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RESEARCH ARTICLE

Multidisciplinary Management of Hepatoblastoma: Three Years of Experience at a Single Centre

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ABSTRACT

Objective: The aim of this study was to report the short-term outcomes of paediatric hepatoblastoma managed by hepatobiliary surgery and paediatric oncology from a single centre.

Methods: Children with hepatoblastoma diagnosed between May 2020 and February 2023 and treated comprehensively in a single centre, were retrospectively reviewed. Management was multidisciplinary and followed the SIOPEL protocols (SIOPEL III-IV).

Results: Eight paediatric patients with a median (range) age at diagnosis of 24 (5-68) months were included. The most common complaint was abdominal distension. There were no patients with PRETEXT stage I. Patients were graded as stage II (n=4), stage III (n=2), and stage IV (n=2). Half of the patients were classified in the standard risk group and the other half in the high-risk group. Chemotherapy was initiated in seven patients, and one was transferred directly to surgery for overt rupture. After neoadjuvant chemotherapy, complete response (CR) was not achieved in any patient, partial response (PR) was achieved in half (n=4), progressive disease and stable disease were present in one patient each, and one patient died. Four patients underwent radical hepatectomy with negative surgical margins after chemotherapy. The median (range) follow-up period was 18 (2-47) months. No recurrence was observed in any patient during follow-up, and the overall and event-free survival rates were 88% and 75%, respectively.

Conclusions: The collective work of surgery and paediatric oncology in management is essential to achieve optimal results.

Keywords: Hepatoblastoma, children, hepatectomy, chemotherapy

INTRODUCTION

Hepatoblastoma is the most common primary malignant liver tumour and accounts for approximately two-thirds of all malignant liver tumours seen in childhood (1-3). They are usually observed in the infantile period and are very rarely encountered after the age of 5 years, but there are case reports of patients older than 10 years (4,5). Although the aetiology of this embryonal tumour, which is known to originate from hepatocyte precursors, is unknown, its association with premature birth, low birth weight (<1500 g), and some familial syndromes, such as Beckwith-Wiedermann syndrome, familial adenomatous polyposis, and trisomy 18, has been well recognised (6-8).

After the diagnosis is made, the stage and risk group of the disease are determined according to both the pretreatment extent of disease (PRETEXT) staging system, defined by The International Childhood Liver Tumour Strategy Group (SIOPEL) based on the involving hepatic sections, evidence of abdominal extrahepatic disease, presence of metastasis, and serum alpha fetoprotein (AFP) levels (9).

The cornerstone of treatment is complete resection, including total hepatectomy and transplantation in selected cases. With the discovery of the sensitivity of this tumour to chemotherapy, cisplatin- and doxorubicin-based chemotherapy regimens that have been added to the treatment protocol have increased the chance of complete resection. Indeed, with the addition of chemotherapy to treatment in the 1980s, survival rates gradually improved, and the 5-year overall survival rates have reached around 80% today (10-12). Moreover, the contribution of improved surgical techniques and most recently developed

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supportive therapies to the improvement in survival cannot be denied. Thus, a multidisciplinary approach is essential in the management of this patient group in which treatment is highly complicated.

In this study, we retrospectively evaluated the clinical characteristics, treatments, and outcomes of paediatric patients diagnosed with hepatoblastoma in a newly established comprehensive treatment (chemotherapy, hepatectomy, liver transplantation, transarterial chemoembolization and radioembolization available) centre in Turkey.

MATERIALS AND METHODS

The charts of children diagnosed with hepatoblastoma between May 2020 and February 2023 and treated comprehensively at our institution were retrospectively evaluated. Patients' demographics, tumour characteristics (histology, location, spread at the diagnosis, relationship with vessels, pre- and post-treatment volumes,) AFP levels (at the diagnosis and during follow-up), complete blood count, liver function tests, surgical procedures, chemotherapy protocols, treatment-related complications, and survival data were analysed.

All patients were discussed in a multidisciplinary council involving paediatric oncology, hepatobiliary surgery, paediatric gastroenterology, radiology, and pathology specialists. The diagnosis was made by biochemical tests, imaging and tumour biopsy. Abdominal ultrasound, computed tomography (CT), and/or magnetic resonance imaging (MRI) were used as imaging modalities.

For staging, the PRETEXT system adopted by the SIOPEL protocol was initially used. Patients were stratified as standard or high-risk based on the SIOPEL guidelines, and chemotherapy protocols were administered according to the risk groups. Patients with tumours limited to no more than three sections (PRETEXT 1, 2, or 3) without any additional risk factors were included in the standard-risk (SR) group, and these patients received cisplatin (80 mg/m^2/day). Patients who met at least one of the following criteria were included in the HR group: tumour involving all four hepatic sections (PRETEXT IV); abdominal extrahepatic disease (any of V+, P+ or E+); presence of metastases (M+); very low serum AFP (<100 ng/mL) levels; and tumour rupture at diagnosis irrespective of PRETEXT (H+). (V+: extension into the vena cava and/or all three hepatic veins (V3), P+: extension into the main and/or both left and right branches of portal vein (P2) , E+ extrahepatic disease except for P+ and V+ that must be biopsy proven (including enlarged lymph nodes on radiological investigation) and these patients received chemotherapy blocks including cisplatin (70- 80 mg/m^2/d), doxorubicin (20-30 mg/m^2/d), and carboplatin (AUC 10.6 mg/mL/min) according to the SIOPEL IV HR protocol.

In principle, resectable or ruptured tumours were surgically removed upfront, whereas patients with unresectable tumours received neoadjuvant chemotherapy. Evaluation of response to neoadjuvant chemotherapy was performed using serial imaging techniques and measurement of AFP levels after each chemotherapy block. Administration of chemotherapy blocks was continued until the appropriate time for surgery, and postoperative TEXT staging was performed before surgery. Response to neoadjuvant chemotherapy was evaluated after all cycles of treatment were delivered before surgery as follows: complete response (CR) defined as no evidence of disease and AFP level in the normal range for age; partial response (PR) defined as reduction in tumour size and decrease in AFP levels by more than 1 log relative to baseline; stable disease (SD) defined as no change in tumour volume or decrease in AFP levels by less than 1 log; and progressive disease (PD) defined as increase in tumour size at any measurement and/or increase in AFP levels detected in three consecutive measurements or weeks. In patients with inadequate chemotherapy response, chemotherapy protocols were escalated to include doxorubicin and carboplatin.

Complete surgical resection was defined as macroscopic total removal of all tumour lesions. The timing of surgery and decision to perform liver resection or liver transplantation were made according to the hepatobiliary multidisciplinary treatment council. Adjuvant chemotherapy was administered in consecutive blocks, considering the agents given in neoadjuvant chemotherapy. After termination of treatment, the patients were followed up with serial abdominal ultrasounds, and serum AFP levels were measured at intervals of 1-3 months.

The study was approved by the hospital ethics committee (approval number: KAEK/2022.03.82), and informed consent was obtained from the parents of the patients.

Statistical analysis

The data were analysed using IBM Statistical Package for the Social Sciences, version 23.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics are presented as mean ± standard deviation and median (minimum-maximum) values. Kaplan–Meier survival analysis was used to analyse overall survival. A $p<0.05$ was considered statistically significant.

RESULTS

During the study period, 10 patients with hepatoblastoma were followed in the paediatric haematology-oncology clinic. Two patients who received some parts of their treatment at other centres as well as patients who were referred for surgery (hepatectomy or liver transplantation) after chemotherapy at other centres, were excluded from this report. Thus, eight patients treated comprehensively at our centre were included with a median (range) age at diagnosis of 24 (5-68) months, and half of the patients were male (4/8) (Table 1). The most common complaint was abdominal distension. In addition, one infant was restless and had crying fits, and another had recurrent febrile and daily episodes of vomiting in the week before diagnosis. A third patient had jaundice and respiratory distress. Except for two patients, borderline prematurity (37 weeks) in one and prematurity (29+5 weeks) in the other, gestational age and birth weights were within normal limits. The premature patient was a twin and was diagnosed with cerebral palsy (CP) and congenital cardiac pathology, defined

Table 1: Baseline features and laboratory data of the patients

Age, months	
Median	24
Range	5-68
Male: female ratio	1/1
Total leukocyte count, 10^9/L	
Mean	12,8
SD	4,8
Hemoglobin, g/dl	
Median	8.2
Range	4,9-10
Thrombocyte count, 10^9/L	
Median	629
Range	198-1212
AST, U/L	
Median	63
Range	28-132
ALT, U/L	
Median	46
Range	5-51
GGT, mg/dl	
Median	128
Range	34-881
Bilirubin, mg/dl	
Median	0.57
Range	0.28-12.5
LDH, mg/dl	
Median	369
Range	290-646
AFP, ng/dl	
Median	237341
Range	4583-1256800
PRETEXT stage, no. of patients, (%)	
I	0
II	4 (50)
III	2 (25)
IV	4 (25)
Risk Groups, no. of patients, (%)	
High Risk	4 (50)
Standard Risk	4 (50)

Abbreviations: AST: aspartate transaminase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, LDH: lactate dehydrogenase, AFP: alpha fetoprotein

as pulmonary stenosis, secundum atrial septal defect, and dilatation of the right ventricular cavity.

Histopathological diagnoses were epithelial (foetal-embryonal) hepatoblastoma in seven patients and epithelial- mesenchymal hepatoblastoma in one patient. There were no patients with PRETEXT stage I. Half of the patients (n=4) were categorised as PRETEXT stage II, and on risk assessment, half of the patients (n=4) were in the HR group. Serum AFP levels were above 100 ng/dL at the time of diagnosis. Thrombocytosis (platelet count >600000/mm^3) was detected in 5/8 patients and >1000000/mm^3 in 2/8 patients. One patient had cholestasis at admission. The baseline features and laboratory data of the patients are shown in Table 1.

Chemotherapy was initiated in seven patients, one of whom died during chemotherapy. One patient was transferred directly to surgery because of overt tumour rupture and bleeding. Patients in the SR group received single cisplatin treatment at the beginning of therapy, and one patient in the HR group received a first cycle with cisplatin, considering her general condition. In patients in the HR and SR groups with insufficient response to chemotherapy, patients were given additional chemotherapy, including cisplatin and doxorubicin or carboplatin and doxorubicin, according to the SIOPEL IV HR protocol. Neoadjuvant chemotherapy response was evaluated in the six surviving patients, CR was not achieved in any patient: PR in four patients, PD in one patient, and SD in one patient. When PRETEXT and POSTTEXT staging were compared, disease regression was noted in 2/6 patients. Two patients had an AFP level >1000000 ng/dL at the time of diagnosis. With neoadjuvant chemotherapy, AFP decreased by more than 1 log in all patients. (Table 2)

Surgical resection could not be performed in three patients. One of them had progressive disease in interim evaluations performed during neoadjuvant chemotherapy sessions, and he was admitted to an external centre and lost to follow-up. The second patient (with CP) responded very well to chemotherapy. Because of her unsuitable general health status for surgery, she was scheduled for transarterial radioembolization, but she was lost to follow-up. When she was re-attended in the 23rd month of the follow-up, her AFP level was found to be 8.9 ng/dl (the level was 414182 ng/dl at the time of diagnosis), and the mass appeared calcified and there was no difference in size. The third patient died preoperatively during neoadjuvant chemotherapy. This patient had severe abdominal distension, cholestasis, and respiratory distress at initial presentation, received three cycles of chemotherapy, and died on the eighth day after the last chemotherapy cycle when she was transferred to the intensive care unit because of decreased urine output and deterioration of renal function. Figure 1 shows the CT images of this patient's tumour involving all segments of the liver at the time of diagnosis.

Five patients underwent hepatectomy. In the patient who underwent emergency right hepatectomy for tumour rupture, multiple small implants on the serosa and distal ileum and the peripyloric stomach and duodenum were left in place. Additional interventions that, on the one hand, would increase the risk of morbidity and mortality in the emergency situation, and on the other hand, would be philosophically non-therapeutic due to rupture, were avoided, and R2 resection was a conscious choice. The remaining four patients underwent hepatectomy, and none had postoperative residual tumours. For one patient who responded well to chemotherapy according to AFP levels (from 121 000 to 136 ng/mL) but did not exhibit any regression due to extensive calcification (present before chemotherapy), a living donor was prepared as a backup option. The tumour could be safely removed with an extended right trisectionectomy with negative margins, and transplantation was not necessary. The median (range) duration of postoperative hospitalisation was 16 (7-22) days. Adjuvant

Table 2: Patient's clinical characteristics, tumor characteristics, chemotherapy, surgery procedures, and outcomes

Patient no:	Age (m)	Sex	Characteristics and spread of the tumor at diagnosis	Pre-text (SİOPEL)	Risk Groups (SIOPEL)	Neoadjuvant chemotherapy cycles	Tumor Size 1	Tumor Size 2	AFP -1	AFP-2	Post-text	Surgery	Adjuvant Chemotherapy cycles	Current status	Follow up (months)
1	**28**	**M**	**Segment II III IV** V (1) P (1)	II	SR	CIS (4) Block A1, A2	786	42	1089000	104	II	Left extended lateral sectionectomy	Block A3	remission	12
2	27	F	Segment V VI P (1)	II	SR	(CIS) (1) Block A1, A2	208	22	414182	16.1	I	-	-	stable disease	23.2
3	5	M	Segment V VI VII VIII+I V (1) P (1) C (1)	II	SR	(CIS) (1) Block A1	491	99	>60500	2891	II	Right hepatectomy	Block A2-A3 Block B	remission	24.8
4	68	F	All segments C (1) F (1) E (1) V (3) P (2)	IV	HR	(CIS) (1) Block A1, A2	1844	-	>60500	-	-	-	None	exitus	2.2
5	21	F	Segment V VI VII VIII F (1) H (1) P (1)	II	HR	-	462+40+ 8+24	-	434506	-		Right hepatectomy + omentectomy	CIS (2) Block (A1) (A2)	remission	9
6	8	M	Segment IV VIII VII V+I V (3) P (1) M (+)	III	HR	Block A1, A2, A3	445	909	4583	130	III	-	-	unfollowed	2.1
7	30	M	Segment II III IV VII I+V VI+VIII C (1) F (1) V (3) P (2) M (+)	IV	HR	Block A1, A2, A3 Block B	877+11+4+2	46	>60500	672	III	Left Hepatectomy+ Left caudate lobectomy	Block C	remission	47
8	8	F	Segment I IV V VII VIII C (1) V (2) P (1)	III	SR	CIS (3) Block A1, A2	550	Similar tumor size increased calcification	12456800	60	III	Right extended trisectionectomy	-	remission	34.3

Abbreviations, and chemotherapy schemes:
Tumor size 1: tumor size at time of diagnosis (cm^3); Tumor size 2: tumor size immediately before surgery after neoadjuvant chemotherapy (cm^3)
Abbreviations:
AFP 1, serum alpha fetoprotein level at the time of diagnosis (ng/dL); AFP2, serum alpha fetoprotein level immediately before pre surgery after neoadjuvant chemotherapy (ng/dL); C (1), caudate lobe involvement; E (1), extrahepatic direct invasion; E2, extrahepatic peritoneal implant; F (1), multifocal tumor; H (1), tumor rupture; V (1), involvement of one hepatic vein; V(2), involvement of two hepatic veins; V(3), involvement of three hepatic veins or inferior vena cava; P (1), involvement of the right or left portal vein; P(2), involvement of main portal vein; M (1), metastases
CIS, cisplatin 80 mg /m^2/day intravenous infusion for 24 hours.
Block A1, Cisplatin 80 mg/m^2/day (D1), cisplatin 70 mg/m^2/day (D8, D15)
Doxorubicin 30 mg/m^2/day (D8, D9)
Block A2, Cisplatin 70 mg/m^2/day (D29, D36, D43)
Doxorubicin 30 mg/m^2/day (D36, D37)
Block A3: Cisplatin 70 mg/m^2/day (D57, D64)
Doxorubicin 30 mg/m^2/day (D57, D58)
Block B: Carboplatin AUC 10.6 mg/mL/min (D1,D22)
Doxorubicin 30 mg/m^2/day (D1,D2,D3,D22,D23,D24)
Block C: Carboplatin AUC 6.6 mg/mL/min (D1, D22,D43)
Doxorubicin 20 mg/m^2/day (D1,D2,D22,D23,D43,D44)
Daily dose equivalents for infants weighing 5-10 kg were as follows: Cisplatin 70 mg/m^2/ day given at 2.3 mg/kg/d; Cisplatin 80 mg/m^2/ day given at 2.7 mg/kg/d; Doxorubicin 20 mg/m^2/day given at 0.67 mg/kg/d; Doxorubicin 30 mg/m^2/day given at 1 mg/kg/d

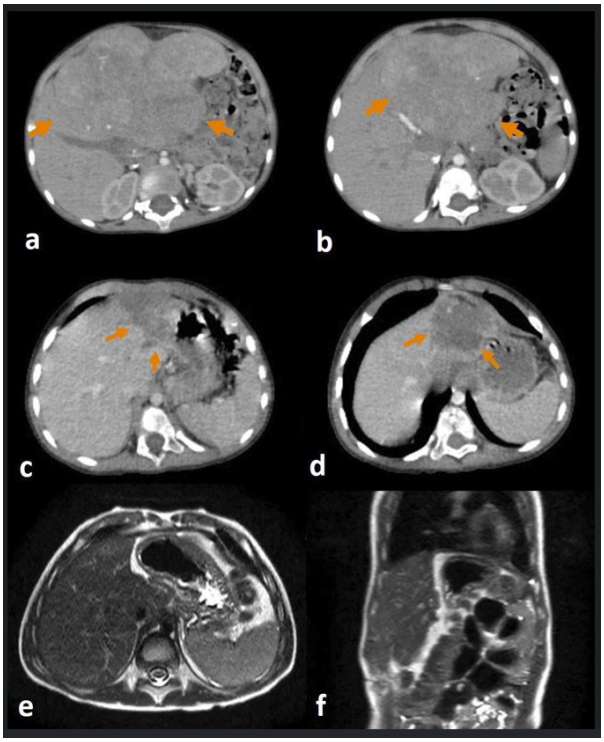

Figure 2: In a 28 month-old boy (case 1); Axial contrast-enhanced CT (a,b) reveals a lobulated, heterogeneously enhancing solid mass lesion in the liver segments II, III, and IV. Follow-up axial contrast-enhanced CT after chemotherapy (c, d) demonstrates a regressing hypodense mass lesion on the portal venous phase in the liver segments II and III. The lesion was located superiorly adjacent to the middle hepatic vein (not shown). An extended left hepatectomy was successfully performed on the patient (e, f).

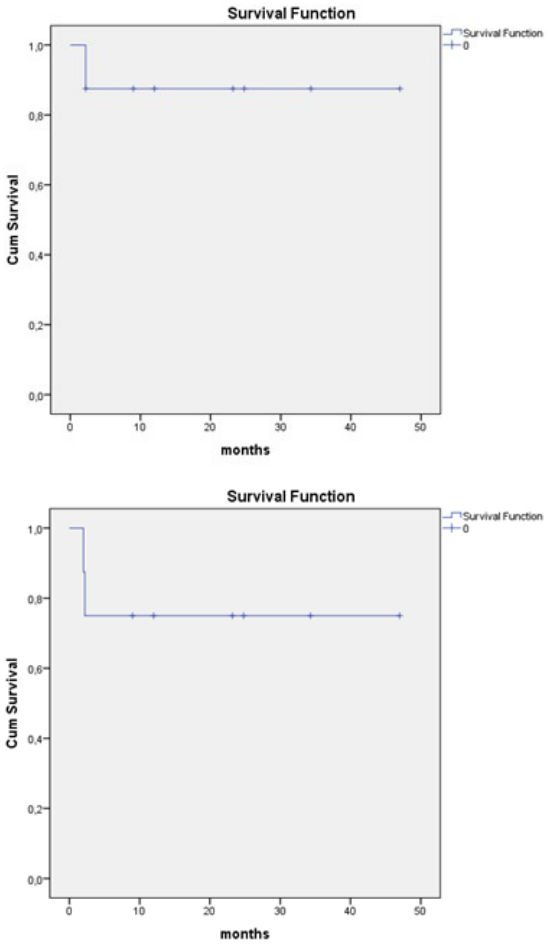

Figure 3: Kaplan-Meier curves of overall survival (OS) and event free survival (EFS) for all patients (n=8).

chemotherapy was administered to 4/5 patients. All patients survived with no evidence of disease at 9, 12, 24, and 47 months after initial diagnosis. Figure 2 shows the preoperative and postoperative CT images of the patient (patient no:1) who underwent a successful extended left hepatectomy.

The median (range) follow-up period was 18 (2-47) months. No recurrence was observed in any patient during follow-up, and the overall survival and event-free survival rates were 88% and 75%. (Figure 3a-b).

Patients received 35 chemotherapy cycles, and 19 neutropenic periods (neutrophil count <500/mm^3) were recorded. Half of the patients (4/8) had >1 and ≤4 episodes of febrile neutropenia and received inpatient intravenous broad-spectrum antibiotics. The patients received treatment with granulocyte colony-stimulating factor (G-CSF) during neutropenic periods. Except for one patient whose general condition had been poor at the time of diagnosis and who also experienced possible chemotherapy toxicity, no chemotherapy-related death or toxicity was reported.

DISCUSSION

According to the Turkish National Paediatric Cancer Registry (2009-2021), primary liver tumours constitute 1.7% (409/24080) of all childhood cancers (13). Surgery is the mainstay of treatment. However, in >60% of patients, resection may not be feasible initially because of locally advanced stage, distant metastatic tumour or large vessel infiltration. At this stage, cisplatin- and doxorubicin-based chemotherapy regimens provide tumour shrinkage in these patients, and the fibrotic and hardened tumour is easily separated from the intact liver tissue. Following neoadjuvant chemotherapy, the surgical resection rate in these patients is approximately 80%. In the remaining 20% of patients, total excision is still not possible, and liver transplantation is considered (14-16). While SIOPEL and the German Society of Paediatric Oncology and Haematology (GPOH) recommend neoadjuvant chemotherapy, surgery, and adjuvant chemotherapy in the management of these patients, some other study groups recommend surgery first and then adjuvant chemotherapy in PRETEXT I-II patients, taking staging and risk groups into consideration (17-21). Dramatic improvement in survival rates with adjuvant chemotherapy has been previously reported (9,22). Guidelines suggest that intrahepatic metastasis and hepatoblastoma recurrence from postoperative residuals are completely or partially reduced with adjuvant chemotherapy (23).

In the present study, neoadjuvant chemotherapy was initiated in all but one patient who underwent hepatectomy due to tumour rupture and bleeding, and the first cycle of

chemotherapy consisted of only cisplatin treatment in 71% of these patients. According to the results of neoadjuvant chemotherapy, the size of the mass decreased in 57% of the patients. The tumour was completely resected without the need for transplantation in 63% of the patients. No patient underwent liver transplantation. At a median follow-up of 18 months, no recurrence was observed in any patient, and OS and EFS rates were 88% and 75%. Shanmugam et al.. reported that all patients with PRETEXT stage I and II hepatoblastoma received neoadjuvant chemotherapy. The authors were able to perform complete surgical resection in 63% of these patients, and 20% of them had undergone liver transplantation. At a median follow-up of 30 months, event-free survival rates were 93% in the SR group and 60% in the HR group (24). Another study compared two patient groups diagnosed with hepatoblastoma who had and had not received neoadjuvant chemotherapy. Overall survival rates were higher in patients who received neoadjuvant chemotherapy, without any significant intergroup difference (88% vs 80%, p=0.95) (23). Küpesiz et al. presented the data of 17 hepatoblastoma patients in their study from Turkey. Surgical resection was performed in 11% of the patients at the time of diagnosis, and neoadjuvant chemotherapy was administered to all remaining patients. Of the patients who received neoadjuvant chemotherapy, 53% underwent complete resection and 40% underwent liver transplantation. The 5-year overall and disease-free survival rates were 88.9% and 80.8%, respectively (16). Another study from Turkey highlighted the better response to chemotherapy in childhood liver tumours in the last two decades and reported 5-year survival rates of patients with hepatoblastoma before and after 1990 as 32.4% and 47%, respectively (25).

Although metastatic disease may appear to have a devastating prognosis, improved outcomes can also be achieved in these patients treated with chemotherapy. In the study where the results of the SIOPEL-4 treatment regimen in HR patients were reported, good results were noted with dose-dense cisplatin-based chemotherapy and radical surgery, especially in high-risk patients with metastatic disease (63% of the patients in the study had lung metastases). All residual tumours could be completely resected in 69% of metastatic patients, and 74% were in CR at the end of treatment; the 3-year EFS and OS were 76% and 83%, respectively (26). One of the two patients in our cohort with metastatic disease was lost to follow-up, but the disease was still progressing even under chemotherapy, whereas the other patient was in remission in the 39th month following chemotherapy.

The results of hepatectomy and liver transplantation in patients with hepatoblastoma were also compared. Yu et al.. reported that hepatectomy increased 1-year OS from 42.9% to 95.7% and liver transplantation from 42.9% to 90% (p<0.0001) (23). Another study from India reported 1-, 3-, and 5-year survival rates in HR patients who had undergone liver transplantation or surgical resection as 91%, 82%, and 73% vs. 100%, 83%, and 83%, respectively. The authors reported that HR hepatoblastoma patients can be treated with excellent results in resource-challenged countries and that surgical resection is comparable to transplantation, despite being surgically challenging (27). In a study from Turkey including transplantation results of 10 patients diagnosed with hepatoblastoma, a survival rate of 90% was reported at the 21st month of follow-up (28). None of the patients included in the present study required liver transplantation. However, complete resection was possible following neoadjuvant chemotherapy.

