)	37 (48.1)	33 (62.3)	
Total (n)	77	53	
Mean Age (month)			0.002
Mean±SS	101.7±64.9	66.1±49.2	
Median (IQR)	97 (103)	56 (62)	
Nutritional Status			
Underweight (n,%)	0 (0)	3 (5.7)	
Normal weight (n,%)	50 (64.9)	41 (77.4)	
Overweight (n,%)	15 (19.5)	7 (13.2)	
Obesity (n,%)	12 (15.6)	2 (3.8)	
Nutritional Status Subgroups			0.02
Underweight+normal weight (n,%)	50 (64.9)	44 (83.1)	
Overweight+obesity (n,%)	27 (35.1)	9 (16.9)	

When the correlation between age (in months) and BMI z-score was examined in the BH4 treatment group, it was found that they were positively correlated with a low degree and this correlation was statistically significant (R: 0.33 and p: 0.017).

In the BH4 treatment group, the median age of the patients in the normal weight+underweight subgroup were found 46 months, and in the overweight+obesity subgroup 137 months (p=0.001). In the dietary treatment group, the median age of the patients in the normal weight+underweight subgroup were found at 96 months, and in the overweight+obesity subgroup at 99 months (p=0.92) (**Table 2**).

When the median annual phe level of the patients in the dietary treatment group and BH4 treatment group were compared, the mean annual phe level of the group that received the diet was found to be higher; 9,6 mg/dl and 4,5 mg/dl, respectively (p <0.001).

Table 2.
Comparison of the median age of normal weight+underweight and obese+overweight children in treatment groups

Groups	Normal weight+ Underweight Mean±SS Median (IQR)	Overweight+ Obesity Mean±SS Median (IQR)	p value
BH4 treatment group, mean age (month)	51.2±34.6 46 (45)	138.7±46.4 137 (84)	0.001
Dietary treatment group, mean age (month)	100.8±67.7 96 (112)	103.4±60.4 99 (77)	0.92

Considering the annual median phe levels in normal-weight patients and obese+overweight patients in the dietary treatment group, the annual median phe levels in obese+overweight patients were higher, but the difference was not statistically significant (p=0.051).

Discussion

Obesity ratios vary within the countries. According to 2011-2012 National Health and Nutrition Examination Survey (NHANES) data in the United States of America, the prevalence of overweight in children and adolescents was reported as 31.8% and obesity prevalence as 16.9% (obesity+overweight 48.7%).[10]

In Turkey, these ratios are lower. The prevalence of overweight is 14.3% and obesity is 6.5% (overweight+obesity, 20.8%).[11] This may because fast-food consumption is less in Turkey and homemade food is widespread. Another reason for this may be the socioeconomic status of the families in Turkey is worse and there may be restrictions in consuming fast-food.

Studies in the literature, the prevalence of obesity and overweight in patients with PKU on dietary treatment was compared with the obesity prevalence of the related country or within the healthy control group.[6-8] In this study, obesity and overweight ratios of patients with PKU on dietary treatment were compared with patients with again PKU patients on BH4 drug treatment. The fact that both of the groups had PKU, showed the positive side of the study, while the median ages of the BH4 treatment group in the study were significantly younger than the dietary treatment group (diet group median age 97 months, BH4 group median age 56 months, p=0.002) constitutes the limitation of the study. BH4 treatment is approved for adults and pediatric patients of 4 years of age and over in 2008.[12] BH4 treatment under age 4 is approved in Turkey in 2015 and this situation causes the BH4 treatment group to be younger than the dietary treatment group.[12]

In this study, the ratio of obesity+overweight in the dietary treatment group was found to be statistically higher 35.1% and the BH4 treatment group was 16.1% (p=0.02). The obesity+overweight prevalence in PKU patients on the dietary treatment group was also higher than the overall obesity prevalence in Turkish children (obesity+overweight ratio of the dietary treatment group was 35.1% and overall obesity+overweight

ratio of Turkish children was 20.8%).[11] Because of a restricted natural protein diet, PKU patients tend to consume carbohydrate rich foods and this may cause excess caloric intake and obesity. In the BH4 treatment group, which they have no diet, the obesity+overweight ratio is lower than the dietary treatment group and also lower than the overall obesity prevalence of Turkish children.

Studies from the USA and European countries, it was emphasized that the obesity prevalence was higher in girls in patients with PKU on dietary treatment, whereas in our study, the ratio of obesity+overweight was higher in boys (female 27%; male 42.5% p=0.33) but this was not statistically significant.[7,8] Considering the overall ratio of childhood obesity in Turkey, the ratio is higher in the male gender which is overweight+obesity ratio in male gender 22.6% and 18.9% in the female gender.[11]

In another multicenter study which is also including Turkey, 8 centers participated in the study with 397 patients.[8] Gokmen Ozel et al.[8] from the Ankara group gave the obesity+overweight ratio lower than our study 19.8%, 35.1% respectively. In the same study, the ratio of obesity was found to be higher in girls, contrary to our study (21.3% girls; 18.7% boys).[8] The study of the Ankara group was done in 2014 but our study was done in 2019. Obesity and the overweight problem is increasing problem over the years. The 5-year difference between the two studies may have caused this difference. Ankara group was the first group that initiates neonatal screening program for phenylketonuria. Their patients are from Ankara and also from the Eastern Anatolia region which socioeconomic status is below the average of Turkey. Nutrition patterns vary from country to country, as well as from region to region within the same country. This may explain the different ratios of obesity among studies conducted in different regions. Kayseri and its surrounding provinces have a diet rich, especially in pastry foods. This situation may have been effective in the high rates of obesity in our study.

In addition, in our patient group, it was observed that the phe levels of the dietary treatment group were higher than the BH4 treatment group (9,6 mg/dl and 4,5 mg/dl, respectively (p <0.001)). The reason for this may be that the BH4 treatment group does not require any dietary treatment. The dietary treatment group has a strict protein-restricted diet and many patients have difficulties in strict compliance with this diet. They can not fully comply with the diet so their phe levels are higher than the BH4 treatment group.

In another study from Portugal, it was found that the ratios of obesity or overweight and the risk of developing metabolic syndrome were higher in the PKU dietary treatment group when compared with the control group but the difference was not statistically significant.[5] There are different results from different countries. This situation may be explained by the fact that different countries have different nutrition styles.

In this study when the relationship between the obese or overweight patients and age was examined, a significant correlation was not found in the dietary treatment group, but a statistically significant correlation was found in the BH4 treatment group in the direction of increasing obesity with increasing age (median age of the normal weight group was 46 months, the median age of the obese/overweight group was 137 months, p=0.001). This situation raises the question of whether if the age of the BH4 treatment group was equal to the age of the dietary treatment group, would there be no statistical difference between obesity rates? However, to reveal this, it is necessary to follow the obesity rates of the same BH4 group in the following years prospectively. It is also important to do more studies that are comparing both the BH4 treatment group and dietary treatment group to see the differences. We also have not much information on how the phenylalanine restricted diet affects the PKU patients in a long-term period.

Conclusion

Obesity and overweight risk of PKU patients on the dietary group are higher than society and also higher than PKU patients who were not on diet. Therefore, attention should be paid not only to the phenylalanine levels of these patients but also to their weight control and dietary content. In the early period, if necessary, calorie restriction should be applied in their diets, or alternative solutions should be produced to increase the compliance of patients who do not comply with the diet. It is necessary to prevent the perception in the patients and also the parents that the phenylalanine restriction in diet is to be seen as the main aim in dietary treatment. It is also important to mention that phenylalanine-free high-calorie foods may not be consumed limitless in patients.

