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Overview

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

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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.
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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.

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

Book Chapter:

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

Entire Book:

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

Software:

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

Online Journals:

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

Database:

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

World Wide Web:

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

URL (Uniform Resource Locator)

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

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Kidney Tumors in Children

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Abstract

Wilms tumor (WT) is an embryonal tumor of the kidneys. It is associated with many oncogenic genetic aberrations and congenital anomalies. Owing to worldwide clinical research and optimized patient care, curative therapy can be obtained in 90% of diagnosed children with WT. The decision of treatment mainly depends on stage, age, histological type, and genetic markers. Except for WT; congenital mesoblastic nephroma, clear cell sarcoma, malignant rhabdoid tumor, and renal cell carcinoma constitute 5% of kidney tumors. Herein, WT and other tumors of the kidney will be emphasized.

Keywords: Wilms tumor, unfavorable histology, kidney tumors

Introduction

Childhood malignant kidney tumors are responsible for approximately 5,5-7% of childhood cancers.[1,2] About 95% of these kidney cancers are Wilms tumor (WT). As a survival advantage is provided with all childhood cancers, the 5-year overall survival for WT is around 93%.[2] Less common types of renal tumors consist of clear cell sarcoma, malignant rhabdoid tumor, congenital mesoblastic nephroma, and cystic differentiated nephroblastoma.[1-3]

1. Wilms Tumor

As mentioned earlier, WT is the most commonly seen renal neoplasia of childhood. Under the age of 15, the incidence is 10.4 cases in one million children and also 0.2 cases per 10,000 infants.[1-4] More than ninety-five percent of patients are diagnosed under 10 years of age. The mean age at diagnosis is about 44-47 months.[5] Around 10% of diagnosed patients present a congenital malformation syndrome, which can enable early diagnosis.[5,6]

1.a. Genetic landscape

Sixty percent of the patients who have congenital anomalies and WT, present nephrogenic rests. Congenital anomalies are composed of hemihypertrophy and also urinary tract anomalies, such as cryptorchidism and hypospadias.[7] The phenotypic syndromes and congenital malformations associated with WT can be found in **Table 1**.

One of the most important genetic alterations which have a remarkable impact on pathogenesis is the loss of the *WT1* gene. WT1 which is a tumor suppressor gene, plays a significant role in cell development, differentiation, and apoptosis. The disease is usually associated with biallelic inactivations of the gene. Wilms tumor, aniridia,

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genitourinary anomalies, and mental retardation (WAGR) syndrome is a WT1-related spectrum, which occurs with the interstitial deletion on chromosome 11 (del(11p13)).[8] The clinical features are aniridia, genitourainary anomalies, and mental retardation. In children with WT, the incidence of this deletion is around 0.4%. The risk of WT development in WAGR syndrome is about 50%, with presenting earlier with a median age of 22 months. In addition to this, WT in children with WAGR tends to be bilateral involvement.[9,10] The other syndromes related to the WT1 gene are Denys Drash and Frasier syndromes. As a part of Denys Drash syndrome, missense germline mutations of WT1 are associated with WT and the risk of WT development is as high as 90% in children with Denys Drash syndrome. However, in Frasier syndrome splice-site mutations are present in WT1 and this syndrome has a lower incidence for WT development.[8-11]

Mutations in the *WT2* gene are also important genetic alterations playing a role in WT development. Altered genetic expressions of two gene clusters located in the WT2 locus which is chromosome 11p15.5 are responsible for Beckwith-Wiedemann syndrome (BWS). Generally, the syndrome is presented with an asymmetric overgrowth of one or more parts of the body. Kidney abnormalities and also hypoglycemia, especially in neonates, can be observed. BWS predisposes to rhabdomyosarcoma, WT, and hepatoblastoma development, especially in the first decade of life.[12,13] Previously, the incidence of BWS in children who have WT was about 1%. However, with the latest population-based studies, the incidence of BWS in patients who have been diagnosed with WT is reported as high as 16%.[14] Besides, the risk of developing WT is higher in the presence of hemihyperthrophy.[15]

Despite all the genetic alterations, which are already known to have a role in pathogenesis and are still being studied, there is also an entity called Familial WT. About 2% of patients with WT have a positive family history of WT. However, the risk for WT development in siblings and offsprings of patients who are diagnosed with sporadic WT is about 1% and 2%, respectively.[16] Two loci have been identified as associated with familial WT, which are 17q12-q21 (FWT1) and 19q13.4 (FWT2).

The genomics of WT have been highly studied as in many other solid tumors of childhood. However, there is a noteworthy study about the genomic landscape of WT, conducted by Gadd et al.[17] This study provided genome-wide sequencing, mRNA, and miRNA expression, also DNA copy number, and methylation analysis on a very large scale. This study has made significant contributions to our understanding of the genetic background of WT, as follows. Firstly, more than one genetic event has an impact on WT development. Different genetic aberrations result in different methylation and gene expression patterns of WT. Also, a large number of candidate genes play a role in WT development, however, most of them are mutated only in less than 5% of WTs. Once and for all, WT arises from recurrent mutations affecting early renal development or either epigenetic regulation.[17]

Children followed up with BWS or other overgrowth syndromes, WAGR, and Denys-Drash, also sporadic aniridia, or isolated hemihypertrophy have significantly increased risk for WT development. Therefore, screening is recommended in such cases, with the primary goal of earlier detection of a small and localized tumor (stage I or II), improve prognosis, and use of less intensive treatment.[18]

1.b. Clinical features

An asymptomatic abdominal mass is the most common presenting symptom, detected generally by the parents when they are bathed or dressed or by pediatricians on a well-child visit. A large, non-tender flank mass is

Table 1.
Syndromes and congenital malformations associated with Wilms Tumor

Overgrowth pheynotype	Non-overgrowth pheynotype
High risk for WT (>20%)	**High risk for WT (>20%)**
Perlman syndrome	WAGR syndrome (WAGR spectrum)
	Denys-Drash syndrome
	Fanconi anemia with biallelic mutations in BRCA2 (FANCD1) or PALB2 (FANCN)
Moderate risk for WT (5-20%)	**Moderate risk for WT (5-20%)**
Beckwith-Wiedemann syndrome	Frasier syndrome
Simpson-Golabi-Behmel syndrome	
Low risk for Wilms Tumor (<5%)	**Low risk for Wilms Tumor (<5%)**
DICER1 syndrome: DICER1 mutation	Bloom syndrome
Isolated hemihypertrophy	Li-Fraumeni syndrome
PIK3CA-related segmental overgrowth including CLOVES syndrome	Hyperparathyroidism-jaw tumor syndrome
9q22.3 microdeletion syndrome	MULIBREY nanism syndrome
Sotos syndrome	Familial Wilms tumor
	Genitourinary anomalies
	Sporadic aniridia
	Trisomy 18

CLOVES; Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal/spinal abnormalities, MULIBREY; Distinctive abnormalities of the (MU)scles, (LI)ver, (BR)ain, and (EY)es, WAGR; Wilms tumor, aniridia, genitourinary anomaly, and mental retardation

usually present. Abdominal pain can accompany in about 40% of patients. A distinguishing finding from the splenomegaly of this mass is that this mass does not move with respiration in the physical examination.[19] Gross and microscopic hematuria occurs in 18% and 24% of patients on admission, respectively. As well, hypertension is another presenting symptom, seen in about 25% of patients, which is caused by activating the renin-angiotensin system. The other less common symptoms on admission can be listed as follows; hypercalcemia, fever, anorexia, and weight loss.[19-21]

Apart from the most common findings, pulmonary symptoms such as dyspnea can be observed in patients owing to pulmonary metastasis. In the case of pulmonary embolism, emergency medical intervention is crucial. Also, the tumor can develop subcapsular hemorrhage, leading to rapid abdominal enlargement, anemia, and severe pain.[19-21] Acute abdomen due to tumor rupture, paraneoplastic polycythemia, Budd-Chiari syndrome, heart failure due to tumor thrombus, and acquired von Willebrand deficiency have been reported.[22] As mentioned earlier congenital abnormalities can be observed in 12-15% of patients in physical examination and imaging studies[23].

1.c. Diagnostic evaluation, differential diagnosis, histology, and staging

As with every diagnostic evaluation in pediatrics, a complete history and physical examination are the first steps. Patients should be judged carefully for signs of associated syndromes such as aniridia, developmental delay, genitourinary anomalies, and hemihypertrophy. The first tests to be performed are whole blood count, urinalysis, biochemical tests, coagulation parameters, and cardiac evaluation.

Generally, the first chosen imaging method is abdominal ultrasonography. However, computed tomography (CT) and/or magnetic resonance imaging (MRI) with contrast are more definitive imaging methods. MRI of the abdomen needs moderate to deep sedation, which is a common concern for clinicians. On the other hand, MRI supplies excellent detail, especially in the case of bilateral involvement and liver metastasis. Detection of contralateral lesions is essential since the stage and treatment of the patient are based on the extent of the tumor.[24,25] The decision of surgical approach or preoperative chemotherapy should be made with the results of imaging studies. In a study carried out by The SIOP-Renal Tumor Study Group (RTSG), online questionnaires were applied to the experts who currently work in the field of pediatric tumors. The aim was to determine pathognomonic imaging findings of pediatric kidney tumors. In this study, WT was generally described as a solid intrarenal mass, with a pseudo capsule, and appears to be heterogenous owing to the hemorrhage, necrosis, and/or cysts inside the tumor. However, it is emphasized that the diagnostic process is not solely based on the MRI findings. In addition to MRI findings, age on admission, and clinical presentation contributes to the differential diagnosis.[26]

Compared with an MRI, a CT scan of the abdomen also confirms a mass of renal origin easily and also provides information about bilateral involvement.[24] However, small bilateral tumors can be missed in helical CT scans. Another important issue about preoperative diagnostic imaging is to determine the intravascular extension of the tumor. Inferior vena cava, atrial involvement, and renal vein involvement should be demonstrated preoperatively to guide safe management. CT scans have been reported to establish cavoatrial thrombus precisely.[27] Radiation exposure is a concern about CT. Nonetheless, a CT scan is a rapid procedure, supplies continuous imaging of the abdomen and chest, with perfect chest detail. The most common metastasis sites in WT are the lungs and liver with 85% and 10%, respectively in metastasized patients. Therefore, imaging of the lungs is vital. CT scan is the most sensitive modality for detecting lung metastasis and pleural effusions.[28,29]

Evaluating the other imaging methods; Fluorine F 18-fludeoxyglucose positron emission tomography (FDG-PET)-CT is not routinely used. Also, there is no need to use a chest X-ray. In the presence of extrapulmonary metastasis, a bone scan or a cross-sectional assessment of the affected site should be considered.[28]

It should be underlined that a definitive diagnosis is only possible with pathological evaluation. However, in a resectable renal mass, such as stage I or II WT, the biopsy is not recommended since it will upstage the tumor to stage III, owing to tumor cells spread during the biopsy. However, in some cases, primary nephrectomy is not possible. In preoperative studies, lymph node status, intravascular extension, and tumor rupture should be judged and clarified. Therefore, a biopsy should be undertaken. In the presence of extended tumor thrombus to the hepatic veins level, tumor involving contiguous organs in which a complete resection can not be possible without the resection of these organs, and extended pulmonary and liver metastasis, primary nephrectomy is not the first choice. After the biopsy, the patient should be treated as stage III. With obtaining a biopsy, histological evaluation can be possible. However, deciding on the tumor histology can be controversial, owing to the heterogeneity of WT.[30]

Neuroblastoma, other kidney tumors, hematoma, and multicystic dysplastic kidney should be taken into account in the differential diagnosis. In the case of blastemal cell predominance, all small round blue cell tumors should be included in the differential diagnosis.[31]

WT exhibits a triphasic histological structure composed of blastemal, epithelial, and stromal cells. However, not all tumors appear to be triphasic. Anaplastic histology is solely the most significant prognostic factor predicting treatment response and survival. Anaplasia occurs in older patients. Two criteria must be met to say anaplasia, which is the presence of hyperchromasia and multipolar polyploid mitotic figures with a marked nuclear enlargement.[32]

The staging system has been developed by National WT Study (NWTS) Group and depends on the pathological, histological, and surgical findings.

Detailed explanations of the staging system are available in **Table 2**. Lymph node sampling and evaluation are recommended in all stages. Generally, 43% of patients are diagnosed with a stage I tumor. However, it should be underlined that regional lymph node evaluation is strongly recommended in these low-risk patients too. As well, lymph nodes should be negative for stage II patients. Tumor rupture, spill to the flank during the surgery, and any kind of biopsy performed before surgery are defined as stage III tumors. Besides the stage, histology has an impact on the outcome and is indicated with the stage.[20] In stage V patients, treatment after definitive surgery relies on the highest stage of the remaining kidneys and the posttreatment pathology.[33]

1.d. Treatment and prognosis

Currently, two treatment approaches are being implemented in the treatment of WT, which are conducted by two large study groups working on WT, the Children Oncology Group (COG), and the International Society of Paediatric Oncology (SIOP). In the COG approach, upfront surgery is recommended, whereas the SIOP approach depends on preoperative chemotherapy in the first step. Postoperative chemotherapy and radiation in selected patients are mutual treatment methods for the two groups. As well, patients younger than 6 months are treated with primary surgery in both groups.[34,35]

Conditions, in which primary nephrectomy is not recommended, are mentioned earlier. In the management of unilateral WT, the COG approach recommends nephrectomy and adjuvant chemotherapy. Whereas, SIOP suggests a neoadjuvant chemotherapy period prior to the surgery. The chemotherapy regimen depends on the stage and the histological findings of the tumor. On the other hand, in the presence of a tumor weight less than 550 gr, age <2 years, and stage I tumor with favorable histology; the necessity of chemotherapy is controversial. These patients can be cured with surgery alone.[36] Radiotherapy (RT) is advised in stage III and IV patients, and it should be underlined that owing to the long-term side effects, the requirement of RT should be evaluated carefully. RT is strongly recommended for patients with unfavorable histology.[37] Recently, the Renal Tumor Study Group (SIOP-RTSG Umbrella), which is a current update of SIOP protocol, recommends the decision of adjuvant RT in localized tumors should be undertaken based on tumor stage and pathologic findings after neoadjuvant chemotherapy and surgical features such as the presence of residual disease, evaluation of resection margins, tumor spillage, also lymph node involvement, and presence of drug-resistant viable tumor cells, as well as histological risk stratification.[38,39] As well, the timing of RT is a highly studied topic in WT treatment. A recent study from National Cancer Database revealed that, in non-metastatic WT adjuvant RT administered within 14 days (≤14 days) after surgery, is related to improved survival.[40]

Once and for all, comparing the two treatment approaches, in the COG approach, initial nephrectomy provides early and accurate histological diagnosis unamended by chemotherapy and staging information. On the other hand, in the SIOP approach, definitive surgery after a preoperative chemotherapy period achieves less tumor spills throughout surgery and also lower stage. Compared with the histological analyzes of primary nephrectomy, histological findings after a preoperative chemotherapy period result in less blastemal and mixed histology types.

