

Evaluation of the Patients Admitted to the Pediatric Emergency Department with Influenza Like Illness During 2009 Influenza A/H1N1 Pandemic Period

2009 Influenza A/H1N1 Pandemisinde Çocuk Acil Servisine Grip Benzeri Hastalık Kliniği ile Başvuran Hastaların Değerlendirilmesi

Ömer Özden, Murat Duman, Pınar Gençpınar, Şule Çağlayan Sözmen, Durgül Yılmaz

Dokuz Eylül University Faculty of Medicine, Department of Pediatrics, İzmir, Türkiye

Abstract

Introduction: In this study, the aim is evaluation of clinical and epidemiological characteristics of the patients presenting to pediatric emergency service with flu like findings.

Methods: Demographical, clinical, laboratory, treatment, hospitalization, and vaccination characteristics of the patients of 1 month-18 years old presenting to Pediatric Emergency Department of Dokuz Eylül University Hospital with influenza-like symptoms in between September 2009-March 2010 have been evaluated.

Results: In the pandemic period 3646 patients were presented with influenza like illness and 902 patients were evaluated in this study. The mean age was 73.4±56.1 (median: 60.0 months) (1-204 months) months. The most affected age group was school children of age between 5 and 14. The age, 42% of patients admitted, was under one year. Presenting symptoms of the patients were determined fever (92%), cough (89%), rhinorrhea (64%), sore throat (40%), myalgia (26%), headache (26%), vomiting-diarrhea (26%), and respiratory distress (3%) in respectively. The rapid antigen test was used in 487 (54%) patients and founded positive in 203 (42%) of them. The pandemic influenza A/H1N1 real time-polymerase chain reaction test was performed in twenty-four (3%) patients, 16 (67%) of them had positive result. The antiviral treatment was started in 357 (90.4%) patients for having a risk factor, in 27 (6.8%) patients for having symptoms of serious illness and in 11 (2.8%) patients as a prophylactic. No patient was died due to pandemic influenza. Twenty-two (2.4%) patients were vaccinated by seasonal influenza vaccine and pandemic virus vaccine while 15 (1.7%) patients were vaccinated by only seasonal influenza vaccine.

Öz

Giriş: Bu çalışmada, çocuk acil servisine pandemik influenza döneminde grip benzeri hastalık bulguları ile başvuran hastaların klinik ve epidemiyolojik özelliklerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Dokuz Eylül Üniversitesi Hastanesi Çocuk Acil Servisi'ne Eylül 2009-Mart 2010 tarihleri arasında grip benzeri hastalık bulguları ile başvuran 1 ay-18 yaş arası hastaların demografik, klinik, laboratuvar, tedavi, hastaneye yatış ve aşılanma özellikleri değerlendirildi.

Bulgular: Pandemi döneminde grip benzeri hastalık tanısıyla başvuran toplam 3646 hastadan 902 tanesi değerlendirmeye alındı. Değerlendirilen hastaların yaş ortalaması 73,4±56,1 (ortanca: 60,0 ay) (1 ay-204 ay) ve en çok etkilenen yaş grubu 5-14 yaş (%44) arası okul çocuklarıydı. Yatırılan hastaların ise %42'sinin yaşı bir yaşın altında idi. Hastaların başvuru semptomları sıklık sırasına göre; ateş (%92), öksürük (%89), burun akıntısı (%64), boğaz ağrısı (%40), miyalji (%26), baş ağrısı (%26), kusma-ishal (%26) ve solunum sıkıntısı (%3) olarak belirlendi. Çalışmada 487 (%54) hastaya hızlı antijen testi yapıldı ve 203 (%42) hastada sonucun pozitif olduğu görüldü. Yirmi dört (%3) hastaya pandemik influenza A/H1N1 gerçek zamanlı-polimeraz zincir reaksiyonu testi yapıldı, 16 (%67) tanesinin sonucu pozitif saptandı. Hastaların 357'sine (%90,4) influenza ilişkili komplikasyonlar için risk faktörü olması, 27'sine (%6,8) ciddi hastalık bulgusu olması ve 11'ine (%2,8) ise profilaktik amaçla olmak üzere toplam 395 (%44) hastaya antiviral tedavi verildi. Pandemi influenzaya bağlı hiç hasta kaybedilmedi. Yirmi iki (%2,4) hastanın mevsimsel influenza ve pandemik virüs aşısı olduğu, 15 (%1,7) hastanın ise sadece mevsimsel influenza aşısı olduğu görüldü.