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Original Article

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The Association Between Platelet Mass Index and Mechanical Ventilation in Pediatric Surgery Cases

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Abstract

Platelet mass index (PMI) is an indicator of platelet functionality. This study aimed to examine the relationship between PMI and mechanical ventilation need in infants less than 1 year of age who underwent gastrointestinal system surgery. We retrospectively reviewed the medical records of cases that underwent gastrointestinal surgery in the last 10 years (2010-2020) at Baskent University Konya Hospital. Demographic data, indications for surgery, age at surgery, preoperative blood tests, hospitalization times, discharge status, mechanical ventilation need and duration, sepsis, accompanying anomalies, recurrent surgery requirements were collected from patient records. The study group (n: 143) was divided into 2 groups as the need for mechanical ventilation (MV; n: 73) and the group that did not need mechanical ventilation (n-MV; n: 70). Data were analyzed with SPSS version 25. PMI was significantly lower in the MV group (1999 Vs 2798, p< .001). 65% of the cases were newborns. Mean gestational age was 34.5 ±4 weeks, and birth weight was 2100 ± 820 g. Most of the cases that need surgical intervention consist of small bowel atresia, esophageal atresia, surgeries due to necrotizing enterocolitis, and anal atresia. Ileus was present in 54% of the patients. The recurrent surgery requirement was 34%. The frequency of accompanying cardiac anomalies was 30.6%, and the rate of proven sepsis was 38.3%. Preoperative 2163 PMI value can discriminate not needing MV with 72% sensitivity and 69% specificity (AUC: .699, p<.001). When the basic characteristics of the groups were evaluated, 83% of the patients who underwent MV were in the newborn group. The birth weight, gestational age, hospital duration, oxygen exposure, culture-positive sepsis rates, total parenteral nutrition (TPN) rates, and duration were found to be significantly higher in patients who underwent MV. While there was no difference in the number of white blood cells in the preoperative blood analysis, the neutrophil-lymphocyte (N-L) ratio, platelet number, albumin values were significantly lower and CRP values were significantly higher in the MV group. There was no difference in the platelet –lymphocyte (PL) ratio. High PMI values can be used as a parameter to discriminate the need for mechanical ventilation.

Keywords: Platelet –mass index, pediatric surgery cases, mechanical ventilation, morbidities

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Introduction

The purpose of mechanical ventilation (MV) is to oxygenate the patient and remove carbon dioxide while trying to minimize damage to the lungs. Historically, positive pressure ventilation was the most widely used ventilation method in newborns.[1] The management of infants receiving MV is largely dependent on personal preference. MV is a complex and highly specialized field in the infancy and newborn period made more complex by the availability of many different modes, techniques, and devices. This process becomes more complicated in preterm babies.[2] Predicting which patients will need MV, extubation failure, and the need for long-term MV remain the subject of serious research.

Highlights

- There is a close relationship between platelets and lungs.
- PMI is very easy to use, calculate, and access.
- PMI may be used as a useful preoperative marker to predict mechanical ventilation in surgical patients.

Platelet mass index (PMI) is a marker of platelet activation and can be easily calculated by multiplying mean platelet volume (MPV) and platelet count. Its use of PMI in cases of bleeding has gained meaning with the understanding that larger platelets produce more reactive and more prothrombotic factors.[3,4] It has been and continues to be the research subject of many studies that are thought to play a role in the physiopathology of inflammation, platelet functions, and mediators secreted in platelets.

This study was aimed to investigate the relationship between PMI and MV in pediatric surgical cases.

Material and Method

In this study, the medical records of infants under the age of 1 who underwent gastrointestinal system operations in pediatric surgery at Baskent University Konya Application and Research Center were examined retrospectively, from January 2010 to December 2020. This study was approved Baskent University Institutional Review Board and Ethics Committee (KA19/182, the 14th of March, 2019). Patient data including age at operation, gestational age, mode of delivery, birth weight, gender, ileus status, number of reoperations, the hospital duration before surgery, the hospital duration after surgery, total hospital stay, invasive mechanical ventilation, and total oxygen exposure duration, discharge or death, preoperative full blood cell indices, and biochemical markers were obtained from medical records. In preoperative blood tests, PMI (mean platelet volume (MPV) * Platelet count (mm^3) /1000) values of all patients were calculated by the formula as described. Using receiver operating curve (ROC) curve analyzes, cut-off values were analyzed to discriminate whether the PMI variable needed MV or not. The best sensitivity and specificity values were determined. Descriptive statistics of scale variables were expressed as mean ± standard deviation (SD) or median (range). Demographic and clinical continuous variables were compared using two independent Student's t-tests for normal distribution and the Mann-Whitney U test for non-normally distributed values. Z scores of skewness, kurtosis, histograms, and Kolmogorov Smirnov statistics were used to understand whether the continuous variables are normally distributed. Categorical variables were compared using Fisher's exact test, Likelihood, or Chi-square test, as appropriate. ROC curve with area under the curve (AUC) was used to define sensitivity and specificity of PMI to discriminate not need for mechanical ventilation. Logistic regression analysis was used to estimate predictors of mechanical ventilation need. The significance level for all tests was determined as $p<0.05$. Data were analyzed using the SPSS software package program version 25.

Results

Of the 143 patients included in the study, 73 were in the MV group and 70 were in the non-mechanical ventilation (n-MV) group. When the basic characteristics of the group were examined, 65% of them were newborns, the mean gestational age was 34.5±4 weeks, and the mean birth weight was 2100±820 g. Most of the cases that need surgical intervention consist of small bowel atresia, esophageal atresia, surgeries due to necrotizing enterocolitis, and anal atresia. Ileus was present in 54% of the patients. The recurrent surgery requirement was 34%. The frequency of accompanying cardiac anomalies was 30.6%, and the rate of proven sepsis was 38.3%. The majority of neonatal surgeries consisted of gastrointestinal malformations (intestinal atresia, esophageal atresia, anal atresia) and surgeries related to necrotizing enterocolitis. Distributions of the cases consisted of 21% (31) congenital small bowel malformations, 15% (22) esophageal atresia, 14% (21) NEC, 13% (19) gastroesophageal reflux, gastrostomy, and hypertrophic pyloric stenosis surgery, 9% (13) anogenital malformations, 7% (11) congenital megacolon, 4% (6) invagination, 2% (4) explorative laparotomy for free air in the abdomen, 2% (4) congenital diaphragmatic hernia and others (13%) including malrotation, colon perforation, britt ileus and constituted the closure of the colostomy. Considering the group statistics, while birth weight (2138 ± 868 gr, p:0.001), week of birth (33.7±4, p: 0.001), age at the time of diagnosis (7, 1-260, $p<0.001$) were significantly lower in the MV group, duration of oxygen use ($p<0.001$), length of hospital stay ($p<0.001$) in both preoperative and postoperative, total parenteral nutrition (TPN) duration ($p<0.001$) and percentage of TPN recipients ($p<0.001$), rates of sepsis ($p<0.001$) and surgery under 1 month ($p<0.001$) were found to be significantly higher (**Table 1**). There was no difference between the groups in terms of gender, need for recurrent surgery, and concomitant complex heart diseases. When the preoperative blood indices were examined, no difference was found between the groups in terms of white blood cell counts and Platelet lymphocyte ratio (PLR), while PMI ($p<0.001$), albumin ($p<0.001$), and platelet values ($p<0.001$) were found to be significantly lower in the MV group (**Table 2**). In addition, preoperative hemoglobin ($p=0.037$), neutrophil-lymphocyte ratio (NLR) ($p<0.001$), and C - reactive protein (CRP) values ($p=0.008$) were significantly higher in the MV group (**Table 2**). In the performed ROC analysis to discriminate

PMI needing mechanical ventilation, a PMI value of 2163 can discriminate not needing MV with 72% sensitivity and 69% specificity (AUC: 0.699, p<0.001), although PMI has a mild and moderate discrimination (**Figure 1**). A regression model which was created scientific knowledge and parameters that could be the risk factors in pairwise comparisons, has been performed to ascertain the effects of the gestational week, proven sepsis, recurrent surgery needs, and PMI on the probability that participants have mechanical ventilation. The logistic regression model was statistically significant, x^2=16, p=0.003. To assess the model fit, Hosmer-Lemeshow statistics was good (p=0.449) The model explained 29% (Naegelkerke R2) of the variance in the mechanical ventilation group, and correctly classified 70% of the cases. In the logistic regression model of independent risk factors predicting the need for MV, it is understood that the most important risk factor was sepsis (p: 0.020, OR: 4.86, 95% CI: [1.277-18.53]) (**Table 3**).