WT with favorable histology has a survival rate greater than 90%. In general, improvements in patient care and management of side effects in childhood cancers have resulted in significant survival advantages. Besides

Table 2.
Staging system for Wilms Tumor

Stage	Definiton
Stage I	-Tumor is limited to kidney and completely resected. -Renal capsule is intact. -No tumor ruptures and biopsies before surgery. -Renal sinus vessels are not involved. -Margins of resection or beyond margins are tumor free. -All sampled lymph nodes are tumor negative.
Stage II	-Tumor is entirely resected and there is no sign of residue. -Regional extension of the tumor (permeation of the renal capsule, or widespread invasion of the soft tissue of the renal sinüs). -Blood vessels outside the renal parenchyma, in the nephrectomy specimen, including those of the renal sinus contains tumor cells. Margins are clear.
Stage III	-There is a postsurgical residue. -Abdominal or pelvic lymph nodes are involved with tumor. -Surface of peritoneum is involved with tumor and contains tumor implants. -Gross or microscopic tumor maintains postoperatively. -Tumor is not entirely resectable because of the involvement of vital organs. -Tumor has ruptured before surgery or spillled during surgery. -Any type of biopsy is undertaken, before surgery. -Tumor is extracted more than one piece owing to the contagious organ involvement. -Even outside the abdomen, extension of tumor to the vena cava thoracicus and heart is taken into account as stage III.
Stage IV	-Hematogenous metastases (lung, liver, bone, brain) -Metastatic lymph nodes outside the abdominopelvic region. -Involvement of adrenal gland by the tumor is not regarded as metastasis and staging depends on all other existing parameters.
Stage V	-Bilateral involvement of kidneys on admission.

these, shortened length of therapy, dosing of irradiation, fields irradiated, and also tailored irradiation therapy have significant contributions to survival and prognosis. Histopathological characteristics and stage have an important effect on prognosis, as mentioned earlier. Besides, another well-known prognostic marker is age on admission. Older age at diagnosis is associated with poor prognosis.[41] On the other hand, in the era of genetic research, molecular markers are documented to have an impact on prognosis. Among them, the most potent predictor of outcome which is associated with adverse outcomes is 1q gain. 1q gain is present in approximately 28% of the cases. Also in low-risk patients; loss of heterozygosity of 11p15 is involved with adverse prognosis and generally relapses.[42]

2. Non-Wilms Tumors

Non-WTs constitute a rare part of childhood kidney tumors. However, controversial to their rarity, sufficient diagnostic management and rapid diagnosis are crucial, owing to the high morbidity and mortality.[43]

2.a. Clear cell sarcoma of the kidney

Clear cell sarcoma of the kidney is an infrequent kidney tumor, presenting between 2-3 years of age. Bone metastasis is present in most cases, therefore bone scintigraphy should be undertaken in staging studies. However, in relapses, brain involvement is present more than bone. Recently, internal tandem duplications in BCL-6 coreceptor (BCOR) and a translocation t(10;17) creating the fusion gene *YWHAE-NUTM2B/E* have been reported to be associated with tumors. The course of the tumor is much more aggressive and recurrent compared to WT. Owing to the intensive treatment regimens, the overall survival has been improved to 86%.[44]

2.b. Congenital mesoblastic nephroma

Congenital mesoblastic nephroma commonly develops in the early infancy period with a median age of 3 months. It may present with abdominal distension, hypertension, hematuria, anemia, vomiting, and hypercalcemia. Curative treatment in most cases is surgery. Patients >3 years of age, cellular type histology, and stage III tumors should be pursued very closely as the disease may recur.[45]

2.c. Renal cell carcinoma

Renal cell carcinoma is the most prevalent kidney tumor in adults, whereas it is rare in childhood. In the presence of localized disease, surgery is the sole treatment method, however in metastatic disease the role of postoperative chemotherapy is controversial and the response is poor. Even though, there is limited evidence, sunitinib, mTOR inhibitors, and also anti-VEGF inhibitors are recommended in metastatic patients.[46]

2.d. Renal medullary carcinoma

Renal medullary carcinoma is a very seldom and very fatal tumor of the kidneys. This tumor almost always develops in patients with sickle cell disease (SCD) or carriers of SCD. There is no standardized treatment method and also owing to the sparseness of the tumor, the screening of patients with SCD is not recommended.[47]

2.e. Malignant rhabdoid tumor of the kidney

In childhood, malign rhabdoid tumor of the kidneys accounts for 1.5-4% of renal malignancies, being a part of the malign rhabdoid tumor family, which are very invasive tumors mainly developing in pediatric age. Other sites, such as the central nervous system, lungs, bone, and soft tissues should be evaluated. Lungs are the most frequent site for metastasis. Patients under the age of 24 months and the existence of distant metastasis are poor prognostic criteria.[48]

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Increase in Odontogenic Cervicofacial Infection Requiring Hospitalization in Children During COVID-19 Quarantine

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Abstract

The aim of this study was to evaluate the effect of Coronavirus disease-2019 (COVID-19) quarantines on children hospitalized for odontogenic cervicofacial infection. The data of patients aged 1 month-18 years, who were followed up with the diagnosis of odontogenic cervicofacial infection in Çanakkale Onsekiz Mart University Hospital between January 2019 and June 2021 was examined, retrospectively. Thirteen patients with a mean age of 8.5±3.8, 7 of whom were male were included in the study. Three of the patients were diagnosed in the pre-COVID-19 period and 10 of them were diagnosed in the second year of COVID-19. Five patients had a known history of dental caries. On physical examination, it was determined that all patients had dental caries in the area corresponding to the infection site. Four patients required abscess drainage, all of whom were presenting in the second year of COVID-19, we isolated *Eikenella corrodens*, *Streptococcus anginosus* and *Streptococcus intermedius* microorganisms in 3 patients. The mean duration of hospitalization was 5.3±3 days. In conclusion, COVID-19 quarantine causes an increase in odontogenic cervicofacial infection requiring intravenous antibiotics and abscess drainage.

Keywords: Child, COVID-19, quarantine, dental caries, hospitalization

Introduction

Since the first case reported from Wuhan, China in December 2019, the Coronavirus disease-2019 (COVID-19) pandemic has resulted in approximately 586 million infections and 6.5 million deaths worldwide as of August 2022.[1] In order to combat the spread of the pandemic in Turkey, curfews and social restrictions were put in place in March 2020. These scope of these restrictions were expanded gradually to include children, as well.[2,3] Turkish Dental Association has advised dental healthcare professionals to post-pone all non emergent interventions and to minimise potential exposure due to airborne water droplets and close contact.[4] Especially in the early phase of the COVID-19 pandemic, dentists and otolaryngologists tended to delay non-acute cases due to their close proximity to the patient's oral and nasal cavity during clinical examination and surgical procedures.[5] Unfortunately, reduced access to primary health care services can inevitably lead to delays in treatment

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and worse outcomes.[6] Odontogenic cervicofacial infections are a known complication of untreated dental infections.[6,7] Thus, it is predicted that there may be a potential increase in the prevalence of cervicofacial region infection and morbidity of patients during the COVID-19 period.[8] Our study focused on determining whether there is an increase in the number of children hospitalized for odontogenic cervicofacial infection during the COVID-19 period compared to previous periods. The aim of this study is to analyze the children we follow with odontogenic cervicofacial infection in our clinic located in a tertiary health center and to share our experiences.

Highlights

- Inadequate dental hygiene is the most important cause of cervicofacial infections.
- Preventive dental health practices have been disrupted in the COVID-19 quarantine.
- The COVID-19 quarantine has increased serious cervicofacial infections.

Material and Method

Study Design and Participants

The data of patients aged 1 month-18 years, who were followed up with the diagnosis of odontogenic cervicofacial infection in Çanakkale Onsekiz Mart University Hospital between January 2019 and June 2021 was examined, retrospectively. Socio-demographic variables as well as clinical features such as presenting symptom, abscess drainage, length of hospital stay (≥24 hours) and laboratory parameters including complete blood count parameters (white blood cell & neutrophil), C-reactive protein and culture results were evaluated from medical records. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (2021/07-12). Written consent was obtained from the parent of the case whose image was used.

Statistical Analysis

The collected data from all groups were imported to Statistical Package for Social Sciences (SPSS) for Windows software, version 23.0 (SPSS Inc., Chicago, USA). Descriptive statistics such as mean ± standard deviation for continuous variables and frequency (n) and percentage (%) for categorical variables were used to summarize participant baseline characteristics.

Results

Seven of the 13 patients followed in our clinic with the diagnosis of odontogenic cervicofacial infection were male. Of the patients, 3 (23.1%) were diagnosed in the pre-COVID-19 period, and 10 (76.9%) patients were diagnosed in the second year of COVID-19 (**Figure 1**). No patients were diagnosed nor admitted in 2020. The ages of the patients were between 3 and 15, with a mean of 8.6±3.8 years. The most common symptom at admission was swelling of the neck and/or face. Five patients had a known history of dental caries. On physical examination, it was determined that all patients had dental caries in the area corresponding to the infection site. The lesion area of eleven patients was evaluated by ultrasonography, and six patients underwent tomography for suspected complications (abscess, etc.). The tomography images of cases number four and twelve are shown in **Figure 2**. In the treatment, cefotaxime plus clindamycin was preferred in 8, ampicillin/sulbactam in 3 and clindamycin in 2 patients. Four patients required abscess drainage, all of whom were presenting in the second year of COVID-19, we isolated *Eikenella corrodens*, *Streptococcus anginosus* and *Streptococcus intermedius* microorganisms in 3 patients. No modification to antibiotherapy was required after the antibiogram of the isolated microorganisms (**Table 1**). The mean duration of hospitalization was 5.3±3 days.

Discussion

The main finding of this study, which included 13 patients, was that rates of odontogenic cervicofacial infections requiring intravenous (IV) antibiotics and abscess drainage in children increased significantly in the second year of the COVID-19 pandemic. Dental caries may the most common chronic disease. The disease is caused by the fermentation of carbohydrates into organic acids by microorganisms in the plaque on the dental surface. Plaque on uncleaned dental surfaces is a biofilm and 70% consists of microorganisms (100 million organisms/mg plaque). In time, the organic acids which are the by-products of the said microorganisms, reduce the pH of the microenvironment below the level at which the enamel will dissolve and demineralise the dentin and enamel. Brushing with fluoride reinforced toothpaste at least twice a day and regular visits to a dentist is deemed necessary.[9,10] It can be predicted that these will be ignored during quarantine periods. Periapical infections of the tooth, an outcome of poor dental hygiene, is shown to be the most attributed cause of cervicofacial infections of odontogenic origin.[5,11] Severe infections of the neck and facial region often require IV antibiotic therapy, surgical interventions and extended hospital stay. Studies have shown that during the COVID-19 quarantine where primary care dentistry practices are disrupted, less patients had presented with dental infections but among those

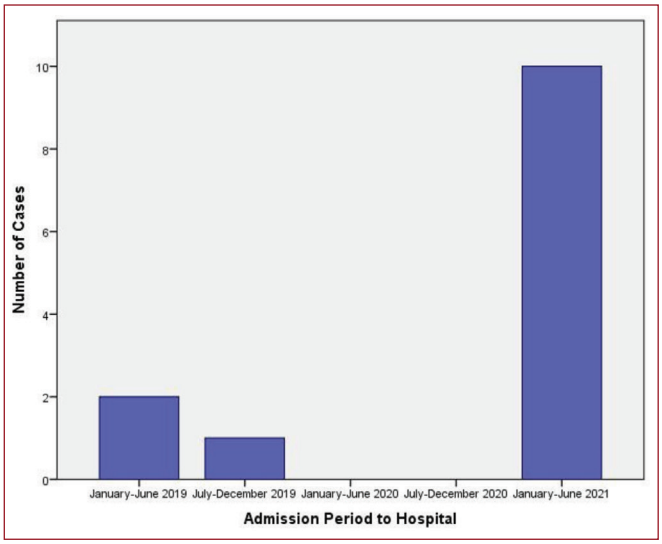

Figure 1. Number of cases in six-month periods before and after COVID-19.
COVID-19: Coronavirus disease-2019

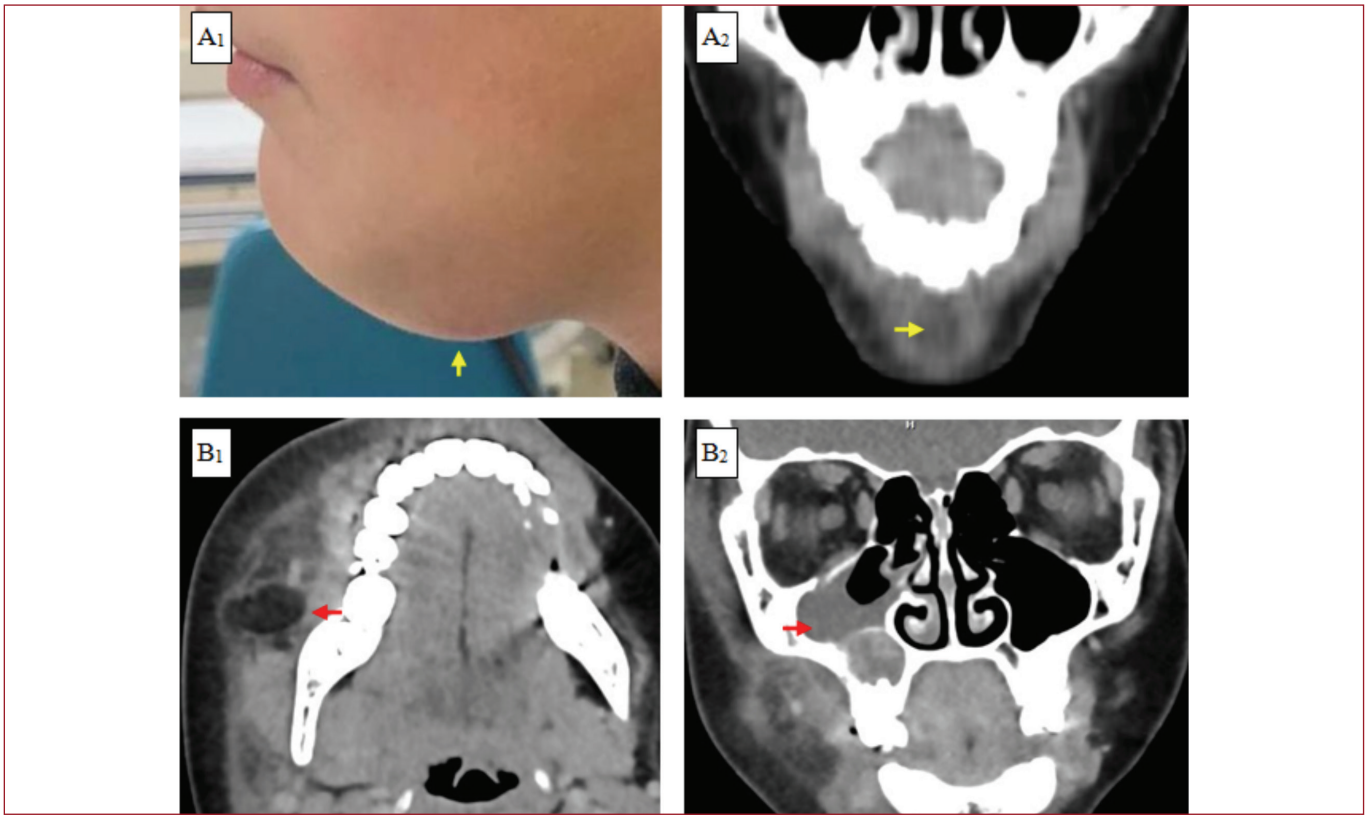

Figure 2. A) In case number four, swelling, redness, warmth and tenderness in the affected area, and a 4x3 cm fluid collection on tomography are shown with yellow arrows. **B)** In case number twelve, a 2x2 cm lobulated contour cystic lesion around the right upper premolar tooth root and tomography image showing odontogenic sinusitis in the right maxillary sinus are shown with red arrows.