Address for Correspondence/Yazışma Adresi: Ömer Özden MD, Dokuz Eylül University Faculty of Medicine, Department of Pediatrics, İzmir, Türkiye
E-mail: dromerozden@hotmail.com **ORCID ID:** orcid.org/0000-0003-0297-5250

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Abstract

Conclusion: The study has been shown that the most affected group was the school age due to pandemic influenza, and the majority of patients admitted to hospital were the age under one year. We thought that early initiation of treatment was important to prevent complications because of the influenza especially in the risk groups.

Keywords: Pandemic influenza, pediatric emergency, influenza rapid test

Öz

Sonuç: Çalışmamızda pandemik influenzadan en çok okul çağı çocuklarının etkilendiği, ciddi hastalık bulguları ile hastaneye yatırılan olguların çoğunluğunun ise bir yaş altı çocuklar olduğu bulunmuştur. İnfluenza komplikasyon gelişimi açısından risk taşıyan hastalarda erken tedavi başlanması, komplikasyon gelişiminin önlenmesi açısından önemli olduğu düşünülmüştür.

Anahtar Kelimeler: İnfluenza pandemisi, çocuk acil, influenza hızlı test

Introduction

Influenza virus infections are a public health problem worldwide due to epidemics. The most important feature of the influenza virus is antigenic change. In this way, influenza virus causes epidemics affecting the whole society every year. In addition, it also causes pandemics that affect the whole world every 10-40 years. There have been three influenza pandemics in the last century. These pandemics, which affected large masses, caused significant economic losses, morbidity, and mortality.¹

Pandemic influenza A/H1N1 virus was first identified in Mexico in February 2009 and rapidly spread throughout the world.^{2,3} The World Health Organization (WHO) raised the influenza pandemic alert level to phase-6 on June 11, 2009. Thus, the first pandemic of the 21st century was declared.⁴

The spread of the virus is by droplet, like classical influenza agents.⁵ The incubation period of the pandemic virus is 1-7 days. In the first 2-3 days of the disease, the amount of virus excreted in respiratory secretions is the highest and this is known to be correlated with fever. Therefore, the period of influenza contagiousness is considered to be 24 hours before the onset of fever and 24 hours after the normalization of fever.^{5,7} The disease has a sudden onset and is characterized by high fever, myalgia, malaise, headache and dry cough. The disease resolves in the majority of patients 3-7 days after the onset of symptoms. Influenza does not usually cause severe illness, but can cause serious and fatal infections in young children, the elderly people and the chronically ill people, who are considered risk groups.⁶ There are many laboratory methods available for diagnosis, treatment and surveillance. Antigenic diagnostic methods such as direct immunofluorescence and rapid tests are used in health care institutions where drug use and infection control are in question and therefore rapid diagnosis is important. In these centers, isolation of the virus and detailed antigenic information are not needed, and high sensitivity and specificity of the test are important.^{3,6,8,9}

The aim of this study was to evaluate the demographic, clinical and epidemiologic characteristics of patients aged between 1

month and 18 years who presented to the Pediatric Emergency Department of Dokuz Eylül University Hospital with influenza-like symptoms during the 2009 A/H1N1 influenza pandemic that affected the whole world, to obtain information to be used in future pandemics, to determine the points to be considered in the follow-up of patients with this information and to contribute to the epidemiologic data on influenza in our country.

Materials and Methods

Patients aged between 1 month and 18 years who presented to the Pediatric Emergency Department of Dokuz Eylül University Hospital with influenza-like illness (ILI) during the influenza virus 2009 A/H1N1 pandemic were included in the study. The case management guideline of the Centers for Disease Control and Prevention (CDC) was used for the clinical definition of ILI.^{3,6} According to this definition, a new-onset axillary temperature above 38 °C and/or sore throat and/or dry cough without any other cause was accepted as ILI and the "pandemic influenza 2009 A/H1N1 follow-up form" was filled out in the pediatric emergency department. In this form, demographic and clinical characteristics, examination and laboratory findings, risk groups, whether they received antiviral treatment, hospitalization, complications and vaccination status were recorded. Patients with complete data on the follow-up form were included in the study. Clinical findings such as body temperature, nasal discharge, cough, sore throat, headache, myalgia, vomiting-diarrhea and respiratory distress were evaluated in all patients. Risk groups for the development of complications were identified as children younger than two years of age, patients with chronic lung, kidney and liver diseases, neurologic, cardiovascular, metabolic and endocrine diseases, chronic aspirin use, immunodeficiency and obesity.^{3,6,7} Signs of severe disease were considered as general condition disorder, extreme restlessness, altered consciousness, moderate to severe dehydration, respiratory distress, convulsions, persistent high fever and clinical deterioration after resolution of influenza symptoms.^{3,6,7}

Laboratory findings, reasons for hospitalization, treatments administered, length of hospitalization, complications, morbidity and mortality of hospitalized patients were evaluated.