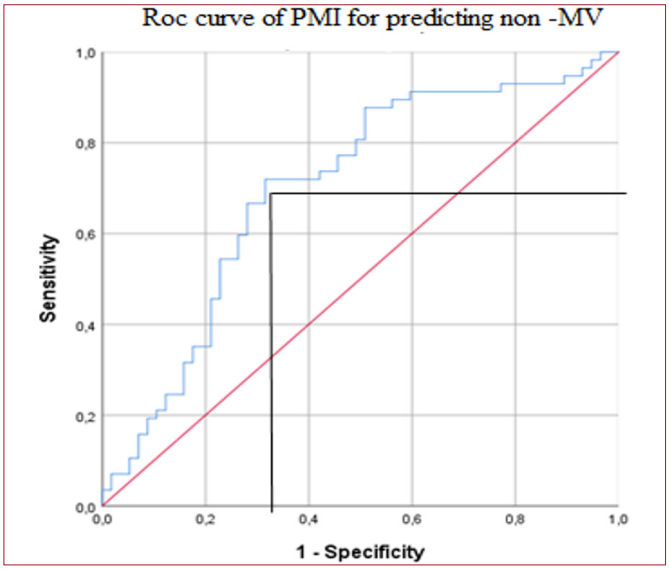

Figure 1. ROC curve showing diagnostic performance of PMI in predicting that will not require mechanical ventilation.

Table 1.
Baseline characteristics of the groups

	MV (n=73)	n-MV (n=70)	P- value
Birth weight gr; Meant±SD	2138±868	2890±780	0.001
Gestational age, Meant±SD	33.7±4	36.5±2	0.001
Gender, Male; n (%)	42 (60)	43 (59)	0.894
Age at diagnosis (day); median (min-max)	7 (1-210)	37.5 (1-360)	<.001
The need for recurrent surgery,median, (min-max)	0 (0-3)	0 (0-4)	0.728
Hospital duration (day); median (min-max)	35 (1-301)	8.5 (1-120)	<.001
Hospital duration before surgery; day median (min-max)	3 (0-64)	1 (0-12)	<.001
Hospital duration after surgery; day median (min-max)	25 (1-288)	7 (1-116)	<.001
The time of Oxygen exposure; day; median (min-max)	19 (1-301)	0 (0-23)	<.001
TPN rate; n (%)	65 (91.5)	20 (28.6)	<.001
TPN duration; median (min-max)	16 (0-232)	0 (0-87)	<.001
Proven sepsis; n (%)	46(65)	8 (11)	<.001
Concomittant hearth desesase; n (%)	35 (49.3)	9 (12.9)	<.001
Concomittant complex hearth desesase; n (%)	6 (8.5)	1 (1.4)	0.116
Surgery less than 1 month old age; n (%)	61 (83.6)	32 (45.7)	<.001

Abbreviations: MV: Mechanical ventilation; n-MV: Non mechanically ventilated; TPN: Total parenteral nutrition; SD: Standart deviation

Table 2.
Preoperative whole blood cell counts, calculated indices and biochemical values of the groups

	MV (n=73)	n-MV (n=70)	P- value
Leucocyte count/mm³ Mean±SD	13232±7250	12085±5420	0.309
Hgb (gr/dl) Mean±SD	14.1± 3.9	12.8±3	0.037
Platelet count /mm³ Mean±SD	222845±129683	374574±173103	<.001
N/L ratio; median (min-max)	1.37 (0.06-52.7)	0.73 (0.1-4.88)	<.001
P/L ratio; median (min-max)	39.2 (8.38-293)	64.9 (2.64-2029)	0.58
PMI ; Mean±SD	1999±1131	2798±1301	<.001
Albumin (gr/dl); Mean±SD	2.88±0.5	3.47±0.6	<.001
Crp (mg/L);median (min-max)	13.8 (0.1-339)	1.2 (0.1-238)	0.008

Abbreviations: MV: Mechanical ventilation; n-MV: Non mechanically ventilated; TPN: Total parenteral nutrition; SD: Standart deviation; PMI: Platelet mass index; N/L ratio: Neutrophil to lymphocyte ratio, P/L ratio: Platelet to Lymphocyte ratio; CRP: C-reactive protein

Table 3.
The logistic regression model to predict mechanical ventilation in pediatric surgery patients

	B	P value	Exp (B)	Confidence Interval (95%)
Gestational age	-0.144	.160	.886	0.709-1.058
The need for recurent surgery	-0.823	.188	0.439	0.129-1.497
Cultur positive proven sepis	1.582	0.020	4.864	1.277-18.530
PMI**	0	0.139	1	0.999-1.000

Abbreviation: PMI: Platelet mass index
** We did not re-scale PMI since it was non-significant variable in the model.

Discussion

MV applications are frequently used in intensive care units both preoperatively and postoperatively, especially in critical patients and neonatal-infant surgery. Invasive mechanical ventilation is required in 35%-64% of pediatric intensive care units all over the world.[7,8] It is known that increased mechanical ventilation time is associated with increased mortality and morbidity.[9] It is very important to investigate whether mechanical ventilation is required and risk factors. As a result of this study, it was concluded that it can be discriminated whether MV will be required with preoperative PMI values.

Okur et al.'s study on the use of PMI as a predictor of neonatal morbidity and mortality in preterm infants, the authors reported that cases with necrotizing enterocolitis (NEC), intracranial hemorrhage (IVH), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and sepsis were included in the study, and found that they had significantly lower PMI values than those who did not.[5] They explained these results with inflammation. In our study, we found a significantly lower PMI in patients who underwent MV, patients who required TPN, and patients who underwent surgery in the newborn, but we did not find a significant difference in the sepsis group. Okur et al. obtained PMI results on two different days from whole blood data taken on day 1 and between 3-7 days. This may have affected the results. The reason for the lack of difference in sepsis in our study was interpreted as the fact that culture-positive sepsis cases consisted of data obtained at any time after surgery, and preoperative PMI values could perhaps shed light on early post-operative periods. In the same study, they found a significant relationship between PMI values calculated from blood taken between 3-7 days and MV, but they did not find a difference between PMI values on the first day. The reason for this seems to be that sepsis and infections developing in the postoperative period affect PMI values.

In the study of Ilhan et al. in which PMI and respiratory morbidities were compared in infants with transient neonatal tachypnea, they found that infants with lower PMI values had longer tachypnea duration, more oxygen need, and more mechanical ventilation need, similar to our study.[6]

Recent studies have shown that the lungs have important roles in platelet function and production. Megakaryocytes produced in the bone marrow come to the lungs through the bloodstream. It differentiates from megakaryocytes to platelets by various signaling systems. Approximately 50% of total platelet production occurs in this way.[10] It has been shown in animal experiments that mediators such as platelet glutathione redox cycle antioxidants released from platelets in the lung after ischemia-reperfusion injury or oxidant stress have effects on endothelial permeability and pulmonary edema are evident in experimental animals with thrombocytopenia.[11-13] In addition, studies have shown the functions of platelets in lung defense mechanisms, inflammation, and remodeling events in healthy lungs.[14]

Conclusion

As a result; we think PMI values, which are accepted as an indicator of platelet functionality, can be used to discriminate the need for mechanical ventilation, especially since the platelets are in a very important and close relationship with the lungs.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

Conflict of Interest: All the authors declare that they have not received any financial support or other benefits from commercial sources for the work described in this paper. They also declare that they have no other financial interests that could create a potential conflict of interest or the appearance of a conflict of interest with about this work.