Table 1.
Characteristics of children followed up with cervicofacial infection of odontogenic origin before and after COVID-19 quarantine

Case	Gender	Age (year)	Admission time	Admission symptom	History of dental disease	WBC (mm^3)	Neutrophile (mm^3)	CRP (mg/dL)	Abscess drainage and culture	Duration of hospitalization (day)
1	Male	14	April 2019	Swelling of the face	-	9.300	8.440	6.4	-	3
2	Female	2.5	April 2019	Swelling of the neck	-	20.100	14.400	2.6	-	3
3	Female	12	December 2019	Swelling of the neck	Dental caries	7.300	4.900	0.6	-	8
4	Male	6	March 2021	Swelling of the neck	Dental caries	17.440	12.900	3.7	+, *E.corrodens*	9
5	Male	8	March 2021	Swelling of the neck	-	13.840	12.240	21.1	-	4
6	Female	6	March 2021	Swelling of the face	-	8.140	3.270	2.7	-	4
7	Female	9	March 2021	Dental pain and swelling of the face	Dental caries	21.700	17.800	1.1	+, no isolated	4
8	Male	6	March 2021	Swelling of the neck	-	5.480	2.260	4.2	-	2
9	Female	8	March 2021	Swelling of the face	Dental caries	11.130	6.610	0.8	-	2
10	Male	15	March 2021	Swelling of the neck	-	7.310	3.930	0.1	-	4
11	Female	4	April 2021	Swelling of the face	-	15.220	9.870	25.1	-	11
12	Female	10	May 2021	Swelling under the jaw	Dental caries	17.950	14.540	6.2	+, *S.anginosus*	10
13	Male	9	June 2021	Swelling of the neck	-	20.520	17.770	7.3	+, *S.intermedius* and *S.anginosus*	6

WBC; White blood cell, CRP; C-reaktif protein, COVID-19; Coronavirus disease-2019

who presented, the percentage of patients requiring IV antibiotic therapy and extended hospitalization had increased.[6,11-14] This has been attributed to the hesitancy of caretakers to potential exposure to COVID-19, limited access to primary dental health care facilities, increased willingness to self-medicate as conservative treatment with analgesic agents and only presenting to a healthcare facility when the pathology becomes unbearable.[6,8,14] It is vital to provide these patients with access to first-line treatment that will allow early intervention in the restrictions to be applied in the possible future waves of COVID-19.[6] In our study, we think that the more frequent cases in the second year of the pandemic are due to the prolongation of the quarantine, neglect of personal oral care practices, the formation/progression of dental caries over time and the disruption of dentist visits.

This study has some potential limitations. Firstly, as it is conducted in a single healthcare centre, the number of cases is low. Secondly, we do not know the impact of the restrictions in the early period of the pandemic, as our hospital only served COVID-19 patients until September 2020.

Conclusion

Disruption of preventive or early intervention oral and dental health practices in children due to the COVID-19 quarantine increases the incidence of dental caries, leading to an increase in the number of odontogenic cervicofacial infections that require IV antibiotics and abscess drainage.

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.

Ethical Approval: The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (approval date: 20/10/21, approval number: 2021-07).

Financial Disclosure: The authors declared that this study received no financial support.

Informed Consent: Written consent was obtained from the parent of the case whose image was used.

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Anxiety Levels of Children with Primary Ciliary Dyskinesia and Their Mothers at the Beginning of the COVID-19 Pandemic and Change in the First Year

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Abstract

We aimed to assess anxiety of children with primary ciliary dyskinesia (PCD) and their primary caregivers at the beginning of Coronavirus disease-2019 (COVID-19) pandemic and change in levels of anxiety in first year with prolongation of pandemic. This was a two-step study; first step was questionnaire-based, conducted via teleconference. In first step, 29 patients and 105 healthy children and their mothers were participated; 25 children with PCD and their mothers were in second step. Demographic characteristics, clinical informations were recorded. Children's and mothers' state and trait anxiety levels were assessed and compared. Anxiety levels of mothers of patients were assessed according to clinical characteristics of children. Mothers' knowledge of COVID-19 and effect of teleconference on their anxiety was evaluated. State anxiety levels in the first year of pandemic of children with PCD and their mothers were also compared. Compared to control group, state anxiety of children in 13-18 age group and trait anxiety of their mothers were lower ($p<0.05$). In both groups, trait and state anxiety of 13-18 years old children and mothers positively correlated. Trait anxiety of mothers of patients negatively correlated with patients' FEV_1 and MEF_{25-75}. Patients' mothers reported feeling less anxiety at the end of teleconference. Anxiety of mothers of patients (especially under 9 years old) had increased as pandemic continued. At the beginning of pandemic, children with PCD were less anxious than healthy children, and their mothers had lower trait anxiety than mothers of healthy children. Being followed for chronic disease and obtaining information about COVID-19 may have reduced anxiety of children with PCD and their mothers. However, as pandemic continues, need to protect their children with PCD from infection, especially of mothers with younger children, may have raised their concerns.

Keywords: Anxiety, children, COVID-19, pandemic, primary ciliary dyskinesia

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Introduction

Primary ciliary dyskinesia (PCD) is a rare chronic genetic disease, and generally presents with recurrent and chronic infections of upper and lower respiratory tracts.[1,2] The diagnosis of a chronic disease in children has a dramatic impact on well-being of themselves and their families, and can be associated with anxiety and depression in both children and their family.[3,4]

In addition to variable respiratory findings, the Coronavirus disease-2019 (COVID-19) pandemic also affected mental health widely in the world, causing psychological problems such as stress, anxiety, depression, insomnia and fear.[5-7] Containment measures caused by pandemic can have destructive effects on mental health, affecting the social health of children as well.[8,9] The stress created by pandemic has increased over time, not only from the risk of infection and death, but also from the disruption of daily routine and social communication.[10]

Highlights

- Primary ciliary dyskinesia (PCD) patients were less anxious than healthy children at beginning of pandemic.
- PCD patients are accustomed to chronic diseases, so they better cope with pandemic.
- Healthy children have never experienced the threat of a serious disease before.
- Mothers of PCD patients exhibited lower trait anxiety than healthy children's.
- Anxiety of mothers of PCD patients may increase as pandemic continues.

The purpose of this study was to measure anxiety of children with PCD and their primary caregivers, as pandemic may increase their anxiety levels, and to evaluate relationship between anxiety levels and clinical and demographic characteristics. Since anxiety levels may increase during pandemic, it was also aimed to see change in anxiety levels in the first year with prolongation of pandemic.

Material and Methods

This study was cross-sectional and two-step. The first step was conducted at the beginning of COVID-19 pandemic between May 23 and June 3, 2020. Patients with PCD aged 0-18 years, who were followed up regularly in pediatric pulmonology department, those who wanted to participate in the study and their primary caregivers were included as the study group. PCD was diagnosed under the guidance of the guidelines published by the European Respiratory Society and the American Thoracic Society for diagnosis of PCD.[11,12] In both guidelines, no single gold standard test has been defined for a definitive diagnosis; and it was stated that nasal nitric oxide, high-speed video microscopy, transmission electron microscopy, immunofluorescence microscopy and genetic analysis could be used in the diagnosis of those with suspected PCD due to their clinical features.[11,12] Control group was populated using snowball sampling since there were restrictions due to COVID-19 pandemic and the implementation of curfews created difficulties in reaching the healthy child group in study time. Children without chronic diseases, any complaints or symptoms, and their primary caregivers included as controls. None of primary caregivers in control group were health workeras. The mothers of all children were their primary caregivers. In all cases, children's primary caregivers were their mothers. Contact with anyone with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and COVID-19 was queried, and those who had a COVID-19 case in their families and/or relatives were excluded from the study.

On March 16, 2020, schools were closed, and strict stay-at-home policies were implemented in Turkey due to COVID-19 pandemic. For this reason, first step of this study was conducted via teleconference. All children and primary caregivers were informed about study. After the aim of the study was explained to all participants, they were informed that they had right to withdraw at any time and not allow their data to be used. Teleconferences were conducted to all participants by the doctor regularly examining each PCD patient and lasted about 20 minutes. During each teleconference, demographic data of children and their caregivers were collected, their anxiety levels, mothers' knowledge of COVID-19, and the impact of teleconference on their anxiety was evaluated.

For both groups, demographic data such as age, gender of children and primary caregiver's age, education level, self-reported health status (obtained by verbally asking whether primary caregiver had a health problem) were recorded. For study group, clinical data including follow-up duration (time between the first admission to the pediatric pulmonology department and the last follow-up), number of hospitalizations during follow-ups, number of referrals to policlinics and sputum cultures positive for any bacteria in the last year, and results of pulmonary function tests (PFT) upon last admission, were noted. PFT data included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), mid-expiratory flow between 25-75% of forced vital capacity (MEF_{25-75}) as the percentage of predicted, and FEV_1/FVC ratio.

The State-Trait Anxiety Inventory for Children (STAI-C) was used for children aged 9-12 years, whose Turkish validity and reliability were approved by Özusta.[13] Children under age of 9 were not surveyed, only their caregivers were surveyed. STAI whose Turkish validity and reliability were confirmed by Oner and Le Compte[14] was used for all caregivers and children aged 13-18 years. Trait subscales measured permanent anxiety; state subscales measured anxiety during COVID-19 pandemic. There are two separate scores for each of the direct and reverse statements in survey. A predetermined and unchanging value is added to the number obtained by subtracting the total score for the reverse statements from the total score for the direct statements. The resulting value is the individual's anxiety score. Higher scores indicated higher anxiety levels.[13-16] In the initial development, the test-retest reliability coefficients ranged from 0.31 to 0.86 (at intervals ranging from 1

hour to 104 days).[16] Permission had been obtained for use these scales.

To assess caregivers' knowledge about COVID-19, a questionnaire based on the "myth busters" section on World Health Organization (WHO) website regarding advice for public related to COVID-19 was prepared by the authors.[17] The statements concerned the weather conditions under which SARS-CoV-2 can survive and spread, the effectiveness of treatment with antibiotics, the prevalence of the disease according to gender, the incidence and mortality risk in children, and the effects of comorbidities and nutrition. The correct answers were recorded as numbers and percentages.

At the end of each teleconference, caregiver was provided with information about the advice provided on the WHO website.[18] Caregivers were then asked to evaluate the effect of the teleconference on their anxiety to categorize as "decreased," "increased," or "unchanged".

Demographic and clinical characteristics of children and caregivers, caregivers' knowledge about COVID-19, and state and trait anxiety scores were compared between two groups, and correlations were investigated.

The second step was conducted between May and June 2021 at the time of their admission to hospital as pandemic restrictions were removed. The state anxiety levels of children with PCD and their caregivers in the first year of pandemic were noted and compared. The number and reason of hospital admissions and hospitalizations of patients during the first year of pandemic were recorded. Therewithal, PFTs of children with PCD were compared before pandemic and in the first year.

This study was conducted with the permission of Gazi University Faculty of Medicine Ethics Committee (date: 22.05.2020, no: 342). All procedures in this study were performed in convenient with the ethical rules and the principles of the Declaration of Helsinki. Since the study was started during the period when the COVID-19 pandemic was widespread, verbal informed consent was obtained in order not to put the individuals at risk, and ethics committee approval was obtained in the form of verbal consent from the individuals.

Statistical Analysis

The IBM SPSS Statistics version 22.0 for Windows (IBM, Armonk, NY, USA) was used for statistical analysis. The conformity of variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk test). For descriptive statistics, categorical variables were expressed as absolute numbers and percentages, and continuous variables were expressed as means ± standard deviations or medians (minimum-maximum). For comparisons between two independent variables, Mann-Whitney U test was used for data not normally distributed, and independent samples t-test was used for normally distributed data. For correlations, Spearman's correlation test was used for data not normally distributed, and Pearson's correlation test was used for normally distributed data. Chi-square tests were used for comparisons of categorical variables between independent groups. Since numerical variables did not normally distribute comparisons between both dependent groups were analyzed with Wilcoxon signed-rank test. It was considered statistically significant when $p<0.05$.

Results

In study and control groups, there were 29 and 105 children and their mothers, respectively. All mothers' and children's demographic characteristics, and clinical data of study group are presented in **Table 1** and **Table 2**, state and trait anxiety levels of children aged over 9 years and all mothers at the beginning of pandemic are in **Table 3** and comparison of mothers' anxiety levels at the beginning of pandemic according to their educational level and self-reported health status were in **Table 4**, respectively.

The percentages of correct answers regarding COVID-19 were 63.8±17.8 in study group and 73.5±13.2 in control group (p=0.009). A statistically significant difference was found in the percentages of correct answers regarding COVID-19 given by mothers according to their education level (below high school vs. high school or above) in both groups [64.3% (range: 28.6-85.7%) vs. 82.1 (57.1-92.9%), p=0.012 and 57.1% (28.6-78.6%) vs. 78.6% (50-100%), p=0.001, respectively].

At the beginning of pandemic, a positive correlation between state and trait anxiety levels of 9-12 years old children was observed in control group (r=0.501, p=0.015). No significant correlation was found in study group (r=0.232, p=0.658). There were positive correlations between state and trait anxiety levels of 13-18 years old children in study and control group (r=0.744, p=0.001 and r=0.484, p=0.008, respectively).

Positive correlations between the mothers' trait and state anxiety levels were found in study and control group (r=0.644, p=0.001 and r=0.557, p=0.001, respectively). The correlations of children's and mothers' anxiety at the beginning of pandemic are presented in **Table 3**.

At the beginning of pandemic, in study group, there was negative correlation between mothers' trait anxiety scores and children's FEV_1 and MEF_{25-75}, although FEV_1 and MEF_{25-75} were within normal limits (r=-0.484, p=0.031 and r=-0.546, p=0.013, respectively). There were no significant correlations between state and trait anxiety scores of mothers and children's clinical features.

In study group, there were no correlations between state and trait anxiety scores of mothers and knowledge about COVID-19 (r=0.100, p=0.605 and r=-0.075, p=0.700, respectively). In control group, no correlation was observed between state anxiety score and knowledge about COVID-19 (r =-0.070, p=0.476), but trait anxiety score positively correlated with knowledge about COVID-19 (r=0.192, p=0.049).

In the first step of the study, at the end of the teleconference, 82.8% of mothers in study group and 39% of mothers in control group reported a reduction in their anxiety levels (p=0.001).