Serum AFP is a tumour marker used in the diagnosis of hepatoblastoma, evaluation of response to treatment, and detection of recurrences after termination of treatment. AFP levels measured in response to chemotherapy have been found to be associated with prognosis, and serial monitoring of serum AFP values has been described as a cost-effective and reliable predictor of outcomes (29-30). Although, in general opinion, AFP levels <100 ng/dL or >1,000,000 ng/dL at the time of diagnosis are unfavourable prognostic factors, different results have also been reported (31-32). In our study, serum AFP levels were not below 100 ng/mL in any patient, but two patients had AFP >1,000,000 ng/mL. In terms of outcome, one of the latter two patients was disease-free at the seventh month, while the other was disease-free at the sixteenth month of follow-up. However, the exact levels of AFP were not known in some patients.

Our study had some limitations. First, this was a retrospective, single-centre study. Second, because our study was conducted in a newly established medical centre, relatively small numbers of patients were followed up, and the follow-up period was relatively short.

In conclusion, we report the results of a cohort of paediatric patients with hepatoblastoma treated by a multidisciplinary team at a newly established centre. According to our results, neoadjuvant chemotherapy is critical to shrinking tumours that are not possible for complete resection and appear in the advanced stages; therefore, liver transplantation may not be necessary in every patient. Adjuvant chemotherapy reduces the risks that may occur, especially due to positive surgical margins. Successful results have been achieved with the SIOPEL protocols. Multidisciplinary management is essential for satisfactory outcomes and high survival rates in these patients.

Ethics Committee Approval: This study was approved by the Clinical Research Ethical Committee of Giresun Training and Research Hospital (Number: KAEK-255, Date: 2023-12-04).

Informed Consent: Informed consent was obtained from the parents of the patients.

Author Contributions: Conception/Design of Study- A.B.; Data Acquisition- İ.T., F.A.B.; Data Analysis/Interpretation- A.B., M.B.; Drafting Manuscript- A.B., M.B.; Critical Revision of Manuscript- A.B., M.B.; Final Approval and Accountability- A.B., F.A.B., İ.T., M.B.

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RESEARCH ARTICLE

Examining Children's Perceptions of Covid-19 Through Drawings: A Case Control Study

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ABSTRACT

Objective: The objective of the present study was to examine the perceptions of children regarding the Covid-19 pandemic through their own drawings and to reveal the impact of the pandemic on children's psychological dynamics through an examination of their perceptions related to the pandemic and draw-and-tell interviews.

Methods: Participants were 60 children aged 6–10 years (30 children diagnosed with COVID-19 in the last six months and 30 healthy children not diagnosed with Covid-19) and their parents. Children diagnosed with COVID-19 were recruited from a state hospital, whereas children in the non-Covid-19 group were recruited from a kindergarten. The children's experiences were examined using drawings, the Children's Apperception Test (CAT), and draw-and-tell interviews. The study employed descriptive and content analysis approaches.

Results: In the descriptive analyses, it was observed that the frequency of colour use was less in the Covid-19 group ($p<.001$) while emotional difficulties such as introversion, regression, and insecurity were higher in this group than in the non-Covid-19 group ($p< .05$). Content analysis revealed that the vital threats posed by the pandemic negatively affected the mental health of all children. Additionally, the external reality experienced by children during the pandemic prevented them from accurately reflecting their actual mental functionality in their responses. Upon comprehensive evaluation of the study results, it was determined that children in both groups exhibited signs of fear, anxiety, depression, aggression, insecurity, introversion, and regression.

Conclusions: The findings of the present study may be beneficial for understanding the psychological effects of the Covid-19 pandemic on children from their own perspectives and may have implications for clinical practise regarding the support that should be offered to children. In psycho-social support interventions for children, it is of critical importance to address the anxiety that may arise from being intensely present and intertwined with their parents, as well as their sensitivity to separation and dependency.

Keywords: Children, Covid-19, Drawing, Anxiety, Depression, Psychosocial Influence

INTRODUCTION

Coronavirus (also known as the coronavirus disease 2019, or Covid-19) emerged in Wuhan, Hubei province, China, in December 2019. World Health Organisation declared a pandemic after it spread rapidly around the world. The disease is caused by the SARS-CoV-2 virus and presents as fever, cough, and difficulty in breathing. The virus is known to be highly contagious, with the potential for transmission from person to person through the release of droplets into the air during the act of talking, sneezing, or coughing. Touching a surface contaminated with the virus and then touching your eyes, mouth or nose can also spread the virus. The rapid person-to-person transmission of COVID-19, coupled with its increased risk of mortality, necessitated the urgent implementation of countermeasures (4, 5). During this period, quarantines were implemented in order to minimise the risk of transmission of the novel coronavirus (6). In accordance with the measures implemented in Turkey to combat the virus, similar to those implemented globally, workplaces and educational institutions

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suspended their operations and individuals were required to quarantine and adhere to social distancing guidelines (7). These measures have resulted in a range of psychological difficulties, in addition to social and economic challenges. The risk of being diagnosed with the disease and the anxiety and fear of contracting the disease affect children and adults alike (8). In addition, various stressors have been identified as negatively affecting the psychological health of children, including prolonged periods of home confinement, frustration, boredom, a lack of knowledge about the disease, isolation from classmates and teachers, a lack of personal space at home, and economic difficulties experienced by families (9, 10). The disruption of daily routines during the pandemic particularly affected young children. In various studies, it has been demonstrated that the majority of children have encountered difficulties in adapting to the measures implemented during this process (11-14) and have exhibited signs of depression, anxiety, and trauma, as well as feelings of fear, frustration, and helplessness (15-17).

During the COVID-19 pandemic, many parents had to reorganise their lives to work at home while caring for their children (18). When family life during the Covid-19 pandemic is examined, one of the positive effects that emerged is the increase in family communication, whereas unrest in the family, psychological problems, and problems related to education and economic conditions have been identified as negative effects (19). In addition to the stress caused by the pandemic, parental stress related to the family has led to increased levels of anxiety in children (20). Although this situation has made it difficult for children to cope with anxiety, it has also increased the internal tension of children who cannot be comforted by their mothers (21). Children whose routines have been disrupted have become even more vulnerable to the effects of the pandemic; in other words, the impact of the pandemic on school-age children at a time when they are playing, learning, and developing peer relationships has hindered the psychological progress of these children. On the other hand, during the pandemic, some parents ignored or were unaware of their children's problems because of their own psychological difficulties (22). It is believed that this situation may have increased the children's sense of loneliness and frustration during the pandemic. According to Winnicott (23), the mother's need for inclusion and care shaped the child's sense of self. The developmental environment that mothers create for their children forms the basis for the child's personality development. The child requires the presence of a caregiver to grow. The most important source of support for the child in difficult situations is the person who performs the "good enough mothering" and "holding" function, namely, the mother. Similar to Winnicot's (23) concept of "holding," Bion's (24) concept of "inclusive functions" refers to a mother who has the ability to alleviate the child's negative experiences, make sense of all these experiences, and make them manageable for the child. The mother's fulfilment of this function is important for their child's internalisation of the same function and effective use of defence mechanisms to cope with feelings of frustration, aggression and sadness caused by external reality. In this context, the absence of a caregiver or the inability of caregivers to perform such functions makes it more difficult for children to cope with negative experiences (25).

The impact of the COVID-19 pandemic on children extends beyond the psychological reactions observed in adults. Children lack the capacity to employ appropriate emotional responses and coping strategies in different situations. Consequently, when children are exposed to the same stressors as adults, they experience heightened stress and greater trauma, and the process they experience has an impact on the foundations of their personality development. The effects of the pandemic on adults have been extensively discussed in numerous studies. On the other hand, the number of studies focused on the effects of the pandemic on children is very limited, and they are largely based on descriptive findings that rely on information obtained from adults rather than children. However, it is important to examine the subjective perceptions and psychological processes of children based on the findings obtained from the children themselves. One of the most effective ways for children to express themselves and reflect on their feelings and inner world is through drawing. Children's drawings are a more robust form of expression and communication than words in understanding their inner world of children (26). As posited by Yavuzer (27), children's drawings represent a highly effective instrument for the comprehension of emotions and can be employed to gain insight into children's inner worlds in the context of psychological assessment. To mitigate and eradicate both the immediate and long-term psychological consequences of the pandemic on children, it is imperative to comprehend children's perceptions of the pandemic and assess the impact of the epidemic on children's psychological development. In accordance with this purpose, the objective is to examine the perceptions of children regarding the Covid-19 pandemic through their drawings, as well as to reveal the impact of the pandemic on children's psychological dynamics through an in-depth examination of their perceptions related to the pandemic and draw-and-tell interviews.

METHOD

Study Group

The study participants were children between the ages of 6 and 10 years and their parents. The participants were selected via the criterion sampling method, which involves selecting a sample of individuals who possess characteristics deemed relevant to the problem in question (28). The main inclusion criterion for this study was a confirmed diagnosis of COVID-19 within the last six months. In this context, the COVID-19 group consisted of 30 children diagnosed with COVID-19 and their parents, while the control group included 30 healthy children and their parents who had not been diagnosed with COVID-19. Consequently, the study included 60 children and their parents (55 mothers and 5 fathers). In addition to the aforementioned inclusion criteria, participants were required to volunteer to take part in the study, have a typically developing child in the specified age range, and complete the study questionnaire in its entirety. Children with special needs and children hospitalised

or undergoing intensive treatment due to COVID-19 were excluded from the study.

Children diagnosed with COVID-19 were recruited from a state hospital in Bursa, whereas children in the non-Covid-19 group were recruited from a kindergarten in Antalya, Türkiye. The rationale behind selecting participants from two distinct cities was to employ an accessible methodology given that data collection was during a pandemic. In accordance with the established protocols, individuals who were not affiliated with educational institutions were prohibited from entering the schools. For this reason, a researcher who was a pre-school teacher in Antalya collected data of children who were not diagnosed with COVID-19. On the other hand, other researchers, who were medical doctors working in a hospital in Bursa collected data on children diagnosed with COVID-19.

Data Collection Instruments

The study employed a variety of methodologies to examine children's experiences, including the analysis of drawings, the completion of an Individual Information Form, the administration of the Children's Apperception Test (CAT), and the conduct of draw-and-tell interviews.

Individual Information Form: The form was prepared by the researchers and administered to the parents to obtain sociodemographic information about the children and their families. Included on the form were questions about the child's age, gender, number of siblings, presence of any chronic disease other than COVID-19 among family members, and family income.

Children's Drawings: In this study, children were asked to draw two separate pictures of their families during the COVID-19 pandemic. The utilisation of family drawings is justified by their status as a projective assessment tool, which enables the examination of children's evaluations of their family relationships, self-perceptions, and emotional and interpersonal interactions within the family unit. On the other hand, family drawings were employed to determine the impact of the pandemic on the family and child, as well as the children's self-perceptions and relationships with their families. Additionally, the drawings were used to assess family dynamics during the pandemic. However, the family drawings were not analysed in isolation; rather, they were employed to assess how the children perceived their family dynamics. The drawings provide insights into the functionality and activity of the family unit from the child's perspective. They also reveal the child's perceptions and psychological defences within the family (29, 30).

Children's Apperception Test (CAT): The CAT is a projective test developed by Bellak and Sorel Bellak (31) that can be administered individually to children aged 3–10 years. The test comprises 10 cards displaying various animal images. The cards are presented to the child in a specific order, after which the child is required to create a narrative for each card. Given the inherent variability in the internal dynamics of each child, their narratives are inherently disparate. The test does not provide any definitive answers; therefore, there are no right or wrong answers. For this reason, a numerical score or scale was employed in the evaluation of the responses provided. The tester recorded the children's stories about the pictures shown and analyzes them in terms of themes such as impulse, perception, conflict, fear, and anxiety. The aim of CAT is to gain insight into the conflicts that children experience by interpreting their unconscious processes in the stories they tell, to identify the figures that are important for the child, and to evaluate the child's attitude towards the mother-father and sibling images. CAT provides the opportunity to assess the child's place in the adult world, the child's aggression in the family, their level of autonomy, and their personality. In particular, the interpretation of unconscious processes is conducted with regard to the narratives of children. Thus, the objective is to comprehend the conflicts they experience, identify significant figures for the child, and assess the child's attitude towards their mother, father, and siblings.

Draw-and-tell interviews: Once the drawings had been completed, the children were interviewed. During the interviews, the children were queried about their drawings, including the identity of the depicted subjects, the content of the figures, and the activities of their family members. Subsequently, open-ended questions were posed to determine the perspectives of children and their families on the impact of the COVID-19 pandemic. In this context, children and their parents were separately asked questions pertaining to their perceptions of the Covid-19 pandemic, their experiences of spending time together at home, and the changes they had observed in their lives since the onset of the pandemic.

Procedure

All data were collected between March 2021 and January 2022. Before the commencement of the study, ethical approval was obtained from the Humanitarian Research Ethics Committee of Akdeniz University (No: 2021A060). Subsequently, hospital management for the COVID-19 group and school management for the non-Covid-19 group were provided with information about the study, and the requisite permissions were obtained for the study to be conducted. The study included parents who volunteered to participate and had children between the ages of 6 and 10, in addition to children who agreed to participate in the study with their parents and exhibited typical development. The fundamental eligibility criterion was a diagnosis of COVID-19 for the group with COVID-19 and an absence of a diagnosis of COVID-19 for the non-COVID-19 group. The children were not subjected to a diagnostic test for the novel coronavirus. For this reason, children with at least one parent who had a positive test result and were quarantined with their families were included in the COVID-19 group. The data in this group were collected via in-person interviews with hospital staff, nurses, secretaries, physicians, or relatives who had been diagnosed with COVID-19 and their children. The interviews were conducted on specific dates after the quarantine period had elapsed. The control group consisted of parents and their children who met the inclusion criteria and were selected by teachers from the volunteer group.

Before the start of data collection, parents of the children were provided with information regarding the study content, and their consent was duly obtained. Furthermore, the children were provided with simplified information about the study, and their consent was obtained. The study was conducted in a hospital setting for the group of children with confirmed COVID-19 cases and in a quiet room at a school for the control group. In both groups, the children were initially provided with 12 coloured crayons and blank pieces of paper, after which they were asked to draw a family. Following the initial drawing, the children were then asked to depict their family during the COVID-19 pandemic. After the completion of all drawings, interviews were conducted with the children to gain their opinions on the drawings. At the conclusion of the study, CAT was administered. To avoid requiring the children and their families to visit the hospital again, CAT was administered to the children on the same day as the other parts of the process in the group experiencing the effects of the Covid-19 pandemic. The interviews with the parents in the COVID-19 group were also conducted on the same day following the completion of the administration of COVID-19 vaccines to the children. In the control group, CAT was administered to children 1 week after the initial assessment. On the other hand, CAT was administered to children in the control group 1 week after they had completed the drawings. In this group, while the administrations were conducted in person with the children at school, the interviews with the parents were conducted online on the specified dates.

In both groups, the Individual Information Form was initially administered to the parents, followed by semi-structured interviews. The duration of each parent interview was approximately half an hour. The duration of each interview with children was approximately 45 min. To prevent fatigue, the researchers ensured that the sessions did not exceed a reasonable duration. The interviews were recorded with the consent of the participants. Once the data collection process was complete, a file was created for each child. The children's drawings and responses to both the CAT and the interviews were compiled and included in the files. The forms completed by the parents and the responses provided during the interviews were also collated and included in the child's file. A code containing the child's age and gender, along with their initials, was written on the cover of each file. The researchers conducted all the administrations to parents and children in both groups.

Data Analysis

In this study, children's drawings were analysed through a process of projective interpretation, employing a descriptive and content analysis approach. The interpretation of the drawings was conducted according to a total of 24 criteria, which were divided into two categories: emotional difficulties (fear, anxiety, depression, introversion, insecurity, aggression, and regression) and drawing composition (the location of the drawing on the paper, use of an eraser, colouring, compartmentalisation, rounding, framing, proportion of figures, omission of family members, omission of body organs, and communication with the tester during the drawing). The criteria were established based on the findings of previous research on children's drawings.

In the context of this study, the drawings were interpreted in accordance with the interpretation guidelines developed by Malchiodi (32) and Yavuzer (27). According to these guidelines, children's drawings provide insight into their emotional states and psychological processes, with criteria including the part of the paper that the child primarily uses and begins drawing on. For instance, figures drawn in the upper panel of the paper may indicate a detachment from reality and features related to being in an imaginary world. The use of the lower panel of the paper is associated with introversion, inadequacy, and depression. The position of the drawings on the right side of the paper may indicate a tendency to reason, suppress emotions, and have expectations about the future. Conversely, drawings on the left may indicate independence, regression, and dependence on the mother. The excessive use of an eraser in children's drawings as well as the inclusion of excessive details and thick drawings that leave marks on the paper may indicate high anxiety. The colours that children frequently utilise when creating drawings are also regarded as reflections of their inner world and emotions. In other words, the more vitality there is in their inner world, the more clearly defined the figures or the more colourful the projection of emotions. Given that the colours chosen by children have psychological meanings, it is possible to offer different interpretations for each child. Consequently, reaching a definitive conclusion is challenging because the meanings attributed to colours may vary from one child to another. Studies have demonstrated that children with various illnesses use specific colours as an indicator of their health condition (33-35). In these studies, the most common colour used by children with various diseases was black. Furthermore, it has been observed that children with these conditions use red more frequently than other colours, as it is associated with blood.

The compartmentalisation of content may indicate a fear of separation from family and withdrawal. The presence of lines or frames around family members was an indication of their unwanted presence. If family members do not derive pleasure from their shared activities, each individual may be depicted as engaged in a separate activity, with a partitioning device present in the image. If children perceive themselves as isolated, they may draw a box or circle around themselves. The order in which family members are drawn is also significant for interpretation. According to Çelik (36), in the paintings of Turkish children, the mother is typically depicted on the left, while the father is on the right. This is thought to be due to the fact that the father is the external representative of the household. Children typically depict themselves in proximity to a person they hold in high regard, indicating a sense of closeness. If children wish to be distant from any individual, they typically depict themselves in a position that is physically distant from that person. In addition, children may also omit certain body parts from their drawings, indicating that they are either uninterested in or concerned about those areas.

For instance, the absence of hands and feet may indicate a lack of confidence, difficulty adapting to one's surroundings, helplessness, aggression, insecurity, and anxiety.

In accordance with these guidelines, three professionals with expertise in child development and psychology conducted independent analyses of the drawings. In order to ensure inter-reliability among the professionals, the results of the analyses were coded on forms and compared by experts. The codings in which experts reached 100% agreement were included in the study. The codings that differed among the experts were included in the study only after all the parties agreed upon it. The results of the analyses are presented in the Results section, accompanied by sample drawings, to facilitate understanding of the interpretations.

In the initial analysis of the results, descriptive analyses of both family drawings were conducted separately. To assess the composition of the drawings, the frequency and percentage values of the specified themes were calculated. To evaluate the characteristics associated with emotional challenges, a score was assigned for each indicator manifesting fear, anxiety, depression, introversion, insecurity, aggression, or regression. Subsequently, the total score was calculated for each emotional domain. The scores for each feature were then aggregated to obtain the total score for emotional difficulties. Descriptive analyses were conducted using SPSS 25 statistical software. Before starting the analyses, a normality test was performed to determine whether the collected data satisfied the normality hypothesis. The results indicate that the data exhibit a distribution that is consistent with a normal distribution. Therefore, a t-test was employed to compare the emotional difficulty scores of the COVID-19 and non-Covid-19 groups. Furthermore, the compositions of drawings and family drawings in the COVID-19 and non-Covid-19 groups were compared using chi-square tests. Furthermore, a descriptive frequency analysis was conducted on the sociodemographic characteristics of the children. The content analysis was conducted after the completion of the descriptive analysis. The drawings of the children were evaluated in conjunction with the findings obtained from the CAT and interviews.

RESULTS

The mean age of children in the COVID-19 group was 8.43 ± 1.28, while in the non-Covid-19 group, it was 8 ± 1.51. The sociodemographic characteristics of the children included in the study are presented in Table 1.

Table 1: *Sociodemographic characteristics of children in the COVID-19 and non-COVID-19 groups*

The Socio-Demographic Characteristics	COVID-19 Group		Non-Covid-19 Group		Total	
	n	%	n	%	n	%
Age						
6	3	10.0	7	23.3	10	16.7
7	5	16.7	5	16.7	10	16.7
8	9	30.0	6	20.0	15	25.0
9	4	13.3	5	16.7	9	15.0
10	9	30.0	7	23.3	16	16.7
Gender						
Girl	13	43.3	17	56.7	30	50.0
Boy	17	56.7	13	43.3	30	50.0
Number of siblings						
No siblings	4	13.3	-	-	4	6.7
One sibling	23	76.7	22	73.3	45	75.0
Two siblings	3	10.0	7	23.3	10	16.7
Three or more siblings	-	-	1	3.3	1	1.7
Family members with chronic diseases other than COVID-19						
Yes	7	23.3	7	23.3	14	23.3
No	23	76.7	23	78.7	46	76.7
Income level						
Low	1	3.3	4	13.3	5	8.3
Average	24	80.0	22	73.3	46	76.7
High	30	16.7	30	13.3	9	15.0

Descriptive analyses

A chi-square comparison of the compositions of the family drawings in the COVID-19 and non-Covid-19 groups is presented in Table 2.

As shown in Table 2, related to the chi-square comparison of the compositions in the family drawings in the Covid-19 and non-Covid-19 groups, only colouring (x^2=12.273, p=.001) and omitted organs (x^2=12.256, p=.028) differed in the Covid-19 and non-Covid-19 groups. According to the results, the use of colour was more frequent in the non-Covid-19 group (n=28) than in the COVID-19 group (n=16). When the omitted organs are examined, it is seen that hands (n=20) were more frequently omitted in the Covid-19 group, while feet (n=16) and arms (n=3) were frequently omitted in the non-Covid-19 group.

A chi-square comparison of the compositions of the drawings of the family during the COVID-19 pandemic in the COVID-19 and non-Covid-19 groups is presented in Table 3.

As can be seen in Table 3 regarding the comparison of the compositions of family drawings during the COVID-19 pandemic using the chi-square test, only colouring (x^2=12.381, p=.001) differed between the COVID-19 and non-Covid-19 groups in terms of composition. An examination of the results revealed that the use of colour was more frequent in the non-Covid-19 group (n=26) than in the COVID-19 group (n=13).

The comparison of emotional difficulties in family drawings between the COVID-19 and non-COVID-19 groups using the t-test is presented in Table 4.

When Table 4, which shows the results of the t-test comparison related to the emotional difficulties in the family drawings, is

Table 2: *Chi-square comparisons of compositions in family drawings between the COVID-19 and non-Covid-19 groups*

Drawing Compositions		Frequency		Chi-Square	df	p
		Covid-19	Non-Covid-19			
The location of the drawing on the paper	Left top	5	12	5.842	3	.120
	Right top	-	-			
	Centre	13	6			
	Left bottom	10	11			
	Right bottom	2	1			
Erasure	Yes	21	13	4.344	1	.067
	No	9	17			
Colouring	Yes	16	28	12.273	1	.001*
	No	14	2			
Compartmentalisation	Yes	2	5	1.456	1	.424
	No	28	25			
Rounding	Yes	1	2	.351	1	.500
	No	29	28			
Framing	Yes	2	4	.669	1	.671
	No	27	26			
Proportion of figures	Disproportionate	-	1	6.631	3	.085
	Normal	19	13			
	Large	8	7			
	Small	2	9			
Omission of family members	Yes	25	22	.884	1	.532
	No	5	8			
Omitted family members	Mother	-	1	2.967	4	.563
	Father	1	4			
	Sibling	4	5			
	Children themselves	-	1			
Omission of body organs	Yes	9	10	.077	1	1.000
	No	21	20			
Omitted organs	Hands	20	13	12.526	5	.028*
	Feet	12	16			
	Arms	1	3			
	Body	1	-			
	Legs	1	1			
	Face	-	-			
Communication with the tester during drawing	Yes	13	14	.067	1	1.000
	No	17	16			

*Note. *p<.05*

examined, introversion [$t_{(44.316)}$=2.064, p<.05] and regression [$t_{(56.470)}$=4.305, p<.01] differed in the family drawings of the Covid-19 and non-Covid-19 groups. The mean scores for introversion (2.67) and regression (1.50) of the non-Covid-19 group were higher than the mean scores of the COVID-19 group. In terms of the drawings of the family during the Covid-19 pandemic, introversion [$t_{(48.481)}$=3.373, p<.05], insecurity [$t_{(52.918)}$=2.798, p<.05] and regression [$t_{(58)}$=2.473, p<.01] differed in the family drawings of the Covid-19 and non-Covid-19 groups. In other words, the introversion (2.87), insecurity (2.67), and regression (1.50) scores of the COVID-19 group were higher than the mean scores of the non-Covid-19 group. In the drawings of the family during the pandemic, it was also seen that the total score for emotional difficulties in the Covid-19 group (17.83) was higher than that of the non-Covid-19 group [$t_{(46.488)}$=2.473, p<.05].

Content Analysis

In the content analysis, children's drawings, CAT, and interview findings were assessed according to age group.