Ethics Committee Approval: This study was approved Baskent University Institutional Review Board and Ethics Committee (KA19/182, the 14th of March, 2019).

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Evaluation of the Relationship between Transcutaneous Carbondioxide Monitorization and End-tidal Carbondioxide and Partial Carbondioxide Monitorization

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Abstract

Non-invasive methods have replaced invasive methods in line with developments in pediatric intensive care units. (Especially methods that enable continuous monitoring) Although arterial carbon dioxide measurement is still the gold standard for the evaluation of alveolar ventilation, the need for continuous monitoring of $PaCO_2$ and the invasive nature of this method have led to the investigation of alternative methods. To evaluate the correlation of transcutaneous CO_2 ($TcCO_2$) monitoring with $PaCO_2$ and $ETCO_2$ in mechanically ventilated patients in peditaric intensive care units. Single-center, prospective, observational cohort study. We enrolled 60 patients between the age of 1 month-18 years who were mechanically ventilated in pediatric intensive care unit for this single-center, prospective, observational cohort study from February 2019 through March 2019. Correlation analysis was performed for arterial $PaCO_2$, end-tidal CO_2, $TcCO_2$ parameters. $P<0.05$ values were considered significant. The Bland-Altman plot was created for determining the agreement between the methods. The correlation of transcutaneous CO_2 and end-tidal CO_2 with arterial $PaCO_2$ was evaluated, both parameters were found to be positively and highly correlated ($r=0.864$, $p<0.001$, $r:0.962$, $p<0.001$, respectively). The mean bias between the arterial carbondioxide mesaurement and transcutaneous measurement was 5.5, and limits of agreement (bias ±1.96 SD) ranged from -13.9 to 2.9. The mean bias between the arterial carbondioxide mesaurement and end-tidal carbondioxide measurement was 2.3, and limits of agreement (bias ±1.96 SD) ranged from -4.1 to 8.6. In 44 measurements (88%), the $TcCO_2$ was ±7.5 mm Hg of the $PaCO_2$. $TcCO_2$ seems to be a good alternative for carbon dioxide measurement, as it is non-invasive and allows continuous monitoring in view of today's intensive care conditions, but arterial $PaCO_2$ measurement is still the gold standard method. Continuous $TcCO_2$ monitoring provides a promising alternative to repeated blood sampling in subjects requiring mechanical ventilation for critically ill children.

Keywords: Transcutaneous, carbondioxide, pediatric intensive care

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Introduction

In recent years, non-invasive methods have replaced invasive methods in line with developments in pediatric intensive care units. (Especially methods that enable continuous monitoring) Although arterial carbon dioxide measurement is still the gold standard for the evaluation of alveolar ventilation, the need for continuous monitoring of $PaCO_2$ and the invasive nature of this method have led to the investigation of alternative methods. Therefore, transcutaneous CO_2 ($TcCO_2$) measurement, which is a painless procedure and allows continuous monitoring, is used in intensive care units with increasing frequency.[1,2] Many studies have also shown that $TcCO_2$ measurement is a good alternative to arterial CO_2 measurement.[1-5]

End-tidal CO_2 ($ETCO_2$) monitoring has been known, heretofore, as a useful tool to follow carbondioxide levels in mechanically ventilated patients. However, several factors affect $ETCO_2$, such as pulmonary edema, obstruction of the airway and low cardiac output which are often found in critically ill patients in peditaric intensive care units.

Highlights

- $TcCO_2$ seems to be a good alternative for carbon dioxide measurement, as it is non-invasive and allows continuous monitoring in view of today's intensive care conditions, but arterial $PaCO_2$ measurement is still the gold standard method.
- Although arterial carbon dioxide measurement is still the gold standard for the evaluation of alveolar ventilation, the need for continuous monitoring of $PaCO_2$ and the invasive nature of this method have led to the investigation of alternative methods.
- End-tidal CO_2 ($ETCO_2$) monitoring has been known, heretofore, as a useful tool to follow carbondioxide levels in mechanically ventilated patients.

Transcutaneous gas exchange monitors measure PaO_2 and $PaCO_2$ on the skin surface to estimate arterial carbon dioxide and oxygen pressure. These monitors provide local warming of the skin. Heat from the sensor expands the capillaries and increases local blood flow. Transcutaneous CO_2 monitors measure $PaCO_2$ emitted throughout the skin by the application of a sensor heated 38°C above body temperature (typically between 40°C and 44°C) to ensure arterialization in the area where the probe is connected. So transcutaneous CO_2 pressure and oxygen saturation are electrochemically measured by the sensor. It should not be forgotten that the deterioration of the patient's ventilation status may result in false positive or false negative results, and this should not be allowed to lead to delay or inaccuracy in the orientation of the patient's treatment. In addition to studies showing good and high compatibility between transcutaneous and arterial blood gas values, studies have also been published that have low compatibility.[6-8] This controversy could be explained by the severity and the heterogenity of the diagnosis.

In this study, it was planned to evaluate the correlation of transcutaneous CO_2 ($TcCO_2$) monitoring with $PaCO_2$ and $ETCO_2$ in mechanically ventilated patients in peditaric intensive care units.

Material and Method

Study design

We enrolled 60 patients between the age of 1 month-18 years who were mechanically ventilated in pediatric intensive care unit for this single-center, prospective, observational cohort study from 1 February 2019-31 March 2019. The exclusion criterias were: Hypotension, using inotropic agent, skin condition that does not allow probe to settle. This study was approved by Clinical Research Ethics Committee of Erciyes Universtiy Hospital (Date: 09.02.2018, Decision No: 2018/78). Informed consent was obtained from the parents of the patients.

Data collection and procedures

$PaCO_2$, end-tidal CO_2 and $TcCO_2$ were measured simultaneously and correlation between these measurements were investigated. $PaCO_2$, end-tidal CO_2 and $TcCO_2$ were measured 4 times from all the patients.

$PaCO_2$: Arterial blood sample is taken from the patients which we follow in intensive care and measured with RAPIDLAB 1265 brand blood gas device in our unit.

End-tidal CO_2: End-tidal CO_2 measurement was performed by micro-side stream method (Capnostream® 20p/Covidien) in patients who were mechanically ventilated in intensive care.

Capno-oxymetry: $TcCO_2$ levels were measured with the help of a probe (V-Sign™ VS-A/P) and a device (SenTec digital Monitor System).