In the second step of this study, two of 29 children with PCD and their mothers who participated in the first

Table 1.
Comparison of children's and mothers' demographic characteristics between the two groups at the beginning of pandemic

	Study group (n=29)	Control group (n=105)	p-value
Children's age (years), mean ± SD	12.2±4.5	8.7±5.3	0.002[a*]
Gender, n (%)			
Female	16 (55.2)	53 (50.5)	>0.05[b]
Male	13 (44.8)	52 (49.5)	
Mothers' age (years), mean ± SD	38.1±7.2	38.2±8.2	>0.05[a]
Mothers' education level, n (%)			
Below high school	23 (79.3)	15 (14.3)	0.001[b*]
High school and above	6 (20.7)	90 (85.7)	
Mothers with health problems[#], n (%) (Allergic, cardiological, gastroenterological, musculoskeletal, rheumatological)	8 (27.6)	12 (11.4)	0.041[b*]

SD; Standard deviation, [a]Independent samples t-test, [b]Chi-square test, *Statistically significant, [#]Obtained by verbally asking

Table 2.
Clinical data of children with primary ciliary dyskinesia at the beginning of pandemic (n=29)

Duration of follow-up (months) (mean ± SD)	60.5±40.3
Number of total hospitalizations during follow-up [median (range)]	1 (0-2)
Number of hospital admissions in the past year [median (range)]	2 (0-3)
Positive sputum cultures in the past year [n (%)]	
Yes	6 (42.8)
No	8 (57.2)
Pulmonary function tests [mean ± SD]	
FEV_1 (%)	90.1±15.4
FVC (%)	91.1±13.4
MEF_{25-75} (%)	97.0±8.8
FEV_1/FVC	85.5±25.2

FEV_1; Forced expiratory volume in one second, FVC; Forced vital capacity, MEF_{25-75}; Mid-expiratory flow between 25 and 75% of forced vital capacity, SD; Standard deviation

Table 3a.
Comparison of children's and mothers' anxiety scores at the beginning of pandemic between two groups

			Study group	Control group	p-value
State anxiety score	**Children**	**Aged 9-12 [median (range)]**	(n=6) 26 (22-30)	(n=33) 29 (21-44)	0.057[a]
		Aged 13-18 [median (range)]	(n=15) 33 (25-51)	(n=39) 40 (23-63)	0.014[a*]
	All mothers (mean ± SD)		(n=29) 37.7±6.5	(n=105) 36.5±8.5	0.479[b]
Trait anxiety score	**Children**	**Aged 9-12 [median (range)]**	(n=6) 27 (24-37)	(n=33) 32 (23-47)	0.094[a]
		Aged 13-18 [median (range)]	(n=15) 34 (24-44)	(n=39) 36 (20-55)	0.130[a]
	All mothers (mean ± SD)		(n=29) 34.0±5.2	(n=105) 47.0±12.7	0.001[b*]

SD: Standard deviation, [a]Mann-Whitney U test, [b]Independent samples t-test, *Statistically significant

Table 3b.
Correlations of children's and mothers' anxiety scores at the beginning of pandemic in two groups

	State anxiety of mothers				Trait anxiety of mothers			
	Study group		Control group		Study group		Control group	
	R_s	P	R_s	P	R_s	P	R_s	P
Children's state anxiety								
Ages 9-12	0.029	0.956	0.233	0.284	-0.058	0.913	-0.010	0.964
Ages 13-18	0.408	0.131	-0.014	0.941	0.092	0.744	0.108	0.577
Children's trait anxiety								
Ages 9-12	-0.433	0.391	-0.084	0.704	0.088	0.868	-0.490	0.018*
Ages 13-18	0.550	0.034*	-0.037	0.847	0.085	0.763	-0.087	0.653

*Statistically significant

survey did not want to participate. The other two had COVID-19 infection during the first year of pandemic. All of 25 children with PCD and their mothers were evaluated. Seven children were under 9, 6 children 9-12, 12 children 13-18 years and 13 (52%) were female in the second step.

The comparison of state anxiety levels of children with PCD and their mothers between beginning and the first year of pandemic was shown in **Table 5**. In addition, state anxiety levels of mothers according to age groups were also shown in **Table 5**.

During the first year of pandemic, 19 (76%) children with PCD admitted to the hospital. Five had admitted only once, the rest more than once. Median number of hospital admission during the first year of pandemic was 2.0 (1.0-8.0). The most common reason (63.6%) for admission was cough and increased sputum. The other reasons were exercise intolerance (18.2%), stomach ache (9.1%) and trauma (9.1%). Sputum analysis was performed on 17 children. While no microorganisms were found in sputum of 16 of them, *Pseudomonas aeruginosa* was detected in one. Only one child was hospitalized during the first year of pandemic for surgery for repair of urethral cord, and there were no other hospitalized children.

PFT could be performed in 15 children. Medians of last FEV_1, FVC, FEV_1/FVC and MEF_{25-75} of patients before pandemic were 88% (67-119), 89% (68-123), 97 (86-110) and 74% (47-129), respectively. Medians of FEV_1, FVC, FEV_1/FVC and MEF_{25-75} of patients in the first year of the pandemic were 83% (62-111), 86% (65-115), 94 (62-107) and 72% (41-119), respectively. No statistically significant difference was observed between the last PFTs before pandemic and PFTs in the first year of pandemic (FEV_1: p=0.132, FVC: p=0.346, FEV_1/FVC: p=0.300 and MEF_{25-75}: p=0.798). The results and comparison of PFTs according to age groups were shown in **Table 6**. No correlations were found between anxiety levels of children and mothers and hospital admission and PFTs of children (p>0.05).

Discussion

The sudden and world-threatening COVID-19 pandemic outbreak has caused considerable anxiety.[19] This study showed that children with PCD aged 13-18 years had lower anxiety levels at the beginning of the pandemic than healthy children. Similarly, their mothers had lower trait anxiety than mothers of healthy children. The state and trait anxiety of all mothers and 13-18 years old children correlated. There was a relationship between trait anxiety levels of 13-18 years old patients with PCD and state anxiety of their mothers. The trait anxiety levels of 9-12 years old healthy children aged also correlated with their mothers' anxiety. The anxiety of mothers of children with PCD has increased as the COVID-19 pandemic continues, and it has been observed that anxiety of mothers with younger children has increased according to age groups in our study.

The studies conducted among children with chronic lung diseases it was noted that these children and their mothers had more anxiety due to COVID-19 pandemic.[20,21] A recent study showed that children with cystic fibrosis had lower anxiety levels than healthy children in COVID-19 pandemic.[22] In Italy, it was shown that during the pandemic, patients with PCD were

Table 4.
Comparison of mothers' anxiety levels at the beginning of pandemic according to educational level and self-reported health status in two groups

		Mothers' educational level			Mothers' self-reported health status#		
		Below high school	High school and above	p	With health problem	No health problem	p
State anxiety	Study group (n=29)	37 (32-59)	34 (30-35)	0.024[a*]	36 (34-53)	35 (30-59)	0.570[a]
	Control group (n=105)	33 (23-56)	35 (23-60)	0.883[a]	33 (23-42)	35 (23-60)	0.397[a]
Trait anxiety	Study group (n=29)	35 (24-45)	29 (28-40)	0.066[a]	35.8±5.0	33.3±5.1	0.315[b]
	Control group (n=105)	36 (24-64)	46.5 (21-78)	0.097[a]	43.1±10.1	47.5±12.9	0.318[b]

[a]Mann-Whitney U test, [b]Independent samples t-test, *Statistically significant, #Obtained by verbally asking

Table 5.
Comparison of state anxiety levels between the beginning of the pandemic and the first year

	State anxiety levels		
	Beginning of the pandemic [median (min-max)]	First year of the pandemic [median (min-max)]	p
Children aged 9-12 years (n=6)	26 (22-30)	28 (23-40)	0.104
Children aged 13-18 years (n=12)	33 (25-51)	37.5 (28-47)	0.055
All mothers (n=25)	35 (30-59)	41 (32-47)	0.025*
Mothers of children:			
aged under 9 years (n=7)	36 (30-42)	42 (35-43)	0.027*
aged 9-12 years (n=6)	34 (33-46)	43 (32-47)	0.207
aged 13-18 years (n=12)	36 (32-59)	39 (32-46)	0.562

Min-max; Minimum-maximum, *Statistically significant

psychologically well, with no increase in parental stress levels; quarantine was thought to give patients with PCD a great sense of security.[23] Similarly, in our study, children with PCD exhibited lower anxiety levels than healthy children at the beginning of pandemic. Children with PCD may cope better because they are more accustomed to living with a disease. Healthy children, on the other hand, had never experienced the fear of a serious disease before. This may explain their higher anxiety levels during the pandemic.

Anxiety is a very easily transmissible emotion. Our findings suggest that children may be affected by their mothers' anxiety, as mothers are role models for their children. It was reported that anxiety levels of both healthy children and children with chronic diseases were associated with their mothers.[24,25] We observed a positive correlation between the trait anxiety levels of 13-18 years old children with PCD and COVID-19-related anxiety of their mothers. Anxiety of both children and mothers interacted each other. Higher levels of trait anxiety in children with PCD may have contributed to increase anxiety of their mothers during the pandemic.

Frequent respiratory tract infections and hospitalizations can cause significant stress and anxiety in families of patients with PCD.[26] Studies showed that children with chronic lung diseases and their parents had higher anxiety levels than the general population.[20,27] We found that mothers of children with PCD had lower trait anxiety than mothers of healthy children. Regular follow-ups may have contributed to reducing their trait anxiety. Mothers of children with PCD are more familiar with diseases and hospitalizations and may have developed coping strategies that help them control their anxiety related to pandemic. Mothers of healthy children, on the other hand, lack such coping strategies; thus, the pandemic may be a more stressful experience for them. In addition, the lower mean age of children in the healthy group than children with PCD may be a reason for the higher level of anxiety in their mothers.

In our study, mothers of children with PCD had lower education levels. Their trait anxiety was lower than that of healthy children's mothers. Emin et al.[28] showed that mothers of children with allergic rhinitis exhibited higher levels of anxiety, although their education levels were not significantly different from mothers of healthy children. Behmanesh et al.[29] found no significant correlation between the education and anxiety levels of mothers of children with asthma. Our findings suggest that mothers with higher education levels may be more aware of public health issues, which can increase their anxiety levels.

Other studies reported no association between FEV_1 and their or their parents' anxiety levels.[30,31] In our study, it was shown that a worsening of FEV_1 and MEF_{25-75} may increase their mothers' anxiety, although FEV_1 and MEF_{25-75} were within normal limits.

In the first step of study, at the end of the teleconference, mothers of patients with PCD reported a greater decrease in their anxiety levels than healthy children's mothers. Talking to the doctor who examined their children regularly and being informed about COVID-19 pandemic may have contributed to this effect.

Researches on the children's mental health and their parents during the COVID-19 pandemic, it was shown that anxiety levels increased.[32-37] In another study, there was no significant relationship between anxiety and the COVID-19 pandemic among adolescents, and it was determined that anxiety was significantly related to gender, not age.[38] It was thought that although children normally do not have any health problems, their anxiety may have increased and their families may be more anxious during the pandemic. Studies showed that the mental health status of parents of children with any disease or disorder may also be affected during COVID-19 pandemic.[10,39] It was also reported that the anxiety levels of caregivers of children with respiratory disorders increased with the COVID-19 lockdown.[40] It was thought that the addition an unknown global situation such as COVID-19 pandemic to these respiratory disorders could have a profound impact on caregivers.[40] Similarly, in our study, it was observed that the anxiety of mothers of children with PCD increased significantly as COVID-19 pandemic continued. It was thought that the anxiety of the mothers due to their children may have

Table 6.
The results and comparison of pulmonary function tests according to the age groups

	Children aged 9-12 years (n=4)			Children aged 13-18 years (n=8)		
	Last before pandemic	First year of pandemic	p	Last before pandemic	First year of pandemic	p
FEV_1 (%) median (min-max)	92.0 (87.0-103.0)	86.0 (76.0-111.0)	0.715	82.5 (67.0-119.0)	70.5 (62.0-99.0)	0.176
FVC (%) median (min-max)	93.0 (85.0-105.0)	83.5 (78.0-115.0)	0.465	83.5 (68.0-102.0)	85.5 (65.0-103.0)	0.933
FEV_1/FVC median (min-max)	96.0 (94.0-103.0)	94.5 (83.0-103.0)	0.593	98.5 (86.0-110.0)	95.0 (62.0-103.0)	0.161
MEF_{25-75} (%) median (min-max)	80.5 (66.0-91.0)	100.0 (72.0-119.0)	0.068	68.0 (47.0-126.0)	54.5 (41.0-89.0)	0.141

FEV_1; Forced expiratory volume in one second, FVC; Forced vital capacity, MEF_{25-75}; Mid-expiratory flow between 25 and 75% of forced vital capacity, min-max; Minimum-maximum, SD; Standard deviation

increased as the pandemic continued, since PCD was especially accompanied by respiratory symptoms and because the respiratory findings of COVID-19 were at the forefront.

The anxiety of children with PCD was expected to increase in our study, however there was no significant change in the anxiety of children with PCD in the first year of COVID-19 pandemic. Since children with PCD felt safer when they stayed at home during pandemic, it was thought that although the pandemic continued, their anxiety might not have increased. In addition, the fact that most of the children with PCD and their families who participated in this study did not have the COVID-19 infection during this period may have caused the anxiety of children to not increase. In our study, no significant change in the anxiety levels of children with PCD according to age groups in the first year of pandemic was observed, while the anxiety of mothers with younger children increased significantly. Recent studies predicted that parents were concerned about the need to protect their children from infection.[10] Therefore, it can be thought that mothers who have children with PCD at a younger age may have higher anxiety as they may have difficulty in protecting their children. At the same time, repeated exposure to news about COVID-19 pandemic could raise anxiety about pandemic.[41]

Restrictions applied during the pandemic (such as social distancing, using a mask) may reduce respiratory symptoms and improve lung function.[42] In the study of asthmatic children by Taytard et al.,[42] less exacerbations, better asthma symptom control during the pandemic period and improved lung function detected after reopening. In our study, last PFT before the pandemic and PFT in the first year of pandemic of patients were similar. Implemented pandemic restrictions may have preserved the lung function, since the patients did not have symptoms such as respiratory tract infection that would affect the lung function.

Our study has some limitations. The sample size was small in both steps of study, and the difference in age distribution of the children in the two groups in the first step of study caused difficulties in evaluating the results. Despite these limitations, our findings may support guiding psychosocial assessment and, if necessary, interventions for children with chronic diseases and their caregivers during such times.

Conclusion

At the beginning of the COVID-19 pandemic, children with PCD had less anxiety than healthy children. Mothers of children with PCD also had lower trait anxiety than mothers of healthy children. In contrast, worsening of FEV_1 and MEF_{25-75} of children may increase trait anxiety of their mothers, although these were within normal limits. Although all mothers were concerned about pandemic, mothers of children with PCD experienced a greater reduction in their anxiety after our teleconference at the beginning of pandemic. Communicating with and obtaining information about COVID-19 from their follow-up doctor may have had a positive effect. Larger, longitudinal studies could provide more information to guide psychosocial assessment and interventions for children with chronic diseases and their caregivers in such extraordinary situations as COVID-19 pandemic.

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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.

Ethics Committee Approval: The study was carried out with the permission of Gazi University Faculty of Medicine Ethics Committee (date: 22.05.2020, decision no: 342). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Informed Consent: Since the study was started during the period when the COVID-19 pandemic was widespread, verbal informed consent was obtained in order not to put the individuals at risk, and the approval of the ethics committee was obtained in the form of verbal consent from the individuals.

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Evaluation of Leukemia and Solid Tumors in Refugee Children in Turkey: A Tertiary Center Experience

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Abstract

Cancer care is progressively became as a significant worldwide challenge. Wars can cause destructions and delays in cancer diagnosis and treatment of displaced people. Cancer cure rates need to be improved in indefensible populations such as refugees. In this study, we purposed to highlight the clinical peculiarities and outcomes of refugee children with cancer in our hospital. Our purpose was to present our findings and contribute to improve the health care for these children. Seventy one refugee pediatric patients admitted to the oncology and hematology units of our hospital between April 2011 and January 2019 were included in this study. The demographic characteristics of the patients at the initial diagnosis, their countries of origin, living conditions, histopathological diagnoses, treatments, relapse, and mortality data were analyzed retrospectively from the patient files. The median age of patients was 6.5±4.5 years, and the male-to-female ratio was 39/32. While 44 patients (61.9%) presented with complaints and had primary diagnoses in our hospital, the remaining 27 patients (38.1%) were diagnosed in their country and applied to our hospital for treatment. Our mean follow-up period was 18.2±18.8 months (1-90 months). As a result, 44 patients (62%) were alive and 22 (31%) were dead. The survival rate without relapse in the second year was 83.6%. Two and five-year survival rates were 77.5% vs. 58.1% respectively. Compared to Turkish children, lower survival rates were found in refugee children. In addition to cancer-specific factors such as tumor type and stage, some problems such as shelter, communication, adherence to treatment, and difficulties supplying medicine may be responsible for lower survival rates in refugee children. Further studies are needed to improve the survival rates of patients.