Influenza A/B rapid antigen test was performed from nasal aspiration specimens of patients who were in risk groups for the development of complications or who had signs of severe disease. Laboratory findings included complete blood count, C-reactive protein (CRP), influenza rapid antigen test, and real time-polymerase chain reaction (RT-PCR) test results.

Ethics committee approval for the study was obtained from the Dokuz Eylül University Non-interventional Clinical Research Evaluation Commission (decision no: 2010/06-06, date: 30.06.2010). Consent for the study was obtained from the legal guardians of all patients.

Statistical Analysis

SPSS 15.0 program was used for statistical evaluation. Quantitative variables were expressed as mean $\pm$ standard deviation and median (minimum-maximum), and qualitative variables were expressed as percentages. Chi-square test was used to compare categorical data. The significance level of the findings was accepted as $p < 0.05$.

Results

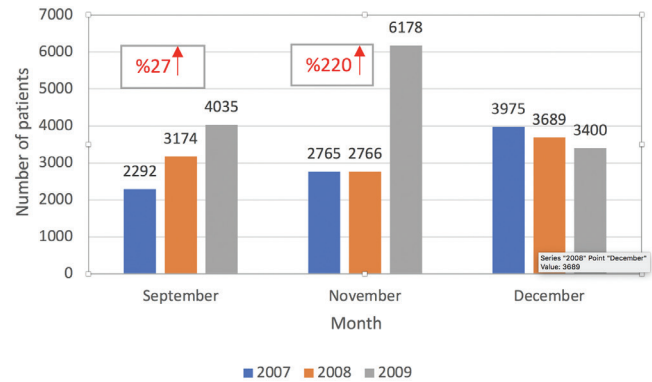
A total of 3646 patients were admitted to our clinic with ILI symptoms between September 2009 and March 2010. Of these cases, 902 patients with complete data were included in the study. During this period, it was found that the number of patients admitted to the pediatric emergency department increased by 27% in October compared to the previous year and by 220% in November, when the cases were most common, compared to the previous year. It was observed that the number of patients started to increase as of the first week of September, peaked in the third and fourth weeks of November and decreased rapidly in December (Graph 1).

Of the patients admitted to the study, 501 (55%) were boys, 401 (45%) were girls, the mean age was 73.4 ± 56.1 months (median: 60.0 months) (1 month - 204 months), and patients aged 5-14 years were mostly affected by the pandemic (Graph 2). The duration of symptoms before presentation varied between 1-10 days, with a mean symptom duration of 2.03 ± 1.55 days. It was observed that 75% of the patients presented to the emergency department within the first 48 hours of symptoms.

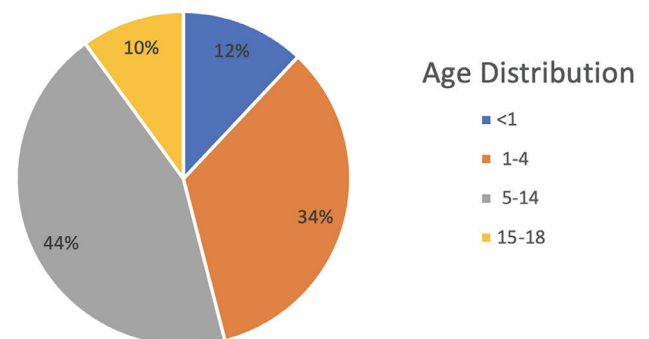
In all cases we evaluated, at least one of the clinical definitions of influenza disease such as fever, cough, sore throat, headache, myalgia, runny nose, vomiting and diarrhea was present. The most common findings in patients admitted to

the emergency department with ILI were as follows: fever (92%), cough (89%), runny nose (64%), sore throat (40%), myalgia (26%), headache (26%), vomiting-diarrhea (26%) and respiratory distress (3%) (Graph 3).