Statistical Analysis

In G-power 3.1.9.2 programme, efect size 0.25 type 1 error was received as 5%, power as 80%. According to this, the number of samples to be taken was calculated as 43. The study was planned to be conducted with 50 patients considering 10% data loss. All statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, ABD) and MedCalc 13.3 (MedCalc Software Inc., Mariakerke, Belgium), with the statistical significance set at $p<0.05$. Frequency distributions were evaluated as number and percentage, continuous variables (measurements) were evaluated as mean±standard deviation. The distribution of the data (normal or not) was determined by performing a Shapiro Wilk test. Pearson correlation analysis was performed for arterial $PaCO_2$, end-tidal CO_2, $TcCO_2$ parameters. $p<0.05$ values were considered significant. The Bland-Altman plot was created for determining the agreement between the methods. Bias was calculated as the main difference between both methods and limits of agreement as the range in which 95% of the differences between 2 methods are expected to lie.[9] An additional analysis was performed to calculate the percentage of data in the bias range, with the measurement percentage range being ±7.5 mmHg because the clinically acceptable agreement between $TcCO_2$ and $PaCO_2$ is ±7.5 mmHg.[10]

Results

A total of 60 patients who were admitted to the Pediatric Intensive Care Unit between 1 month and 18 years of age were included in the study. 10 patients who had measurement problems and impossible optimal monitoring were excluded from the study. Of the patients who participated in the study, 26 were boys (52%) and 24 (48%) were girls. The median age of the patients was 14 months. (min: 2-max: 168) According to the admission diagnoses of the patients, 6 (12%) patients due to respiratory, 10 (20%) patients due to neurological problems, 16 (32%) patients due to cardiac problems, 6 (12%) patients due to renal failure, and 12 (24%) patients due to endocrinological problems were admitted to intensive care (**Table 1**).

Table 1
Characteristics of study subjects

Characteristics	Values
Age, mean±SD (month)	14±11.3
Male, sex n (%)	26 (52)
Body weight (min-max)	13.7 (10.2-35)
BMI (min-max)	24.7 (18.4-31.2)
Body Temperature oC (min-max)	36.6 (36.1-37.2)
Diagnosis at the admission n (%)	
Respiratory problems	6 (12%)
Neurological problems	10 (20%)
Cardiac problems	16 (32%)
Renal problems	6 (12%)
Endocrinological problems	12 (24%)
Blood gases, mean±SD	
pH	7.32±0.9
$PaCO_2$, mmHg	51±3.7
$TcCO_2$, mmHg	45.1±4.2

When the correlation of transcutaneous CO_2 and end-tidal CO_2 with arterial $PaCO_2$ was evaluated, both parameters were found to be positively and highly correlated (r=0.864, p<0.001, r:0.962, p<0.001, respectively) (**Figure 1,2**).

The median $PaCO_2$ was 41 mmHg (IQR 35–51 mmHg), with a range 21–76 mmHg. The median $PTcCO_2$ was 43 mmHg (IQR 32–49 mmHg) with a range of 27–74 mmHg. The median end-tidal CO_2 was 38 mmHg (IQR 28–47 mmHg), with a range 18–66 mmHg.

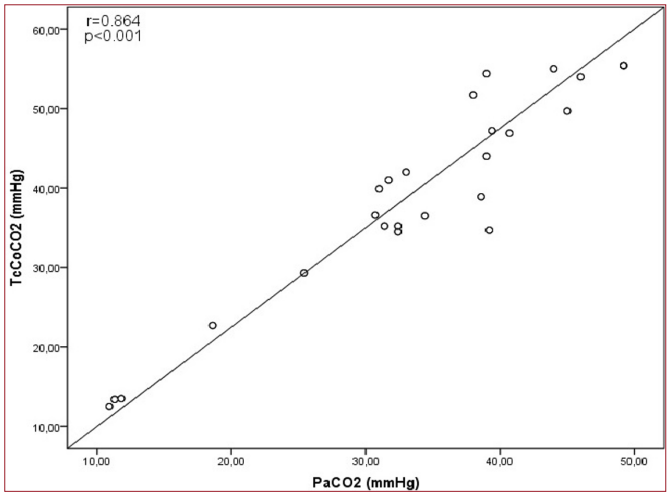

Figure 1. Correlation graphic between $PaCO_2$ and $TcCO_2$

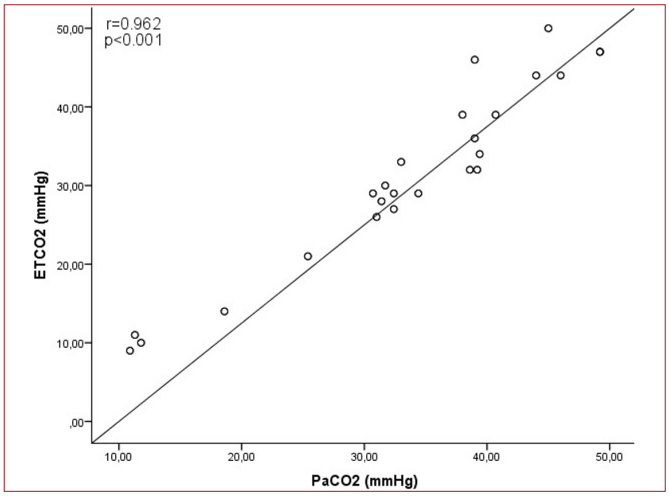

Figure 2. Correlation graphic between $PaCO_2$ and $ETCO_2$

The mean bias between the arterial carbondioxide mesaurement and transcutaneous measurement was 5.5, and limits of agreement (bias ±1.96 SD) ranged from -13.9 to 2.9. (**Figure 3**) The mean bias between the arterial carbondioxide mesaurement and end-tidal carbondioxide measurement was 2.3, and limits of agreement (bias ±1.96 SD) ranged from -4.1 to 8.6. (**Figure 4**) In 44 measurements (88%), the $TcCO_2$ was ±7.5 mmHg of the $PaCO_2$.

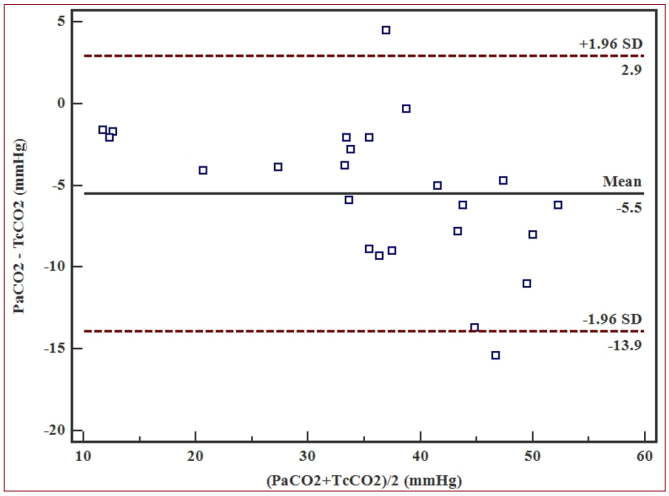

Figure 3. Blant-altman analysis for $TcCO_2$ versus $PaCO_2$. Bias (continous line), limits of agrement (bias±1.96, dashed lines) are shown in graph. Each square indicates the bias the bias of a single patient.

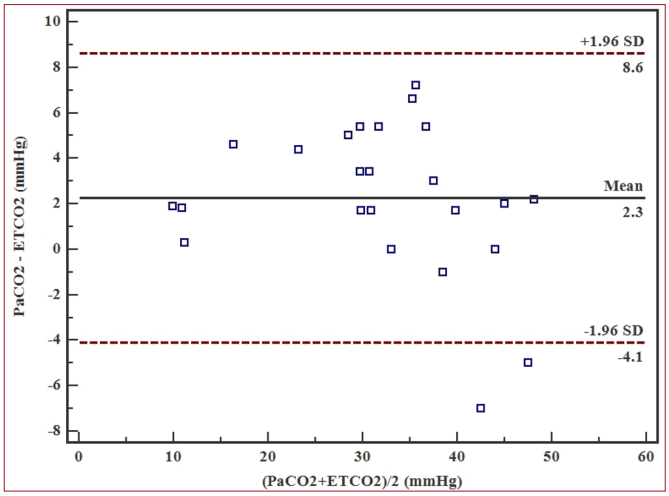

Figure 4. Blant-altman analysis for $ETCO_2$ versus $PaCO_2$. Bias (continous line), limits of agrement (bias±1.96, dashed lines) are shown in graph. Each ssquare indicates the bias the bias of a single patient.