Six-year-old children: All six-year-old children in the Covid-19 and non-Covid-19 groups demonstrated a similar understanding of social distancing, cleaning, mask wearing, lockdown, the inability to attend school, and the use of a computer at home, as evidenced by their drawings and interview responses. Upon examination of the drawings and responses provided in the interview, it became evident that the children exhibited a general awareness of the precautions that needed to be taken, including spending time with family members, and the continued necessity for distance education using technological devices such as smartphones and tablets. A common finding in CAT drawings was that children employed various manic defences against their inner tension and concerns regarding loss. Upon examination

Table 3: *Chi-square comparisons of family compositions during the COVID-19 pandemic in the COVID-19 and non-Covid-19 groups*

Drawing Compositions		Frequency		Chi-Square	df	p
		Covid-19	Non-Covid-19			
The location of the drawing on the paper	Left top	9	17	6.100	4	.192
	Right top	1	-			
	Centre	10	4			
	Left bottom	8	7			
	Right bottom	2	2			
Erasure	Yes	21	14	3.360	1	.058
	No	9	16			
Colouring	Yes	13	26	12.381	1	.001*
	No	17	4			
Compartmentalisation	Yes	18	16	.271	1	.795
	No	12	14			
Rounding	Yes	3	2	.218	1	1.000
	No	27	28			
Framing	Yes	14	7	.845	1	.438
	No	16	12			
Proportion of figures	Disproportionate	2	-	3.146	3	.370
	Normal	15	18			
	Large	10	8			
	Small	2	4			
Omission of family members	Yes	8	3	2.805	1	.179
	No	21	26			
Omitted family members	Mother	4	3	4.393	4	.355
	Father	6	8			
	Sibling	1	5			
	Children themselves	3	2			
Omission of body organs	Yes	8	3	2.805	1	.179
	No	21	26			
Omitted organs	Hands	18	15	7.168	6	.306
	Feet	15	16			
	Arms	1	-			
	Body	1	-			
	Legs	3	-			
	Face	1	-			
Communication with the tester during drawing	Yes	15	16	.067	1	1.000
	No	15	14			

*Note. *p<.05*

of the CAT and interview responses, it was determined that children exhibited difficulty in processing negative emotions and aggression, resulting in the use of secondary-level defence mechanisms such as suppression, rationalisation, and isolation. The results revealed a prevalence of depressive findings, with most children expressing concerns about loss and harm. When the drawings, CAT, and interview responses were examined together, it was determined that the children in both groups had difficulties in psychologically processing negative emotions such as aggression and resorted to defence mechanisms such as suppression, rationalisation and isolation. Findings related to insecurity, depression, and anxiety were seen to be prominent, especially in the drawings of the COVID-19 group (See Figure 1).

Figure 1 depicts a family during the pandemic, with a 6-year-old girl belonging to the COVID-19 group. It can be observed that the use of colour is notably constrained. Organs such as the hands, arms, and feet are absent, the bodies are angular, and the lines are dashed. The virus figure is particularly noticeable.

Seven-year-old children: In the drawings of the COVID-19 group, findings related to Covid-19, such as the virus, disinfectant, and drawings of sick family members, were observed with regularity. The absence of hands and feet was a common feature in most drawings, in both the COVID-19 and non-Covid-19 groups. It was observed that some paintings exhibited thick lines. It is also notable that a significant proportion of the drawings in the COVID-19 group depicted stick figures (see Figure 2). In the initial drawings of the Covid-19 group, while the family was depicted together engaged in an activity, it was observed that the number of family members decreased in the drawings during the pandemic. In these drawings, the

Table 4: *Comparison of Emotional Difficulties in Family Drawings between the COVID-19 and Non-Covid-19 Group*

Drawing	Emotions	COVID-19		Non-Covid-19		t	df	p
		M	SD	M	SD			
Family	Fear	2.17	0.87	2.37	0.89	-.878	58	.384
	Anxiety	2.23	1.33	2.37	0.93	-.450	58	.654
	Depression	2.97	1.50	2.83	1.29	.370	58	.713
	Introversion	2.43	1.79	2.67	0.96	2.064	44.316	.045*
	Insecurity	2.13	1.46	1.70	0.84	1.413	46.271	.164
	Aggression	1.07	0.94	1.40	0.72	-1.534	58	.130
	Regression	1.27	0.52	1.50	0.61	4.305	56.470	<.01**
	Total	14.27	6.44	12.97	3.85	.949	47.338	.347
Family during the COVID-19 pandemic	Fear	3.53	1.14	3.40	1.04	.475	58	.637
	Anxiety	2.77	1.57	2.47	1.07	.864	58	.391
	Depression	3.27	1.31	3.00	1.31	.370	58	.713
	Introversion	2.87	1.66	1.67	1.03	3.373	48.481	.001*
	Insecurity	2.67	1.37	1.37	0.10	2.798	52.918	.007*
	Aggression	1.23	0.86	1.63	0.81	-1.858	58	.068
	Regression	1.50	0.63	0.83	0.59	4.224	58	<.01**
	Total	17.83	5.81	14.80	3.37	2.473	46.488	.017*

*Note.*p<.05, **p<.01*

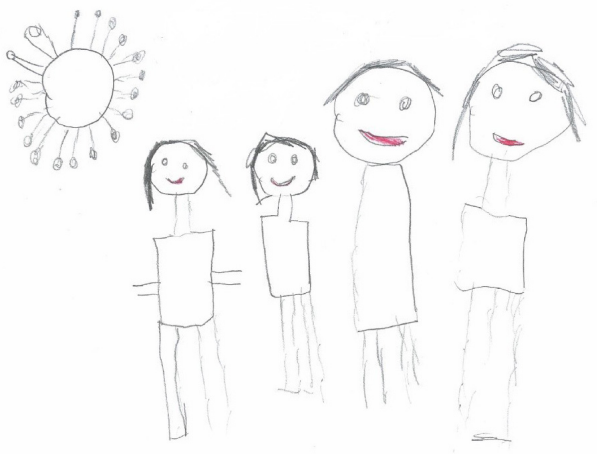

Figure 1: Drawing of a 6-year-old girl with COVID-19 diagnosis

boundaries between spaces were highlighted, and family members were depicted in different rooms. In particular, it was observed that the father was absent from some compositions. Upon examination of the CAT results, it became evident that the impact of the pandemic was evident, as evidenced by the incorporation of masks into the narratives. In the COVID-19 group, the capacity to be alone was diminished, and loneliness emerged as a pervasive emotion. The pandemic occurred when children should have been engaged in activities that facilitate learning, formation of new relationships, participation in activities, and contact with their social environment. The development of cognitive and social capacities marked this period of life. While this age group was expected to disassociate from edipal objects, observations in CAT stories indicated that this disassociation was not sufficient. A lack of clarity emerged regarding the delineation of roles, the protection of boundaries became challenging, sexual curiosity intensified, and the suppression mechanism employed proved ineffective. This age group, which is at the beginning of the formation of the upper self, experienced difficulty in controlling their impulses.

In both the CAT and drawings, duality was observed rather than individuation. A synthesis of the findings from the drawing, CAT, and interview revealed an increase in the need for protection and feelings of loneliness, while the capacity to be alone decreased. In all cases, the findings indicated a regression in mental development, a lack of sufficient functionality of the suppression mechanism that should be activated at this age, and the use of both the suppression mechanism and defence of denial. Although these observations were consistent across both groups, they were more prominent in the COVID-19 group.

Figure 2 depicts a family during the pandemic, specifically a 7-year-old boy in the COVID-19 group. The drawing exhibit compartmentalisation, excessive detailing, the omission of family members, and limited use of colour.

Eight-year-old children: Upon examination of the content of the drawings, it was observed that the symbolic expressions exhibited a notable decline, while more depressive themes became increasingly prevalent in the group depicting the impact of the Covid-19 pandemic. In both groups, while families were depicted together in nature in the initial drawings, it was observed that the number of people decreased or family members were distant from each other in the family drawings during the pandemic

Figure 2: Drawing of a 7-year-old boy with COVID-19 diagnosis

period (see Figure 3). This finding was observed in both groups. In the drawings depicting the pandemic, it was observed that children in the COVID-19 group either completely removed their parents from the drawings or drew them in a distant place. In the CAT story context, the use of the suppression defence, which is specific to the latency period, is a prominent feature. Responses in which the suppression defence was not effective also emerged in CAT cards. It can be postulated that the vividness of the impulsive world, which is still close to the edipal period, is the reason for this. The emergence of "fear" themes that were incongruous with the latent content on the cards, followed by responses in which the perception was distorted, and animal name answers pointing to the problematic of bonding were also noteworthy. In the case of the mother cards, responses indicating a lack of ability to approach the mother and oral satisfaction also indicated that inclusion was difficult. On the other hand, the undoing defence was frequently observed in interviews and narratives about the aftermath of the pandemic. When the CAT responses of children and their initial family drawings were examined together, it became evident that themes of aggression and depression were present. A commonality between the CAT and pandemic drawings was the perception of the outside world as dangerous and the inability of children to manage such perceptions. The pandemic drawings of the COVID-19 group exhibited some common characteristics, including the depiction of houses, viruses, drawings with thick contours, and the omission or erasure of hands. In the CAT responses of this age group, the names of animals were frequently used to indicate the theme of fear and attachment problems. When all drawings, CAT, and interview results were assessed together, themes related to the difficulties experienced while staying together in the house and the need for separation as a defence were observed in both groups. In particular, the COVID-19 group exhibited difficulties in coping with the realities of the external world, which can be attributed to the superego.

Figure 3 shows an 8-year-old girl's drawing of her family during the pandemic. In the drawing, several features are evident, including the use of the lower portion of the page for drawing, the compartmentalisation of the image, incorporation of brown and black colours, and application of thick contours.

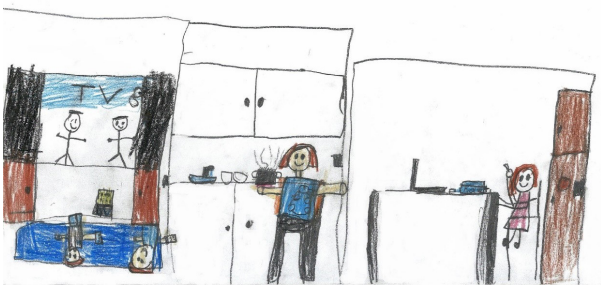

Figure 3: Drawing of a 8-year-old girl without COVID-19 diagnosis

Nine-year-old children: The drawings of both the COVID-19 and non-Covid-19 groups exhibited common features, such as virus, masks, and patients. In many drawings in both groups, the hands and feet were absent, and the drawings were in the form of stick figures (see Figure 4). However, this finding was more evident in the COVID-19 group. Findings related to the search for strong parental figures who offer support and protection, difficulty in distinguishing between the self and the other, and vulnerability to the dangers of the outside world were observed in both groups.

In the drawings of the Covid-19 group, the high degree of emotional distress manifested in the form of a strong desire for care, inclusion, and protection, as well as an increased concern about being harmed, was particularly noteworthy. The majority of drawings in this group included observations on the intensity of conflict within the family and the difficulty of maintaining familial cohesion. Narratives that attempted to understand the circumstances and difficulties involved in articulating their experiences were notable. In contrast to the COVID-19 group, in which almost all eyes were drawn as dots, the non-Covid-19 group included detailed depictions of eyes. Upon evaluation of the CAT results, it was observed that the boundaries of privacy were exceeded. This resulted in a concomitant increase in sexual curiosity and guilt, as well as a high desire for care and protection, accompanied by an increase in anxiety about being harmed. Additionally, denial and manic defences were employed. In the cards, it was observed that children exhibited a desire to distance themselves from their parents and a desire for separation according to their age. However, as evidenced by the responses, this separation was not fully achieved. When the family drawings, CAT, and interview findings were assessed together, it was observed that children in both groups resorted to defences such as denial and suppression.

Figure 4 depicts the family during the pandemic, including a 9-year-old boy in the COVID-19 group. The lack of quality and richness in the drawing, the omission of the hands and feet, the mask, and the absence of colour use are notable features.

Ten-year-old children: In both groups, while the family drawings typically commenced with the depiction of the same-sex parent, who served as the object of identification for children during this developmental period, it was notable that pandemic drawings commenced with the inclusion of

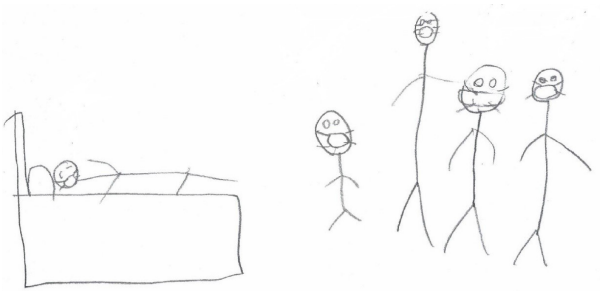

Figure 4: Drawing of a 9-year-old boy with COVID-19 diagnosis

spatial elements such as beds, carpets, televisions, computers, and armchairs. In addition, elements of the pandemic, such as masks, disinfectants, and viruses, were also included in the drawings. While domestic themes were prevalent in the narratives of the Covid-19 group, in the non-Covid-19 group, the majority of drawings depicted external elements such as the sky, trees, and activities like going on a picnic or going for a walk (Figure 5). In the COVID-19 pandemic drawings, objects that created barriers between family members were common, and family members were mostly shown in different rooms. The initial family drawings depicted family members in a linear configuration. However, in the pandemic drawings, some family members are depicted in restricted areas, while others are depicted in distant and separate areas.

In both groups, family members were depicted and represented according to generational differences. In the protocols, the perception of a dangerous outside world and concerns about being harmed were identified as common findings. In the CAT responses of both groups, the aggression and fear of harm were observed at expected levels in children in this age group. Responses indicated that children in the latency period exhibited more aggressive fantasies and concerns about harm than anticipated, and suppression was ineffective in most protocols. It was observed that the consequences of the pandemic, including illness and death, served as an external reality that increased early aggressive fantasies and concerns about harm. Furthermore, the expected quality of suppression from the latency period was not realised. When the drawings, CAT, and interview responses were collectively assessed, it was observed that the children employed various defence mechanisms, including suppression, regression, and rationalisation, in response to internal concerns and conflicts. In particular, regression was identified as a common phenomenon in the pandemic drawings of children in both groups, and in the CAT and interview results. However, this finding was more evident in the COVID-19 group. It is noteworthy that the regression findings increased in the drawings of the pandemic and the CAT results for the non-Covid-19 group.

Figure 5 depicts the family of a 10-year-old girl in the non-Covid-19 group during the pandemic. The image depicts a family engaged in an outdoor activity. Additionally, it is noteworthy that the figures are positioned in the lower left corner of the page and are depicted in miniature.

Figure 5: Drawing of a 10-year-old girl without COVID-19 diagnosis

DISCUSSION

The study investigated children's perceptions of COVID-19 through an analysis of their drawings. To achieve this, a descriptive and content analysis approach was employed. In the descriptive analysis, the use of colour in the COVID-19 group was less diverse and varied than that in the control group. These findings are consistent with those of previous studies on children with various diseases. In a study by Dolidze et al. (37), in which the drawings of 293 sick children were examined, the authors found that children used significantly fewer colours than controls. In other words, most children commonly used a single colour for their entire drawing. In some studies, the use of red was found to be associated with pain (38, 39) and black with depression (36). In this context, it is hypothesised that the use of fewer colours, as well as the use of colours such as black and red, may indicate physical symptoms such as pain, sadness, and depression in individuals diagnosed with Covid-19. While the omission of hands was an intriguing finding in the family drawings of the COVID-19 group, it was observed that the omission of feet was more prevalent in the non-Covid-19 group. The absence of hands in most drawings may be associated with difficulties in intervening, lack of control, and a sense of powerlessness. The absence of feet in the drawings may indicate a perceived lack of control over one's circumstances, which necessitates external support (40). On the other hand, a reduction in the use of colour and the exclusion of organs in pandemic drawings were observed in both groups. It is postulated that this phenomenon can be attributed to the impact of the pandemic on children in both groups.

When the emotional difficulties depicted in the drawings of the two groups were compared, introversion and regression were observed as common findings. However, the emotional difficulties observed in the pandemic drawings of the COVID-19 group were found to be more pronounced than those observed in the non-Covid-19 group. It is believed that restrictions imposed during the pandemic may have contributed to increased parental dependence and introversion. Furthermore, concerns about the pandemic, in addition to dependence and introversion, may have prompted children to frequently employ

regression as a coping mechanism. When the drawings were evaluated in general, a notable observation was that regression, manifested by a reduction in detail and quality, was a prevalent phenomenon in the majority of children in both groups, particularly in the pandemic drawings. Regression, which refers to a child's inability to display a skill they have acquired and return to more juvenile behaviours instead of the behaviours expected from their age, is defined as a psychological defence and considered to be one of the most evident consequences of sickness and hospitalisation on children (41). Some findings in the literature support this theory and the findings of this study. For example, in a study conducted by Erdem Atak et al. (35), which aimed to examine the psychological states of 31 hospitalised children and their perceptions of illness through drawings, findings related to emotional difficulties such as anxiety, depression, and regression were found to be common features. In another study conducted by Tiryaki et al., (42), which aimed to examine the Covid-19 perceptions of 17 children aged between 7 and 11 years, it was found that the majority of the children included in the study had high levels of anxiety. In this context, regression is thought to have occurred as a common finding in children during the pandemic period, regardless of whether they had COVID-19 or not.

In the content analysis of the study, when the family drawings, CAT, and interview responses were assessed together according to age group, it was found that the threats to life and health caused by the pandemic had an impact on the mental functioning of all children. Furthermore, it was determined that the children could not reflect their true mental functioning levels in their responses due to the external reality they were experiencing. During the lockdowns, children were required to remain at home with their parents, which resulted in social isolation and limited social contact. The loss of everyday peer-to-peer contact and mobility has created difficulties for children. In this new reality, isolation has emerged as a significant risk factor for the deterioration of psychological processes (43). The fact that most images, particularly in the 7-9 age group, depicted stick figures may indicate that the mental processes of the children were not as advanced as expected of their age. The observation that children predominantly depicted a closed mouth in a straight line may mean that they were reticent in expressing themselves or encountered difficulties in expressing their emotions. The pandemic had a profound impact on children at a developmental stage when they should be engaged in activities such as learning, forming new friendships, participating in activities, and maintaining contact with their social environment. While this age group is expected to exhibit psychological differentiation from their parents, it is believed that this separation was not sufficient. Roles within the family were mixed, sexual curiosity increased, and the mechanism, including suppression, was not sufficiently functional during lockdowns with parents during the pandemic. It is expected that this age group will require social interaction with their peers. In this context, it can be posited that the absence of parents in drawings may indicate a need for emotional distance in the children's mental world. The presence of houses, viruses and omitted hands in pandemic drawings may indicate a lack of perceived safety despite external dangers. Drawing with thick contours may reveal aggressive impulses in an attempt to establish a boundary with the outside world and to protect oneself. Furthermore, the removal of images of the mother and father from the drawings and some detailed house drawings may indicate that children have a greater need for inclusion and protection during the pandemic. The age of 8-9 is a critical period in the development of the superego, which is defined as a structure that creates the psychological principles, values, and rules of the personality and emerges with feelings of guilt in daily life. In this age period, the superego becomes more compatible with the expectations of the external world (44). However, it is believed that children had difficulty controlling their impulses and the superego, which is the reflection of the "holding" caregivers, appeared to be not fully internalised, resulting in difficulties in coping with the expectations of the external world.

In terms of psychosexual development, children at this age are expected to engage in learning processes, new activities, and peer relationships by starting school after the impulsivity of the edipal period (45). However, the reality of the pandemic was experienced instead. From this perspective, maintaining physical proximity with parents who were already challenging to disengage mentally may have impeded the children's capacity for psychological growth. These findings indicate the use of suppression defences specific to the latency period. However, the CAT cards demonstrate that these defences are not sufficiently functional. It can be proposed that the impulsivity resulting from continued proximity to the edipal period may have contributed to this dysfunctionality, as evidenced by the CAT responses, which revealed persistence of the children's edipal conflicts. In addition, in this age group, a tendency to rely on concrete and sensory objects in drawings was observed, and CAT responses were observed with some frequency. The behaviours of talking to the practitioner and asking questions during the drawing process may indicate a need for approval, dependence, and support.

In the drawings of the 10-year-old, the aspects of the pandemic, including masks, disinfectants, and viruses, were evident. These details may indicate that the source of internal conflict is the risk of disease caused by the pandemic. In addition, the excessive presence of house figures in the second drawing may indicate a shift in psychological investment and conflict from the external world, such as school and friends, to home and domestic relations. In addition to the elements of the external environment, such as the sky and trees, the narratives depicted in the drawings, including those of going on a picnic and going for a walk, reflect the children's desire to reconnect with the outside world that they were deprived of. In the non-Covid-19 group, the initial drawings depicted scenes from the natural environment, whereas the subsequent images typically portrayed scenes from the domestic setting. The emotional difficulties were more evident in the domestic drawings. Similar findings were obtained in a study that examined lockdown drawings of 151 children (46). In the study, while family members were depicted together and in a positive light

in the children's outdoor drawings, sadness and loneliness were prominent in the lockdown drawings. This finding, which was also evident in this study, may be indicative of the emotional ambivalence of children in the non-Covid-19 group towards the lockdown.

The CAT responses of both groups demonstrated that the mother images exhibited inclusive functions. With the exception of one protocol, a nurturing and positive love object projection was observed. However, it was observed that this "holding" figure was not sufficiently internalised, and the children could not utilise effective coping strategies. This may be attributed to the caregivers' inability to provide a secure environment and to cope with their own anxiety. The fact that the parents were infected with COVID-19 may have prevented the successful fulfilment of this "holding" function. In this context, it was observed that the suppression of negative emotions and inner conflicts was unsuccessful in most protocols. Duan et al. (47) observed that children affected by disasters are unable to develop appropriate emotions and coping techniques. Consequently, children were more negatively affected by the COVID-19 pandemic and experienced greater stress than adults. In parallel with this suggestion, this study observed that the consequences of the pandemic on morbidity and mortality increased early aggressive fantasies and concerns about harm. Consequently, expected suppression did not occur in this age group. When the CAT and interview responses were assessed together, it was observed that the desire to be cared for and protected was high, and parental dependency and sensitivity to separation from the parents increased. In the context of the pandemic, children were prohibited from physically attending schools, which represented the only opportunity for them to develop as autonomous individuals. Conversely, there was an observed increase in instances of parental intervention and control over personal space. As a result, it can be argued that the intense co-existence and intertwining with parents increased the anxiety of both parental intervention and dependency. It was also observed that children in both the COVID-19 and non-Covid-19 groups in this age group frequently employed the regression defence mechanism in CAT. The observed increase in dependency and expressed concerns and sensitivity about separation may be indications of regression as a defence in children in both groups.

This study is significant in that it presents the psychological effects of the COVID-19 pandemic on children from their own perspectives. In light of the fact that the generation that has grown up with the global COVID-19 pandemic will continue to experience its effects for an extended period, it is anticipated that this study will retain its relevance in the future and have significant implications. However, besides the strengths of the study, some limitations of the study should also be mentioned. First, the data for this study were collected from two different cities. The cities of Antalya and Bursa are both metropolitan cities in different regions. It was assumed that the pandemic conditions did not differ between the two cities and that they were similar in terms of sociodemographic characteristics. However, selecting children diagnosed with COVID-19 from a hospital in Bursa and children not diagnosed with COVID-19 from a kindergarten in Antalya may have introduced bias or error into the study. Therefore, it is essential to exercise caution when interpreting the results of comparisons between children with and without a confirmed diagnosis of COVID-19. In addition, it should be noted that these findings may not be solely attributable to the effects of the pandemic. The drawings made by the children and their responses in the CAT and interviews may have been influenced by a number of factors, including the severity of their experiences with the pandemic, their socio-economic status during the pandemic, their parents' reactions to the pandemic, and the child's general personality characteristics. It is recommended that the aforementioned confounding factors be considered when interpreting the responses. It is also recommended that further studies on the long-term effects of the pandemic be conducted in the future, with a particular focus on controlling the effects of these confounding factors.

CONCLUSION

In conclusion, this study offers valuable insights into the psychological impact of the COVID-19 pandemic on children, based on their experiences. The findings may have clinical implications for the provision of appropriate support to children to help them cope with the psychological effects of the pandemic. In psycho-social support interventions for children, it is crucial to address the anxiety that may arise from being intensely present and intertwined with their parents, as well as their sensitivity to separation and dependency. It is equally important to facilitate self-development by encouraging separation from parents and peer relationships. The fact that the mortality rates of children during the pandemic were lower than that of adults and that the clinical picture was milder in children has led to a reduced number of reported paediatric patients compared with adults; therefore, the difficulties experienced by children during the outbreak were the subjects of less concern compared with adults. However, it is believed that the psychological effects of the pandemic will be more severe and longer lasting in children than in adults, and the developmental effects of the pandemic in children may become more evident in the long run. For this reason, it is of great importance to monitor the development of children affected by the COVID-19 pandemic. It is imperative for mental health professionals to consider the long-term consequences of the pandemic when assessing psychological difficulties in children. Similarly, devising functional support mechanisms for children and their families, with a particular focus on online psychological support. Furthermore, it is vital to maintain these mechanisms in an active state and to update them in accordance with the identified needs of the affected population during the pandemic.

Ethics Committee Approval: This study was approved by the ethics committee of Humanitarian Research Ethics Committee of Akdeniz University (No: 2021A060).

Informed Consent: Written consent was obtained from the participants.

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RESEARCH ARTICLE

Effect of the COVID-19 Pandemic on Mothers' Breastfeeding Status

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ABSTRACT

Objective: This study was conducted descriptively to evaluate the impact of the COVID-19 pandemic on the breastfeeding status of mothers with infants aged 0-24 months.

Methods: The study was conducted at the Ankara City Hospital in the breastfeeding support/relactation clinic and mother-infant bonding service between December 2021 and May 2022. A sample of 511 mothers who applied to the clinics mentioned during the study period, agreed to participate in the research, and met the research criteria was formed. Research data were collected using a Descriptive Data Form.

Results: The average age of the mothers was 28±4.7 (18-44), and 51.66% had a caesarian delivery. Approximately 54.41% of the mothers were university graduates. During the pandemic, it was determined that 13.0% of the mothers experienced breastfeeding-related problems, and all mothers who experienced problems hesitated to go to the hospital. It was found that 12.14% of the mothers had COVID-19 during pregnancy, and 69.70% of the mothers who had COVID-19 did not continue to breastfeed. The rate of mothers who stated that they did not receive any information about breastfeeding during the COVID-19 period was 57.6%, and the rate of mothers who had breastfeeding problems after quarantine was 17.50%. During their hospital stay due to COVID-19, it was determined that 48.7% of the mothers breastfed their babies, 41.0% fed expressed breast milk and formula,and 10.3% fed only formula.