Keywords: Refugee children, cancer, survival

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Introduction

Turkey is the country that hosts the most refugees in the world and continues to be home to the world's largest refuee population. Refugees are defined as those who are pushed to part from their houses in consequence of persecution by The United Nations High Commissioner for Refugees. According to the data, in Turkey, approximately 3.6 million Syrians, 172 thousand Afghans, 142 thousand Iraqis, 5,700 Somalis, 39 thousand Iranians, and 11.7 thousand other country refugees are under temporary protection status as of July 2019. In Turkey, there are nearly 1.4 million refugees are under the age of 15 and more than 800,000 are between the ages of 15 and 24.[1] Over 98 percent of refugees in Turkey live in peri-urban, urban, and rustic areas, generally placed in rented houses or relatives' homes, while the remaining live in Temporary Accommodation Centres.

Highlights

- In refugees cure rates of childhood cancer need to be improved.
- Besides cancer-specific factors such as stage and tumor type, some problems such as shelter, communication, difficulties supplying medicine, and compliance to treatment might have been responsible for lower survival rates in refugee children.

Cancer care is progressively became as significant global challenges, in consequence of financial, global, social, and health inference. Wars and conflicts can conduce great devastation and disruption to patients already being treated for malignancy, and delays in the diagnosis and treatment of these people. Patients with malignancy are undefended to such contingencies that affect the standard of medical care they take, and the medications for the disease treatment.[2] They usually present in advanced disease and further complications develop in these patients. These patients' outcomes are poor due to poor living conditions and hygiene, along the limited access to care, health education, and facilities available to them. In their asylum countries, they are often unfamiliar with the health-care system, and not enrolled in screening programs.[3,4]

The Turkish Disaster and Emergency Management Presidency has supported health services, basic daily needs, and regular education institutions, since the beginning of the crisis in 2011.[5] A Temporary Protection Regulation was passed by The Turkish State to make legal the situation of immigrants, thus achieving free healthcare and medicine including cancer treatment. Primary or secondary care centers refer to the refugees who need to special care tertiary care centers.[6]

To the best of our knowledge, in Turkey, limited number of studies have been reported including refugee children with cancer in the literature.[7] Therefore we aimed to highlight the number and clinical peculiarities and outcomes of refugee children in tertiary care hospital. Our purpose was to present our findings and could understand the problems to advance the health care for refugee children.

Material and Methods

This study was designed to appreciate the clinical and social characteristics of cancer patients among refugee children. The study group comprised of refugee children with leukemia or solid tumor who were on treatment between April 2011 to December 2018 in our hospital. Descriptive data consisting of demographics, histopathological diagnosis, the countries of origin, living conditions, previous and current treatments, treatment compliance, relapse or progression status, outcomes, relapse, and mortality data were retrospectively analyzed from the patient's medical records. All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki. Informed written consent has been taken from parents or guardians before the study (Ethics committee approval: University of Health Sciences Turkey, Ankara City Hospital, approval no: 23.12.2022, E2-22-3020).

Statistical Analysis

Statistical analyses of the study was performed using SPSS 16 statistical programme. Categorical variables were stated as numbers and percentages, and mean ± standard deviation, minimum-maximum, and median values were used for expressing numerical variables. To compare the differences between groups, the Student t-test was used and Mann-Whitney U test was used for comparisons of median values. As the time from treatment to death, regardless of disease recurrence was defined overall survival. Kaplan-Meier method was applied to estimate survival curves. For the estimation of survival, adjusted hazard ratio and 95% confidence interval were used. $P<0.05$ was defined as statistically significant.

Results

A total of 71 refugee children who were admitted to our center with a diagnosis of malignancy were included in the study. The median age of our patients was 6.5±4.5 years (11 months-12 years), and the female-to-male ratio was 32/39. The countries of our patients were as follows; 36 of our patients were from Syria (50.7%), 16 were from Iraq (22.5%), 7 were from Afghanistan (9.9%), and 12 were (16.9%) from other countries. Primer diagnoses of the patients were as follows; 12 children with acute lymphoblastic leukemia (ALL) (16.9%),10 children with brain tumors (14%), 9 children non-Hodgkin lymphoma (12.6%), 8 children with neuroblastoma (11.2%), 5 children with rhabdomyosarcoma (7%), 5 children with retinoblastoma (7%), 4 children with Ewing sarcoma/PNET (5.6%), 3 patients with Langerhans cell histiocytosis (4.2%), 3 patients with acute myeloid leukemia (AML) (4.2%), 3 patients with Wilms tumor (4.2%), 2 patients with Hodgkin lymphoma (2.8%), 2 patients with squamous cell carcinoma (2.8%), 2 patients with osteosarcoma (2.8%), and the other 3 patients with germ cell tumor, hepatoblastoma, nud-midline carcinoma. Tumor and patients' characteristics are summarized in **Table 1**. Communication was achieved using an official translator for patients' families. In total, 45 families (63.3%) had a consanguineous marriage, and 22 (30.9%) were between first cousins. The reason

for migration was mostly ongoing war for 50 families (70.4%) and health problems and war for the others. Conditions of shelter revealed that 49 families (69%) were living in rented houses, and 22 families (31%) were living in guesthouses.

Of 71 patients, 44 patients (61.9%) presented with complaints and had a primary diagnosis in our hospital, the remaining 27 patients (38.1%) were diagnosed in their country and applied to our hospital for treatment. Of the 27 patients who were diagnosed in their country, 21 patients (29.6%) had begun treatment in their country but could not be completed due to war or inadequate health care. The diagnoses of 27 patients diagnosed in their country were as follows: 3 patients with a brain tumor, 3 patients with retinoblastoma, 3 patients with ALL, 3 patients with relapsed ALL, 2 patients with rhabdomyosarcoma, 2 patients with Wilms tumor, 2 patients with Ewing sarcoma/PNET, 2 patients with relapsed Hodgkin lymphoma, the others were neuroblastoma, Burkitt lymphoma, Langerhans cell histiocytosis, osteosarcoma, AML, relapsed Wilms tumor, relapsed anaplastic large cell lymphoma (ALCL), relapsed neuroblastoma.

All patients were treated with appropriate chemotherapy protocols for histopathological diagnosis. The patients with ALL received the ALL-BFM 2009 protocol,[8] and patients with AML were treated with the AML-BFM-2013 protocol.[9] Patients with neuroblastoma received the TPOG neuroblastoma 2009 protocol.[10] Patients with non-Hodgkin lymphoma, Burkitt lymphoma, and ALCL received the NHL-BFM protocol.[11] Patients with rhabdomyosarcoma received the RMS 2005 protocol.[12] Vincristine, etoposide, and carboplatin (VEC protocol) was used are for patients with retinoblastoma.[13] Patients with Ewing sarcoma received the Euro-EWING 99 protocol.[14] Patients with Langerhans cell histiocytosis received the LCH-IV protocol.[15] Patients with Wilms tumor received the NTWS-5 protocol.[16]

Table 1.
Patient and tumor characteristics

Characteristics	n (%)
Median age, years (range)	6.5±4.5 (11 months-12 years)
Gender	
Male/female	39/32
Countries	
Syria	36 (50.7%)
Iraq	16 (22.5%)
Afghanistan	7 (9.9%)
Others	12 (16.9%)
Diagnosis	
Acute lymphoblastic leukemia	12 (16.9%)
Brain tumors	10 (14.1%)
Non-Hodgkin lymphoma	9 (12.6%)
Neuroblastoma	8 (11.2%)
Rhabdomyosarcoma	5 (7%)
Retinoblastoma	5 (7%)
Ewing sarcoma/PNET	4 (5.7%)
Langerhans cell histiocytosis	3 (4.3%)
Acute myeloid leukemia	3 (4.3%)
Wilms tumor	3 (4.3%)
Hodgkin lymphoma	2 (2.8%)
Squamous cell carcinoma	2 (2.8%)
Osteosarcoma	2 (2.8%)
The others	3 (4.3%)
Sheltering of families	
Rented house	49 (69%)
Guesthouse	22 (31%)

Treatment change was performed in 11 patients (15.5%) who showed progression without responding to primary or relapse treatment. These patient's diagnoses were as follows; 2 patients with Ewing sarcoma, the others were respectively Hodgkin lymphoma, Burkitt lymphoma, neuroblastoma, Wilms tumor, rhabdomyosarcoma, Langerhans cell histiocytosis, nud-midline carcinoma, ALCL, and ALL. Treatment modalities consisted of neoadjuvant and adjuvant chemotherapy, surgical resection, radiotherapy, and bone marrow transplantation. According to their treatment protocol, surgical resection was performed in 30 patients and 6 patients received radiotherapy. Furthermore, bone marrow transplantation was performed in 6 patients (8.5%). Four of these were autologous and two were allogeneic stem cell transplantation. The diagnosis of transplant patients was as follows; 2 patients with neuroblastoma, the remainings were respectively, Ewing sarcoma, ALL, relapsed ALL, and relapsed ALCL. Seven patients (9.9%) relapsed an average of 9±6.1 months after the end of treatment. The median follow-up period was 18.2 months (1-90 months). After a median follow-up 22 (31%) patients died due to primary refractory or relapsed disease. Five patients' latest status is unknown because of the discontinuation of the treatment and follow-up. The survival rate without relapse of our patients in the second year was 83.6% (**Figure 1**). Two and five-year survival rates of the whole group were 77.5% vs 58.1% respectively (**Figure 2**).

Treatment modalities, side effects, and outcomes are shown in **Table 2**. The most common side effect was febrile neutropenia in 21 patients (29.5%). All patients with febrile neutropenia were hospitalized and given antibiotic therapy. The chemotherapy compliance rate

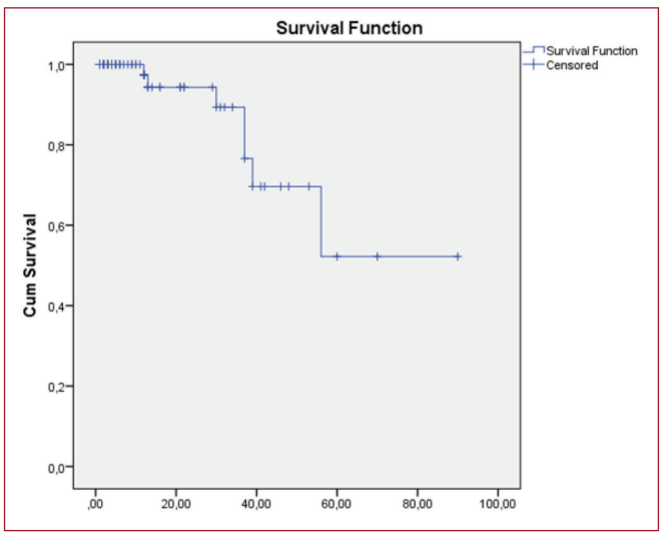

Figure 1. Relapse-free survival rates of our patients.

for patients was 87.3% (n=62). Statistical analysis failed to show a significant relationship between the living site (rented house or guesthouse) and the compliance rate of the patients. Additionally, there was no significant relationship between the living site and the febrile neutropenia episode (p>0.05).

Discussion

In this retrospective study, we aimed to investigate the types of cancer and outcomes seen in refugee pediatric patients in our tertiary hospital.

Most of the people were affected by the war in Syria, and most of them came from cities where a war was going on. Actually, they frequently explain their reason for migration was the war. Providentially, they achieved a health institution in Turkey once possible.

Refugee children's cancer treatment is interrupted, or a new cancer is developed while living in host countries. They usually present with advanced disease and experience further complications. Because of living conditions and poor hygiene, such as limited accession to the health care, and resources available to them, these patients have poor outcomes. In their countries they are not record in screening programs.

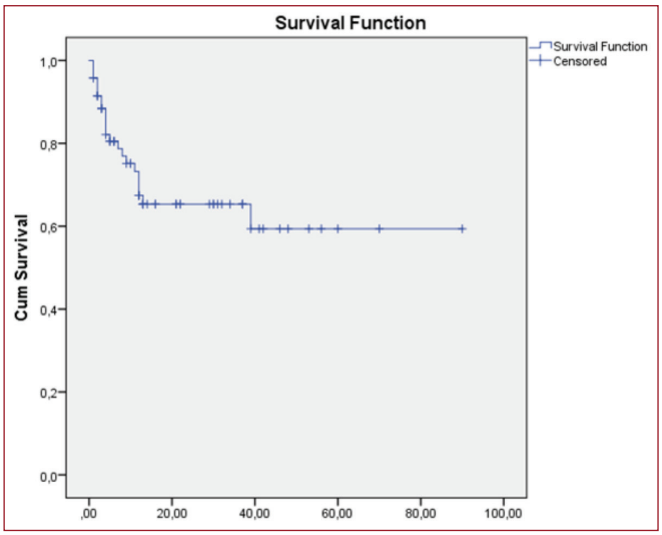

Figure 2. Two and five-year overall survival rates of patients.

Table 2.
Treatment modalities, side effects, and outcomes

	n (%)
Treatment modalities	
Chemotherapy	71 (100%)
Radiotherapy	6 (8.5%)
Surgery	30 (42.2%)
Bone marrow transplantation	6 (8.5%)
Autologous	4 (5.7%)
Allogenic	2 (2.8%)
Side effects	
Febrile neutropenia	21 (29.5%)
Fungal infection	5 (7%)
Paraplegia	1 (1.4%)
Portal hypertension	1 (1.4%)
Dilated cardiomyopathy	1 (1.4%)
Final status	
Deceased	22 (31%)
Alive	44 (62%)
Unknown	5 (7%)

Communication difficulties and language differences are another obstacle to be overcome in the treatment for refugee patients. Even though, a translator or telephone translation service were ensured by the Turkish Government, often not enough translators could be found. In case of need health personel who can speak Arabic was helped.

For inpatients, all of the medication was ensured in the hospital but sometimes for outpatients, medications were a problem, as medications take longer to provide because all prescriptions have to be registered by government agencies.

In our study, the chemotherapy compliance rate was 87.3%, and the compliance rate was to be poor, especially in outpatient settings whom uses oral drugs, for example,patients whom in the maintenance phase of leukemias or lymphomas.

Similarly to developing countries and Turkey, leukemia, lymphoma, and CNS tumors were found to be the most common cancers in our study. Most of the patients (n=44, 61.9%) were diagnosed in Turkey. The patients' chemotherapy compliance rate was not bad, 87.3%, and the most common side effect was febrile neutropenia in 21 patients (29.5%). Although we expected more frequent febrile neutropenia attacks in patients with poor hygienic conditions and staying in the guesthouse, there was no statistically significant difference in febrile neutropenia and complication rates between those staying at home and in the guesthouse.

In Turkey, the 5-year survival rate in children with cancer, including solid tumors and leukemias, was found 69.5%.[17] In another study, Kebudi et al.[18] reported 7-year survival rates of 74% in patients with cancer at specific cancer centers in Turkey. Yağcı-Küpeli and Özkan[19] reported that refugee children had a lower treatment compliance and high frequency of advanced/metastatic disease compared to Turkish children. In our study, the 5-year survival rate of refugee children with cancer was found to be lower than those of Turkish children, that five-year survival rate was 58.1%.

Cancer in refugees causes a major burden on the health systems of the host countries. Patients and their families were confronted with some problems such as hygiene, communication, language barriers, shelter, difficulties in supplying medicine, and compliance with treatment. Advanced or relapsed disease in diagnosis and these socioeconomic problems adversely affect the prognosis and survival of these patients. Therefore, we concluded that there may be significant challenges for cancer patients with early diagnosis. One reason may be the difficulty to reach the free screening program of the Turkish Ministry of Health on the other hand when they have a proven cancer diagnosis, they easily reach health system facilities and get treated with chemotherapy, radiotherapy, and surgical operations.