Discussion

Arterial $PaCO_2$ is still the gold standard for the evaluation of alveolar ventilation but the desirable method for estimating $PaCO_2$ value in a critically ill child is the method that provides non-invasive, reliable and continuous monitoring.[5] This is one of the most detailed studies comparing two different non-invasive techniques for continuous carbon dioxide measurement with arterial blood gas carbon dioxide measurement (the gold standard method of alveolar ventilation) in patients undergoing mechanical ventilaiton in a pediatric intensive care unit. The main finding of the present study is that $TcCO_2$ monitoring is an appropriate method for continuously measuring PCO_2 in ventilated patients. In critical patients receiving respiratory support, closely monitoring cardiorespiratory changes and instantly recognizing clinical worsening are very important for follow-up and treatment. Therefore, continuous monitoring of CO_2 levels with $TcCO_2$ has the potential to prevent many of the known problems associated with end-tidal CO_2 monitorization in critically ill children.

There have been many studies in newborns, adults and children to demonstrate the relationship between $PaCO_2$ and $TcCO_2$, but there are still studies that show that there is correlation, as well as studies that suggest otherwise.[11-17] In a study of patients admitted to the emergency department with respiratory problems, the mean difference between $PaCO_2$ and $TcCO_2$ was 1 mmHg with limits of agreement of -3.4 to 5.6 was found by Delerme et al.[5] Perrin et al.[18] found a bias of 0.13 mmHg with limits of agreement of -3.9 and 3.7 mmHg in asthmatic patients. Different from previous studies, we found the mean bias between the arterial carbondioxide mesaurement and transcutaneous measurement was 5.5, and limits of agreement (bias ±1.96 SD) ranged from -13.9 to 2.9. We explain this worse results with the higher $PaCO_2$ levels of our patients. While mean $PaCO_2$ of our patients is 51 mmHg, mean $PaCO_2$ of previous studies are respectively 39 and 36 mmHg. Our findings are consistent with the findings of other authors, who argue that the reliability and accuracy of this method decreases in patients with high levels of $PaCO_2$.[2,19]

In previous studies, the predicted range for $TcCO_2$ was assumed to be ±7.5 mmHg and 81.2% of cases remained within this range.[13] Another study by Anoopindar et al.[20] found that 83.2% of cases remained within this range when the estimated range of ±7.5 mmHg was accepted. Our study also found that 88% of the cases were in this range consistent with the literature.

Anoopindar et al.[20] reported that they did not find a significant association between high lactate levels, high doses of inotropes (higher vasoactive inotrope scores) and $TcCO_2$ 5 mmHg higher than $PaCO_2$. In previous studies, a decreased correlation between $PaCO_2$ and $TcCO_2$ was observed at epinephrine doses as high as 0.3 ug/kg/min.[21] In our study, 5 of 12 patients with cardiac problems received such a high dose of inotrope, but we did not see this association in our subgroup. It is possible that most children with cardiac disease did not have low cardiac output at the time of measurement so they had enough cardiac output to ensure skin perfusion.

In a study on non-invasive carbon dioxide monitorization conducted by Tobias et al.[21] regression analysis revealed an r value of 0.9693 when comparing transcutaneous versus arterial $PaCO_2$ values and an r value of 0.8745 when comparing end-tidal versus arterial CO_2. Consistent with these findings, in our study the correlation of transcutaneous CO_2 and end-tidal CO_2 with arterial $PaCO_2$ were both found to be positively and highly correlated (R:0.864, $p<0.001$, r:0.962, $p<0.001$, respectively).

There are some limitations in our study. The first was that our number of patients was small. The second was although higher temperatures increased the reliability of the $TcCO_2$ measurement we use the V-Sign Sensor 2 (which heats up to 42°C) probe to avoid injury and burns. The third was that due to the low number of patients with respiratory problems, we were unable to obtain clear data on the differences from alveolar dead space between end-tidal CO_2 and $PaCO_2$/ $TcCO_2$. And also this is a single-centre study and one type of sensor device was used.

Conclusion

As a result, $TcCO_2$ seems to be a good alternative for carbon dioxide measurement, as it is non-invasive and allows continuous monitoring in view of today's intensive care conditions, but arterial $PaCO_2$ measurement is still the gold standard method. This study shows that continuous $TcCO_2$ monitoring provides a promising alternative to repeated blood sampling in subjects requiring mechanical ventilation for critically ill children. But further research is needed for the reliability of $TcCO_2$ measurement especially in special patient groups (tissue perfusion impaired, severe ARDS, shock, etc.)

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

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Case Report

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Valproic Acid-Induced Priapism in a Child

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Abstract

A complete or partial involuntary erection that occurs in absence of a sexual stimulation and lasts longer than four hours is defined as priapism. Etiology usually includes sickle cell disease or hematologic malignancies. Less common causes include trauma, spinal cord injury, medications, congenital syphilis, parotitis, Fabry's disease and retroperitoneal sarcoma. Priapism is a urologic emergency that varies by ischemic and non-ischemic episodes. Ischemic injury to cavernous tissues leads to erectile dysfunction. Early recognition of priapism, determination of the type and the treatment are crucial in preventing potential long-term complications caused by priapism. With this case of priapism caused by a treatment with valproic acid, it was aimed to point out priapism which is a urologic emergency.

Keywords: Priapism, valproic acid, children, pediatric emergency, urologic emergency

Introduction

A complete or partial involuntary erection that occurs in absence of a sexual stimulation and lasts longer than four hours is defined as priapism. Etiology usually includes sickle cell disease or hematologic malignancies. Less common causes include trauma, spinal cord injury, medications, congenital syphilis, parotitis, Fabry's disease and retroperitoneal sarcoma.[1] Treatment of this urological emergency aims prevention of erectile dysfunction and psychological sequelae.[2] There is still no widely accepted algorithm for management of priapism in children. Most cases of priapism improve with treatment of the underlying disease. However, refractory cases are managed conservatively by corporeal irrigation. Some cases require a corporeal cavernous-spongious shunt.[1]

With this case of priapism caused by a treatment with valproic acid, it was aimed to point out priapism which is a urologic emergency.

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Case

An eight year-old male patient admitted to our pediatric emergency department with complaints of unease for 3 days and having a seizure half an hour ago. The patient with no remarkable family history had mental-motor retardation due to hypoxic-ischemic encephalopathy and history of being treated with valproic acid for 4 years with diagnosis of epilepsy. His general condition was moderate, he was in the postictal phase with a SpO_2 of 93-95%, body temperature of 36.7°C, heart rate of 102/min, blood pressure of 102/67 mmHg and respiration rate of 24/min. On physical examination, he had penile erection with relatively glans penis (Figure 1). During taking the history, it was learned that this condition was present for three days and he had no history of trauma. Examination of the other systems was normal. Laboratory work-ups requested for etiology of priapism were found to be normal. The patient was consulted with department of urology, a corporeal aspiration was performed and a blood gas analysis was requested, which was consistent with ischemic priapism (PO_2: 25 mmHg, PCO_2: 82 mmHg, pH: 7.21). Low rate of blood flow within cavernous arteries were also consistent with ischemic priapism. A cavernous aspiration was performed; however, because of failure to achieve detumescence and a history of priapism that had lasted longer than three days, treatment with a surgical shunt was considered. However, his parents refused due to mental-motor retardation of the patient. Treatment with terbutalin at a dose of 0.05 mg/kg/dose every 8 hours was initiated. The patient was considered to have valproic acid-induced priapism and the medication discontinued. Patient's complaint of priapism improved three days after discontinuation of the medication.