Conclusions: It was observed that mothers needed breastfeeding counselling during the pandemic.

Keywords: Pandemic, breastfeeding, breastmilk

INTRODUCTION

The coronavirus infection (SARS-CoV-2) that started in Wuhan, China, in December 2019 has rapidly spread and caused infections in countries around the world. By the end of January, with the spread of COVID-19 to 19 countries, the World Health Organisation (WHO) declared it a "Public Health Emergency of International Concern." Because of the millions of deaths caused by COVID-19 worldwide, it was declared a pandemic in March 2020 (1).

As COVID-19 spread worldwide, countries prevented the spread of the infection through measures such as maintaining social distance and personal isolation at home. Flexibilities in public and private sector work arrangements, such as staggered shifts and remote work, were introduced. Schools switched to distance learning, and meetings and events were cancelled. These measures have changed the daily flow of individual and societal life and have affected all members of society in various ways (1-3).

the COVID-19 pandemic has also affected the breastfeeding process of mothers, just as it has affected every aspect of life. Studies have reported no transmission of the virus through breastfeeding. However, the spread and alarming level of this infection has caused fear and panic among mothers. Mothers have been unable to attend prenatal classes, receive breastfeeding education, or even seek healthcare facilities for their breastfeeding difficulties after childbirth (4-8).

Policies regarding breastfeeding after SARS-CoV-2 infection have varied among pregnant women. The World Health Organisation (WHO) recommended breastfeeding during the SARS-CoV-2 infection outbreak. It emphasised that breastfeeding mothers wearing masks and paying attention to breast hygiene before breastfeeding and hand washing before and after touching the baby would be sufficient (9). Studies have not found the COVID-19 virus in amniotic fluid, cord blood, placenta, or breast milk (7,10,11). The SARSCoV-2 virus is transmitted through close contact between individuals and droplets. It can also be transmitted through the enteral route, conjunctival mucosa, or

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contaminated surfaces (12). Therefore, transmission through droplets between the mother and baby should be carefully considered. However, because of the novelty of the infection, there is limited research on this topic (13).

Although it has been published in the literature that the SARS-CoV-2 virus does not pass through breast milk, it is known that the risk of transmission through contact and droplet infection, as well as the restrictions imposed in social life and anxieties, have affected the breastfeeding period. Therefore, this study was conducted as a descriptive study to evaluate the effects of the COVID-19 pandemic on the breastfeeding status of mothers with infants aged 0-24 months.

METHODS AND PROCEDURES

Study Type
The study was conducted as a descriptive research.

The Research Question
Has breastfeeding of mothers' babies been negatively affected during the COVID-19 pandemic?

Location and Time of the Study
The research was conducted at Ankara City Hospital in the Maternal Support Breastfeeding/Relactation Polyclinic (Breastfeeding/Relactation Support Clinic) and the Mother-Baby Bonding Unit between December 2021 and May 2022.

Population and Sample
The study population consisted of a total of 4.498 mothers who applied to Ankara City Hospital Mother Support Breastfeeding/ Relaxation Polyclinic (2.102) and Mother-Baby Bonding Unit (2.396) between January and December 2020. The required sample size was calculated to be a minimum of 380 using a formula commonly used when the population is known. A sample of 511 mothers with children aged 0-24 months, who applied to the specified clinics during the study period, agreed to participate in the research, and met the research criteria was included in the study.

Inclusion Criteria:

- Mothers with children aged 0-24 months,
- Proficient in Turkish
- No communication problems
- Mothers who agreed to participate in the study.

Data Collection Tools Descriptive Data Form
The form prepared by the researchers consists of 48 questions, following the literature. The form includes four questions related to the sociodemographic characteristics of the mothers, eight questions related to the birth characteristics of the mother and the baby, 17 questions related to the mothers' breastfeeding status during pregnancy and after childbirth, seven questions related to the mothers' knowledge about infant feeding, and 12 questions related to the examination of the mothers' characteristics regarding breastfeeding and feeding their babies during the COVID-19 pandemic.

Implementation of the Research
The research data were collected by the researcher either through face-to-face interviews or using the Google Forms survey tool, based on the mothers' preferences. The approximate time to complete the survey form was 10-15 minutes.

Ethical Considerations of the Research
Written permission was obtained from the Zonguldak Bülent Ecevit University Human Research Ethics Committee (25.11.2021/105435) and the Ankara Provincial Health Directorate to conduct the research. Before starting the study, the participants were provided with information about the purpose and research plan, and their consent was obtained. The names of the participants were not used. At the beginning of the Google Forms survey, a voluntary consent form was included. After providing their consent on the form, participants proceeded to answer the survey questions.

Data Analysis
SPSS 16.0 software was used for data analysis. For the analysis of the data obtained in the study, frequencies and percentages were used for categorical variables. Descriptive statistics such as minimum and maximum scores, mean, standard deviation, and median values were used to identify continuous variables.

Limitations and Challenges Encountered in this Research
The results obtained from this study are limited to the time in which the study was conducted and the responses provided by the participants to the data collection tools used in the study.

RESULTS

The mean age of the participating mothers was found to be 28.34±4.72 years, with a range of 18.00-44.00. The average gestational age of the infants was 38.96±3.42 weeks, with a range of 32.00-42.00. It was determined that mothers breastfed their infants until an average age of 12.22±3.81 months, with a range of 0.00-24.00 months. When examining the educational status of the mothers, it was found that 30.33% (n=155) had completed high school education and 54.41% (n=278) had completed university education (Table 1).

Table 1: Distribution of maternal and infant socio-demographic characteristics (n=511)

Characteristic	Mean±SD Median (Min-Max)	
Mother's age	28.34±4.72 27.00 (18.00-44.00)	
Gestational age	38.96±3.42 38.00 (32.00-42.00)	
Postpartum age (in months)	12.22±3.81 (00.00-24.00)	
Breastfeeding duration (in months)	16.44±4.62 (00.00-24.00)	
Mother's educational status	**n**	**%**
Literate	2	
Primary school	12	0.39
Middle school	64	2.35
High school	155	12.52 30.33
University	278	54.41
Total	**511**	**100.0**

Approximately 48.34% (n=247) of the mothers gave birth through spontaneous vaginal birth, and

72.02% (n=368) gave birth at a state hospital. Among the mothers who had a caesarian section, 20.71% (n=54) stated that their first childbirth was also a caesarian section, 12.85% (n=34) chose caesarian section due to pelvic constriction, and 15.47% (n=41) chose caesarian section due to health problems (Table 2).

During the pandemic, 13.0% (n=66) of the mothers experienced breastfeeding-related problems, and all of these mothers hesitated to go to the hospital. Among the 66 mothers who expressed hesitation, 82.9% (n=54) stated that they hesitated to go to the hospital because of the fear of contracting COVID-19 (Table 3).

It has been determined that most mothers (87.86% (n=423)) do not contract COVID-19 disease. In addition, 76.13% (n=66) of the participants stated that they had contracted COVID19 after childbirth. During the COVID-19 period, 79.54% (n=70) of the participating mothers reported that they were not hospitalised, while 20.46% (n=18) stated that they were hospitalised (Table 4).

Among the mothers who had COVID-19 after childbirth, 30.30% (n=20) continued to breastfeed. Among the mothers who continued breastfeeding, 71.21% (n=47) stated that they did not feel anxious while breastfeeding, whereas 28.79% (n=19) expressed anxiety. When asked about the duration of not being able to breastfeed due to COVID-19 infection, 22.72% (n=15) stated 14 days, 10.61% (n=7) stated 15 days, 3.03% (n=2) stated 20 days, and 1.52% (n=1) stated 21 days. It was determined that 42.4% (n=28) of the mothers sought information on how breastfeeding should be done during COVID-19, and among those who sought information, 86.5% (n=32) received it from healthcare professionals, 5.41% (n=2) from the internet, and 5.41% (n=2) from social media (Table 4).

After the quarantine period, 82.50% (n=33) of the mothers reported no problems related to breastfeeding, whereas

Table 2: Distribution of birth-related characteristics of mother and baby (n=511)

Characteristic		n	%
The type of birth	Spontaneous vaginal birth Caesarian section	247 264	48.34 51.66
Place of birth	At home Public hospital Private hospital University hospital	1 368 127 15	0.20 72.02 24.85 2.93
Reason for caesarian Delivery (n=264)	Recurrent caesarian section Mother's health problems Pelvic stenosis Inverted position Foetal bradycardia Decreased amniotic fluid Makrozomi Before preeclampsia Multiple pregnancy Cordent tanglement Early birth Intrauterine growth restriction	54 41 34 32 23 16 23 13 9 8 8 3	20.71 15.47 12.85 12.07 8.57 5.86 857 4.97 3.5 3.12 3.12 1.17

Table 3: Distribution of mothers' characteristics during the COVID-19 pandemic period (n=511)

Characteristic		n	%
Having problems with breast feeding	Yes No	66 445	13.0 87.0
Do not hesitate to go to the hospital (n=66)*	Yes No	66 0	13.0 0.0
If yes, why	Due to fear, COVID-19 transmission Because of the crowd Due to curfew	54 6 6	82.9 8.55 8.55
Presence of COVID-19 disease	I didn't pass I spent	423 88	87.86 12.14
COVID-19 time to get sick (n=88)	Post-natal During pregnancy	66 22	76.13 23.87
COVID-19 hospital treatment (n=88)	Yes No	18 70	20.46 79.54

17.50% (n=7) reported experiencing problems. When asked about the problems, they mentioned the baby being hospitalised due to a COVID-19 infection, a decrease in the mother's milk supply leading to the baby not latching, and the baby getting used to bottle feeding in the hospital and refusing to breastfeed (Table 4).

48.7% (n=19) of the mothers breastfed their babies, and 41.0% (n=16) fed them with expressed breast milk and formula. While feeding their babies, 52.8% (n=19) of the mothers used a

Syringe, 22.2% (n=8) used a bottle, and 16.7% (n=6) used a spoon (Table 4).

Table 4: Distribution of mothers' characteristics of breastfeeding their babies during the COVID-19 pandemic period (n=66)

Characteristic		n	%
Breastfeeding during COVID-19 disease	Yes No	20 46	30.30 69.70
Anxiety during breastfeeding	Yes No	20 46	30.30 69.70
Duration of not breastfeeding during COVID-19 disease	1 day 6 days 14 days 15 days 20 days 21 days	10 12 14 7 2 1	15.15 18.18 22.72 10.61 3.03 1.51
Breastfeeding information during	Yes No	28 38	42.4 57.6
Where is the information obtained?	Health workers TV Internet Social media	32 1 2 2	86.5 2.7 5.41 5.41
Having trouble breastfeeding after quarantine	Yes No	33 7	82.5 17.5
If yes, the problem	My baby was hospitalised due to COVID-19 My baby was also in intensive care, my milk decreased, he started not to breastfeed Refused the breast	2 2 3	28.67 28.67 42.66
Baby's diet*	Breast-feeding Formula Breastmilk+formula	19 4 16	48.7 10.3 41.0

*Mothers gave more than one answer

DISCUSSION

It is a well-known fact that breastfeeding has many benefits for both the other and the baby's health, and economically. Therefore, breast milk is considered the ideal food for babies, ranking first. The most suitable way to obtain and maintain breast milk is through breastfeeding. Breastfeeding is a feeding method that promotes the healthy physical and psychological development of babies. WHO has emphasised the importance of exclusive breastfeeding for the first six months of a baby's life to ensure their healthy growth and development (14,15).

Despite the known benefits of breast milk, uncertainties during the pandemic can cause mothers to experience different concerns. During the pandemic, the transmission routes of the SARS-CoV-2 virus,the uncertainty surrounding breastfeeding, and the disruption of breastfeeding counselling, health education, and healthcare services are believed to have contributed to the problematic completion of this process for mothers (16).

SARS-CoV-2 infection becomes more critical during sensitive periods of women's lives, such as pregnancy, childbirth, and the postpartum period. It was determined that 87.86% of mothers did not have COVID-19. Among 88 mothers who had COVID-19, 76.13% were infected after childbirth and 23.87% were infected during pregnancy. In a study examining the anxiety and depression caused by COVID-19 in pregnant women, 137 pregnant women were examined, and 44.5% of them tested positive for COVID-19 (17). The low rate of COVID-19 infection among mothers in the study is thought to be due to their concerns about protecting their own and their babies' health during the pandemic, which may have led them to comply with lockdown measures, hygiene, and distancing rules.

The study found that 20.45% of mothers with COVID-19 were hospitalised. In a study by Pereira et al. (2020) conducted on 22 mothers, 11 of them (50%) were symptomatic, and four of all patients received COVID-19 treatment before delivery, whereas four received treatment in the post partum period(18). In another study conducted in Turkey, it was reported that 8.2% of pregnant women diagnosed with COVID-19 received

hospital treatment, whereas 91.8% received home treatment (17). Pregnancy is a physiological condition that makes women more susceptible to respiratory complications from viral infections. The physiological changes in the immune and cardiopulmonary systems of pregnant women increase the risk of developing more severe diseases if they become infected with respiratory viruses. In a study that examined 1918 cases during the influenza pandemic, the mortality rate was reported as 26% in the general population, whereas it was 37% among pregnant women (19). Although studies are still ongoing, there is currently no specific treatment proven to be effective and reliable for COVID-19 infection (20,21,22).

The study found that 69.70% of mothers who had COVID-19 after pregnancy did not continue to breastfeed. The management of breastfeeding varied at the beginning of the COVID-19 pandemic. While there are publications supporting breastfeeding during the COVID-19 pandemic (23,24), there are also publications suggesting not breastfeeding during this period (25,26). As COVID-19 continued, new and updated opinions were formed by investigating the management and transmission routes of the disease. Initially, the prevailing views endorsed the separation of the mother and baby during the breastfeeding period, but later it was recommended to support breastfeeding (27,28).The transmission routes of SARSCoV-2 in infected newborns have been investigated, but no study has shown that breastfeeding (29-31). It is believed that the differences in breastfeeding during the pandemic may be due to the uncertainty of this period and the fact that COVID-19 is a newly discovered virus. Among mothers who continued breastfeeding during the quarantine period, 28.79% expressed anxiety while breastfeeding. The pandemic has caused parental anxiety regarding breastfeeding and breast milk (32,33). Pregnancy and the postpartum period are emotionally sensitive times characterised by intense emotions. Pregnant and postpartum women experience greater anxiety during the pandemic because they are concerned not only about their own health but also about the health of their infants, whom they are responsible for nurturing, breastfeeding, and protecting (34). Studies have indicated an increased likelihood of depressive symptoms and anxiety in women during pregnancy and the postpartum period during COVID-19 (35,36). The rapid progression of the COVID-19 pandemic has led to uncertainties in pregnancy and breastfeeding. this uncertainty may be the reason for the anxiety experienced by breastfeeding mothers. In a study conducted during the COVID-19 pandemic, it was observed that 13.0% of mothers encountered problems related to breastfeeding, and all mothers experiencing problems hesitated to go to the hospital. Among mothers expressing hesitation, 82.90% stated that they were reluctant to go to the hospital because of concerns about contracting COVID-19. Similarly, studies have found that individuals hesitated to enter healthcare facilities and postponed hospital appointments during the COVID-19 pandemic (37-42). In a study by Nazik et al. (2020) that evaluated the impact of the COVID-19 pandemic on prenatal care services received by pregnant women, it was found that women received fewer prenatal care services compared with the pre-pandemic period, with more than half of the pregnant women receiving fewer than four prenatal care visits during their pregnancies (38). Yildiz et al. (2021) conducted a retrospective cross-sectional study and found that women made fewer prenatal visits in 2020, during the ongoing pandemic, compared with 2018 and 2019 (39). Wu et al. (2020) found that women feared hospital visits during the pandemic, and more than half of the women cancelled or postponed their hospital appointments (40). Lockdown measures during the pandemic and people's fear of contracting the disease have disrupted routine healthcare cheque-ups.

After the quarantine period, 82.50% of mothers reported not having any problems related to breastfeeding, whereas 17.50% reported experiencing problems. The identified problem incl udedthebabybeinghospitalizedduetoaSARS-CoV-2infection,a decrease in the mother's milk supply, resulting in the baby not latching or refusing to breastfeed. Although there is no evidence of breastfeeding transmission of SARS-CoV-2 (7), the evidence regarding the safety of breastfeeding in infants of suspected or confirmed COVID-19 mothers is limited because of horizontal transmission. In addition, breastfeeding is not recommended for mothers undergoing ongoing treatment because it is yet unknown whether antiviral drugs pass into breast milk (20). It has been reported that if a subsequent COVID-19 test of suspected or confirmed COVID-19 mothers yields a negative result, the infants can be breastfed (26). Problems such as a decrease in the mother's milk supply and the baby not latching or refusing to breastfeed may have occurred due to the interruption of breastfeeding in infants of suspected or confirmed COVID-19 mothers.

CONCLUSION-SUGGESTIONS

Continuing the breastfeeding process, which is vital for the baby, should not be interrupted during the COVID-19 pandemic that has affected the entire world. The newborn should continue to receive breast milk in the most effective way by following all hygiene rules specified during the COVID-19 period.

Health professionals, especially healthcare professionals, should provide detailed information and support to mothers about breastfeeding their babies and ensure the continuation of breastfeeding during the pandemic.

Women should be supported with evidence-based practises and their confidence should not be undermined in making decisions for themselves and their babies. Safe information regarding the COVID-19 pandemic should be provided to mothers and expectant mothers through evidence-based practises, official guidelines, and national and international recommendations. Especially during the pandemic, midwives should advocate natural childbirth for women. It is recommended to plan advanced scientific research in this regard.

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RESEARCH ARTICLE

Investigation of Withdrawal, Controlling Difficulty, Disorder in Functionality, and Social Isolation in Problematic Internet Use in Adolescents

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ABSTRACT

Objective: Problematic internet usage, a significant and growing global problem in adolescents, is associated with the risk of future behavioural problems. This research explains the relationships between the factors affecting problematic Internet use among adolescents using the Structural Equation Modelling technique.

Methods: The study group comprised 756 adolescents studying in different schools. Descriptive statistics of the variables, confirmatory factor analysis, and structural equation modelling were used in the data analysis.

Results: A positive relationship was obtained between deprivation and control difficulty, impairment of functioning, and social isolation. It was found that the effect of impairment of functioning and social isolation on control difficulty was statistically significant. In addition, the study determined that the relationship between impairment of functioning and social Isolation was significant. When the coefficients related to path analysis were tested, it was found that the effect of impairment of functioning on deprivation was not statistically significant, whereas the effect of control difficulty and social isolation on deprivation was statistically significant.

Conclusions: There is a positive relationship between deprivation and problematic internet use, control difficulty, and social isolation, and a negative relationship with impaired functioning. In addition, it was concluded that the model created for the path analysis showed a good fit.

Keywords: Adolescents, Problematic Internet Use, Behaviour, Mental Health

INTRODUCTION

The Internet is a tool that makes significant contributions to people's lives by enabling people to access new information quickly and to correspond with other people quickly, and its use has increased at an incredible rate. Features such as mobile applications, education and entertainment opportunities, access to social media, and the mobile Internet make Internet use indispensable in daily life. Accessibility of the internet can lead adolescents to spend more time than they originally planned. For these reasons, the buildup in internet use brings with it important problems and dangers, as well as many benefits. Despite the many benefits that the Internet provides to individuals and society, a new problem area, namely excessive abuse of the Internet, has emerged. One of them is Problematic internet usage (PIU), that is, internet addiction (1).

Problematic internet use, a significant and growing global problem among adolescents, is associated with the risk of future behavioural problems (2). Problematic internet use was identified as features such as the inability to prevent the desire to use the internet excessively, the emergence of physical, mental, and social problems due to excessive use of the internet and computer, the emergence of excessive irritability and aggression when not connected to the internet, the inability to control the time waste on the internet, the increasing time waste on the internet, increasing and worsening of the individual's work and social life (3, 4). Problematic internet usage is considered a syndrome with many dimensions, consisting of behavioural and cognitive symptoms that produce negative results in social, professional, and academic aspects (4).

Although problems in the use of the internet, which is an important area of life in people's lives, can be observed at any

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age, the biggest risk group is young people between the ages of 12-18. Adolescents mostly use the internet for different purposes, such as doing their homework, communicating with their friends in their spare time, searching for answers to issues that interest them, and realising themselves in a place where they feel strong. When studies on adolescents are conducted, it is observed that the social development of children who use the internet for a long time and spend their time playing games is significantly retarded. These adolescents' self-confidence was low, their anxiety level was high, and an increase in aggressive behaviours was observed. While the useful use of the Internet provides many opportunities for adolescents to develop, its problematic use can also bring many risks to adolescents' lives (5).

This study is designed to address the relationships between the factors affecting the PIU of students in two schools determined in the centre of Istanbul, with the Structural Equation Modelling (SEM).

METHODS

Study Design and Participants

A cross-sectional study design was used in the study. We conducted the research between September 2019 and February 2020 in two public secondary schools with the students during the study period. There is still no clear way to determine sample size in structural equation modelling (6). The minimum sample size targeted for sufficient sample size in the study was calculated using the most common sampling formula. Aslan & Yazıcı (2016) reported a risky internet usage prevalence rate of 20.9%, focusing on the young population in Turkey (7), and a sample size of 391 students was calculated. The sample size was larger than that estimated in our study. Following approval from the ethics committee, necessary permissions were obtained from the Turkish Ministry of National Education and the Governorship of Istanbul. The inclusion criteria for this study group: age between 12 and 18 years, ability to read and write in Turkish, and who did not have a diagnosis of intellectual disability, and provision of consent from parents with a form for students before (completed the informed consent form). Adolescents with any diagnosed diseases and without consent forms were also excluded from the study. The questionnaires were explained to the students by the researchers. After students were informed that their participation was voluntary and they could leave without reason, a personal information form and internet addiction scale were distributed to the students during class hours as hard copies. The questionnaires were filled out by the students and were collected by the researchers. A total of 770 students from both schools agreed to participate in the study; however, 14 questionnaires were deemed missing or unsuitable.

Data Collection Tools

In the study; The Personal Information Form and Internet Addiction Scale were used.

Personal Information Form: The researchers developed this form consisting of open-ended and closed-ended questions from the works of literatüre (3, 5). Participants answered questions regarding self-identified gender, age, school, family type, parental work status, and Internet presence at home.

Internet Addiction Scale (IAS): This scale created for the Turkish Population. Turkish validity and reliability of the IAS were made. The IAS is comprised of 35 items scored using a five-point Likert-type scale, and each content is scored between 0 and 5. The IAS has four sub-factors as identified "Withdrawal", "Controlling difficulty", "Disorder in Functionality" and "Social Isolation". The Cronbach's alpha coefficient was calculated to be 0.94. In our research, exploratory factor analysis (EFA) for structural validity and confirmatory factor analysis (CFA) to examine the accuracy of factor structure were used. The total signified variance in the IAS is 47,463% (8). In this research, the total internet addiction scale had good internal consistency. The Cronbach's alpha level was α=0.93.

Statistical Analysis

While measuring the findings obtained in this study, SPSS 22.0 and LISREL 8.7 Statistics packages were used. The sociodemographic characteristics of the adolescents were analysed descriptively. Confirmatory factor analysis and validity and reliability tests were performed on the answers provided by the adolescents to the questions on the Internet Addiction scale, and the validity and reliability of the scale were provided. Then, the hypotheses of the model designated by the structural equation modelling were tested. SEM is a comprehensive statistical paradigm that allows testing hypotheses regarding the relationships between observed and covered variables (9). SEM includes many statistics and considers more than one parameter at the decision stage; thus, it is expressed as a powerful quantitative analysis (12). The results were evaluated at a 95% confidence and at $p<0.05$ significance.

We hypothesise that problematic internet usage is correlated with withdrawal as follows:

H1a: Functionality disorder affects Withdrawal in adolescents.

H1b: Controlling difficulty affects Withdrawal in adolescents.

H1c: Social isolation affects withdrawal in adolescents.

Ethical Considerations

In order to carry out the research, ethics committee confirmation was acquired because of the meeting of the Non-Interventional Research Ethics Committee of Bezmialem Vakif University, which was dated 07/11/2019 and numbered 17848. Following confirmation by the ethics committee, necessary permissions were obtained from the Turkish Ministry of National Education and the Governorship of Istanbul to apply the questionnaire to the students. This study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Demographic Characteristics

The demographic characteristics of the adolescents are presented in Table 1. The mean age of the adolescents who participated in the research was 16.01±1.15 years. It was found

that 63.0% of the students were male, their family types were nuclear families (81.3%, n= 755), mothers of 73.1% of students, and fathers of 7.9% of students were not working. In addition, it was determined that most respondents (83.9%) used the Internet at home (Table 1).

Table 1: Descriptive statistics on participants

Gender	**n**	**(%)**
Girl	279	37.0
Boy	476	63.0
Total	755	100.0
Family Type	**n**	**(%)**
Nuclear family	614	81.3
Extended family	116	15.4
Split family	25	3.3
Total	755	100.0
Internet presence in the home	**n**	**(%)**
Yes	634	83.9
No	122	16.1
Total	756	100.0
Age	**mean**	**S.D.**
	16.01	1.158

Confirmatory Factor Analysis (CFA) Results for the Internet Addiction Scale

Before moving on to the parameter estimations of the model, we checked whether the variables provided the normality assumption to determine an appropriate estimation. The results of single and multiple normality tests of the data were examined. According to these results, all factors used in our model were analysed using the Shapiro-Wilk normality test, and it was shown that the input was not fit for distribution using the Henze-Zirkler multiple test (HZ=1.406; $p<0.05$). While parameter estimation is performed in CFA and SEM, it is important to determine whether the variables satisfy the assumption of normality. In this case, before starting the analysis of the models, the Henze-Zirkler multiple normality test for the variables was used. Because of the Henze-Zirkler Multiple normality tests, it was found that the variables were not fit for normal distribution (HZ=1.406; $p<0.05$). As a result, the "Diagonal Weighted Least Squares Method" was used for parameter estimation in CFA and SEM.