We acknowledge that the current study has several limitations. Retrospective design of the study, and the limited number of patients could not be generalized to the entire refugee children in Turkey. Our median follow-up period was 18.2 months (1-90 months) and it was relatively adequate. Recommendations to increase the prevention, diagnosis, and treatment of cancer in refugee children include improved health systems and screening programs, and innovative financing schemes. Information for refugee patient's families, about how and when to look for medical care should be more appropriate, that this could detect cancers at early stages and would lead to better prognosis and less-costly treatment for these patients.[20]

Conclusion

Our data showed that cancer survival rates are lower in refugee children, and further prospective studies are needed to determine and improve the socioeconomic problems affecting survival rates in these patients.

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Does the Use of Multiplex PCR Contribute to the Management of Paediatric Emergency Physicians in <2-Year-old Children with Acute Respiratory Infections?

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Abstract

Multiplex polymerase chain reaction (PCR) is used to detect respiratory viruses in pediatric emergency departments, but its indications and interpretation of results must still be clear. In the present study, we examined the effect of detecting a viral agent with multiplex PCR on patient management. Infants and toddlers, aged between 1-24 months, who presented to the pediatric emergency department with respiratory tract infection complaints and underwent multiplex-PCR between 1 January 2014 and 28 February 2020 were included in the study. Patients with at least one agent detected were considered as the study group, and patients without detection were considered as the control group. The same design was implemented only for patients with chronic diseases. A total of 1106 patients were recruited [median age: 6.7 months (range: 2.9-13.0 months)]. Seven hundred and eighty-nine in the study group and 317 in the control group. There were no significant differences between the groups in hospital admissions (study group: 271 admissions; control group: 89 admissions; p=0.055), length of hospital stay duration [mean ± standard deviation: 3.09±7.87 days (study group) and 2.6±7.79 days (control group); p=0.045], or antibiotic use [234 patients (study group) and 77 patients (control group); p=0.078]. When these variables were examined only for those with chronic diseases, there was no difference again. Although multiplex PCR is an ideal method with high sensitivity, specificity, and cost-effectiveness, the limits of its clinical application need to be clarified. We did not observe significant differences in the treatment of patients with detected viral agents.

Keywords: Pediatric acute respiratory infection, pediatric emergency, polymerase chain reaction

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Introduction

Acute respiratory infections (ARI) in children are one of the most common causes of emergency department visits and paediatric hospitalisations. Almost 40-60% of hospital visits and 30-40% of hospitalisations among children seem to be due to ARI.[1,2] Also, these infections are one of the most important causes of death in children under the age of 5.[3] Although most of the causes of ARI are viral, unnecessary antibiotic prescriptions continue.[4,5] This increases antibiotic resistance and is a concern for the future.

Highlights

- Multiplex-polymerase chain reaction (PCR) is a method with high sensitivity and specificity in rapid viral diagnosis and allows more than one factor to be studied simultaneously.
- Few studies on its effect on patient management have presented different results.
- Clinicians did not make any changes in patient management on antibiotic use and hospital admission with the results of multiplex PCR.
- In patients with chronic disease, antibiotic use, hospitalisation, and length of hospital stay were higher.

The viral causes of ARI can be detected by viral culture, direct immunofluorescence assays (DFA), rapid antigen tests, and nucleic acid tests.[6] Apart from nucleic acid tests, other tests are no longer preferred due to their important limitations. Viral culture is a time-consuming method and requires expertise rather than advanced technology. Direct immunofluorescence tests and rapid antigen assays can give results in relatively short time compared to viral cultures. However, their sensitivity and specificity are lower, and they can only be used for specific viruses.[7]

Monoplex polymerase chain reaction (PCR) test is one of the nucleic acid-based methods. It can detect single viral pathogens such as RSV and influenza viruses. Because it can detect one pathogen at a time, it is a time-consuming method for ARI. Another nucleic acid-based method is the multiplex PCR test. With multiplex PCR tests, it is possible to detect a wide range of respiratory viruses.[8] Its specificity and sensitivity are higher than other methods. In addition, it requires a shorter time and is cost-effective.

Based on clinical features, it is not always possible to distinguish between viral and bacterial infections in patients with ARI. It is aimed to make this distinction with rapid viral diagnostic tests. Studies on diagnostic methods other than PCR tests have shown that these tests provide a reduction in antibiotic use, hospitalisation, and length of stay.[9,10] Similar results are expected with PCR tests, but studies show that multiplex PCR tests do not lead to decreases in hospital admissions, shorter hospital stays, or less antibiotic use for children with ARI.[11,12]

In appropriate indications, we take multiplex PCR tests from some patients with ARI symptoms, like many hospitals. The aim of this study is to determine whether the multiplex PCR results of patients with respiratory symptoms affect patient management in the paediatric emergency department.

Materials and Methods

In a controlled clinical trial, nasal wash specimens (NWS) were obtained to evaluate multiplex PCR diagnostic method for ARIs in pediatric patients. From 1 January 2014 to 28 February 2020, NWS was obtained from children with ARI symptoms such as fever, rhinorrhea, nasal congestion, cough, or respiratory distress. Infants and toddlers were included in the study, so patients younger than two years and older than one month were included.[13] Since the latest guideline published by the American Academy of Pediatrics does not recommend using NWS in newborns, patients younger than one month were excluded from the study.[14] The study was conducted in Hacettepe University Hospital Pediatric Emergency Department where approximately 70000 patients presented annually. The study was approved by the Institutional Review Board of the Hacettepe University (date: 15.03.2022, decision no: 2022/05-02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Multiplex PCR (Bosphore Respiratory Pathogens Panel Kit v4, Anatolia Gene Works, Turkey) was used to detect viral agents in NWS following the manufacturer's instructions. Multiplex PCR assays were performed for 17 pathogens (RSV A, RSV B, influenza viruses A and B, adenovirus, parainfluenza viruses 1, 2, 3, and 4, human bocavirus, coronaviruses 229E, HKU1, OC43, and NL63, human metapneumovirus, rhinovirus, enterovirus). Patients with at least one viral agent as a result of PCR were considered the study group, and patients without any agent were considered the control group.

Demographic characteristics, presenting symptoms at admission, vital findings, laboratory and imaging tests, treatment methods, type of respiratory support (if done), hospital admission, admission to the intensive care unit, length of hospital stay, and clinical outcomes of patients were retrospectively investigated from medical records. Additionally, results of multiplex PCR for respiratory tract pathogens in the NWS were recorded.

ARI was defined as a new episode of respiratory symptoms of the upper and/or lower airways. Upper respiratory tract infection was defined as respiratory symptoms without abnormalities in lung auscultation (e.g., rhinorrhea, nasal congestion, sore throat, erythematous pharynx, earache or erythematous eardrum). Lower respiratory tract infection (LRTI) was defined as respiratory symptoms with abnormalities in lung auscultation (e.g., rales, crackles, crepitations, wheezing, or prolonged expiration).

The hospital admissions of the patients with the same complaints related to respiratory tract infection within 7 days after the first hospital admission were accepted as revisit. It was not accepted as a revision due to other symptoms and diagnoses.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows 22.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov) to determine whether they were normally distributed. Numerical measurements were presented with mean and standard deviation or medians with interquartile range based on distribution; qualitative data with numbers and percentages. According to the distribution of numerical variables, a paired sample t-test or Mann-Whitney U was performed to investigate the differences between the groups. For categorical variables, a chi-square test or Fisher exact test was performed. The possible factors determined by the univariate analysis were then analysed with a multiple logistic regression model. The p-value <0.05 was considered statistically significant.

Results

Patient Enrollment

The medical records of patients administered to the paediatric emergency department between 2014 and 2020 were retrospectively reviewed using the hospital database. Patients who obtained NWS due to suspected respiratory tract infection were screened. During the 6-year period, NWSs were performed on 2382 patients. According to the inclusion criteria of our study, the number of patients aged 1-24 months who obtained NWS were 1121. Fifteen of them were not included in the study because of missing clinical data. A total of 1106 patients were recruited in this study. **Figure 1** shows the flowchart of patient enrollment.

Main Characteristics of Patients

Demographic and clinical characteristics are presented in **Table 1**. At least one viral agent was detected in 789 (71.3%) patients. Seven hundred and eighty-nine patients were included in the study group and 317 (28.6%) patients were in the control group. The median age, sex, chronic disease, and revisit rates of both groups were found to be close to each other. Cough, rhinorrhea and wheezing were statistically more found in the study group (p<0.001). The rash was greater in the control group (p<0.001). When laboratory test results were compared, the neutrophil-lymphocyte ratio was higher in the study group (p=0.016), while C-reactive protein was higher in the control group (p=0.024).

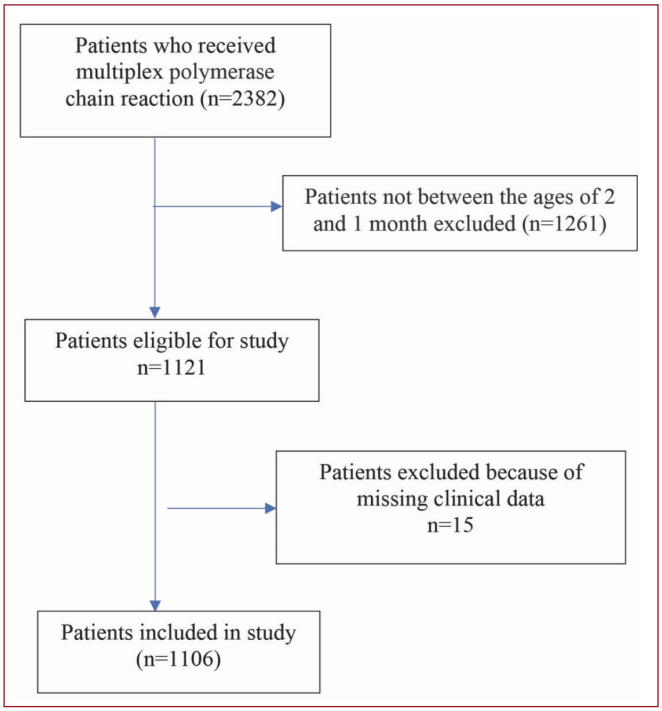

Figure 1. Flowchart of patient enrollment

Outcomes

Regarding the main objectives of this study, chest X-ray, inhaler salbutamol, oseltamivir, and oxygen therapy with mask were higher in the study group (p=0.001, p<0.001, p<0.001, p=0.026, respectively). In addition, the duration of hospitalisation was longer and statistically significant (p=0.045). Although antibiotic treatment and hospitalisation were higher in the study group, no statistically significant differences were found (**Table 1**).

Among viral agents, rhinovirus was detected most frequently in 288 (26.0%) patients, while RSV A/B was detected in 263 (23.7%) patients, and influenza A/B was detected in 184 (16.6%) patients (**Table 2**). The coinfection rate was 13.8%. Coinfection was detected with two agents in 121 (10.9%) of the patients and three agents in 14 (1.2%) (**Table 3**, **Figure 2**).

Two hundred and seventy-six patients in the study had at least one chronic disease. The distribution of these chronic diseases is as follows: cardiovasculer disease 84, pulmonary disease 45, neuromuscular disease 44, renal disease 24, gastrointestinal disease 29, hematological disease 43, metabolic disease 14, malignancy 13 patients. Humanrhinoviruses are the most common viruses detected in patients with chronic diseases. Antibiotic use, hospitalization, and the length of hospital stay were higher in the study group, but no statistically significant difference was found.

Discussion

This study is one of the rare studies examining the utilization of multiplex PCR in the pediatric emergency department. Multiplex PCR testing has replaced the old methods, and its routine use in practice has become

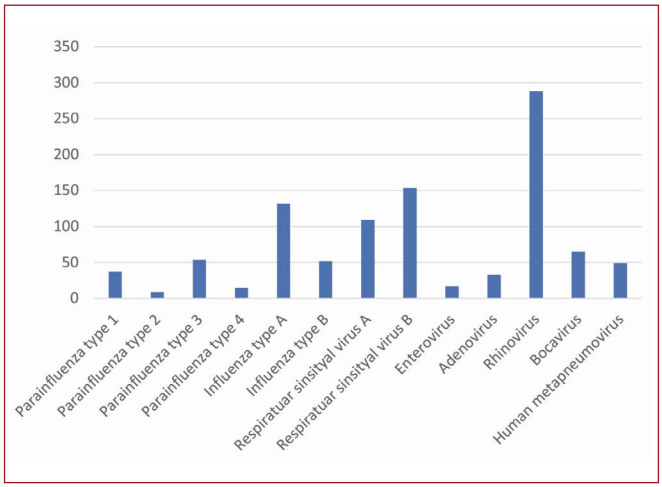

Figure 2. Distribution of viral agents

widespread in the last decade.[15] Studies on the subject mostly show the distribution of detected viruses according to seasons and years.[6,16-18] In addition, there are studies investigating other rapid viral diagnosis methods, such as DFA and viral culture, and showing that hospitalization rates and hospital stays of patients are shortened.[9,10] However, at the time of these studies, multiplex PCR was not used. Furthermore, DFA and viral culture were compared in these studies, and the DFA result time may be shorter than the viral culture. Studies on the clinical effect of the multiplex PCR assay are limited. The main goals are to determine the indications of virus PCR and to improve our ability to interpret the results from a clinical point of view.

The present study observed that the detection of a viral agent as a result of multiplex PCR did not affect the

Table 1.
Demographic and clinical characteristics of the patients

	Viral agent (+) (n=789)	Viral agent (-) (n=317)	p-value
Age, month (median, IQR)	6.5 (2.8-13.5)	7.1 (3.6-13.2)	0.737
Sex			
Male	443 (56.1%)	175 (55.2%)	0.775
Female	346 (43.9%)	142 (44.8%)	
Chronic disease	195 (24.7%)	81 (25.5%)	0.685
Revisit	45 (5.7%)	15 (4.7%)	0.540
Symptoms			
Fever	482 (61.1%)	204 (64.4%)	0.266
Highest measured fever, °C, (median, IQR)	38.5 (38.0-39.0)	38.6 (38.0-39.3)	0.325
Cough	588 (74.5%)	160 (50.5%)	**<0.001**
Rhinorrhea	388 (49.2%)	112 (35.3%)	**<0.001**
Wheezing	198 (25.1%)	42 (13.2%)	**<0.001**
Respiratory distress	91 (11.5%)	33 (10.4%)	0.601
Vomiting	171 (21.7%)	68 (21.5%)	0.971
Diarrhea	89 (11.3%)	38 (12%)	0.739
Rash	37 (4.7%)	46 (14.5%)	**<0.001**
Restlessness	56 (7.1%)	26 (8.2%)	0.519
Cyanosis	29 (3.7%)	16 (5%)	0.292
Symptom duration before admission, day, (median, IQR)	2 (1-4)	2 (1-4)	0.885
Vital signs			
Tachycardia	183 (23.2%)	71 (22.4%)	0.841
Tachypnea	190 (24.1%)	52 (16.4%)	**0.016**
Hypoxia	156 (19.8%)	56 (17.7%)	0.459
Hypotension	2 (0.3%)	0	0.369
Laboratory and imaging tests			
White blood cell count, $\times 10^9$/L, (median, IQR)	10.2 (7.7-10.3)	10.0 (7.0-14.2)	0.194
Neutrophil count, $\times 10^9$/L, (median, IQR)	3.6 (2.0-6.6)	3.7 (2.0-6.6)	0.962
Lymphocyte count, $\times 10^9$/L, (median, IQR)	4.5 (3.1-6.2)	4.3 (2.9-6.1)	0.232
Neutrophil-lymphocyte ratio (NLR), (median, IQR)	0.87 (0.42-1.80)	0.78 (0.37-1.66)	**0.016**
C-reactive protein level, (median, IQR), mg/L	0.81 (0.31-2.18)	0.88 (0.35-2.76)	**0.024**
Chest X-ray	557 (70.6%)	191 (60.3%)	**0.001**
Management			
Inhaler salbutamol	265 (33.6%)	64 (20.2%)	**<0.001**
Oral antibiotic	234 (29.7%)	77 (24.2%)	0.078
Intravenous antibiotic	227 (28.8%)	75 (23.6%)	0.093
Oseltamivir	314 (39.8%)	85 (26.8%)	**<0.001**
Oxygen with mask	65 (8.2%)	14 (4.4%)	**0.026**
High flow nasal cannula	47 (6.0%)	15 (4.7%)	0.423
Non-invasive mechanical ventilation	16 (2.0%)	2 (0.6%)	0.725
Mechanical ventilation	6 (0.8%)	2 (0.6%)	0.818
Hospitalization	271 (34.3%)	89 (28.0%)	0.055
Pediatric intensive care unit admission	19 (2.4%)	6 (1.8%)	0.602
Duration of hospitalization (mean ± SD)	3.09±7.87	2.6±7.79	**0.045**