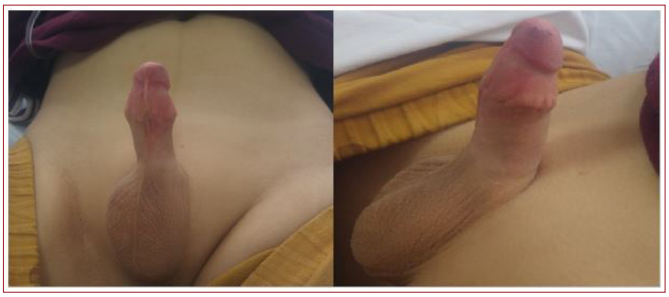

Figure 1. A case of valproic acid-induced priapism

Discussion

Priapism has three distinct types: Ischemic (veno-occlusive, low-flow), non-ischemic (arterial, high-flow) and stuttering (intermittent, recurrent ischemic). Ischemic priapism is the type which is usually painful and the most common in children. Its etiology includes hematologic disorders, history of medication use (α-Adrenergic receptor antagonists, anticoagulants, antidepressants, antipsychotics, antihypertensive drugs, hormones, vasoactive drugs), malignancies and neurological disorders.[3,4] Main objective of the treatment is rapid restoration of cavernous blood flow in order to prevent end organ damage and erectile dysfunction. Hypoxia and acidosis lead to cavernous fibrosis within four hours and focal necrosis within 24 hours and diffuse necrosis within 48 hours.[5] Non-ischemic priapism is a rare condition that occurs in case of an irregular high arterial blood flow to the corpora cavernosa due to rupture of cavernous artery secondary to a penile, perineal or pelvic trauma. Painful, recurrent, self-limiting long-lasting erections that may precede ischemic priapism is called stuttering (recurrent) priapism.[6,7] History, physical examination and blood taken from the corpora cavernosa can differentiate ischemic from non-ischemic priapism. Blood taken from the ischemic priapism has a pH<7.25, pO_2<30 mmHg and is dark-colored, whereas in the non-ischemic variant, it has a pH>7.30, pO_2>50 mmHg and is bright red. A color Doppler of penis and perineum is the gold standard for access to blood flow to the corpora cavernosa and differentiates the ischemia from normal-high-flow non-ischemic priapism.[8]

The basis for mechanism of action of drug-induced priapism is development of hypoxia and ischemia due to irregular tonus of smooth muscles localized in penile vascular tissues.[9] In the literature, an adult case of valproic acid-induced priapism, similar to ours, was published by Bansal et al.[10] Our case is the first pediatric case report of valproic acid-induced priapism.

Conclusion

Priapism is a urologic emergency that varies by ischemic and non-ischemic episodes. Ischemic injury to cavernous tissues leads to erectile dysfunction. Early recognition of priapism, determination of the type and the treatment are crucial in preventing potential long-term complications caused by priapism.

Author Contributions: Concept: E.T, A.Y, F.A, A.O.K; Design: E.T., A.Y; Analysis or Interpretation: E.T, A.Y, F.A; Literature Search: E.T, A.Y, A.O.K; Writing: E.T, A.Y.

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Case Report

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Bladder Papilloma as a Rare Cause of Urogenital Bleeding in a Prepubertal Girl

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Abstract

There are different causes of urogenital bleeding in prepubertal girls. These include vulvovaginitis, urinary infections, urethral prolapse, urethral caruncle, vaginal foreign bodies, hormonal causes, tumors, posterior labial fusion, lichen sclerosis. Among the tumors, rhabdomyosarcoma and papilloma are prominent. In this article, a case of urogenital hemorrhage due to papilloma located at the base of the bladder was presented and the relevant literature was reviewed.

Keywords: Bladder papilloma,urogenital bleeding, girl

Introduction

Urogenital bleeding is a rare problem in prepubertal girls.[1,2] Vaginal, urethral, bladder lesions, foreign body, hormonal problems, vaginal-urinary infections, and tumors are among the causes of bleeding.[3-5] In cases, detailed anamnesis is important. An external and internal genital examination and hormonal studies, pelvic ultrasonography should be performed. If it is considered necessary, urethra and bladder should be examined with cystoscopy. Urethral, cervix, and bladder tumors should be excluded.[2]

In this article, a case of bladder papilloma, which was determined as the cause of prepubertal bleeding in a 7-year-old girl, was presented and the relevant literature was reviewed.

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Case

A seven-year-old girl presented with the complaint of bleeding when urinating for about 7 days. It was learned that there was no bleeding disease in the family. Physical examination; height 129.5 cm (60th percentile), weight 24 kg (46th percentile), blood pressure 105/85 mm/Hg, pulse 72/min, pubic-axillary hair, and thelarche were not detected. The external genital examination was normal. In laboratory examinations, hemoglobin was 11 g/dl, white blood cell was 7200 mm^3/blood, and platelet count was 265,000 mm^3/blood. In the urine examination, pH 5, density 1025, blood (peroxidase) +++, leukocyte esterase ++, nitrite negative, abundant erythrocytes, 8-10 leukocytes were detected in microscopy. Pelvic ultrasonography findings were consistent with prepubertal period. In hormonal evaluation; LH was <0.1 mIU/mL and estradiol was 7.09 pg/ml. When other causes were ruled out, it was decided to examine the urethra and bladder cystoscopically. Large and small hemorrhagic lesions were observed at the base of the bladder with cystoscopy and a biopsy was taken. In the pathological examination of the material taken, a papillary structure containing fibrovascular core in the bladder surface epithelium, which supports the diagnosis of papilloma, and urothelial epithelial lining that does not show increased atypia (HE×10, HE×20) (**Figure 1 a,b**). Laser coagulation was performed on the papilloma lesions by performing cystoscopy again. The complaints of bloody urine disappeared in the patient.

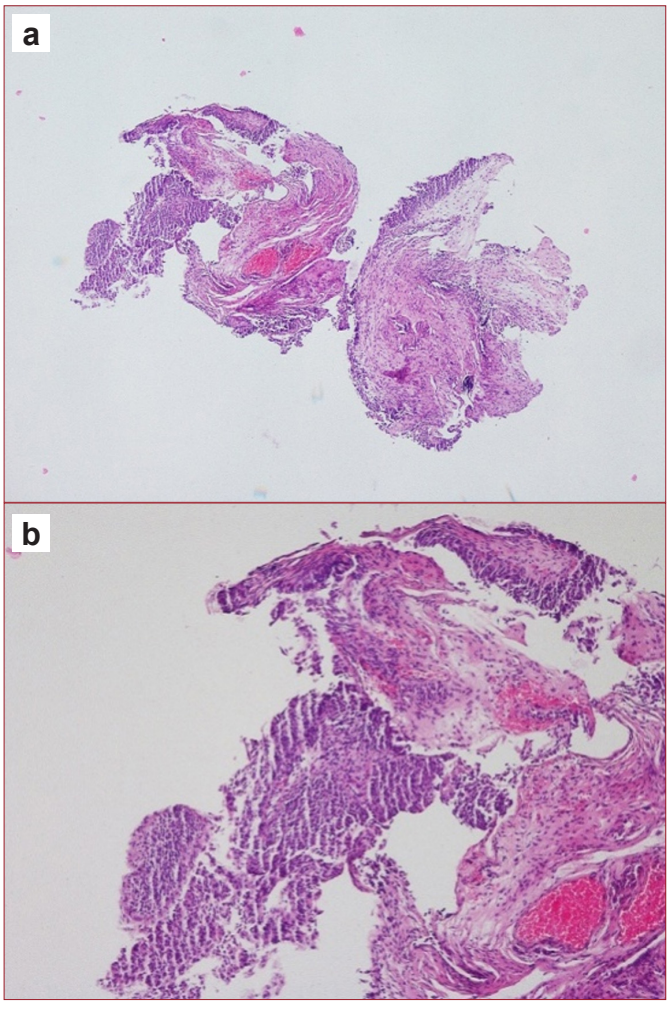

Figure 1. In the histopathological examinations, papillary structure containing fibrovascular core in the bladder surface epithelium and he urothelial epithelium were observed(HE×10 **(a)**, HE×20 **(b)**.