When the reliability analysis values of the scale are examined; CFA and Cronbach's alpha internal consistency ($\alpha=0.93$) are suitable for the IAS. In addition, the standardised coefficient worths of the 4 sub-dimensions of the Internet addiction scale are statistically important ($p<0.05$). Since Cronbach's Alpha coefficient values are ≥ 0.80, the scale is highly reliable (13) (Table 2). With all test results of the SEM installed in Fig. 1, it is seen that the research model fit index values of the installed model, values were found as Chi-square/df (cmin/df) (3.96)), GFI (0.98), CFI (0.98), NNFI (0.97), NFI (0.97), SRMR (0.064), and RMSEA (0.063). They were acceptable and the results were within the limits of a good fit (10). Thus, the values indicate that the data support the model.

Table 2: Cronbach's alpha values

Factor	**Cronbach Alpha**
Withdrawal	0.857
Controlling Difficulty	0.843
Disorder in Functionality	0.840
Social Isolation	0.867

Results of Structural Equation Model Analysis

Exploring correlations between withdrawal, controlling difficulty, disorder in functionality, and social isolation, withdrawal showed a positively high intensity or moderately positive correlation with other research variables ($p<0.05$) (Table 3).

Table 3: Correlations among the study variables

Factor	**Mean**	**SD**	**1**	**2**	**3**	**4**
1. Withdrawal	29.97	8.93	1.000	0.642*	0.570*	0.495*
2. Controlling Difficulty	22.35	7.83		1.000	0.681*	0.510*
3. Disorder in Functionality	15.18	6.04			1.000	0.621*
4. Social Isolation	12.35	5.63				1.000

*p<0.05 SD: Std. Deviation

Fig. 1 and Table 4 indicate the results of the SEM analysis installed to demonstrate how much PIU is linked to withdrawal, controlling difficulty, functional disorder, and social Isolation in adolescents. The equations for the coefficients in Table 4 are given below.

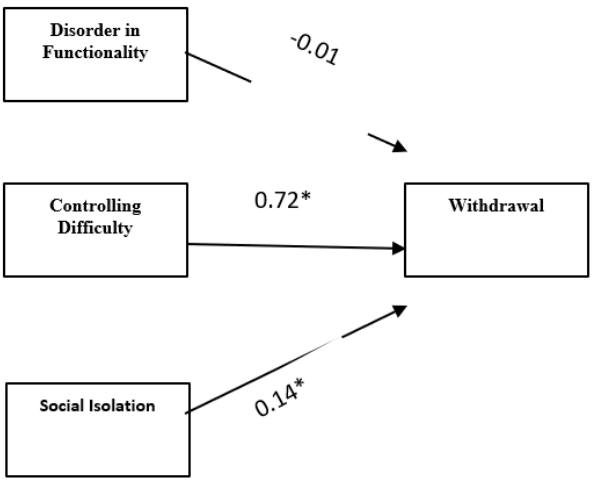

Figure 1: SEM Path diagram.

Withdrawal=0.01*Disorder in Functionality+0.51* Controlling difficulty+0.10*Social isolation (1)

When the coefficients related to Equation (1) are examined in the table, it was observed that controlling difficulty and social isolation significantly affect withdrawal statistically ($p<0.05$). However, functional disorder did not significantly affect withdrawal ($p >0.05$). The R2 values of the factors are expected to exceed 0.50, which is the acceptable limit (14). The coefficient of determination was R2 = 0.65 in our study. It was observed that 65% of the changes in controlling difficulty and social isolation that explained withdrawal from PIU in adolescents were explained by this model (Table 4). In this case, although the H1a hypothesis is not supported, the H2a and H3a hypotheses are supported.

Table 4: Path Factors in the SEM

Path	Unstandardised β	Standardised β	S.E	t	p	R^2
DF → Withdrawal	-0.01	-0.01	0.075	-0.07	0.944	
CD → Withdrawal	0.51	0.72	0.061	8.30	0.000*	0.65
SI → Withdrawal	0.10	0.14	0.046	2.12	0.034*	

*p<0,05 DF: Disorder in Functionality CD: Controlling Difficulty SI: Social Isolation S.E.: Standard Error

DISCUSSION

The internet has become a necessary need in people's lives; however, PIU can have a negative effect, especially on adolescents. There is a lack of studies determining many correlates of PIU worldwide (13). This research aimed to investigate the factors affecting PIU among adolescents undergoing SEM.

The average age of the adolescents participating in the research was similar to that of the studies conducted with adolescents (14, 15). Regarding PIU, males were associated with more PIU symptoms. Male gender was positively related to behavioural problems. In line with previous research, symptoms related to PIU were found to be effective because of the high number of male students in our study (16,17,18). According to the data of the Turkish Statistical Institute (TSI) regarding internet usage in Turkey, while it was 72.9% for persons in the 16-74 age group in 2018, it increased to 87.1% in 2023. In addition, in 2023, it was observed that 97.5% of homes have access to the internet. This is an indication of how widespread the Internet is across the country, as in our study (19). Accessing the Internet at home and living in a nuclear family affect students, which may lead to social isolation or other problems, such as stress, anxiety, depression, and social isolation (20,21). This situation turns into PIU, as observed in our study.

Measurement models were created for the scale used in this study, and the subdimensions that explain each concept meaningfully and the expressions in these dimensions were determined by CFA. For the test results of the Internet addiction CFA Model, it can be concluded that the CFA model is steady and significant because its values are acceptable and are within the limits of good agreement (12, 22). The Cronbach's Alpha values were ≥ 0.80 and have a high degree towards one. In this case, the Internet addiction scale is valid and reliable, according to the CFA and Cronbach's alpha coefficient values. Thus, the answers given by the adolescents to the questions were found to be generalisable (11, 23).

PIU is as important an addiction as substance addiction; it can be considered a group of behavioural problems (26) or behavioural control problems (25). Addictive behaviours to relieve mental effects can be used as coping strategies however these behavioural models are more difficult to handle in the long term (20). It has been stated that withdrawal, which is the most serious emotion among addicted students, is due to problematic internet usage (8). In a similar study, it was observed that as the daily internet usage time increased, the withdrawal, controlling difficulty, and disorder scores in functionality increased statistically (26). This study showed a positive relationship between withdrawal and controlling difficulty, functional disorder, and social isolation. Furthermore, it was determined that the variables controlling difficulty and social isolation in internet usage affected withdrawal. H1b and H1c were accepted in line with this result. Based on these results, it can be concluded that withdrawal is common in the presence of problematic internet use. Withdrawal affects the negative impact of internet use on daily routines, which can lead to isolation from normal life, breakdown of daily routines and roles, and thus sociable and academic problems (12, 27, 28). It was found in our study that controlling difficulty, which was affected by the disorder in functionality and social isolation, and the relationship between the disorder in functionality and social isolation was also significant. Consistent with earlier research, the finding that controlling difficulty supports these links for PIU symptoms demonstrates that students experience control difficulties (25, 26). In addition, disorder in functionality did not have a significant effect on withdrawal; thus, H1a was rejected. In PIU, the cause of functional disorder may be loss of control, poor physical health, and social isolation. Asocial adolescents may have a higher problem with control disorders than others (2). More time spent on the internet can increase social isolation. Studies on the psychological profiles of Internet users have found a relationship between social anxiety, social isolation, and PIU (29,30,31). Morahan-Martin (1999) and Kim, LaRose, and Peng (2009) also emphasised the relationship that excessive use of the Internet leads to social isolation (32, 33). Social isolation rates are higher among individuals who are not addicted. People with Internet addiction also refuse other communications and work because they are too busy with the Internet (34, 35). Similarly, et al. (1998) reported that internet-addicted students delay their daily important communication with their families and friends because they spend excessive time online (36). Social isolation in internet addiction is also related to a lack of social skills and shyness. People who lack social skills in daily life use online activities to socialise, and this

may cause PIU and create negative life experiences that can lead to unhappiness (32). The inability of virtual social support provided via the Internet to turn into permanent relationships in real life continues to increase social problems and create a vicious circle (37).

CONCLUSION

It can be seen that there is a restricted amount of studies that determine the variables that predict PIU, and recent studies have led to quantitative methods. From this perspective, we believe there is a need for qualitative research to determine the variables that have the power to predict problematic internet use (38). In addition, experimental and longitudinal studies with different variables are useful in the future. Adolescents generally prefer the internet for various reasons in terms of their desire for acceptance and relationship building. Therefore, it is necessary to create environments where adolescents can meet their social needs in real life instead of the virtual world and increase their social skills. Therefore, especially from adolescents, families, teachers, and field experts, opportunities should be created for children to express their feelings. It may be beneficial for mental health professionals and school nurses to focus on awareness-raising activities with young people to prevent this addiction.

Limitations

There are some limitations in this study, which is aimed to fill the gap in this field, as in previous studies, since there are few studies in the literature in which SEM analysis is performed using macro data. Although there are many factors associated with withdrawal, hypotheses were established based on studies conducted with adolescents, dependent independent variables were determined in this direction, and the relationship between them was analysed with the help of SEM. In the research prepared for this purpose, 756 usable data were obtained. Therefore, the findings are valid only for the research scope and cannot be generalised. The addiction level of individuals' internet use was defined using only a scale, and no clinical interviews were conducted.

Ethics Committee Approval: This study was approved by the ethics committee of Non-Interventional Research Ethics Committee of Bezmialem Vakif University, which was dated 07/11/2019 and numbered 17848.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study-M.B.S. ; Data Acquisition- S.B.; Data Analysis/Interpretation- S.B., M.B.S.; Drafting Manuscript- M.B.S., S.B.; Critical Revision of Manuscript- S.B., M.B.S. ; Final Approval and Accountability- M.B.S., S.B.

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RESEARCH ARTICLE

Impact of Maternal Nutrient Consumption on Human Milk Macro Nutrient Composition: A Cross-Sectional Study

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ABSTRACT

Objective: To increase the production of human milk, mothers must have an adequate, balanced, and healthy diet. This study investigated the effect of maternal food consumption on the macronutrient composition of breast milk.

Methods: This cross-sectional descriptive study included 46 mothers. Food consumption and breast milk content of mothers were analysed on postnatal days 1, 5, and 15. Macro and micronutrient values consumed by the mothers were evaluated using the BeBis programme. Breast milk was analysed with Miris HMATM device.

Results: In repeated measurements until mature milk was secreted (days 1st, 5th and 15th), the amount of carbohydrates and fat in breast milk gradually increased, whereas the amount of protein decreased. A significant negative correlation was observed between the amount of carbohydrates and energy consumed by mothers on the 5th day and the amount of breast milk proteins. There was a significant positive correlation between the amount of carbohydrates in the mothers' food consumption on the 15th day and the amount of carbohydrates in their breast milk.

Conclusions: The effect of nutrient consumption of the mothers in the study group in the last 24 h on the macronutrient levels of breast milk was evaluated. It was observed that maternal food consumption affected the macronutrient composition of breast milk during the three follow-ups. In repeated measurements, the nutrients consumed by the mothers affected the breast milk (transitional milk, and mature milk) content.

Keywords: Nutritional Consumption, Human Milk, Macronutrient, Composition

INTRODUCTION

With human milk, the most natural food for infants, all the nutrients needed by infants in the first months of life are met, almost half of them are met in the following six months, and nearly one-third of them are met until the age of two years (1). It is known that human milk differs in terms of its macro and micronutrient content; each mother's human milk is unique to her infant, and its content changes according to the infant's needs (2,3).

Changes in the content, structure, and amount of human milk, especially in the first two weeks after birth. The amount of colostrum secreted within the first 5 days after birth is less than that of mature milk, but it differs in terms of its richness in immunological compounds and proteins (4-7). Human milk contains many bioactive compounds and micronutrients (vitamins, minerals, and trace elements) necessary for infant growth and development (2,3). The composition and amount of human milk are affected by factors such as the lactation period, maternal nutrition, and genetic characteristics, duration and frequency of human feeding, the time between two human feeding sessions, human feeding technique, and the gestational and postnatal age of the infant (8-11).

A mother should have an adequate, balanced, and healthy diet to increase milk production (12,13). The nutrients that mothers consume change human milk production and composition (13,14).Nutritional patterns of mothers during the postpartum period vary in different geographies and countries. Furthermore, the socioeconomic status variable also showed differences in increasing the consumption of basic nutrients, especially during the postpartum period. Purchasing power and cultural differences can cause changes in the most consumed

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foods. Some studies have indicated that the nutritional content of human milk is affected by many factors (2-5,10-12). There are only a few studies in the literature that investigated the impact of maternal nutritional status on human milk content. The aim of this study was to examine the impact of maternal nutritional status on the content of human milk.

MATERIAL AND METHODS

Study Design

This cross-sectional descriptive study was conducted in the neonatal unit of a university hospital in Istanbul. This study aimed to examine the relationship between newborn characteristics and human milk nutritional content. The STROBE Statement was used in the design, planning, implementation, and reporting of the cross-sectional, descriptive study.

Sample size and inclusion criteria

The study population consisted of mothers who gave birth in the hospital where the data were collected, and the sample consisted of 46 mothers who met the selection criteria. The minimum sample size required for the study was calculated via power analysis. In this context, the required minimum sample size was found to be 34 under the assumption of a 5% first-type error margin, one-to-one group distribution rate, 80% study power, and therefore a 20% second-type error, and an effect size of 0.50 according to a double-sided hypothesis and Cohen's standard effect sizes. To increase the study power, it was planned to include 50 mothers in the sample. When the data collection process was terminated, four mothers were excluded from the sample because there were missing data, and 46 mothers comprised the study sample.

Sample selection criteria

a) Singleton pregnancy b) the infant's gestational age is >35 weeks

Exclusion criteria

b) The presence of a congenital anomaly in the newborn that will prevent the infant's sucking (cleft palate, cleft lip, etc.) b) the presence of a disease in the mother that may affect human milk content (diabetes, hypertension, hypothyroidism, etc.) c) The presence of an infectious disease in the mother, such as HIV, hepatitis B, hepatitis C, etc., known to be transmitted through human milk d) the mother's not coming to the 5th-day and 15th-day postpartum controls.

Data collection tools

The data were obtained using a data collection form (including socio-demographic and obstetric characteristics of mothers and infants, nutritional habits of the mother) prepared by the researchers as a result of the literature review (14,15). The mothers were asked to record the nutrients they consumed in the last 24 h on the day they came for control. The BeBis programme (16) was used to calculate the mothers' nutritional consumption. Human milk content was analysed using a Miris HMATM device. Human milk samples for analysis were obtained using the hand-express method. Samples were taken as foremilk before the human feeding session.

BeBis Programme: The programme analyzes macro and micronutrients when the nutritional consumption during the day and their amounts are entered into the programme. A researcher entered the nutrients into the BeBis programme.

Miris HMATM (Uppsala, Sweden): The energy and macronutrients (protein, fat, and carbohydrate) in human milk were analysed using the Miris HMATM device. The Miris HMATM device was certified by the International Organisation for Standardisation (ISO 9622: 1999). The Miris HMATM analyzes 2 mL of human milk in approximately 2 min. Milk was taken from the mother's wand into a syringe and analysed using the Miris HMATM device. The Miris HMATM device calibration and cleaning were performed as recommended by the researcher on the day of data collection.

Intervention and data collection

Mothers who gave vaginal birth and their infants are discharged after 24 h if there are no health problems, and those born by caesarean section are discharged after 48 h. The initial control of newborns after discharge is performed within 72 h, according to the requirements. A researcher filled out the data collection form by conducting face-to-face interviews with the mothers.

Mothers who met the selection criteria were included in the study. 2 ml milk samples were collected from the right human at least 2 h after human feeding within the first 24 h after delivery, on the 5th and 15th days after delivery, analysed with Miris HTAM. Macronutrient content values were obtained approximately 3 min after the human milk sample was placed into the analyser. The mothers recorded the nutrients and amounts consumed within 24 h and brought the records with them when arriving at control.

Data analysis

The data obtained from the study were evaluated in the SPSS 21.0 package using parametric and nonparametric descriptive statistical analyses. The conformity of variables to the normal distribution was investigated using histograms and the Kolmogorov-Smirnov test. When presenting descriptive statistics, mean, standard deviation, and median values were used. Pearson's correlation analysis was conducted to determine the relationship between quantitative variables. Statistical significance was set as $p<0.05$.

Ethical considerations

Voluntary consent was obtained from all participants. The study was approved by the ethics committee (XXX University XXX Faculty of Medicine Clinical Research Ethics Committee; Date:09.08.2019;No:991). All participants provided informed consent before answering the questionnaire.

RESULTS

The mean age of the mothers in the study group was 28.6±5.5 years, 95.7% were unemployed, 60.8% gave birth by caesarean section, the mean pre-pregnancy body weight was 67.8±9.9 kg,

the average weight gain during pregnancy was 12.7±5.4 kg, and the mean weight on day 1st postpartum was 73.3±10.3 kg (Table 1).

It was found that 65.2% of the infants were male, the mean gestational age was 38.9±1.1 weeks, the mean birth weight was 3389±406 g, and 82.6% of the infants weighed appropriate for gestational age (AGA), according to the Lubchenco curve (Table 2).

The carbohydrate content of colostrum, transitional milk, and mature milk increased as 4.7 g/100 mL, 5.6 g/100 mL, and 6.5 g/100 mL, respectively; the fat content increased as 2.2 g/100 mL, 3.3 g/100 mL, and 3.5 g/100 mL; protein values decreased as 4.1 g/100 mL, 1.97 g/100 mL, and 1 g/100 mL; and calories as 68.50 kcal/100 mL, 67.4 kcal/100mL, and 68.4 kcal/100 mL, respectively. The mothers' nutritional consumption within the last 24 hours were determined on days 1, 5, and 15 postpartum in the following manner: carbohydrate 150.1±107.7 g, 251.2±90.2 g, 251.5±91 g, protein 23.7±19.6 g, 75.5±57.7 g, 78.7±46.7 g, and fat 28.4±26.7 g, 80.5±36.4 g, 79.1±34.5 g. Likewise, the number of calories consumed increased as 969.3±721.7 kcal, 2050.4±640.2 kcal, and 2148.5±591.3 kcal, respectively (Table 3).

Table 1: Sociodemographic characteristics of the mothers (N=46)

Characteristics		n (%)	
Education	Literate	16 (34.7)	
	Primary education	17 (36.9)	
	Secondary education	13 (28.4)	
Employment status	Employed	2 (4.3)	
	Unemployed	44 (95.7)	
Income status	Income more than expenses	2 (4.4)	
	Income equals expenses	28 (60.8)	
	Income less than expenses	16 (34.8)	
Family type	Nuclear	19 (41.3)	
	Extended	27 (58.7)	
Mode of delivery	Vaginal	18 (39.2)	
	Caesarean section	28 (60.8)	
Continuous medication administration	No	43 (93.5)	
	Yes	3 (6.5)	
		Mean±SD	**Median**
Maternal age (years)		28.6±5.5	27.5
Pre-pregnancy weight (kg)		67.8±9.9	68.0
Total weight gain during pregnancy (kg)		12.7±5.4	11.0
Weight on day 1 postpartum (kg)		73.3±10.3	71.8
Maternal height (cm)		159.3±6.0	160.0
Number of living children		2.7±1.1	3.0

Table 2: Infant characteristics (N=46)

Sex	Female	16 (34.7)	
	Male	30 (65.3)	
Birth weight according to gestational age	*AGA	38 (82.6)	
	**SGA	8 (17.4)	
		Mean±SD	**Median**
Gestational age (weeks)		38.9±1.1	39.0
Birth weight (g)		3389±406	3335
Birth length (cm)		51.5±1.9	51.0

*AGA: Appropriate Gestational Age **SGA: Small gestational age.

According to the results of the BeBis programme, upon examining the correlation between the nutritional consumption by the mothers during the 24-hour period on days 1st , 15th, and 15th, postpartum and human milk macronutrient levels, there was no significant correlation between the nutritional consumption by the mothers on the first day and human milk macronutrient levels. There was a significant negative correlation between the energy and carbohydrate content of the nutritional consumption by the mothers on day 5th postpartum and the levels of human milk proteins. A significant positive correlation was detected between the amount of carbohydrate in the mothers' nutritional consumption on day 15th postpartum and the carbohydrate levels in the human milk (Table 4).

DISCUSSION

It is known that maternal nutrition influences the composition of human milk, and the macro- and micronutrient content of human milk should be sufficient for the healthy nutrition, growth, and development of infants (14,15). This study was conducted to examine the effects of maternal nutrition on the human milk content.

The daily protein requirement of feeding mothers increases for the synthesis of milk proteins and cell regeneration. It is recommended that a woman of childbearing age should consume an average of 0.8 g/kg protein per day, and it is recommended to add 19 g of protein daily to her diet during pregnancy and lactation (16). The average daily protein consumption by mothers in our study group was 23.7 g on day 1 postpartum, 75.5 g on day 5th postpartum, and 78.7 g on day 15th postpartum. When the recommended amount of protein (0.8 g/kg) in the literature was calculated according to the mothers' average weight (73.3 kg), the required daily average protein intake was 58.6 g/day, and the required average protein intake was 77.6 g/day when adding 19 g that should be consumed additionally by human-feeding mothers in the postpartum period. The amount of protein consumed by the mothers daily was similar to the recommendations. There was no significant correlation between the amount of protein consumed by the mothers daily (days 1st , 15th, and 15th, postpartum) and human milk protein and other macronutrients. Likewise, a study conducted with 117 mothers in Italy found no significant correlation between the amount of

Table 3: Distribution of the nutrients in human milk and nutritional consumption by the mothers (N=46)

Human milk nutrients (in 100 mL)	Day 1		Day 5		Day 15	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Carbohydrate (g)	4.7±1.2	4.6	5.6±1.2	5.9	6.5±0.8	6.6
Fat (g)	2.2±0.9	2.1	3.3±0.6	3.1	3.5±0.8	3.4
Protein (g)	4.1±1.6	4.4	2.0±1.0	1.7	1.0±0.3	1.0
Energy, kcal	68.5±16.3	62.5	67.4±10.4	68.0	68.4±9.5	68.5
Nutritional consumption by the mother (per day)	**Day 1**		**Day 5**		**Day 15**	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Carbohydrate (g)	150.1±107.7	145.6	251.2±90.2	239.9	251.5±91.0	246.4
Protein (g)	23.7±19.6	13.9	75.5±57.7	64.8	78.7±46.7	74.7
Fat (g)	28.4±26.7	20.9	80.5±36,4	73.1	79.1±34.5	74.0
Energy (kcal)	969.3±721.7	800.5	2050.4±640.2	1911.0	2148.5±591.3	2132.6

protein consumed by mothers daily and the levels of human milk protein (17).

The mother's nutritional status and content can affect the composition of human milk and thus the infant's nutrient intake (15). Nutritional requirements are higher in infancy than in other age periods. The composition of human milk changes over time according to infants' changing needs (2,3,18). There was a negative correlation between the carbohydrates consumed by the mothers and the energy they received and the human milk protein in our study group on day 5th postpartum. There was a positive correlation between the amount of carbohydrates consumed by the mothers on day 15th postpartum and the carbohydrate content of human milk. The amount and quality of protein in human milk are not affected by the mother's diet. However, providing protein support to the mother increases the protein concentration and free amino acid content of the milk (18). Hascoët et al. (19) revealed a positive correlation between the carbohydrate consumption of the mother and the levels of human milk protein, carbohydrates, and lipids. Bzikowska et al. (20) investigated the impacts of maternal and infant factors on human milk content and found that maternal nutrition affected the amount of human milk carbohydrates. Magnel et al. (21) reported no correlation between maternal nutrition and the amount of human milk carbohydrates. More research using larger samples is needed in this area because the literature on maternal nutrition and breast milk content is scarce, and there is no consistent evidence.

No correlation was detected between the amount of fat consumed by the mothers in our study group and human milk macronutrient levels. Maternal fatty acid intake affects the fatty acid profile of human milk (1). Samur et al. (22) examined the mothers' nutritional consumption for three days using the BeBis programme and revealed that Turkish women frequently consumed flour products, margarine and desserts, and trans fats, and there was a significant correlation between human milk fatty acids and trans fats consumed by mothers. The research results and the literature differ, which may be related to the foods consumed by the mothers participating in the study within the last 24 h. A systematic review by Keikha et al. (23) evaluated 43 studies on human milk composition and maternal nutrition. There was no correlation between maternal nutrition and macronutrient levels in the human milk composition, but there was a correlation with micronutrients. Likewise, Fouani and Mahmoudi (24) stated that maternal nutritional status affects micronutrients rather than macronutrients in human milk. Rakıcıoğlu et al. (25) investigated changes in human milk content when fasting mothers in Turkey did not consume water and other foods for approximately 8-10 hours per day. It was determined that the intake of all nutrients of the fasting mothers decreased, but it did not significantly affect the growth of human milk macronutrients or infants. The energy of human milk is provided by macronutrients such as fat and carbohydrates (22). The approximate daily caloric intake of the mothers in our study group was 969, 2050, and 2148 kcal on day 1 postpartum, day 5 postpartum, and 2148 kcal on day 15th postpartum. It is recommended that mothers should consume 2300-2500 kcal of energy daily during human feeding (16,26). It was observed that mothers consumed fewer calories than recommended. It has been reported that the macronutrient content of human milk is high in different cultures and age groups, regardless of the number of pregnancies, despite changes in maternal nutritional status (27,28).

There was a significant negative correlation between the amount of energy consumed by the mothers and the human milk proteins on day 5th postpartum, but there was no correlation in the measurements performed on days 1st and 15th postpartum. Minato et al. (29) also demonstrated that the amount of energy that the mother received from her food did not affect the amount of energy in her milk. Yang et al. (30) did not find a correlation between maternal macronutrient consumption within the last 24 h and macronutrient concentrations in human milk. The fact that the human milk content did not change, despite the low amount of nutrients and energy taken by the mothers, was associated with fat burning. The results obtained with repeated measurements in our study group can be considered parallel to those obtained by Yang et al. and Minato et al.