IQR; Interquartile range, SD; Standard deviation

Table 2.
Evaluation of the management of the patients with chronic disease according to multiplex polymerase chain reaction results

	Viral agent (+) (n=195)	Viral agent (-) (n=81)	p-value
Oral antibiotic, n (%)	56 (28.7%)	20 (24.6%)	0.495
Intravenous antibiotic, n (%)	89 (45.6%)	36 (44.4%)	0.856
Oseltamivir, n (%)	69 (35.4%)	21 (25.9%)	0.127
Pediatric ward admission, n (%)	107 (54.8%)	42 (51.8%)	0.647
Pediatric intensive care unit admission, n (%)	14 (7.2%)	4 (4.9%)	0.492
Duration of hospitalization, (mean ± standard deviation) day	7.83±13.7	7.07±13.6	0.813

Table 3.
The number of certain pathogen coinfected with another pathogen

Pathogen	HPIV1	HPIV3	HPIV4	InfA	InfB	HRV	HMPV	ADV	HBoV	RSVA	RSVB	Enterovirus
HPIV 1		0	0	0	0	4	0	0	0	0	1	0
HPIV 3			0	0	0	6	0	0	0	0	1	0
HPIV 4				0	0	1	0	0	0	0	0	0
Inf A					2	10	0	1	4	9	7	0
Inf B						5	0	0	1	3	1	0
HRV							2	4	5	13	7	1
HMPV								0	0	0	0	0
ADV									1	1	1	0
HBoV										2	3	0
RSV A											2	1
RSV B												0
Enterovirus												

ADV; Adenovirus, HBoV; Human bocavirus, HMPV; Human metapneumovirus, HPIV; Human parainfluenza virus, HRV; Human rhinovirus, InfA; Influenza A virus, InfB; Influenza B virus, RSV; Respiratory syncytial virus

patient's use of antibiotics, hospitalisation, and length of hospital stay. The results suggest that although physicians apply for this assay when possible, they only consider the result of the assay a little when deciding on the patient's antibiotic treatment and hospitalisation. Wishaupt et al.[12] examined the use of multiplex PCR for ARIs in the pediatric population and found that antibiotic use was similarly higher. Also, Oosterheert et al.[19], who investigated the clinical consequences of viral RT-PCR diagnostic results in a randomized controlled trial involving adults, found results similar to those in our study. Excessive use of antibiotics is not expected. There may be different reasons for this. First, it was not expected that the multiplex PCR results would influence the decision to start antibiotic treatment because these results become available 12 to 24 hours after sampling. Multiplex PCR can be expected to affect the duration of antibiotic use rather than the rate of antibiotic initiation. This data could not be investigated in our study because they were unavailable. Wishaupt et al.[12] also did not detect a change in the duration of antibiotic use. Another reason antibiotic use was higher in the study group may be that doctors do not want to interrupt or change an antibiotic treatment that had been started. Doctors may be making this decision because they are concerned about bacterial superinfections. Also, in the present study, it was observed that more chest X-rays were taken in these patients. Imaging may have caused more antibiotics to start. Considering that the hospitalizations and respiratory support needs of the patients with viral agents are somewhat high, these patients have a more severe clinical course, and therefore more antibiotics are preferred.

Other possible clinical effects of multiplex-PCR use in patients with respiratory tract infections are hospitalisation and length of hospital stay. No effect was observed in this area either. Similar to the decision to start antibiotics, hospitalization is a situation mainly decided according to the patient's clinical condition and follow-up. The effect of the multiplex PCR test may be on hospital stay and patient isolation. We could not evaluate isolation in our study because of the limited availability of isolated rooms in our emergency department. Oosterheert et al.[19] found no decrease in hospital stay, similar to our study. Andrews et al.[20] compared the effect of routine laboratory-based tests such as culture, serology or batch molecular testing with the FilmArray® RP panel, which is a multiplex PCR test, on the length of stay in adults with respiratory tract infections and found no difference. Isolation of patients according to viral PCR results and thus prevention of infectious diseases is a targeted situation in this regard.[15] In extraordinary situations, such as during the COVID-19 pandemic, this indication is an important reason for using viral PCR.

When we look at the frequency of viral pathogens without considering the month or season, the rhinovirus was detected as the most common viral agent. Appak et al.[6] reported that rhinovirus/enterovirus was the most common agent in their study in which they examined patients diagnosed with viral respiratory infection with the use of multiplex PCR in pediatric patients. Zhang

et al.[21] in their study, examined respiratory tract viruses in children and adults. They found human bocavirus as the most common agent. In our study, the presence of rhinovirus may result from the inclusion of patients with all respiratory tract infections, not just LRTIs. Knowing the frequencies and seasonal distributions of the factors may be necessary for the emergency physician to make preparations before the possible increases in the amount of an agent.

The use of multiplex PCR in chronic disease (i.e., cancer patients, immunodeficiency patients, cystic fibrosis) is an area that needs further study in the literature.[12] The use of multiplex PCR in this group of patients will provide a more accurate flu diagnosis and may be more appropriate for the use of neuraminidase inhibitors.[8] On the other hand, the detection rates have been higher in asymptomatic individuals with a chronic disease than in asymptomatic individuals without such a condition. Therefore, false positivity can be seen.[22] However, it is clear that further studies are needed on the use of multiplex PCR in the treatment of specific groups such as cystic fibrosis, immunodeficiency patients, and cancer patients.[8]

Although multiplex PCR is practically requested, it does not seem to contribute to patient management. However, detecting the viral agent and making the treatment specific to the patient is an important step for precision medicine. Algorithms can be produced to increase the contribution of multiplex PCR to patient care. These algorithms should be in different ways according to the patients who will be followed up and outpatients. Furthermore, in recent studies on this subject, the use of multiplex PCR is being investigated together with other examinations (sputulum, procalcitonin, etc.) is being investigated. The goal is to interpret the results of multiplex PCR together with other tests, especially in patients with chronic disease, to de-escalate or stop antibiotic treatment for the individual patient by minimising exposure to antibiotics and improve targeted use of antibiotics. The duty of the emergency services in this regard is to apply this test in the emergency department within the first 24 hours after the application, so that multiplex PCR can be used especially in the management of hospitalized patients.

Study Limitations

The present study had several limitations. Children were evaluated at a single center. Additionally, the study was not double-blind and did not have long-term follow-up information. Patients with chronic disease were not divided into subgroups. The duration of antibiotic use could not be evaluated because it was not found in the patient's medical records. The patients were selected only from patients with respiratory tract infections, admitted to the emergency department, and not classified according to their diagnosis.

Conclusion

Multiplex PCR is a relatively rapid, sensitive and highly specific method that is now routinely used to detect respiratory tract viruses. NWS enables the detection of the viral agent in the patient admitted to the pediatric emergency department with respiratory symptoms, but it does not seem to be of significant benefit to the clinician on patient management. On the other hand, there are not many studies in the literature on the effect of NWS on patient management, especially in patients with chronic diseases. Studies in which a larger number of patients with chronic diseases are evaluated will make significant contributions to the literature.

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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.

Ethics Committee Approval: The study was approved by the Institutional Review Board of the Hacettepe University (date: 15.03.2022, decision no: 2022/05-02).

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

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Case Report

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Pragmatic Management of Hand Involvement in Extended Oligoarticular Juvenile Idiopathic Arthritis: Ultrasound-guided Serial Interphalangeal Joint Injections

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Abstract

Small-joint involvement, including the interphalangeal joints of the hand, is less common in oligoarticular juvenile idiopathic arthritis (JIA). Ultrasound (US)-guided joint injections are also plausible for children. However, US-guided injections into pediatric small joints make the tips and tricks special because of the more difficult injection technique and greater risk of potential complications than with large joints. Here, we report the tips and tricks of serial US-guided interphalangeal joint injections in a male child with oligoarticular JIA who progressed to extended polyarthritis after an initial 6-month follow-up.

Keywords: Hand, interphalangeal joint, injection, ultrasound, juvenile idiopathic arthritis

Introduction

The role of musculoskeletal ultrasound (US) in diagnosis and treatment decisions in juvenile idiopathic arthritis (JIA) is controversial in some areas. On the other hand, US guidance is now a necessary reality for almost all joint injections in children, similar to adults.[1] However, US-guided injections into pediatric small joints make the tips and tricks special because of the more difficult injection technique and greater risk of potential complications compared with large joints, as well as the child's moodiness and/or possibly the limited experience of the clinician. Therefore, we report both our experience with the injection technique and protocol, and the patient's clinical outcomes after serial steroid injections into the interphalangeal (IP) joints.

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Case Report

A 12-year-old male who was followed up with the diagnosis of oligoarticular JIA was referred to our clinic for intra-articular corticosteroid (IAC) injection due to flare of synovitis in the IP joints of the hands. His complaints started four years ago with pain and swelling in the proximal IP (PIP) joint of the 2nd finger on the right hand. Antinuclear antibodies were also positive while rheumatoid factor was negative at the time of JIA diagnosis.

After the initial 6-month follow-up, synovitis developed progressively in the other small joints of the hand. He was then given methotrexate (subcutaneous, 15 mg weekly), naproxen (oral, 500 mg daily) and folic acid (oral, 5 mg twice weekly). However, there was exacerbation of synovitis in some joints of his hands 2 months ago.

On physical examination, there was swelling and mild tenderness in the IP joint of the 1st finger and PIP joint of the 2nd finger on the right hand, and the PIP joints of the 3rd and 5th fingers on the left hand (**Figure 1A**). Also, there were limitations in varying degrees of flexion range of motion in the affected joints. On the pain assessment, the mean numeric rating scale (NRS, 0-10) score for these joints was 6. Sonographic evaluation of both hands revealed active synovitis characterized by synovial effusion, synovial hypertrophy, and hypervascularity in the affected joints. Other than mild anemia, routine biochemistry and other laboratory tests including acute phase reactants were within normal limits.

US-guided IAC injection was planned for the affected joints of the patient. After getting written consent, the IP joint was visualized longitudinally on the dorsal side of the hand with US under sterile conditions. Then, the lateral side of the joint was entered using the out-of-plane technique with a 26G needle (**Figure 1B**). After the needle tip was seen in the joint, the appropriate dose of triamcinolone hexacetonide was injected into the joint (**Figure 1C**). The same procedure was repeated in the form of 2.5 mg triamcinolone hexacetonide injections at 1-month intervals for the other affected joints of the patient. No side effects were observed after the injections. The average NRS was 1 at the patient's 1-month evaluation after the last injection. The swelling resolved completely in 3 of the 4 swollen joints of the patient and partially resolved in one (**Figure 1D**). A 5-point Likert scale (1=very dissatisfied, 2=not satisfied, 3=none, 4=satisfied, and 5=very satisfied) was used to evaluate the overall satisfaction of the patient with the treatment. The patient evaluated his satisfaction after the serial injections as very satisfied (5).

Discussion

Oligoarticular JIA mainly involves the lower extremity joints such as the knee and ankle. However, small-joint involvement, including the IP joints of the hand, is more rare.[2] Here, we present a male patient who slowly progressed to extended oligoarticular JIA, which is known as a poor prognosis criterion, after the first

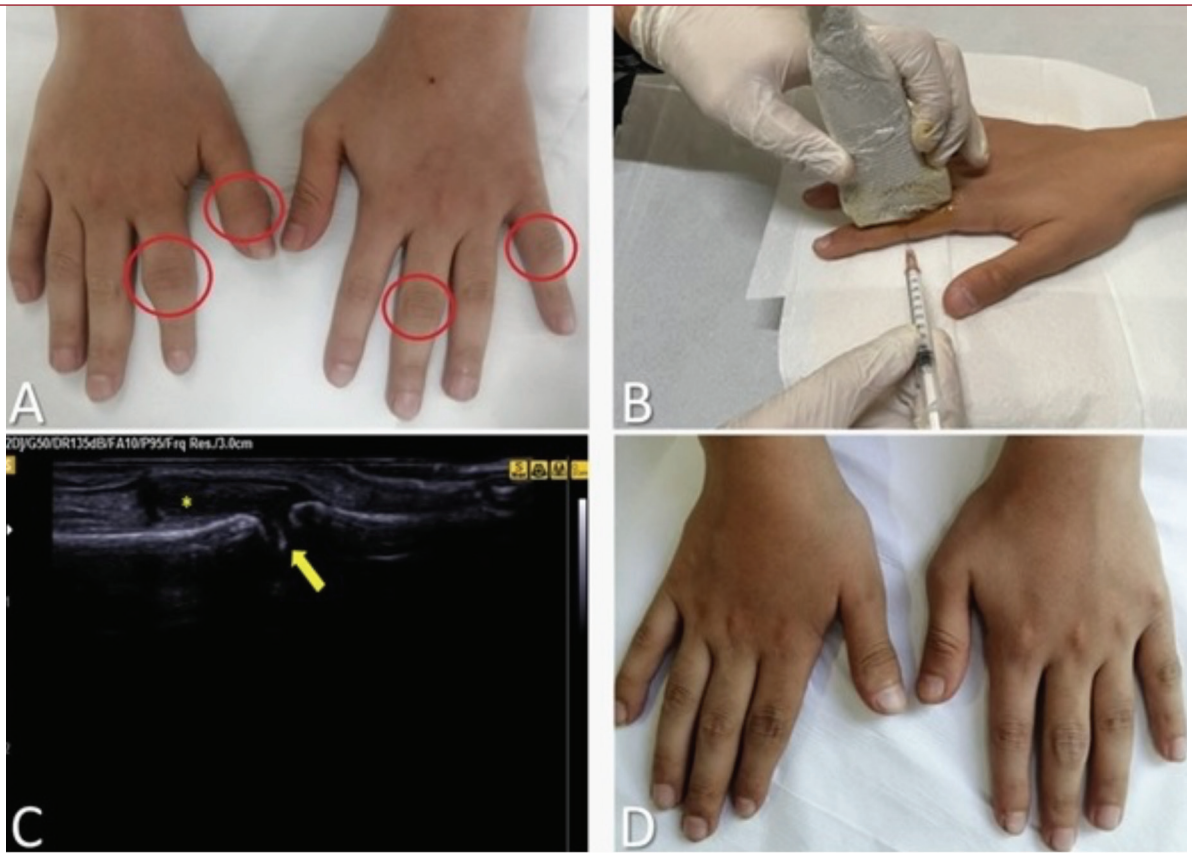

Figure 1. A) Arthritis in the 1st finger IP and 2nd finger PIP joints on the right hand and the PIP joints of the 3rd and 5th fingers on the left hand (pre-injection). **B)** Position of the hand and US probe for US-guided PIP joint steroid injection, and the position of the needle for insertion into the joint with the out-of plane technique. **C)** US image of IP joint injection. Synovial hypertrophy and effusion (star); intra-articular steroid particles (arrow). **D)** Control at 1 month after serial injections. In the right hand, arthritis of the 1st finger IP, 2nd finger PIP and left hand 5th finger PIP joints healed completely, there was no swelling; partial improvement in the PIP joint of the 3rd finger on the left hand, slight swelling.