Discussion

Tumors are rarely involved in the etiology of prepubertal urogenital hemorrhages in girls. Urethral and bladder localized papilloma can be seen in boys and girls.[3] Papilloma constitutes 1-2% of urothelial tumors.[6] Some authors explain that papilloma lesions are not true neoplasia, but as a hyperplastic reaction of Brune cells against irritative agents or chronic inflammation.[3] However, the general opinion is that the papilloma is a true neoplasm of the urogenital system.[7] Kunze E et al.[8] divide the lesions into two as trabecular and glandular patterns. Trabecular type papilloma is more common, the clinical picture is similar to cystitis in cases of glandular type papilloma.[9]

Conclusion

If urogenital bleeding is observed in prepubertal girls, foreign bodies and tumors should be investigated under general anesthesia, in addition to careful physical examination, and papilloma located in the urethra and bladder should be investigated by cystoscopy. Endocrine tests, pelvic ultrasonography and magnetic resonance should be performed in necessary cases.[1-3,6]

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

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Image Corner

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A Case of Pulmonary Tuberculosis Detected While Being Investigated with a Preliminary Diagnosis of Covid-19 Infection

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A 15-year-old female patient, who had no previous history of illness, had the complaint of intermittent cough and chest pain for 2 months. Two days ago, she applied to the hospital with difficulty in breathing added to her complaints. Tomography (CT) was planned due to the presence of pneumonic infiltration in the left lung (**Figure 1**) in the chest radiography of the patient who was hospitalized in the intensive care unit due to respiratory distress. The patient was referred to us after Covid-19 was considered. On physical examination, there was bilateral diffuse crackles in the lung with auscultation and respiratory sounds were decreased in the left lung. Its oxygen saturation was determined as 89% on room air, RR: 28/min. Pathologically in laboratory evaluation; Erythrocyte Sedimentation Rate:56 mm/hour, C-reactive protein:8 mg/dl. The patient was admitted to the pandemic service with the pre-diagnosis of Covid-19 infection and Pneumonia. There was a history of smoking 1 pack per day for 2-3 years. The pneumonia treatment of the patient was arranged as Ceftriaxone and Azithromycin. Covid-19 PCR Tests taken resulted as Negative. In thoracic CT imaging, it was evaluated as significant by the radiology in terms of tuberculosis (TB) (**Figure 2**). The PPD of the patient was evaluated as negative with 3 mm (BCG single scar). There was no known history of tuberculosis contact in the family history. With the diagnosis of "Pulmonary Tuberculosis" with the diagnosis of sputum ARB (++), anti-tuberculosis treatment consisting of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol was initiated due to cavity-widespread pulmonary TB. The patient, whose need for oxygen decreased during follow-up, was discharged on the 10th day of his treatment, with outpatient follow-up planned.

In some individuals, tuberculosis bacillus reacts and multiplies, causing the development of post-primary TB. Although the post-primary TB radiological findings may overlap with the findings of primary TB, it has some distinctive findings such as preferring the upper lobes, not following lymphadenopathy, and a tendency to create cavitation.[1] Tomography provides important contributions in the detection of parenchymal pathology and lymphadenopathies in patients who are evaluated with the pre-diagnosis of tuberculosis, or in patients with suspected tuberculosis clinically but without radiographic findings.[2] In this period when Covid-19 infection is common, tuberculosis should be kept in mind in patients with long-term cough.

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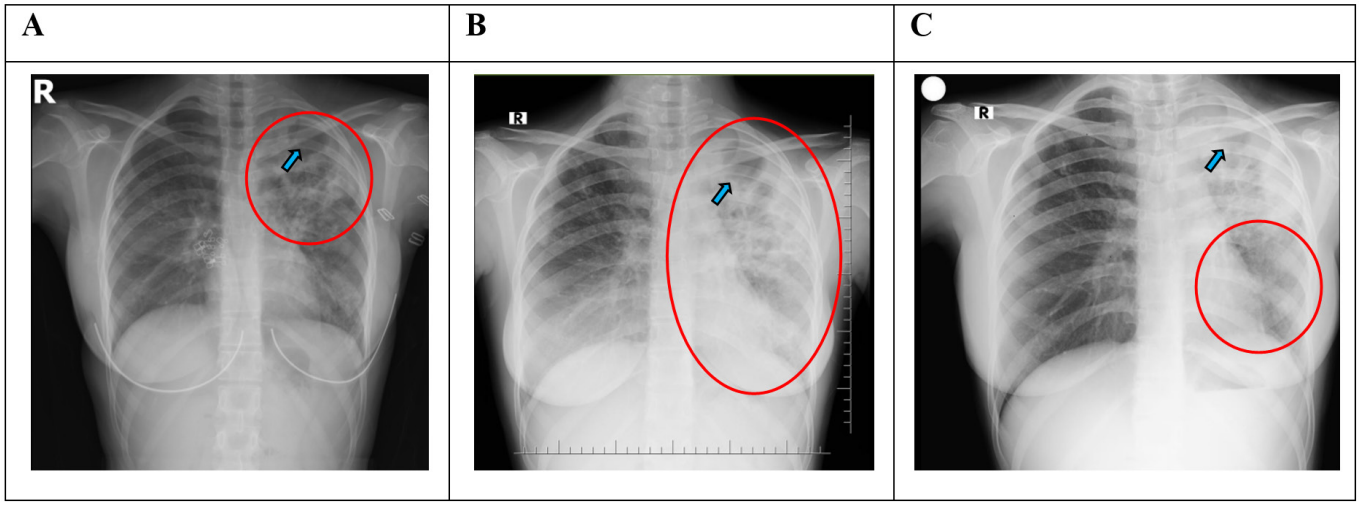

Figure 1. A) Chest radiography two months ago: There are reticulonodular infiltration areas and cavitary lesion in the left lung. **B) Reference Chest radiography:** Significantly increased reticulonodular infiltration areas are seen in the left lung compared to the old radiograph. **C) Chest radiography in the third week of treatment:** Radiological findings in the left lung partially regressed.

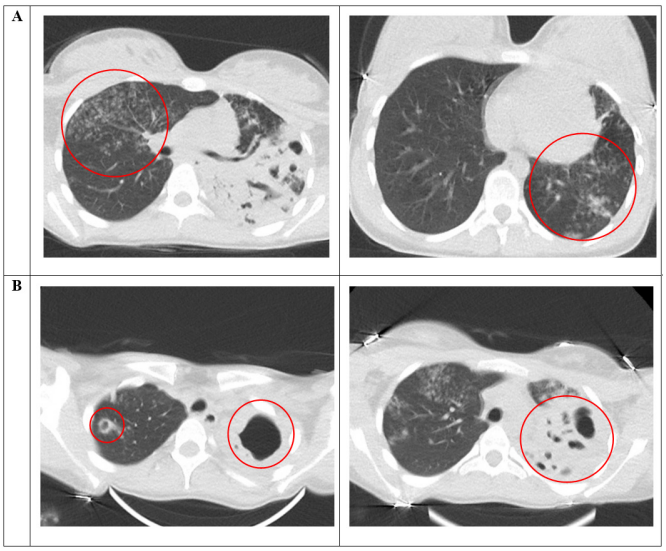

Figure 2. Thorax CT imaging; A) More prominent reticulonodular infiltration areas in the upper lobe of both lungs, lower lobe of the left lung, and upper lobe of the left lung. **B)** Cavitary lesions in the upper lobe of both lungs and upper lobe of the left lung with a larger diameter reaching 7 cm in the upper lobe of the left lung.

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