Table 4: Correlation between maternal daily nutritional consumption and human milk nutrients (N=46)

Nutritional consumption by the mother		Human milk nutrients			
		Day 1			
		Carbohydrate	Fat	Protein	Energy
Energy	r	0.181	-0.189	-0.205	-0.189
	p	0.228	0.208	0.172	0.207
Water	r	0.228	-0.032	-0.213	-0.128
	p	0.128	0.831	0.156	0.395
Protein	r	0.161	-0.110	-0.077	-0.026
	p	0.284	0.468	0.612	0.864
Fat	r	0.157	-0.129	-0.182	-0.168
	p	0.298	0.394	0.226	0.263
Carbohydrate	r	0.162	-0.218	-0.273	-0.236
	p	0.282	0.146	0.067	0.114
		Day 5			
Energy	r	0.129	-0.132	-0.359	-0.258
	p	0.391	0.380	**0.014**	0.083
Water	r	-0.231	-0.026	-0.137	-0.007
	p	0.122	0.863	0.362	0.966
Protein	r	-0.035	0.028	-0.267	-0.193
	p	0.819	0.852	0.072	0.198
Fat	r	-0.020	-0.027	-0.116	-0.060
	p	0.894	0.857	0.441	0.690
Carbohydrate	r	0.242	-0.139	-0.348	-0.230
	p	0.105	0.357	**0.018**	0.124
		Day 15			
Energy	r	0.208	-0.205	0.094	-0.105
	p	0.165	0.172	0.535	0.488
Water	r	0.265	0.004	-0.010	-0.022
	p	0.075	0.981	0.945	0.883
Protein	r	0.232	0.119	0.210	0.001
	p	0.121	0.430	0.161	0.993
Fat	r	0.162	-0.116	0.043	-0.064
	p	0.281	0.444	0.778	0.672
Carbohydrate	r	0.377	-0.057	0.178	0.009
	p	**0.010**	0.706	0.237	0.952

*Spearman's Correlation Test

Unlike other studies, it was observed that maternal nutrition (especially carbohydrate consumption) affected the macronutrient (protein, carbohydrate) content of human milk in repeated measurements performed at different times in our study group. There was a positive correlation between the carbohydrate content of maternal nutrition on day 15th postpartum and the carbohydrate value of human milk on day 15th, but the amount of fat and protein consumed by the mothers did not affect human milk content. The difference of our study from other research may be related to the data collection method, nutritional culture, and the time of human milk examination. Further studies examining maternal nutrition and human milk content in different cultures are recommended.

Limitations

The results obtained from this study are limited to women with similar socioeconomic characteristics who gave birth at a university hospital.

CONCLUSION

Repeated measurements (days 1st, 5th, and 15th postpartum) revealed that the amount of carbohydrates and fat in human milk gradually increased while the amount of protein decreased. There was a significant negative correlation between energy and carbohydrate content in the nutritional consumption by mothers on day 5 postpartum and the levels of human milk proteins. Additionally, there was a significant positive correlation between the carbohydrates consumed by the mothers on day 15th postpartum and human milk. The maternal nutritional consumption affects the human milk (transitional milk and mature milk) content. These results may not show a direct causal relationship. Further studies are required.

Adequate and balanced nutrition during the preconception, pregnancy, and human feeding periods is important for mother and baby health. Optimal nutrition provided in the first 1000 days of life, during which neurodevelopment is rapid, affects healthy growth and development. Support mother and baby nutrition through counselling, guidance, and training for physicians, midwives, and mothers who have important roles in mother and child health services during the first thousand days of life. Midwives should determine deficiencies in nutritional information and provide trainings in line with current and evidence-based information starting from the preconception period onward to expectant mothers.

Ethics Committee Approval: This study was approved by the ethics committee of İstanbul University Faculty of Medicine Clinical Research Ethics Committee; (Date:09.08.2019;No:991).

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

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RESEARCH ARTICLE

Febrile Seizures: The COVID-19 Pandemic and Beyond

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ABSTRACT

Objective: Febrile seizures are common reasons for admission to paediatric emergency departments. There is evidence suggesting that the frequency, severity, and seasonal distribution of non-COVID infections have changed since the removal of measures during the COVID-19 pandemic. These changes may also impact febrile seizures, which are known to be triggered by infections.We aimed to reveal the frequency and seasonal distribution of febrile seizures during the COVID-19 pandemic and after the removal of social restrictions and measures.

Methods: Patients who presented to the emergency department with a febrile seizure were grouped as having first or recurrent febrile seizure, and demographic data were reported. The patients were then grouped according to the period of the pandemic as follows; the first year of the pandemic (Group 1), the second year (Group 2), and the period after the removal of measures (Group 3). The groups were compared in terms of the number of patients, seizure age, seizure duration, seizure frequency, season of admission, seizure type, seizure status at the time of admission to the emergency department (stopped or ongoing), and electroencephalography (EEG) findings.

Results: A total of 248 patients who presented with 272 febrile seizures were included. There were 34, 105, and 132 patients in Groups 1, 2, and 3, respectively. There were no significant differences among the three groups in terms of recurrent febrile seizures, continuation of seizures upon admission to the emergency department, duration of seizures, treatment requirement in the emergency department, or ratio of focal seizures ($p>0,05$). However, the number of febrile seizures increased in groups 2 and 3. There was seasonal variation in febrile seizures, with a decrease in autumn and an increase in winter. The majority of patients in all groups was under 3 years of age.

Conclusions: In this study, we attributed the decrease in the number of febrile seizures in the first year of the pandemic period and its increase in the subsequent years to the effects of the pandemic on the course of infections. The seasonal shift observed in febrile seizures after the removal of precautions may also reflect changes in the period of infection. Understanding that pandemics cause epidemiological changes in infections and related comorbidities is important for the early prediction and management of infections and their comorbidities.

Keywords: Febrile seizure, Covid-19, Pandemic, Child

INTRODUCTION

Febrile seizures are the most common seizure disorder of childhood and affect 2-5% of children (1,2). Febrile seizures are caused by genetic and environmental factors. Viral infections with fever are associated with febrile seizures. As viral infections increase seasonally, febrile seizures also increase. Therefore, changes in infections may affect the distribution and frequency of febrile seizures (3).

The first case of COVID-19 in our country was reported in March 2020, and the pandemic quickly spread nationwide. At the beginning of the pandemic, non-COVID infections and related emergency applications decreased significantly because of physical distancing measures, mandatory mask wearing, and travel precautions. After May 2022, pandemic measures were gradually lifted in our country. Following the removal of these measures, non-Covid infections increased. During this period, we observed an increase in the frequency, severity, and duration of infections compared with before the pandemic. This observation led to the hypothesis that these changes might affect emergency visits and fever-triggered seizures and that the lifting of measures would result in an increase in non-COVID infections and consequently an increase in febrile seizures. For this reason, we examined patients who presented to the emergency department with febrile seizures before and after the implementation of the pandemic measures.

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MATERIAL AND METHODS

The data of patients who presented to the emergency department with febrile seizures during and after the pandemic were retrospectively examined. During the 1-year period before the pandemic, the number of patients presenting with febrile seizures was determined, but detailed data could not be accessed.

Patients who presented with febrile seizures were included in the study. Patients diagnosed with central nervous system infection, symptomatic seizures, or fever-triggered epilepsy seizures were excluded.

The demographic data of the patients were examined by dividing them into two groups: patients with first febrile seizures and patients with recurrent febrile seizures. The groups were compared in terms of age, gender, seizure type, seizure onset type, number of patients with generalised tonic clonic (GTC) seizures, electroencephalography (EEG) findings, family history of febrile seizures and epilepsy, and presence of fever at first admission.

Patients who presented to the emergency department with febrile seizures after May 2020 were divided into three groups: Group I, patients admitted in the first year of the pandemic (1 May 2020–1 May 2021); Group II, patients admitted in the second year of the pandemic (1 May 2021–1 May 2022); and Group III, patients admitted in the period after the removal of pandemic measures (1 May 2022–1 May 2023). The groups were compared according to age, recurrent febrile seizures, seizure status upon admission, seizure duration, need for antiseizure treatment, and seasonal distribution.

Ethics Approval

This study was conducted in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Giresun University with register number 2023/01.

Statistics

Statistical analyses of the study were performed using the trial version of SPSS 22.0 (SPSS Inc., Chicago, IL) package software. Kolmogorov-Smirnov test was employed to examine whether the quantitative variables were suitable for normal distribution. Independent groups were compared using the Mann–Whitney U or Kruskal-Wallis H test for variables that were not normally distributed. The relationship between qualitative variables was examined using chi-square analysis. The descriptive statistics of the quantitative variables that conformed to the normal distribution are presented as mean ±standard deviation, and the descriptive statistics of the quantitative variables that were not normally distributed are presented as median (min-max) or mean ±standard deviation. Descriptive statistics for qualitative variables are expressed as frequency (%).

RESULTS

In total, 248 patients who presented with 272 febrile seizures were examined. Among these seizures, 140 occurred in girls and 132 in boys. The mean age was 32.8±27.8 months. A total of 19 patients experienced seizures that continued upon admission to the emergency department. The seizures of 5 patients lasted more than 15 min. Seizure onset was focal in 14 patients. Of the 14 patients, 175 presented with their first febrile seizure and 97 with recurrent febrile seizures. The mean age of patients with recurrent febrile seizures was significantly higher than that of patients with first febrile seizure ($p<0.001$). There were no significant differences between the groups in terms of sex distribution, seizure duration, seizure type, family history of epilepsy and febrile seizures, or presence of epileptic activity on EEG (Table 1). Similarly, the seasonal distribution of febrile seizures and recurrent febrile seizures showed no significant variation (Table 2). In the 1-year period before the pandemic (1 May 2019-1 May 2020), 65 patients presented to our emergency department with febrile seizures. The detailed data for these patients could not be accessed.

Table 1: Comparison of febrile and recurrent febrile seizure data

	FS n:272	First FS* n:175	Recurrent FS* n:97	p*
Age(mean ± SD) median (%)	32.8+27.8 24.5	28.91±21.85 21	40.05±35.23 29	**<0.001** **
Gender (M/F)	140/132	85/90	55/42	0.199
Ongoing seizure at admission	19 (7)	15 (8.6)	4 (4.1)	0254
Seizure duration of >15 m	5 (8.9)	5	0	0.145
Seizure duration of >10 m	10 (17.9)	9	1	0.072
Seizure duration of >5 m	18 (67.9)	15	3	0.137
Focal-onset seizures	14 (4.8)	9	5	1.00
GTC(%) seizure	80 (29.5)	52 (29.9)	28 (28.9)	0.609
Family history of epilepsy (%)	59 (21.8)	32 (18.4)	27 (27.8)	0.071
Family history of FS (%)	127 (46.9)	80 (46)	47 (48.5)	0.695
Epileptic activity in EEG (%)	20 (20.8)	13/49	7/47	0.249
Fever at admission(%)	216 (81.5)	137 (81.1)	79 (82.5)	0.934

*P= Comparison of Fs and RFs groups **Mann-Whitney U test. EEG:Electroencephalography F:Female FS:Febrile seizure m:minutes GTC:Generalised tonic clonic seizure M:Male

There were no differences between the groups in the frequency of first or recurrent febrile seizures, seizure status upon admission to the emergency department, seizure duration, treatment requirement, and focal onset frequency (Table 3).

Considering the distribution of febrile seizures, no significant seasonal differences were observed between the first and second years of the pandemic. However, after these measures were implemented, the number of patients with febrile seizures decreased in autumn and increased in winter, although there was no statistical difference between the groups (Table 3). The expected peak of febrile seizures in autumn did not occur, shifting to winter months (Figure 1). There was no difference in the rate of recurrent febrile seizures between the pandemic period and after the measures were lifted (comparing the

Table 2: Seasonsal distribution of febrile seizures.

	Spring	Summer	Autumn	Winter	Total	p
First FS	34 (19.4)	51 (29.1)	35 (20)	55 (31.4)	175	0,225
Rekpurrent FS	26 (26.8)	19 (19.6)	17 (17.5)	35(36.1)	97	
Total	60(22.1)	70(25.7)	52(19.1)	90(33.2)	272	

FS:Febrile seizure

Table 3: Distribution of febrile seizures by age

	Pandemic-1st Year n:34 (Group1)	Pandemic-2nd Year n:105 (Group 2)	After lifting social isolation measures are lifted n:132 (Group 3)	p
Age (mean ± SD) median	26±19.64 18	29.04±17.61 25	37.78±34.8 27	0.49
Age<3 (%)	29 (85.2)	80 (76.2)	78 (60.4)	0,02
FS	24 (70,6)	70 (66,7)	81 (60,9)	0,47
Recurrent FS	10 (29,4)	35 (33,3)	52 (39,1)	
Emergency admission				
Ongoing seizure	4 (11,8)	9 (8,6)	6 (4,5)	0,246
Without seizure	30 (88,2)	96 (91,4)	126 (95,5)	
Seizure duration				
>5 m	3 (8,8)	4 (3,8)	11 (8,3)	0,334
<5 m	31 (91,2)	101 (96,2)	122 (91,7)	
Seizure stopped without				
medication	25 (73,5)	76 (72,4)	95 (71,4)	0,96
with medication	9 (26,5)	29 (27,6)	38 (28,6)	
Focal	1 (2,9)	4 (3,8)	9 (6,8)	0,487
Generalise	33 (97,1)	101 (96,2)	124 (93,2)	
Spring	7 (20,6)	17 (16,2)	36 (27,1)	
Summer	8 (23,5)	27 (25,7)	35 (26,3)	0,254
Autumn	9 (26,5)	25 (23,8)	18 (13,5)	
Winter	10 (29,4)	36 (34,3)	44 (33,1)	

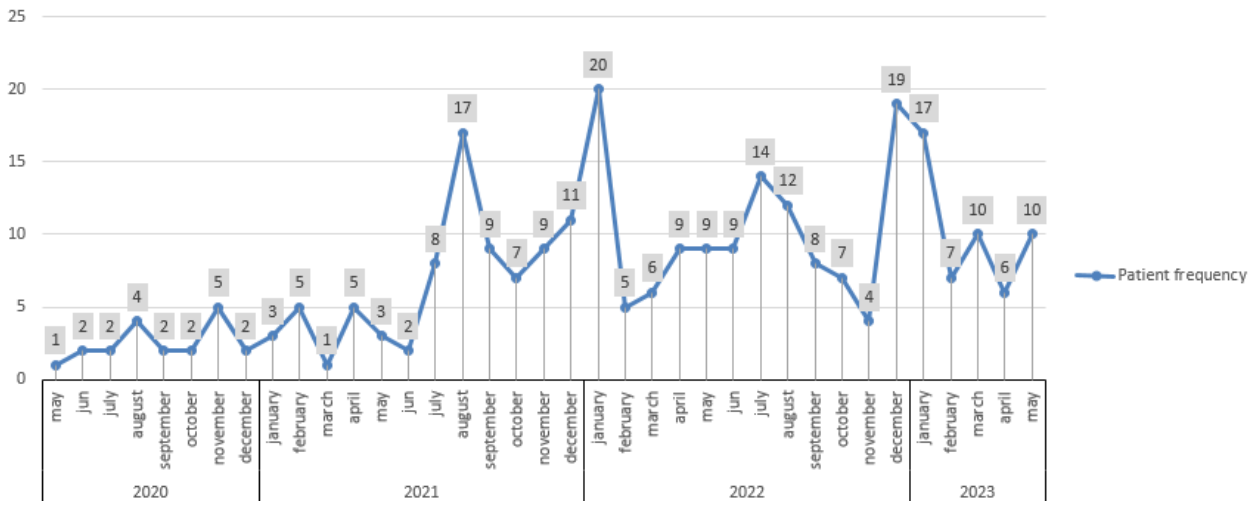

Figure 1: Patient distribution by months.

1st Year of the pandemic and after the measures were lifted p=0.398, comparing the 2nd Year of the pandemic and after the measures were lifted p=0.435, comparing the 1st and 2nd Year of the pandemic p=0.831).

DISCUSSION

Febrile seizures are one of the most common conditions in paediatric neurology practise. COVID-19-related febrile seizures have been reported at rates ranging from 0.5% to 5.7% in the literature (4, 5, 6). In a case–control study by Hanlon et al. focusing on COVID-19 infection, febrile seizures were observed in 2.7% of patients with COVID-19. The study concluded that there was no increased risk of febrile seizures associated with COVID-19 (4).

The COVID-19 pandemic encompassed three distinct periods: closure (group 1, first year), ease of measures (group 2, second year), and removal of measures (group 3). In the present study on the course of febrile seizures during the pandemic period, we did not find any statistically significant differences in the frequency of first febrile or recurrent febrile seizures, seizure status at admission to the emergency department, seizure duration, treatment requirement, or focal onset frequency between the first year of the pandemic, the second year, or the 1-year period after the measures were lifted. However, there was an increase in the number of febrile seizures during the second and third years after implementation of the measures, and a seasonal shift was observed in febrile seizures.

In this study, the number of patients was significantly lower in group 1. Due to the widespread use of masks and social distancing, there was likely a decrease in respiratory virus infections, which was indirectly reflected in the reduced number of febrile seizures triggered by infection and fever. There was a rapid increase in the number of cases in the second year of the pandemic (group 2), and the number rose further in the third year when the measures were lifted. This led us to hypothesise that compliance with measures decreased from the second year of the pandemic onwards, and non-covid infections increased following the removal of measures. Additionally, we detected a seasonal shift in the occurrence of febrile seizures. We hypothesised that this might be related to the shift in infection periods. The literature contains studies from various countries on the course of infections during and after the pandemic. According to a study conducted by Agha et al. in New York, it was observed that the RSV (Respiratory Syncytial Virus) peak, which is usually observed between September and February in the years 2016-2019, was not observed in 2020. Instead, there was a shift of RSV infection to the spring months of 2021, specifically from March to May. (7). Similarly, New York health surveillance data showed that the RSV peak occurred later and remained at a lower level in 2020-2021, but peaked earlier and was higher than expected in 2022-2023. The same findings are also applicable to influenza infection (8). In a similar study conducted in Australia, it was shown that although the RSV epidemic typically started in April before the pandemic, it began in late September 2020 (9). In Park et al. in Korea, the pre-pandemic period (March 2016-February 2020) was compared with the pandemic period (March 2020-February 2022). The incidence of febrile seizures increased dramatically in autumn during the pandemic and decreased significantly in spring. The same study reported a decrease in influenza and an increase in parainfluenza virus throughout the pandemic. Although the pathogens and epidemic periods vary, seasonal shifts are common in these studies. In this study, we observed a seasonal shift in infection-related febrile seizures, which is consistent with the literature (Figure 1).

In the 1-year period before the pandemic (1 May 2019-1 May 2020), 65 patients presented to our emergency department with febrile seizures. During the first year of the pandemic, there was a significant decrease in febrile seizures (n: 34). However, we observed an increase in the number of patients presenting with febrile seizures during the second year of the pandemic (n: 105) and further in the third year (n: 132) when the measures were lifted. This increase coincided with a noticeable increase in the severity and frequency of non-COVID infections in our daily practise compared to previous years, contributing to the expected increase in febrile seizures. Studies in the literature have also indicated a post-pandemic increase in infections. A study from China reported increases of 70.9% in Mycoplasma infections, 259.5% in influenza, 9.8% in parainfluenza, 174.3% in RSV, and 35% in bocavirus infections (10). A review from Germany highlighted that pandemic measures initially reduced infections, but their cessation increased invasive group A streptococcal infections. The study also noted, similar to our findings, a shift in the timing of infections outside the usual period (11). In Italy, following the lifting of restrictions, a study observed changes in the epidemiology of respiratory syncytial virus (RSV), leading to increased hospitalisation rates (12).

In a study from Israel, social restrictions led to a significant decrease in infectious disease morbidity, but non-SARS-CoV viruses resurged in the months following the easing of measures, particularly affecting children under the age of 3 (13). Early-life exposure to microorganisms is linked to the development of robust immunity (14). Precautionary measures and lockdowns during the pandemic may have prevented infants, especially those in their early years and without prior exposure to microorganisms, from developing strong immune systems. This could explain the increased susceptibility observed in children aged 3 years. In our study, most patients in all three groups were under 3 years old (85.2%, 76.2%, and 60% respectively by year). In group 3, the proportion of patients aged 3 years was the lowest ($p<0.05$).

In a study conducted in our country in 2011, the clinical findings of 1385 patients with febrile seizures were recorded, with a mean age of 22.2±1.24 months (15). In the current study, the mean age was 28.91±21.85 (median 21) in the group experiencing their first febrile seizure during the first year of the pandemic, and 26±19.64 (median 18) in the first year of the pandemic. The median age of all groups was 36 months (Table

1, 3). Our study included patients aged under 5 years, which is consistent with the literature, as this age group is most affected by infections that increased following the lifting of restrictions.

In a study examining RSV and non-RSV bronchiolitis in Italy, there was a significant decrease in bronchiolitis and other respiratory infections during the SARS-CoV-2 quarantines (2020-2021), followed by a general increase in cases in the subsequent season, 2021-2022. It was observed that patients in 2021-2022 required more intensive care than children in the previous four seasons (16). Based on these findings, it can be inferred that reduced exposure to infections in 2020-2021 led to decreased immunity and more severe infections in 2022.

In this study, we hypothesised that the number of febrile seizures decreased in the first year of the pandemic and increased in subsequent years because of the pandemic's impact on infection patterns. The increase in febrile seizures and their seasonal distribution, mirroring infection trends, suggest similar fluctuations in our country as well.

Limitations of the study

This study was constrained by its retrospective design and the absence of specific infectious agents.

In conclusion, our study supported the hypothesis that the frequency and seasonal distribution of febrile seizures may vary during pandemic periods. Recognising that pandemics induce epidemiological shifts in infections and associated comorbidities is crucial for the early prediction and management of these conditions.

Ethics Committee Approval: This study was approved by the ethics committee of Giresun University with register number 2023/01.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- B.D.D., E.T., C.C.K.; Data Acquisition- B.D.D., E.T.; Data Analysis/Interpretation- B.D.D., C.C.K.; Drafting Manuscript- B.D.D.; Critical Revision of Manuscript- E.T., C.C.K.; Final Approval and Accountability- B.D.D., E.T., C.C.K.

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RESEARCH ARTICLE

The Assessment of Congenital Laryngeal Lesions in Infants with Stridor

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ABSTRACT

Objective: In neonatal stridor, various conditions can be responsible as well as laryngomalacia. These conditions can be quite rare and the treatment of these diseases could be complicated. The purpose of this study is to identify the laryngeal pathologies and to discuss our approach in infants with chronic stridor.

Methods: The hospital charts of infants with stridor undergoing rigid laryngotracheobronchoscopy in our hospital in 2018-2022 were retrospectively reviewed.

Results: 107 children were enrolled to the study. The most frequent diagnosis was laryngomalacia (isolated and seen with secondary airway lesions (SALs)) (74 patients, 69.1%). 10 patients (9.3 %) had subglottic stenosis which caused stridor or dyspnea. Regarding other laryngeal lesions, in 8 patients (7.47 %) the diagnosis was laryngeal edema and 8 patients (7.47 %) had tracheomalacia. SALs which occurred with laryngomalacia were seen in 16 patients of our series (14.9 % of all cases). Surgery was performed in 11 of patients. Stridor was resolved in % 80 of laryngomalacia patients at about 2 years of age with only follow up.

Conclusions: In neonatal stridor, various conditions can be responsible as well as laryngomalacia. Referral of infant to otorhinolaryngologists and examination with flexible and rigid endoscopy is necessary for the assessment of stridor. The examination of the airway with the rigid endoscopy under general anesthesia without intubation on operating room with the cooperation of the anesthesiologist may provide the surgical intervention together with simultaneous inspection especially in the patients with severe stridor and systemic diseases.

Keywords: Stridor, Infant, Laryngomalacia, Stenosis, Endoscopy

INTRODUCTION

Stridor in pediatric patients is common symptom caused by turbulent air flowing through a narrowed airway (1,2). It can be inspiratory with obstruction at the supraglottic and glottic level, biphasic at the subglottic level and expiratory with obstruction in the trachea (1). Stridor in pediatric age group caused by viral croup, epiglottitis and foreign bodies represents acute stridor and requires emergent management. Chronic stridor is seen especially in neonatal and infantile period and usually caused by congenital laryngeal anomalies such as laryngomalacia, subglottic stenosis, vocal cord paralysis and subglottic hemangioma (2).

Laryngomalacia is the most seen congenital problem. During spontaneous respiration especially with inspiration, the supraglottic structures, specifically the epiglottis and aryepiglottic folds, close onto over the airway like a lotus flower due to their weak cartilage structure (3). The lesions that seen together laryngomalacia such as subglottic stenosis, tracheomalacia, vocal cord paralysis are called secondary airway lesions (SALs) (3,4). These lesions have clinical importance in several aspects. Firstly, surgical intervention may be required in cases of subglottic stenosis and cord paralysis that mostly seen ones. Secondly, even if surgical intervention is performed, it would be more appropriate to follow up for a period of time for accompanying laryngomalacia because of the nature of its. In this case, since stridor will continue even if it decreases, it is important to accurately diagnose whether only these lesions are present or whether they are present together with laryngomalacia in order to accurately predict the clinical outcome of the patient. Therefore, it is of great importance to perform an endoscopic examination of every patient who has stridor even if we guess likely having laryngomalacia to diagnosis SALs seen together with laryngomalacia. However, when conditions known to be associated with large airway lesions are taken into account, the prevalence of SALs

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associated with laryngomalacia is contrary to expectations. In fact, the prevalence of SALs is not fully revealed in the literature. The increased prevalence in some publications may be a result of the inclusion of patients with other pathologies and over-diagnosis for these lesions (5).