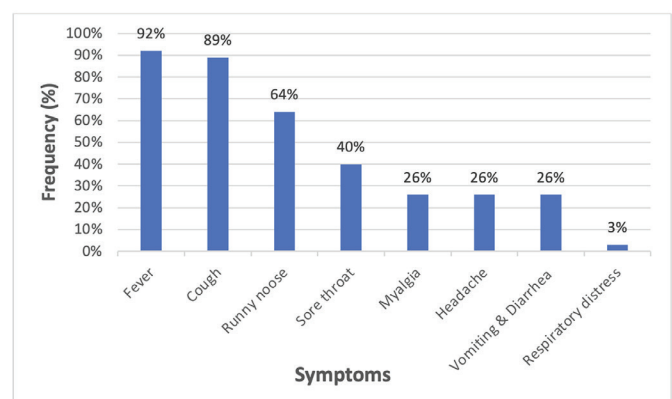
In the emergency department, 132 (14%) patients had a temperature $\leq 37.9^\circ\text{C}$, 486 (54%) had a temperature $38-38.9^\circ\text{C}$ and 284 (32%) had a temperature $\geq 39^\circ\text{C}$. Four hundred and fifty-one (50%) of the patients had risk factors for



Graph 1. The impact of pandemic influenza on emergency room patient load
*Percentage rates indicate the increase in the number of patients presenting to the emergency room in October-November 2009 compared to 2008



Graph 2. Age distribution of cases (%)



Graph 3. Patients' presenting symptoms

influenza-related complications. The most common risk factor was age less than two years (50.1%). Other risk factors were chronic lung disease (35.5%), neurologic disease (5.1%), cardiovascular disease (2.7%), metabolic disease (2.2%), renal-hepatic disease (1.8%), immunodeficiency (1.3%), hematologic disease (0.9%) and chronic aspirin use (0.4%). Treatment was given to 85% of patients with risk factors.

Signs of influenza-related serious illness were present in 27 (3%) patients. Respiratory distress was detected in 24 (89%) patients and was the most common serious illness finding. Febrile convulsion was detected in one of the other three patients, moderate to severe dehydration in one patient and altered consciousness in one patient. Risk factors were not present in 33% of the patients with serious illness. All patients with signs of severe illness were hospitalized and followed up and antiviral treatment was initiated.

Laboratory evaluation was performed in 111 (12%) of the patients. The mean leukocyte count was 10000 ± 5000 ($1700-22400$) mm^3 . Leukocytosis was found in 24% and leukopenia in 8% of the patients. CRP was found to be elevated in 50 (45%) patients and the mean CRP value was 22.1 ± 42.4 (median: 8.4) (0.2-314). Chest radiography was performed in all patients with lung auscultation findings on examination. Radiologic findings were detected in 44 (75%) of the patients. Consolidation was found in 23 (52%) patients and peribronchial prominence and increased ventilation were found in 21 (48%) patients.

In the study, 487 (54%) patients underwent influenza rapid antigen test and 203 (42%) were positive. Twenty-four (3%) patients underwent pandemic influenza A/H1N1 RT-PCR test and 16 (67%) were positive. Influenza rapid antigen test was performed in 59 (44%) of 132 patients with fever ≤ 37.9 °C, and it was found positive in only 2 (3%) patients. Of 486 (54%) patients with a body temperature between 38-38.9 °C, 257 (52%) underwent influenza rapid antigen test and 82 (32%) were positive; 171 (60%) of 284 (32%) patients with a body temperature ≥ 39 °C underwent influenza rapid antigen test and 119 (70%) of these patients were positive. The positive rate of rapid antigen test was statistically significant in patients with a body temperature ≥ 39 °C compared to patients with a body temperature of 38-38.9 °C ($p < 0.001$).

Antiviral treatment (oseltamivir) was initiated in 395 (44%) patients. Treatment was initiated in 357 (90.4%) patients because of risk factors for influenza-related complications, in 27 (6.8%) patients because of evidence of severe disease and in 11 (2.8%) patients for prophylactic purposes. Antiviral treatment was started in 80% of patients within the first 48 hours after the onset of symptoms. Of the 395 patients who started antiviral treatment, 22 (5.5%) had drug side effects in the form of nausea and vomiting after drug intake.