6 months of follow-up. Young children with prominent swellings on their hands may also experience more appearance-related stress. Our patient expressed this as “I will feel better if the swelling in my hands improves rather than pain”.

The patient we report here had only one joint involvement (PIP joint in the 2nd finger of the right hand) at the time of diagnosis. Other joint involvements developed progressively over the years. Because of this slow progression, IAC injections were administered before biological disease modifying anti-rheumatic drug treatments. IAC injections are a joint-targeted treatment option that provides rapid symptomatic and functional recovery in oligoarticular JIA and should be considered primarily for any joint involvement. In addition, a multicenter study revealed that concomitant use of methotrexate in patients may be associated with higher and longer efficacy for IAC.[3]

Although joint injections are widely performed in JIA, uncertainties remain regarding the technique, frequency of administration, which steroid to use and doses. The most preferred steroid for joint injections is the long-acting triamcinolone hexacetonide. Some authors recommend applying methylprednisolone acetate to small or difficult-to-assess joints because of the risk of subcutaneous atrophy and hypopigmentation.[4,5] However, Young et al.[6] reported the results of US-guided injection into small, medium, and large joints in patients with JIA, and applied triamcinolone hexacetonide or acetonide to IP joints, and these side effects were reported in only 2.5% of all injections (localization unclear). US allows imaging of the needle tip as well as the distribution of the steroid within the joint. In addition, avoidance of excessive distension with the volume of the injected material (i.e., steroid) in small joints, absence of steroid contamination to the metal part or tip of the needle before injection, and immobilization after injection are among the safety measures.[5,7]

Another dilemma regarding joint injections in JIA is whether to give a single or multiple injections in one session. The most important limitations of multiple IAC injections are that it requires general anesthesia or sedation in most children, the prolongation of the procedure and follow-up time, and the increased risk of potential systemic side effects associated with higher total steroid dose.[5,8] Although the procedure compliance of our young child case was good, we performed a joint injection in one session because the technique of injection into the small joints was difficult and the patient did not want anesthesia or sedation. We then repeated the same procedure with an interval of 1 month. In the following sessions, it was observed that patient compliance with the procedure increased even more. This may be due to the dramatic improvement of pain and swelling after the first injection, and possibly due to verbal information given to the patient about the procedure with US images. Therefore, in our opinion, individual injection planning in children with JIA may be a more accurate approach. A simplified injection protocol for multiple joints, as in this case, may be an alternative to the difficulties of multiple injections.

Conclusion

In summary, IP joint injection can be safely performed in selected children with JIA under US guidance, without anesthesia or sedation. In addition, serial injections for delicate joints in patients resistant to conventional therapy may be an alternative to the difficulties and risks of multiple injections.

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Pneumococcal Meningitis with Serotype 7 Who Develops 12. Nerve Paralysis

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Abstract

Meningitis is an inflammatory disease of the leptomeninges surrounding the spinal cord and brain. *Streptococcus pneumoniae (S. pneumoniae)* is the most common cause of bacterial meningitis in infants and children older than one month. In this report, we present a 13-month-old infant who, after receiving three doses of the 13-valent conjugated pneumococcal vaccine, had nervus hypoglossus paralysis as a result of serotype 7 *S. pneumoniae* meningitis. She was admitted into our center with complaints of high fever for 2 days, apathy that started in the last 24 hours, and a tendency for sleeping. Penicillin and ceftriaxone susceptible *S. pneumoniae* grew in cerebrospinal fluid culture. Antibiotic treatment was completed in six weeks as she had a millimetric abscess in MR imaging. Considering common variable immunodeficiency in the patient who was examined for immunodeficiency, intravenous immunoglobulin treatment was started. The physical examination results of the patient were entirely improved. In conclusion, meningitis is a pediatric emergency with a high mortality and complication rate. If meningitis is managed on time and correctly it can heal without sequelae. Vaccination is crucial for prevention. Despite vaccination, although rare, infection with vaccine strains may occur. Patients infected with vaccine strains may require evaluation in terms of immunodeficiency.

Keywords: *Streptococcus pneumoniae*, meningitis, nervus hypoglossus paralysis

Introduction

Meningitis is an inflammatory disease of the leptomeninges surrounding the spinal cord and brain. *Streptococcus pneumoniae* (*S. pneumoniae)* is the most common cause of bacterial meningitis in infants and children older than one month. The incidence of pneumococcal meningitis decreased after the initiation of routine vaccination against *Pneumococci*.[1] 13-valent pneumococcal conjugate vaccination (PCV13) in Turkey. It includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. Despite this, pneumococcal meningitis continues to be a major factor in the morbidity and mortality of children.[1] So far, 100 different serotypes have been defined for *Pneumococci*.[2] As the frequency of invasive pneumococcal diseases caused by vaccine serotypes decreases, the rate of unvaccinated serotypes increases.[1] Pneumococcal vaccines have been developed to provide effective vaccination protection, particularly in young infants. These vaccines are effective in reducing transmission and are protective against invasive disease.[3] However, the disease can also be seen with the

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serotypes contained in the vaccine strains. In this report, we describe a 13-month-old child who developed nervus hypoglossus paralysis due to serotype 7 *S. pneumoniae* meningitis after receiving three doses of the 13-valent conjugated pneumococcal vaccine (PCV13).

Case Report

A 13-month-old female patient with no prior history of any disease was admitted to our center with complaints of high fever for 2 days, apathy that started in the last 24 hours, and a tendency for sleeping. She received the 3rd dose of 13-valent conjugated pneumococcal vaccine 23 days ago. She had a lower respiratory tract infection 1 month ago and used antibiotics for 1 week. It was one week before the pneumococcal vaccine. On physical examination of the patient, the fever was 38.9 ˚C. She was throwing her head back and she had neck stiffness. The fontanel was 1x0.5 cm open, with normal camber. Other system examinations were normal. In the blood tests, C-reactive protein: 209 mg/L, procalcitonin: 89.6 ng/mL, white blood cell (WBC): 15700/mm³, hemoglobin: 9.2 g/dL, thrombocyte: 299000/mcL. In fundus examination papillae stasis was not observed. Brain computerized tomography imaging was normal. Cerebrospinal fluid (CSF) was examined by lumbar puncture. CSF glucose was 2 mg/dL and protein was 148 mg/dL, concomitant blood sugar was 110 mg/dL. CSF direct examination of thoma slide showed 70 WBC/mm³, they were neutrophils and Gram-positive diplococci were observed in gram staining. Vancomycin (60 mg/kg/day), ceftriaxone (100 mg/kg/day), acyclovir and dexamethasone treatments were started. Fever continued for 2 more days. *S. pneumoniae* signal was seen in CSF culture on day 2. Acyclovir treatment was stopped. She took the dexamethasone treatment for 48 hours. Consciousness and general condition improved. On the fifth day her tongue was deviated to the right inside the mouth (**Figure 1**) to the left outside the mouth (**Figure 2**), nervus hypoglossus palsy was considered. Brain magnetic resonance imaging (MRI) revealed increased contrast enhancement in leptomeningeal structures and an appearance consistent with millimetric abscess in the left frontal region. There was not an infarct shown in brain MRI. We did not perform any other brain imaging for infarction. In her daily examination, the deviation of the tongue to the right decreased and completely resolved within 1 month. Penicillin and ceftriaxone susceptible *S. pneumoniae grew* in CSF culture. Chocolate agar method was used and the minimum inhibitory concentration (MIC) of penicillin was 0.25. The serotyping result was type 7 (type 7 subtype could not be determined). Antibiotic treatment was completed for 6 weeks as she had a millimetric abscess in MRI. Although there was no history of frequent illness it was speculated that there might be a common variable immunodeficiency (CVID) or combined immunodeficiency (CID). Despite 3 doses of pneumococcal vaccine, she developed pneumococcal meningitis. Serum immunglobulin G: 9.3 g/L, immunglobulin: 0.69 g/L, immunglobulin A: 0.6 g/L were normal for her age. CD3: 22.6%, CD4: 16.3%, CD8: 5.9% and CD16 + CD56: 2.1% were low for her age. Intravenous immunoglobulin (IVIG) treatment was started, genetic testing was sent for CVID and CID, there are no test results yet. The patient's physical examination findings improved completely. MRI findings regressed. Hearing test and eye examinations were normal. The patient's follow-up continues in the polyclinic.

Discussion

S. pneumoniae, Neisseria meningitidis and *Haemophilus influenzae* constitutes the primary etiology of bacterial meningitis.[4] An association has been reported with pneumococcal meningitis and pneumonia in 15-25% of cases, with pneumococcal meningitis and acute otitis media in 30% of cases.[5] Our case also had a history of lower respiratory tract infection 1 month ago. The incidence of pneumococcal meningitis decreased significantly after the addition of the heptavalent conjugated pneumococcal vaccine (PCV7) to the infant immunization program.[1] With the licensing of expanded PCV10 and PCV13 conjugate vaccines in 2009 and 2010, diseases caused by vaccine serotypes have decreased by more than 90 percent, but overall disease

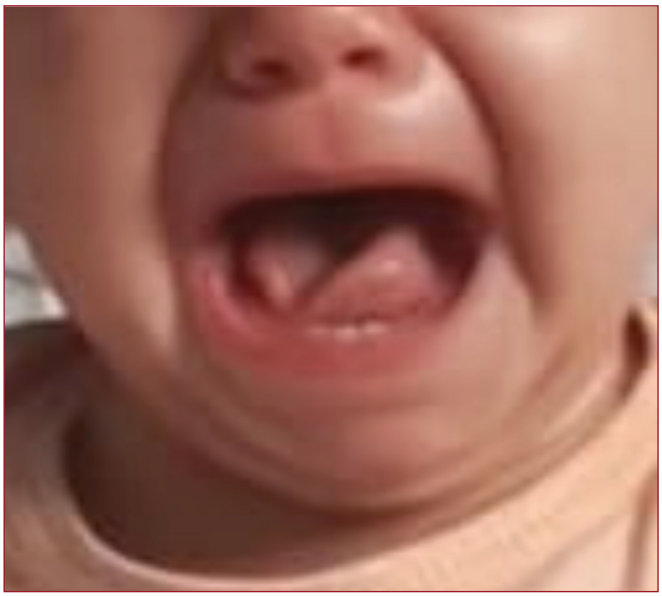

Figure 1. Her tongue was deviated to the right inside the mouth

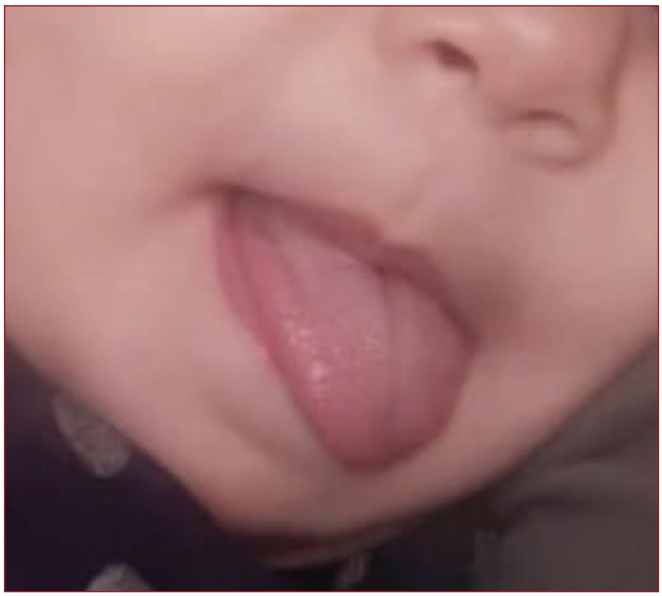

Figure 2. Her tongue was deviated to the left outside the mouth

rates remain high with serotype change.[6] Although it is reported that vaccine failure is rare, cases that become infected despite vaccination are reported. In a study of 161 pediatric cases vaccinated with PCV13 in the United Kingdom, vaccine failure was found to be 0.66/100,000.[7] The reasons for vaccine failure may be related to the patient, the vaccine, and the vaccine administration methods. The patient's immunodeficiency status, age, and eating disorder are important factors in vaccine failure.[3] In Turkey, infection rates were found to be 25% between 2008 and 2014 despite vaccination.[8] Our case's 13 valences pneumococcal vaccination was completed. It was determined that she was infected with type 7, one of the strains included in this vaccine. A poor response to vaccines is seen in common variable immunodeficiency. According to studies, presentation with meningitis has been reported in 25% of CVID patients. An immunological deficiency that renders the host defense inadequate against potential bacterial pathogens may facilitate hematogenous spread. In the literature, pneumococcal meningitis has been reported in a 22-year-old female patient with CVID.[9] The CVID genetic result of our patient has not been revealed yet, but due to the test results, IVIG treatment was started by considering CVID. Bacterial meningitis has fever and present with signs of meningeal irritation. Meningeal irritation findings can be seen such as nuchal rigidity, irritability, confusion or change in mental status, headache, photophobia, nausea, vomiting.[10] Our case had high fever, nuchal rigidity, and neck hyperextension. Pneumococcal meningitis requires detection of S. pneumoniae in CSF by techniques such as culture, gram stain and polymerase chain reaction (PCR). A positive blood culture is also diagnostic in a patient with CSF pleocytosis. Gram staining is positive in approximately 90 percent of children with pneumococcal meningitis.[11] In our case, Gram-positive diplococci were observed in gram staining and *S. pneumoniae* was grown in its culture. While penicillins were the first choice in treatment, in 1974 penicillin-resistant *Streptococcus pneumoniae* meningitis has been described. Over the years, multi-antibiotic resistance has also developed widely. As in our case, it is recommended to start vancomycin and ceftriaxone or cefotaxime in empirical treatment.[12,13] Treatment should be revised according to culture - antibiogram sensitivity.[12] The benefits and harms of dexamethasone in children with suspected pneumococcal meningitis are uncertain and should be evaluated on a patient basis.[14] A decrease in antibiotic resistance has been observed after vaccination applications all over the world. However, ongoing studies have shown that non-vaccine serotypes have increased and that these serotypes have increased in the rate of antibiotic resistance. Data on serotype distribution and antibiotic resistance after KPA13 application in Turkey are limited. In the USA, after KPA7, penicillin-resistant *Pneumococci* decreased by 81%, especially under the age of two. In a study involving eight hospitals in the USA, ceftriaxone resistance in pneumococcal meningitis decreased from 13% to 3% after KPA13. According to the review in which four studies performed after KPA7 application in Europe were examined, it was reported that penicillin resistance decreased from 48% to 29% in children under the age of five, and cephalosporin resistance decreased by 10%.[15]

When the penicillin MIC values of isolates obtained from children under the age of five with meningitis were examined in a single-center study conducted in our country and published in 2021, it was determined that 38.8% of the isolates were resistant.[15] A wide variety of complications can be seen due to pneumococcal meningitis. Cerebral edema and increased intracranial pressure, convulsions, hearing loss, cranial nerve palsies, hemiparesis, quadriparesis, ataxia, cerebrovascular abnormalities, subdural effusion or emphysema, hydrocephalus, brain abscess, behavioral and developmental disorders can be seen among the complications.[14] In our case, brain abscess and transient 12th cranial nerve palsy developed. Cranial nerve palsies are well-known complications of basal meningitis, particularly in patients with tuberculous meningitis.

Conclusion

Meningitis is a pediatric emergency with a high mortality and complication rate. If managed on time and correctly can heal without sequelae. Vaccination is very important in prevention. Despite vaccination, although rare, infection with vaccine strains may occur. Patients with vaccine strain infections may need to be assessed for immunodeficiency, as was the reported case.

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