Most of congenital airway lesions such as laryngomalacia and tracheomalacia usually resolve by only follow up (2,6). However, rare congenital anomalies of airway such as subglottic stenosis, laryngeal webs, cysts and subglottic hemangioma require medical or surgical treatment (1,7). Presence of congenital laryngeal lesions and synchronous airway problems and various comorbidities are seen frequently in neonatal intensive care unit (2).

Management of a newborn with stridor, with or without respiratory distress, could be established with safe airway and evaluation of laryngeal structures (6). Flexible or rigid laryngoscopy can be used in otolaryngology departments easily for assessment of infant airway (6,8). Rigid laryngotracheobroncoscopy may provide the chance to intervene the pathology simultaneously during the examination. During rigid laryngotracheobroncoscopy under general anesthesia, if surgical intervention is required, the collaboration between the otolaryngologist and anesthesiologist is indispensable to ensure successful operative outcomes (9).

In this study, we have reviewed our experience in patients with chronic stridor requiring hospitalization and rigid endoscopy under general anesthesia. Our aim is to investigate whether management of pediatric patient with stridor with rigid endoscopy is always necessary.

MATERIAL AND METHODS

Patients

Ethical approval and Funding: This study was approved by Baskent University Institutional Review Board (Project no: KA19 / 412) and supported by Baskent University Research Fund.

The records of patients between 0-24 months of age who underwent laryngotrachobronchoscopy for chronic stridor between January 2018 and January 2022 in our tertiary hospital reviewed retrospectively. Cases with acute stridor caused by acute inflammation such as epiglottitis, croup, foreign bodies, trauma and oronasopharyngeal lesions such as choanal atresia were excluded.

Surgical Procedure

Direct rigid laryngoscopy with/without tracheobronchoscopy was performed under general anesthesia in operating room. The patient was induced with either intravenous sedation with typically propofol (Propofol %1; Fresenıus, Avusturya Gmbh., Avustria) or inhalational anesthetic with usually sevoflourane (Sevorane %100; Aesica, Queenborough Ltd., England) and then maintained at a proper depth anesthesia with spontaneous ventilation. Intubation was not performed. The laryngoscope was performed and 0° Storz-Hopkins telescope (ranging from 1.7 mm to 4 mm) was used for airway examination. The hypopharynx, larynx, subglottis, trachea and bronchi were evaluated systematically and documented photographically. When saturation drops below 80% during the procedure, the anesthetist warns the otorhinolaryngologist. In this case, the otorhinolaryngologist removes the endoscope and gives the patient to the anesthesiologist for ventilation and recovery of saturation. Then the procedure continues again. In this way, the airway is examined in detail.

The airway was sized with uncuffed endotracheal tube to determine the grade of stenosis according to Myer-Cotton classification (10). If surgical intervention was necessary, intubation was done and surgery was performed.

Data Collection

In each case, the following parameters were assessed: age at onset, sex, symptoms, diagnosis, synchronous airway lesions, presence of associated neurological and/or congenital anomalies, need for surgery and treatment modalities, negative situation during anesthesia, time of follow up, complications and time to resolution of symptoms.

The outcome of the patients in this study was classified as good outcome, poor outcome and death. The good outcome means normal daily life without any symptoms; the poor outcome means unresolved problems with/without tracheotomy.

Statistical Analysis

Statistical analysis (SPSS) (Version 22, Chicago IL, USA) was used for statistical analysis of the data. Chi-square test and Anova test was used for comparison of the two groups. Significance level in statistical evaluations was accepted as $p<0.05$.

RESULTS

A hundred and seven children were included in this study. There were 65 (60.7 %) male and 42 (39.2%) female children. The age of onset of symptoms was between 0-17 months and was within 12 months in 82 patients (76.6%). The most frequent symptom was stridor (58 patients, 54.2%) followed by dyspnea with 45 patients (42%) (Figure 1).

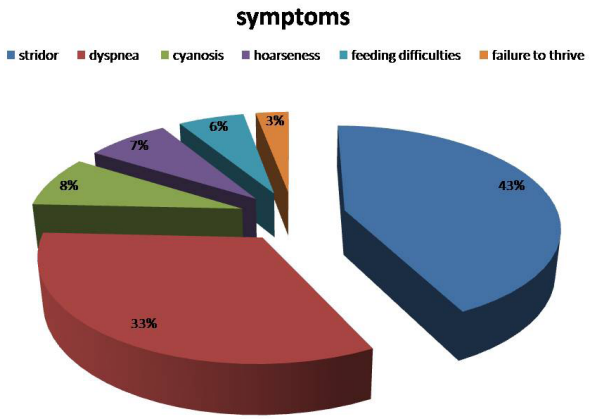

Figure 1: Presenting symptoms in patients evaluated with stridor

The most frequent diagnosis was laryngomalacia (isolated and seen with secondary airway lesions) (74 patients, 69.1%). Ten of all patients (9.3 %) had subglottic stenosis causing stridor or dyspnea. Regarding other laryngeal lesions, there was laryngeal edema in 8 patients (7.47 %), tracheomalacia in 8 patients (7.47 %).

Figure 2 summarized the patients with diagnosis of laryngomalacia. Secondary airway lesions (SALs) which occurred with laryngomalacia were seen in 16 patients of our series (14.9 % of all cases). The most seen SAL was subglottic stenosis in 5 patients. Seventy-four patients had laryngomalacia and 60 of them was mild whereas 12 of them was moderate and 2 of them had more serious disease (Figure 3). Among the patients with laryngomalacia, 7 of them (7/74 9,4 %), were operated because of SALs and outcome of these patients was good. In 59 patients of this group (59/74, 80%) stridor resolved with only follow-up at the end of 36 months. Eight patients of them (8/74, 10,6%) had associated comorbidities with poor outcome.

Subglottic stenosis was seen in 10 patients (9.3%) and 5 of them have seen together with laryngomalacia and one of them had been undergone endoscopic laser operation with good outcome (Figure 4). Vocal cord paralysis was seen in 6 patients (5.6%) and 2 of them was managed with tracheotomy.

The presence of associated anomalies and/or diseases of the patients in this study were also recorded and the results were

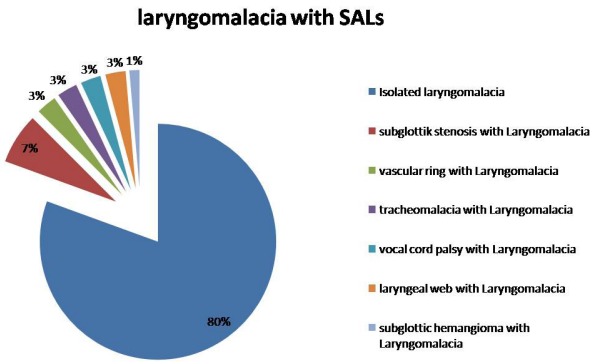

Figure 2: Diagrams of patients with Laryngomalacia

Figure 3: Severe isolated Laryngomalacia

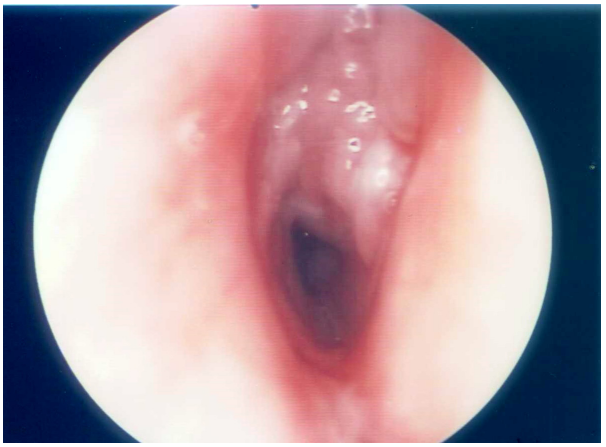

Figure 4: Subglottic stenosis

given in Table 1. Twenty-eight patients (26.1%) had various comorbidities. The percentage of prematurity in this study was 39.2% (42 patients). Features of our patients were summarized in Table 1.

Our patients were followed- up during 2 years (2- 24 months). The surgery was performed in 11 patients (10.2%) in all series. Endoscopic surgery was performed in 9 of these patients (81,8 %) with good outcome.

The outcome of the patients in this study was analyzed and shown in Table 2. Tracheotomy was applied in 7 patients (6.54%) and there were 9 deceased patients (8.41%) in our series. The infectious disease or comorbidity was the most common cause of death rather than laryngeal disorders. Tracheotomy was requiring mostly in the patients with comorbidities and the patients with tracheotomy had mostly poor outcome or deceased.

DISCUSSION

Laryngomalacia is the most common cause of newborn stridor and airway obstruction with an incidence of 35-75% (6). The most important symptom of laryngomalacia is inspiratory stridor which worsens at 4-6 months, improve at 8-12 months and will resolve by 12-18 months of age (6,10). The severity of symptoms of laryngomalacia are mild, moderate and severe. Severe form sometimes may require surgical management (6). In our study, the frequency of laryngomalacia was found as 69.1 % and is compatible with literature. However, in our study there was no surgical treatment for laryngomalacia. Most of our cases were resolved by only follow-up at mean age of 17 months.

We separately evaluated secondary airway lesions seen together with laryngomalacia in this study. Because, even if we diagnose and treat these secondary lesions, unless the accompanying laryngomalacia improves, the patient's complaint decreases but will not go away, and this will affect the patient's outcome. Additionally, our goal is also to determine how often isolated laryngomalacia is seen. In fact, laryngomalacia is a condition improved by just waiting and growing of the patient. Thus,

Table 1: Features of patients undergone Laryngotracheobronchoscopy.

N=107	Isolated Laryngomalacia (n= 58, 54,2%)	Laryngomalacia with SALs (n=16, 14,9%)	Pathologies other than laryngomalacia (n=27, 30,9%)	p
Operating age (mean, mo)	11.2 months	9.7 months	12 months	>0.05
Gender (M/F) M (n=65, 60.7 %) F (n=42 , 39.2%)	45/13	10/6	14/13	>0.05
Diagnosis				
• Subglottic stenosis	-	5	5	
• Vascular ring	-	2	-	
• Tracheomalacia	-	2	6	
• Laryngeal web	-	2	2	
• Hemangioma	-	1	2	
• Cord paralysis	-	2	4	
• Vallecular cyst	-	2	-	
• Papillomatosis	-	-	3	
• Tracheal stenosis	-	-	2	
• Granulation	-	-	1	
• Edema	-	-	8	
Comorbidities				
• Prematurity (n=42, 39,2%)	30	5	7	>0.05
• Systemic diseases (n= 28, 26,1%)				
CNS	6	2	2	>0.05
CVS	6	2	2	
Multipl Anomalies	2	2	-	
Down Syndrome	2	-	-	
Operation (n=11)				
• Open surgery	-	2	-	
• Endoscopic excision	-	4	4	
• Endoscopic dilatation and laser	-	1	-	

M: Male, F: female, CNS: Central Nervous System, CVS: Cardiovascular System, SALs: Secondary airway lesions.

Table 2: Clinical outcome results in patients evaluated in this study.

		Tracheotomy (+) (n: 7), (6,54 %)	Tracheotomy (-)	p
Good outcome (n: 80), (74,7 %)	Comorbidities (+)	-	46	-
	Comorbidities (-)	-	34	
Poor outcome (n: 18), (16,8%)	Comorbidities (+)	3	14	>0.05
	Comorbidities (-)	-	1	
Exitus (n: 9), (8,41 %)	Comorbidities (+)	2	5	>0.05
	Comorbidities (-)	2	-	

this study may be guiding in terms of correct information to the family, especially in the primary care setting, and correct manipulation of a newborn with stridor. In our study, we found the frequency of secondary airway lesions as 14.9 % and the most seen anomaly with laryngomalacia was subglottic stenosis which had major significance. Therefore, we thought that every patient with congenital chronic stridor should be undergone laryngotracheobronchoscopy.

Laryngomalacia may occur as isolated or in association with any other anomalies of airway or other systemic diseases with an incidence of 7.5-64 % in literature (1). Krashin and et al (11) claimed that secondary airway lesions seen together with laryngomalacia were found as a low rate of 7.5 % and had minor significance. They advocated that routine search of synchronous lesions was unnecessary in children with laryngomalacia (11). However, in literature many studies are present about importance of secondary airway lesions. Sakakura et al (2) found that 47.3% of their patients had at least one synchronous lesion and 56.4% had various comorbidities. Rifai et al (5) found the prevalence of SALs as 7.7% and claimed that the prevalence is much less than previously believed. However, they maintain their practice of full airway examination for all patients with severe symptoms.

Fiberoptic flexible endoscopy has been become as preferred diagnostic tool in the congenital stridor nowadays (8). Dynamic anatomical motion and distortion of the airway's structures

during breathing like laryngomalacia can be evaluated with fiberoptic endoscopy (11). However, rigid laryngoscopy may be superior in detailed evaluation of airway anatomy especially in examination of the posterior glottis area and subglottic stenosis (7,11). Rigid laryngotracheobroncoscopy is also necessary for diagnosis and management in many airway lesions that can be seen together with laryngomalacia (12). We thought that the preference of fiberoptic or rigid endoscopy in congenital stridor is dependent on the severity of the patient. If the infant has severe stridor with comorbidities such as cardiovascular disease, failure of thrive; the examination of the airway with the rigid endoscopy under general anesthesia without intubation in operating room may be safer than fiberoptic examination under policlinic conditions without anesthesia. However, of which diagnostic tool for laryngeal examination of infant with stridor is used, nasal and nasopharyngeal examination must be done due to significant airway compromise in neonates with nasal obstruction (12,13).

In many tertiary care pediatric hospitals, the patients with stridor are managed by a multidisciplinary team comprised of otolaryngologists, pediatrist, anesthesiologists, nutritionists, speech pathologists, and nurses. Management includes both medical optimization and surgical interventions, including endoscopic and open airway surgery. Preoperative optimization of the patient's comorbidities is paramount for favorable surgical outcomes (9).

Many comorbidities and many systemic diseases can be seen together with congenital airway diseases (2,7). Moreover, the infants with congenital airway diseases are susceptible to many infectious diseases which may be directly cause of death (2,12). In this study, 26 % of patients (28 patients) had suffered from systemic diseases and this condition affected the clinical outcome (Table 2). The most common comorbidity together with congenital airway diseases in our study was cardiovascular anomalies and central nervous system anomalies. Sakakura et al (2) also found that cardiovascular diseases were the most seen comorbidities in their patients with a percentage of 51 %. Prematurity can be also seen as comorbidity and is blamed for many airways congenital lesions (1,14). Martins et al (14) found that 27.3% of 55 patients were premature and Yuen et al (1) showed that 4 premature infants were present in their series of 26 children. However, Aksoy et al (15) said that prematurity and intubation were not absolutely essential for congenital airway cysts. Our prematurity rate was 39% and we thought also that congenital airway lesions were not absolutely together with prematurity.

The association of gastroesophageal reflux (GER) with congenital airway lesions especially laryngomalacia is well investigated in the literature (1,6). GER was found as responsible for many severe symptoms of laryngomalacia and other airway lesions (6, 16). Yuen et al (1) documented that the incidence of GER with laryngomalacia was 42.3%. In our series, unfortunately the frequency of GER in congenital airway lesions was not examined.

In our series 10.2 % of patients (11 patients) had been undergone operation because of congenital airway anomalies. These operations were usually endoscopic surgeries and were performed for secondary airway lesions (Table 1). Any patient with isolated laryngomalacia had not been undergone surgery in our study. Because most of the isolated laryngomalacia patients in our study improved with time. Indeed, our patients were followed- up by 2 years and in 80 % of them, stridor resolved with only follow-up at the end of 24 months. In this series, patients with laryngomalacia or secondary airway lesions had also severe comorbidities and had usually tracheotomy. Tracheotomy and comorbidities were primary responsible from our patient's outcome (Table 2). 9 patients (8.41%) had deceased because of systemic primary diseases. Neither laryngomalacia nor secondary airway lesions seen together with laryngomalacia has directly affected the outcome in our study as similar in the literature.

In our study, we found that the most important cause of death was comorbidities or infection while investigating the most frequently seen congenital airway lesions. Sakakura et al (2) found that tracheotomy was one of the most related factors for outcome regardless of congenital laryngeal lesions. Nisa et al (17) concluded in their study that if the newborn with bilateral vocal cord paralysis had major comorbidities affecting their normal development, they had poor functional outcomes and would be tracheotomy-dependent. According to our results, we thought also, tracheotomy determined the end-results. However, in patients with tracheotomy, rules of tracheotomy surgery and the ability and knowledge of nurse in intensive care units were very important. These factors could be cause of elongation of period with tracheotomy and end result of the outcome. This opinion requires proof with future studies.

Vascular ring is aberrant right subclavian artery and also can be rare cause of congenital chronic neonatal stridor (17). In literature, it is pointed that congenital anomalies of aortic arch and its branches are rare but important causes of stridor and can be managed with surgery. In our series, 2 patients with vascular ring were operated with good outcome. Adamczuk et al (18) concluded that chronic congenital stridor was an interdisciplinary problem. In this regard, Asha'ari ZA et al (19) claimed that combined physician-surgeon airway endoscopy gave a high diagnostic yield and provided more efficient management with severe airway problems. In our hospital we did not apply endoscopy with pediatricians at the same time. However, all patients with chronic stridor were evaluated and consulted with pediatricians and were examined for circulatory and central nervous system anomalies as a cause of stridor.

The most important weak point of the study is that some information such as reflux and tracheotomy care could not be obtained due to a retrospective nature. Despite this weakness, this study offers a comparative analysis about congenital stridor.

CONCLUSION

As a conclusion, in neonatal stridor, various conditions can be responsible as well as laryngomalacia. Referral of all infants with stridor to otorhinolaringologists and the examination with

flexible and rigid endoscopy is necessary for the assessment of airway. The examination of the airway with the rigid endoscopy under general anesthesia without intubation in operating room may provide simultaneous inspection and surgical intervention especially patients with severe stridor and with systemic diseases. It is thought that a multidisciplinary approach is much more important in stridor management rather than evaluating the airway with a rigid or flexible endoscope.

Ethics Committee Approval: This study was approved by the ethics committee of Baskent Univercity Institutional Review Board (Project no: KA19 / 412)

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CASE REPORT

Paediatric PFAPA Syndrome: an Easily Missed Diagnosis

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ABSTRACT

PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis) syndrome is an autoinflammatory condition characterised by recurrent febrile episodes associated with aphthous stomatitis, pharyngitis, and cervical adenitis. It typically presents before the age of 5 years, with over 60% of cases occurring in males. The prevalence of PFAPA is unknown, but over 500 cases have been reported. The syndrome is diagnosed on the basis of clinical manifestations and is a diagnosis of exclusion. It is characterised by episodes of fever lasting for 3–6 days, with recurrences every 3–8 weeks. Patients are usually asymptomatic between episodes and show normal growth. The aetiology of PFAPA is unknown, it is considered an immune-mediated disease characterised by cytokine dysfunction. Genetic factors may also play a role, as suggested by the strong familial clustering of the syndrome. There is no specific treatment for PFAPA, and its management is based on controlling the symptoms and preventing future episodes.

Keywords: PFAPA syndrome, Periodic fever, Auto-inflammatory, Child

INTRODUCTION

PFAPA (Periodic fever-aphthous stomatitis- pharyngitis - adenopathy) syndrome is an autoinflammatory disorder that typically occurs in preschoolers and is characterised by periodic fever, aphthous stomatitis, pharyngitis, and adenitis. It typically presents before the age of 5 years, with over 60% of cases occurring in males. The prevalence of PFAPA is unknown, but over 500 cases have been reported (1)

The diagnosis of PFAPA syndrome is based on clinical findings, which include at least three febrile episodes lasting up to 5 days and occurring at regular intervals, pharyngitis plus adenopathy or aphthous ulcers, good health between episodes, and elevated acute-phase reactants during a febrile episode but not between episodes. Blood tests may be performed to measure substances that indicate inflammation (2).

PFAPA syndrome is easily missed by practitioners when dealing with recurrent pharyngitis, aphthosis, or stomatitis, which would delay appropriate management. Treatment of PFAPA syndrome is optional and depends on the frequency and severity of flare-ups; it can include glucocorticoids, such as a single dose of prednisone or betamethasone, which, when administered at the onset of an episode, can dramatically abort fever attacks in a few hours. Tonsillectomy may also be considered in some cases (3).

CASE REPORT

An 8-year-old male child presented to the dermatology outpatient clinic with recurrent aphthous stomatitis since the age of 5 years. He was the first child of consanguineous Algerian parents, and his pregnancy, labour, and postnatal development were uneventful. The episodes occurred almost regularly, every 4 weeks, and lasted 8-10 days, accompanied by fever and pharyngitis. Upon admission, physical examination revealed superficial, aphthous lesions on the inner side of the cheeks, tongue, and lips, cervical adenitis, tonsillitis, concomitant elevated temperature at 39°C, vague abdominal pain, and diffuse arthralgia (Figures 1 and 2).

Laboratory findings showed elevated inflammatory biomarkers (high C-reactive protein > 18 mg/l, no exact titration provided and elevated erythrocyte sedimentation rate > 30 mm at the first hour), whereas blood count and smear did not show any

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Figure 1,2: Recurrent aphthous ulcers in two episodes. Left: on the lower lip; Right: on the tongue

haematological abnormality. A further biopsy to rule out any underlying condition such as atypical infections or other rare pathologies that may present with symptoms similar to those of recurrent tonsillitis. It revealed a non-specific, lymphocytes-histiocytes infiltration.

The modified Marshall's criteria were used to finally diagnose the patient with PFAPA syndrome.

Following a short course of steroids (two days of Prednisone, 2mg/kg/day), colchicine was initiated to prevent attacks, and tonsillectomy was scheduled with ENT surgeons.

DISCUSSION

PFAPA syndrome is a periodic fever syndrome of unknown cause that was first described in 1987 by Marshall et al. (4).

It is an autoinflammatory disorder characterised by recurrent, abrupt episodes of fever that resolve spontaneously within a few days, along with pharyngitis, oral aphthous lesions, and cervical lymphadenitis. Other symptoms, such as abdominal pain, arthralgia, arthritis, headache, rash, diarrhoea, and nausea/vomiting, have also been reported during attacks (2).

Moreover, the syndrome's aetiology is unknown, and the proposed contributors to pathogenesis include infection, abnormal host immune responses, or a combination of both. The presence of variants in inflammasome-related genes, mostly in NLRP3 and MEFV, suggests a possible role of these genes in PFAPA pathogenesis. However, none of these variants alone seem to be relevant to the disease aetiology, suggesting an oligogenic or polygenic background (5).

Approximately 90% of cases of PFAPA syndrome manifest before the age of five, as was the case with our patient. Recurrences of symptoms occur periodically, with intervals of 3–8 weeks initially, and then with longer intervals as the child ages (6).

Our patient's odyssey is not uncommon: due to the complex non-specific presentation of PFAPA, patients often undergo multiple diagnostic tests and procedures, including intravenous perfusions of antibiotics(7); which can lead to a delay in diagnosis and inappropriate treatment strategies (8,9).

The diagnosis of PFAPA syndrome can be challenging because of its diverse clinical presentation and lack of specific diagnostic criteria. Typically, diagnosis is made by exclusion, and the differential diagnosis should include disorders depicting a periodic fever, such as recurrent tonsillitis, streptococcal infection, juvenile idiopathic arthritis, Behçet's disease, cyclic neutropenia, familial Mediterranean fever, TRAPS syndrome, and mevalonate kinase deficiency (1,10) . Less common autoinflammatory diseases, such as Cryopyrin-Associated Periodic Syndrome (CAPS) and Tumour Necrosis Receptor-Associated Periodic Syndrome (TRAPS), must also be excluded (11).

The diagnostic criteria for PFAPA syndrome have low specificity, and the adoption of new, more specific criteria is crucial to better identify the syndrome and provide a correct and rapid diagnosis. The lack of gold standard criteria for PFAPA syndrome has led to difficulties in establishing classification criteria (5,10,11) . To address this, the Eurofever Registry and the Paediatric Rheumatology International Trials Organisation have published a modified set of criteria for PFAPA syndrome, which has been validated and shown to have high specificity and sensitivity (12). The new criteria provide a more specific and evidence-based approach to the diagnosis of PFAPA syndrome (Table 1).

The management of PFAPA eases symptoms, shorten the duration of fever, and prevent recurrence. Various treatment strategies have been used and demonstrated variable efficacy for treating attacks. The different therapeutic options for PFAPA syndrome encompass the following (5,13) :

1. Corticosteroids: Glucocorticoids are considered the mainstay of treatment for PFAPA syndrome and are frequently used in managing fever episodes. A short course of steroids, with a single dose of prednisone (1–2 mg/kg) or betamethasone (0.1–0.2 mg/

Table 1 : New criteria for PFAPA diagnosis according to Gattorno et al (12).

Criteria	Description
Regularity	Recurrent fevers with a duration of 3-6 days and a frequency of at least one episode every 4-8 weeks
Aphthous stomatitis	Oral ulcers that occur during fever episodes or within 24 to 48 hours of fever onset
Pharyngitis	Sore throat or redness of the pharynx during fever episodes or within 24 to 48 hours of fever onset
Cervical adenitis	Tender or enlarged cervical lymph nodes during fever episodes or within 24 to 48 hours of fever onset
Exclusion of other diseases	Exclusion of other periodic fever syndromes, autoimmune diseases, and infections
Response to the treatment	Complete resolution of symptoms within 24 to 48 hours of treatment with corticosteroids

kg) administered at the onset of an episode, can dramatically resolve symptoms, shorten or even end the episode

2. Colchicine has shown efficacy in some patients and may help prevent future episodes in some children

3. Cimetidine has been suggested as an effective prophylactic treatment for PFAPA and has relieved symptoms in a subset of patients

4. Tonsillectomy may prevent future episodes in some children: in more than 80% of children, tonsillectomy has been reported to cure PFAPA, but the best timing for this treatment is unclear.

5. Nonsteroidal anti-inflammatory drugs have poor results in amending PFAPA symptoms and are not considered a primary treatment option.