Thirty-three (3.6%) of the patients were hospitalized, the mean age of these patients was 34.9 ± 41.4 months (median: 18 months) (2-144 months) and 42% of the hospitalized patients were over one year old. The most common reason for hospitalization was pneumonia ($n=28$; 69.6%). Other reasons for hospitalization were febrile convulsions, dehydration and altered consciousness. Influenza-related risk factors were present in 27 (82%) of the hospitalized patients. The most common risk factor was being younger than two years of age ($n=18$, 54%). There were no deaths due to pandemic influenza 2009 A/H1N1 during the study period.

Of the 902 patients in the study, 15 (1.7%) received seasonal influenza vaccine and pandemic influenza vaccine together, while 22 (2.4%) received only seasonal influenza vaccine. Three of the patients who received pandemic influenza vaccine presented to the emergency department within 48 hours after vaccination. Two of these patients presented with pain and redness in the vaccinated arm and one presented with a fever of >37.9 °C. The other 12 patients presented to the emergency department with symptoms of ILI within 2-7 days after vaccination.

Discussion

The influenza A/H1N1 pandemic, declared by the WHO as the first pandemic of the 21st century, first started in Mexico in March 2009 and spread rapidly around the world. The pandemic virus is a subtype of influenza that has never been encountered before and therefore people are generally susceptible.⁴ The attack rate of pandemic virus infection has been reported to be 20%.⁹

With the pandemic, there has been a significant increase in the patient load admitted to emergency departments with ILI clinic all over the world. In the northern hemisphere, the number of patients affected by the pandemic virus and admitted to the emergency department reached the highest level on the third and fourth patient of November.⁶ Similar findings have been obtained in other studies and it has been shown that the patient load in pediatric emergency departments increases by 150-200% during periods of intense pandemic.¹⁰ In this study, similar findings were found in parallel with the literature (Graph 2). These results clearly show the increase in emergency department workload due to the pandemic. It is thought that the excessive media attention to the pandemic, the sensitivity and anxiety in the society and the daily reporting of death cases were effective in this increase.

Pandemic influenza infection mostly affected school-age children and young adults (5-24 years).^{2,3,11} Studies have shown that outbreaks usually occur during periods when

schools are open and that school-age children are most frequently exposed.¹¹ In addition, it has been shown that the rate of spread of pandemic influenza is highest in school-age children (36%).¹¹ Epidemiologic data have shown that children and young adults are more susceptible to pandemic influenza infection than older people.^{3,6,7,12,13} In our study, similar to the data in the literature, it was found that school-age children were most frequently affected by pandemic influenza (Graph 2).

In studies, the most common symptoms in patients with pandemic influenza A/H1N1 were reported to be fever (94%) and cough (92%).^{14,15} Clinical findings are similar in seasonal and pandemic influenza. However, vomiting and diarrhea complaints, especially in children, have been reported to be higher in pandemic influenza (approximately 25%), whereas this rate is much lower in seasonal influenza.^{2,6,7} In our study, both the most common symptoms of pandemic influenza and the rate of nausea and vomiting symptoms were similar to the literature (Graph 3).

It has been shown that influenza infection is more severe in patients with risk factors for influenza-associated complications.^{3,6} CDC reported that approximately 70% of patients hospitalized for pandemic influenza had at least one risk factor for influenza complications.⁶ In our study, similar to the literature, 82% of patients with severe disease findings and hospitalized had at least one of the risk factors for influenza-associated complications. It is an expected result that patients with risk factors will have a more severe course. Therefore, it is considered vital that patients who have risk factors for influenza-related complications during the pandemic period and who show symptoms of ILI should be admitted to a healthcare institution early and antiviral treatment should be started within the first 48 hours of symptoms. Recent data show that 25% of hospitalized pediatric patients, 42% of high-risk outpatients and 75% of children younger than two years with influenza did not receive antiviral treatment based on evidence and guidelines.¹⁶⁻¹⁸

It has been reported that CRP and white blood cell counts of children with pandemic influenza are generally within normal limits for the patient's age.¹⁹ In our study, the proportion of patients with leukocytosis, leukopenia or elevated CRP was found to be higher compared to the literature. The reason for this is that only cases with severe disease findings were examined and it is thought that bacterial coinfection may be present in these cases. In the literature, the rate of bacterial coinfection in pandemic influenza cases with complications was reported to be between 23-39%.^{20,21}