6. Biologics like interleukin-1 inhibitors have been efficient in some studies but require further confirmation.

Even if such treatments are useful for managing PFAPA episodes, there is no evidence that treatment can modify the natural history of PFAPA syndrome. The main goal of treatment is to ease symptoms, shorten the duration of fever, and prevent recurrence

CONCLUSION

PFAPA syndrome is a periodic fever, autoinflammatory disorder characterised by recurrent, abrupt episodes of fever that resolve spontaneously within a few days, along with pharyngitis, oral aphthous lesions, and cervical lymphadenitis. The challenges in diagnosing PFAPA syndrome include its diverse clinical presentation, lack of specific diagnostic criteria, and unknown aetiology.

Treatment for PFAPA syndrome is primarily symptomatic, with the goals of easing symptoms, shortening the duration of fever, and preventing recurrence

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CASE REPORT

Approach to Vaccine Hesitancy: A Case Report Conveying the CASE Approach*

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ABSTRACT

Vaccine hesitancy is a concept that has persisted from the time smallpox vaccine was first introduced to this day. When encountering vaccine-hesitant caregivers in clinical practice, it is important to approach vaccine hesitancy in accordance with evidence-based practices to effectively utilise the limited time available. Our case describes a 6-month and 20-day-old patient admitted to the paediatric ward with acute bronchiolitis and missed vaccinations. The patient's mother revealed that she did not get the infant vaccinated after 2 months of age because she was influenced by people around her. A structured interview was conducted with the mother following the CASE method. After the interview, the mother decided to get her baby vaccinated. The infant received Hepatitis B, diphtheria, tetanus, acellular pertussis, inactivated polio, Haemophilus influenzae type b, and conjugated pneumococcal vaccines on the day of discharge. Subsequent clinic visits confirmed adherence to the vaccination schedule.

Keywords: Child, interview techniques, vaccination hesitancy

INTRODUCTION

Vaccine hesitancy is not a new phenomenon, dating back to the time when Edward Jenner introduced the smallpox vaccine in England in the 1800s (1). However, vaccine hesitancy has become increasingly prevalent and has been identified as one of the top ten threats to global health by the World Health Organisation in 2019 (2). Vaccine hesitancy is described as delayed acceptance or refusal of some vaccines, whereas vaccine refusal is described as not accepting any of the vaccines despite the availability of vaccination services (3).

A decline in vaccination rates leads to an increased incidence of infectious diseases. Measles is a prominent example among childhood infectious diseases. "Canary in the coal mine" analogy is often used for measles and vaccination services (4). Miners used to send canaries into coal mines before descending because the birds were highly sensitive to toxic gases. If the canary showed signs of distress, it indicated a gas leak in the mine (5). Similarly, measles serves as an early indicator of challenges in vaccination and basic healthcare services, being a highly contagious yet preventable disease through successful vaccination (4). The global measles vaccination rate was reported as 81% in 2021, whereas it was reported as 96% in our country (6). However, between March 2022 and February 2023, our country ranked second in the WHO European region with 466 reported measles cases (7).

Given the rise in indicative measles cases, addressing vaccine hesitancy in parents has gained increased importance and urgency in childhood immunization. This case presentation discusses an approach to a family experiencing vaccine hesitancy and provide a brief literature overview.

CASE REPORT

A 6-month and 20-day-old girl presented to the paediatrics clinic with a cough for the previous week and a fever for the last day. Physical examination revealed bilateral rales, intercostal retractions, a heart rate of 117 beats/min, and a respiratory rate of 55 breaths/min with tachypnoea. Other system examinations were unremarkable. Laboratory tests showed no abnormalities in complete blood count, kidney and liver function tests, or electrolytes. C-reactive protein was negative.

* We thank our patient and her family for letting us share their case.

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Chest X-ray was consistent with acute bronchiolitis. She was admitted to the paediatric ward with a preliminary diagnosis of acute bronchiolitis. The patient was started on intravenous hydration, inhaler salbutamol and budesonide therapy, and intermittent oxygen support through a mask.

Medical history revealed a full-term pregnancy with a birth weight of 4090 g at 39 weeks 5 days. The patient was regularly given iron and vitamin D supplements as recommended by her physician and was breastfeeding along with complementary foods. Upon inquiry, it was discovered that the infant received Hepatitis B vaccinations at birth and at 1 month, but subsequent vaccinations were not continued. While her treatment for bronchiolitis was continued successfully, consultation with social paediatrics was planned for the patient with missed vaccinations.

The day before discharge, the mother and baby were evaluated, and the CASE (Corroborate, About me, Science, Explain/Advise) method was used for communication with the mother. The steps of the interview are summarised in Table 1 (1).

Table 1: Interview technique for caregivers with vaccine hesitancy and the CASE approach (1)

Corroborate: Acknowledge the caregiver's concerns and find a point on which you can agree.
About me: Describe what you have done to build your knowledge and expertise on the subject.
Science: Define what science says.
Explain/Advise: Explain your advice to the caregiver, based on science.

Following the CASE method, the mother's concerns about childhood vaccinations were identified. She expressed concerns about potential side effects of vaccines that were suggested by her close relatives, leading her to worry and decide against getting her child vaccinated at and after the 2nd month. Feedback was provided to convey understanding of the mother's concerns (Corroborate). Subsequently, information was provided about our practices regarding vaccines and our expertise in the field (About me). Using examples based on scientific evidence, the benefits of vaccines in our country were emphasised, demonstrating that the benefits outweigh potential side effects (Science). The mother was advised to complete the child's vaccinations as soon as possible for the child's health, and it was emphasised that our own children were fully vaccinated (Explain/Advise). Specific attention was paid to maintaining a respectful tone throughout all communication steps. The conversation dialog with the mother is shown in Figure 1.

On the day of discharge, the mother decided to get her child vaccinated, and the infant received hepatitis B, diphtheria, tetanus, acellular pertussis, inactivated polio, *Haemophilus influenzae type b* (DTaP-IPV-Hib pentavalent vaccine), and conjugated pneumococcal (PCV-13) vaccines in the hospital. As the patient was older than 3 months of age, a purified protein derivative (PPD) skin test was performed, and BCG vaccination for tuberculosis was planned according to the result with a referral to the Family Health Centre. After informing the mother about potential side effects (local reactions, fever, etc.) of the vaccines, the patient was discharged. At the outpatient clinic follow-up one month later, a second dose of PCV-13 and a second dose of DTaP-IPV-Hib pentavalent vaccine were

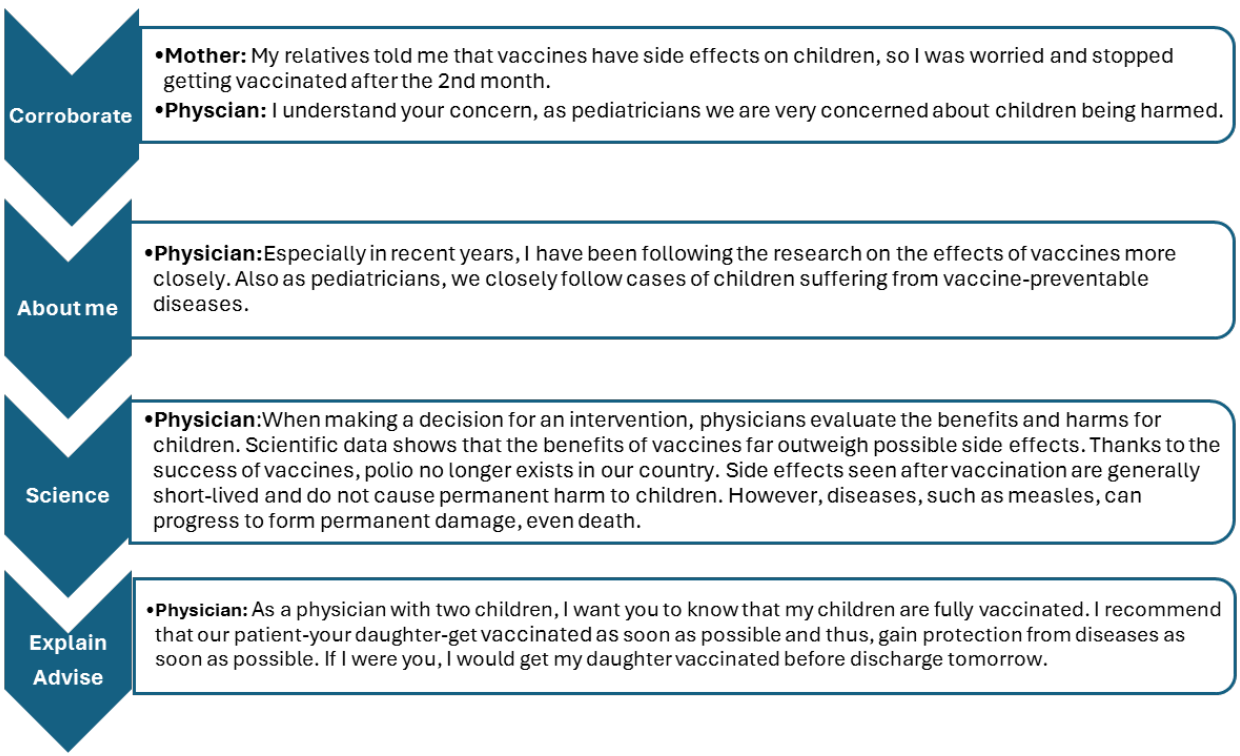

Figure 1: Implementation of the CASE approach.

administered to the 8-month-old patient. In the subsequent month, at 9 months of age, the third dose of DTaP-IPV-Hib pentavalent vaccine, oral polio vaccine, and measles vaccine were administered, completing the catch-up vaccination schedule. The mother was advised to continue the routine vaccination schedule of Expanded Immunisation Programme at and after 12 months of age.

DISCUSSION

The current surge in measles cases may be considered a warning sign for challenges in vaccination implementation. Therefore, engaging with caregivers with vaccine hesitancy and aiming to complete vaccinations for their children has become more crucial. The utilisation of appropriate communication techniques and evidence-based discussion methods when interacting with families can lead to positive changes in vaccination decision-making (8).

Comprehending the reasons behind vaccine hesitancy, a concept ranging from delaying one vaccine to refusing all vaccines, is crucial. The World Health Organisation categorises these reasons into three main groups: contextual influences, individual and group influences, and vaccine/vaccination-specific issues. Contextual influences include communication and media, politics and policies, anti-vaccination lobbies, geographical barriers, and the pharmaceutical industry. Individual and group influences include personal experiences with past vaccinations, perception of vaccination as a social norm, knowledge and awareness of diseases and vaccines, and perception of risk/benefit. Lastly, vaccine-related influences include the method of vaccine administration, design of the vaccination schedule, role of healthcare professionals, and costs for vaccination (9). In this study, mother's vaccine hesitancy originated from the influences of her vaccine-sceptical environment.

Various approaches exist to aid physicians with limited time to conduct structured interviews with vaccine-hesitant caregivers. These include the CASE approach (Corroborate, About me, Science, Explain/Advise), AIMS approach (Announce, Inquire, Mirror, Secure), and motivational interviewing techniques (8, 10-12). Effective communication skills form the basis of these approaches. Rather than directly conveying scientific information about vaccines to parents, a more effective discussion is achieved by eliciting emotions such as empathy, compassion, and trust in healthcare professionals (8). A study using motivational interviewing techniques showed a decrease from 9% to 6.4% in families with vaccine hesitancy in comparison to standard paediatric care (13). However, no research has compared the effectiveness of these different approaches for vaccine hesitancy. Further studies are needed to determine which method is more effective and feasible in achieving positive outcomes.

Studies show that caregivers primarily rely on healthcare professionals for information about vaccines and consider physicians to be the most trustworthy source (8, 14). Physicians' approaches can influence vaccine-hesitant caregivers to change their decisions and have their children vaccinated. On the other hand, a study showed that 37% of paediatricians discontinued follow-ups of unvaccinated children. It is recommended that discussions about vaccination should be conducted at every visit of unvaccinated children, and these children should not be discontinued from follow-up (8, 13).

CONCLUSION

In conclusion, when encountering caregivers with vaccine hesitancy, creating a communication environment characterised by respect and empathy, understanding caregivers' concerns, providing accurate information grounded in specific scientific evidence, positioning oneself as a reliable and determined source of guidance in the eyes of family as the child's healthcare provider, and ensuring ongoing dialogue about vaccination during subsequent visits until the family decides to vaccinate contribute to the management of vaccine hesitancy by healthcare professionals.

Informed Consent: Written consent was obtained from the participants' parents.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Ş.K., E.Ş., İ.K. ; Data Acquisition- Ş.K., E.Ş., İ.K.; Data Analysis/Interpretation- Ş.K., E.Ş., İ.K.; Drafting Manuscript- Ş.K., E.Ş., İ.K. ; Critical Revision of Manuscript- Ş.K., E.Ş., İ.K.; Final Approval and Accountability- Ş.K., E.Ş., İ.K.

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CASE REPORT

Ventricular Septal Defect Repair in a Patient with Hydrocephalus

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ABSTRACT

Congenital heart diseases may be associated with different syndromes or anomalies. Congenital hydrocephalus is a rare disease that leads to increased intracranial pressure due to fluid accumulation through obstruction of intracranial aqueduct flow, Arnold Chiari and Dandy–Walker malformations, or abnormally increased fluid production into intracerebral ventricles. Increased intracranial pressure may produce many problems during the anaesthesia for any operation. Moreover, the postoperative period may be complicated by hydrocephalus. In severe cases, shunt replacement may be necessary. The case reported here is a 10-month-old infant with ventricular septal defect repair diagnosed with hydrocephalus and postoperative early follow-up findings.

Keywords: Ventricular septal defect, hydrocephalus, congenital heart disease

INTRODUCTION

The incidence of congenital hydrocephalus (CH) has been reported to be 0.5–0.8 per 1000 in the population (1). It results in undesirable fluid accumulation in the brain. The most frequent cause of CH is spina bifida, which is described as a multifactorial neural tube defect presented in a ratio of 3/100000 live births (2). In the case of spina bifida, meningomyelocele can be seen. Isolated congenital hydrocephalus may have a quiet normal outcome in general as high as 60 % (3). Poor outcome depends on the association with central nervous system anomalies in addition to the thickness of the cortical mantle (3). In the literature, there is limited acknowledgement that reports the challenging features of the CH associated with congenital heart disease (CHD) (3,4). The most related CHD's are patent ductus arteriosus, atrial septal defect, ventricular septal defect (VSD), coarctation of the aorta, tetralogy of Fallot, bilateral v. cava superior, bicuspid pulmonary valve, hypoplastic pulmonary valve, aortic atresia, dextrocardia, atrioventricular septal effect, and mitral and tricuspid insufficiency (3,4). Acyanotic CHD is frequent in this association (3). Management techniques in the operating room and postoperative period are challenging (3–5). In our case report, we present the successful repair of a VSD in a 10-month-old infant diagnosed with CH who had previously undergone surgical repair for meningomyelocele. During the VSD repair stage, CH was carefully monitored because of the undesirable clinical course worsening.

CASE REPORT

A 10-month-old infant was diagnosed with spina bifida and CH in a routine control. Further imaging tests were performed because of cardiac murmur. VSD was detected on the echocardiogram. In the first month, the patient underwent surgery for meningomyelocele. Postoperative follow-up was uneventful, and an echocardiogram was performed for the monitoring of VSD.

During follow-up, the patient had an insufficiency with swallowing reflex and was being fed via a nasogastric catheter. A ventriculoperitoneal shunt (VPS) was planned. However, the cardiac condition was found to be more of a priority than CH, so it was decided to perform VSD repair. Surgical indications were 10 mm perimembranous VSD, pulmonary artery hypertension of 40 mmHg, Qp/Qs >1,5 and frequent hospitalisation for recurrent respiratory tract infections. Informed consent was obtained from the patient's relatives.

Preoperative evaluation was performed, and no abnormality was detected in blood tests. The VSD was repaired using the transatrial

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approach. Induction of anaesthesia was made in normocarbia, normoxic, and normothermic situations, and vital parameters were within the normal range. Cardiopulmonary bypass (CPB) was established in mild hypothermia, and VSD repair was performed using a polytetrafluoroethylene graft. During CPB, brain circulation was monitored using near-infrared spectroscopy to maintain adequate blood supply. Postoperative blood loss was within an acceptable range, and thrombocyte suspension was not required. After 24 h, the patient tolerated the extubation, and the arterial tension was within the normal range. The neurological evaluation was normal. The possibility of intracranial haemorrhage was assessed by cranial ultrasound and was not found. The patient was discharged on the 10th day. No complications developed. Four months later, the patient underwent an operation for a VPS. Early follow-up for VSD repair was normal.

DISCUSSION

CH is frequently associated with central neurological system pathologies (6). The association between CH and Fallot tetralogy has been published in a case report (7). In addition, associated CHDs in CH have been reported in the literature as follows: VSD, atrioventricular septal defect, patent ductus arteriosus, coarctation of the aorta, atrial septal defect, congenitally corrected transposition of major arteries, and mitral and tricuspid valve regurgitations (3). Bicuspid aortic valve and pulmonary stenosis may be associated with CH (5). Double aortic arch has been reported as associated with CHD in only one case (8), and hypoplastic left heart and ectopia cordis were reported by Garne (1). Crawford stated in his study that CHD is strongly related to poor outcome in CH (3). Of the 11 children, 4 died early months in that series, and complex CHD added an additional risk for mortality even though corrective surgery was realised (3). Unfortunately, the mechanism of additional mortality risk was not mentioned in previous studies.

As Crawford stated, cardiac repair should be performed as a priority because of the cardiac condition of the patient (3).

Singh stated that left-to-right shunt due to double aortic arch, patent ductus arteriosus, and atrial septal defect might complicate the anaesthesia procedure for VPS operation (8). They preferred to manage the patient at the time of anaesthetic induction with hyperventilation to reduce cerebral blood flow while maintaining adequate PaO2 and avoided pulmonary vasodilation by lowering FiO2 and/or hypoventilation (8).

In some cases, surgical treatment of hydrocephalus requires a VPS operation; however, some case reports mentioned a requirement for a conversion of VPS to a ventriculoatrial shunt because of peritoneal fluid accumulation related to different factors (7). In these cases, an appropriate central venous pressure (CVP) ranged between 10 and 12 mmHg was obligatory to provide drainage of the excessive cerebral fluid (7). In case of right heart insufficiency and increased CVP, intracranial pressure could not be properly decreased. CHD by itself requires serious surgery and a long postoperative intensive care unit survey because of drainage after surgery, infections, pulmonary oedema caused by cardiopulmonary bypass (CPB) circulation. These postoperative reasons may trigger changes in acute phase reactant proteins, particularly serum albumin and protein levels. The cytokine storm after CPB generally leads to different degrees of capillary endothelium dysfunction. In conclusion, wide corporeal oedema and third space fluid accumulation due to extravasation occurred. In addition, as mentioned previously, increased CVP may lead to intracranial fluid accumulation (7). Therefore, in CH and CHD associations, intracranial fluid accumulation following cardiac surgery can be observed (9).

Moreover, CHD must be repaired under high-dose heparin for CPB. The risk of intracranial haemorrhage may be aggravated by thrombocyte dysfunction due to CPB circulation, thrombocytopenia, rebound phenomenon of heparin, perioperative arterial hypertension, or increased APTT and INR values due to acute liver dysfunction during postoperative monitoring. In our case, utilisation of high-dose heparin didn't result any intracranial haemorrhage and it is safe when careful perioperative follow-up is implemented. To the best of our knowledge, the association between CH and CHD is rare, and there are a few studies and limited case reports in the literature. It requires further studies to reveal the incidence of fluid accumulation after CHD surgery in patients with CH.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

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ERRATUM

Erratum to: Pregnancy in Patients with Thalassemia: A Single-Center Study

DOI: 10.26650/jchild.2024.1352861

Erratum: It was noticed after the publication of the article titled 'Pregnancy in Patients with Thalassemia: A Single-Center Study' in the 2024/24(1) issue of the Journal of Child that the name and institution of the author Zeynep Karakaş were not included in the article file.

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You can access the updated version of the article through the following link:
https://iupress.istanbul.edu.tr/tr/journal/jchild/article/pregnancy-in-patients-with-thalassemia-a-single-center-study

DESCRIPTION

Journal of Child is an international, scientific, open acces, peer-reviewed official publication of Istanbul University, Faculty of Medicine, Department of Child Health and Diseases and Istanbul University, Institute of Child Health. It is a quarterly journal published in March, June, September and December. Starting from January 2023, except for the articles in process, the journal has started to consider manuscripts in English for evaluation and publication language has become English.

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Journal of Child aims to contribute to the literature by publishing high quality original articles, reviews focusing on key subjects and contemporary developments, and case reports in the field of child health and diseases.

The journal welcomes articles about internal and surgical medicine as well, provided that these are related to child health and diseases. The target group of the journal consists of academicians, researchers, professionals, students, related professional and academic bodies and institutions.

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- Research participants should participate in the research voluntarily, not under any coercion.
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PEER REVIEW POLICIES

Only those manuscripts approved by its every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. After plagiarism check, the eligible ones are evaluated by editor-in-chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope.

The editor hands over the papers matching the formal rules to at least two national/international referees for double-blind peer review evaluation and gives green light for publication upon modification by the authors in accordance with the referees' claims.

Responsibility for the Editor and Reviewers
Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors. Editor-in-Chief provides a fair double-blind peer review of the submitted articles for publication and ensures that all the information related to submitted manuscripts is kept as confidential before publishing.

Editor-in-Chief is responsible for the contents and overall quality of the publication. He/She must publish errata pages or make corrections when needed.

Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers. Only he has the full authority to assign a reviewer and is responsible for final decision for publication of the manuscripts in the Journal.

Reviewers must have no conflict of interest with respect to the research, the authors and/or the research funders. Their judgments must be objective.

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees must be ensured. In particular situations, the editor may share the review of one reviewer with other reviewers to clarify a particular point.

Peer Review Process
Only those manuscripts approved by its every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. After plagiarism check, the eligible ones are evaluated by Editor-in-Chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope.

Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors and ensures a fair double-blind peer review of the selected manuscripts.

The selected manuscripts are sent to at least two national/international referees for evaluation and publication decision is given by Editor-in-Chief upon modification by the authors in accordance with the referees' claims.

Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers and is responsible for final decision for publication of the manuscripts in the Journal.

Reviewers' judgments must be objective. Reviewers' comments on the following aspects are expected while conducting the review.

- Does the manuscript contain new and significant information?
- Does the abstract clearly and accurately describe the content of the manuscript?
- Is the problem significant and concisely stated?
- Are the methods described comprehensively?

- Are the interpretations and consclusions justified by the results?
- Is adequate references made to other Works in the field?
- Is the language acceptable?

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees is important.

AUTHOR GUIDELINES

Manuscript Organization and Submission

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje.org/icmje-recommendations.pdf). Author(s) are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at https://dergipark.org.tr/en/pub/jchild Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Author(s) are required to submit the following documents together with the manuscript and must ensure that the abstract and keywords are in line with the standards explained in below.

- **Copyright Agreement Form**
- **Author Form and ICMJE Potential Conflict of Interest Disclosure Form**
- **Ethics Committee Approval**
- **Cover Letter to the Editor**
- **Title Page:** A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, academic degree(s) and ORCID ID(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: A Turkish and an English abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Abstracts of Case Reports and Reviews should be unstructured. Abstracts should be 250 words.

Keywords: Each submission must be accompanied by a minimum of 3 to a maximum of 6 keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (http://www.nlm.nih.gov/mesh/MBrowser.html) .

Manuscript Types

Original Articles: The main text of original articles should be structured with Introduction, Material and Method, Results, Discussion, and Conclusion subheadings. Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in

accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Review Articles: Manuscripts prepared by experts who have received an invitation letter from the Journal of Child have knowledge on the subject of the article and whose knowledge is reflected in the number of publications and citations in the international literature are welcomed. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

Revisions

When submitting a revised version of a paper, the author(s) must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed

by the author's reply) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 20 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 20-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author(s) and their publication approval is requested within 2 days of their receipt of the proof.

Reference Style and Examples

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Blasco V, Colavolpe JC, Antonini F, Zieleskiewicz L, Nafati C, Albanèse J, et al. Long-term out come in kidneyrecipients from do norstreated with hydroxyethylstarch 130/0.4 and hydroxyethylstarch 200/0.6. Br J Anaesth 2015;115(5):797-8.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study KidneyInt: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktivitelerive Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. SağlıkBilimleriEnstitüsü, DoktoraTezi. 2007.

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIElD/cid.htm.

CHECKLIST

- **Cover letter to the editor**
  - The category of the manuscript
  - Confirming that "the paper is not under consideration for publication in another journal".
  - Including disclosure of any commercial or financial involvement.
  - Confirming that the statistical design of the research article is reviewed.
  - Confirming that last control for fluent English was done.
  - Confirming that journal policies detailed in Information for Authors have been reviewed.
  - Confirming that the references cited in the text and listed in the references section are in line with NLM.
- Copyright Agreement Form
- Author Form
- Permission of previous published material if used in the present manuscript
- Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.
- Statement that informed consent was obtained after the procedure(s) had been fully explained. Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in "Guide for the Care and Use of Laboratory Animals".

- **Title page**
  - The category of the manuscript
  - The title of the manuscript both in Turkish and in English
  - Short title (running head) both in Turkish and in English
  - All authors' names and affiliations (institution, faculty/department, city, country), e-mail addresses
  - Corresponding author's email address, full postal address, telephone and fax number
  - ORCIDs of all authors.
  - Acknowledgement (if exists)

- **Main Manuscript Document**
  - The title of the manuscript both in Turkish and in English
  - Abstracts both in Turkish and in English (250 words)
  - Key words: 3 - 6 words both in Turkish and in English
  - Main article sections
  - References
  - All tables, illustrations (figures) (including title, description, footnotes)