It has been reported that the initial chest radiographs of children with mild symptoms of pandemic influenza are often normal, abnormal radiologic findings are detected

in a very small number of children, and the most common finding is excessive ventilation in the lungs with peribronchial prominence.²² The most common abnormal findings on chest radiographs of children hospitalized due to pandemic influenza have been reported as bilateral, symmetric and multifocal consolidation areas and ground-glass opacities frequently accompanying them.²² Similar to the literature, the most common radiologic finding in this study was lung parenchymal consolidation, and peribronchial prominence and increased ventilation followed it in the second frequency. It has been stated that rapid antigen tests with high sensitivity and specificity can be used in the pandemic period for diagnosis due to the rapid spread of influenza, short incubation period, prevention of unnecessary antibiotic use and the necessity to start antiviral treatment within the first 48 hours.^{23,24} Influenza rapid antigen tests detect influenza A, but cannot detect influenza A subtypes. Since 99.4% of the influenza A subtype circulating during the pandemic period was pandemic influenza, it was announced by WHO that the positivity detected could be accepted as pandemic influenza.^{6,24} In our study, a significant correlation was found between the degree of fever and rapid antigen test positivity. In the literature, it has been reported that the amount of virus excreted by inhalation in influenza infection correlates with fever and is highest in the first 2-3 days of the disease.^{6,9} Since approximately 75% of the patients in our study were evaluated within the first 48 hours after the onset of symptoms, the test reliability was considered to be high.

WHO and CDC have recommended pandemic influenza A/H1N1 treatment for children with a high risk of complication-mortality or with signs of severe disease. It has been reported that starting neuraminidase inhibitors (oseltamivir or zanamivir) as soon as possible, especially within the first 48 hours of symptoms, will provide the most benefit.^{6,25,26} In this study, it was observed that treatment was started within the first 48 hours in 80% of patients with risk factors and severe disease findings. Early initiation of treatment in appropriate cases is thought to have prevented death or serious complications in any patient. Many studies have reported nausea and vomiting as the main side effect of oseltamivir in children, with vomiting occurring in approximately 15% of children receiving oseltamivir.²⁵⁻²⁷ In this study, nausea and vomiting after oseltamivir intake was less common than reported in the literature.

In our study, it was found that the rates of vaccination against both seasonal and pandemic influenza were quite low during the pandemic influenza period. Similarly, in many studies, it has been reported that the rate of vaccination acceptance is lower than expected.^{28,29} In studies, the reasons for not being vaccinated in the population have been stated as not

trusting the vaccine, thinking that they will not get pandemic influenza, believing that the disease is mild and insignificant, and not being in the risk group for vaccination.^{28,30} Studies have also shown that the rate of pandemic influenza vaccination was significantly higher in patients who received seasonal influenza vaccine.^{29,30} In this study, in parallel with the global data, all patients who received pandemic influenza vaccine also received seasonal influenza vaccine. Three of our patients who received pandemic influenza vaccine had mild vaccine side effects, but none of them developed a serious vaccine-related reaction. In our country, the rate of post-vaccine adverse reactions has been reported as 3.62 (100,000).³¹

Study Limitations

The limitation of our study is that it is a single-center study. In order to see the effect of the pandemic period more clearly in our country, multicenter epidemiological studies with a larger number of patients are needed. In this way, it will be possible to prepare for future pandemics at the national level. Our study will contribute to national pandemic data.

Conclusion

In our study, it was found that school-age children were mostly affected by pandemic influenza, and the majority of patients hospitalized with severe disease findings were under two years of age. It is thought that early treatment initiation in patients at risk for the development of influenza-related complications and close follow-up of patients with severe disease findings are important in terms of complications, morbidity, and mortality.

Ethics

Ethics Committee Approval: Ethics committee approval for the study was obtained from the Dokuz Eylül University Non-interventional Clinical Research Evaluation Commission (decision no: 2010/06-06, date: 30.06.2010).

Informed Consent: Consent for the study was obtained from the legal guardians of all patients.

Footnotes

Authorship Contributions

Concept: Ö.Ö., M.D., Design: Ö.Ö., M.D., Data Collection or Processing: Ö.Ö., M.D., Analysis or Interpretation: Ö.Ö., M.D., P.G., Ş.Ç.S., D.Y., Literature Search: Ö.Ö., M.D., P.G., Ş.Ç.S., D.Y., Writing: Ö.Ö., M.D., P.G., Ş.Ç.S., D.Y.

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