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Documented 2009 H1N1 influenza A infection in pediatric liver transplant patients – Description and follow-up of 7 patients

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Background/aims: *There is a paucity of data regarding pediatric liver transplant patients from Turkey and less so globally. We report here 7 pediatric cases with documented H1N1 nove Influenza A infection.* ***Material and Methods:*** *7 pediatric liver transplant patients on immunesuppression, tested positive with PCR for 2009 H1N1 Influenza A, have been analyzed retrospectively. All patients were commenced oseltamivir treatment and 6 patients continued to take their immunosuppressive treatment.* ***Results:*** *All patients (n=7) survived H1N1 novel Influenza A infection without any sequela. 1 patient has been admitted to Intensive Care Unit and has been discharged without any sequela. There was no graft dysfunction or loss during the infection episode.* ***Conclusion:*** *2009 H1N1 Influenza A infection did not cause any mortality among our patients. Oseltamivir treatment may have played a role for improving in our patients' condition. Immunosuppression can be continued in pediatric liver transplant patients with close monitoring of vital signs and graft function.*

Key words: Liver transplant, child, H1N1 influenza A

Karaciğer nakli olmuş 7 çocuk vakada 2009 influenza A infeksiyonu

Amaç: *Ülkemizde ve daha az oranda dünyada, pediyatrik karaciğer nakilli hastalarla ilgili, 2009 H1N1 İnfluenza infeksiyonu hakkında çok sınırlı bilgi yayımlanmıştır. Amacımız, merkezimizde takip edilmiş 7 karaciğer nakilli vakada H1N1 infeksiyonu bulgularını ve 6 aylık takip sonuçlarını tartışmaktır.* ***Yöntem ve Gereç:*** *Eylül - Kasım 2009 tarihleri arasında, PCR yöntemi ile pozitif saptanmış 7 karaciğer nakilli çocuk vakanın dosyası bu çalışmada retrospektif olarak incelenmiştir. Hastaların hepsine oseltamivir tedavisi başlanmıştır. 6 vakanın immunsupresyonu bu süreç içinde kesilmemiştir.* ***Bulgular:*** *Vakalarımızın hepsi (n=7), 2009 H1N1 infeksiyonunu sekelsiz geçirdiler. 1 vaka Çocuk Yoğun Bakım Ünitesi'nde izlenmiştir. Vakalarımızda nakledilmiş karaciğere ait kayıp veya disfonksiyon, infeksiyon ve takip süresince gözlenmemiştir.* ***Sonuç:*** *2009 Influenza A infeksiyonu, merkezimizde takip edilen çocuklarda mortaliteye neden olmamıştır. Oseltamivir tedavisinin bu duruma katkısı olmuş olabilir. Pediyatrik vakalarda immunsupresif tedavinin devamı, vital bulguların ve graft fonksiyonlarının yakından takip edilmesi şartıyla, mümkün olabilir.*

Anahtar kelimeler: Karaciğer nakli, çocuk, H1N1 influenza A

INTRODUCTION

Influenza A can be a significant risk factor for patients with liver transplantation, leading even to the loss of the graft. The 2009 influenza A outbreak was declared as a major threat for humanity by the World Health Organization (WHO). Children with liver transplant can be considered at more risk due to their immunosuppressive treatment. We report here seven pediatric cases with liver

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transplant and documented H1N1 influenza infection, of which six were under tacrolimus (TAC) treatment at the time of infection (Table 1). None of the patients was taking prednisone, and all survived the infection without any sequelae. In Turkey, there has been no case series reported about the outcome of pediatric liver transplant in patients with 2009 H1N1 influenza infection. We report here a pediatric case series from a single institution with liver transplant.

MATERIALS AND METHODS

Seven patients admitted to our institution between September and November 2009 were analyzed retrospectively in this study. All patients tested positive for H1N1 influenza A with polymerase chain reaction (PCR). After November 2009, there was no available test material for H1N1 influenza, and whether treated or not, patients with suspected H1N1 influenza were excluded from this study.

Case 1:

A nine-year-old boy, transplanted when he was eight years old with underlying Wilson disease, was diagnosed with upper respiratory tract infection (URTI) with the complaints of fever, fatigue, cough, and rhinorrhea during a regular visit to the transplant clinic. His symptoms started two days before the clinic visit. He had been on TAC and mycophenolate mofetil (MMF) immunosuppressive treatment since the time he was transplanted. His last physical examination before the onset of symptoms was unremarkable. All of the patient's laboratory results are shown in Table 2 in detail. He was commenced on oseltamivir treatment 75 mg twice daily po. H1N1 PCR result was positive. He completed a five-day course of oseltamivir treatment without any complications. He did not have any complications or morbidity attributable to 2009 H1N1 flu or the treatment itself. After seven months of follow-up, he did not show any signs of acute or chronic rejection of the graft.

Case 2:

A 14-year-old boy with autoimmune hepatitis, who had a liver transplant one year before, was seen in the transplant clinic with rhinorrhea and cough for three days. He had been on TAC and MMF since the transplant. He was admitted to the hospital and commenced on oseltamivir treatment for five

Table 1. Demographics of the patients

Case	Sex	Current Age	Age at LTX	Age at Infection	Follow-up *	Underlying Disease	Immunosuppressive Treatment
1	M	10 $^{10/12}$	9 $^{2/12}$	10 $^{3/12}$	7	WD	TAC
2	M	13	11 $^{8/12}$	12 $^{6/12}$	6	AIH	TAC
3	M	2 $^{8/12}$	1 $^{6/12}$	2 $^{2/12}$	6	HB	TAC
4	M	8 $^{4/12}$	7 $^{4/12}$	7 $^{10/12}$	6	CC	TAC
5	M	13 $^{6/12}$	8 $^{2/12}$	12 $^{11/12}$	7	CC	NONE
6	M	4 $^{10/12}$	3 $^{10/12}$	4 $^{4/12}$	6	HEP A, ALF	TAC
7	M	2 $^{2/12}$	7/12	1 $^{1/12}$	6	EHBA	TAC

M: Male. LTX: Liver transplantation. WD: Wilson disease. AIH: Autoimmune hepatitis. HB: Hepatoblastoma. CC: Cryptogenic cirrhosis. HEP A: Hepatitis A. ALF: Acute liver failure. EHBA: Extrahepatic biliary atresia. TAC: Tacrolimus. * represented in months

Table 2. Laboratory data of the patients

	PRE TAC	PERI TAC	PRE WBC	PERI WBC	PRE CRP	PERI CRP	PRE ALT/AST	PERI ALT/AST	POST ALT/AST
Case 1	8.4	7.4	5600	5800	0.4	1.7	39 / 44	38 / 42	34 / 41
Case 2	6.8	7.2	8490	4700	0.7	1.2		16 / 26	27 / 34
Case 3	6.2	9.2	4200	6100	15.2	9.9	19 / 36	21 / 55	13 / 27
Case 4	9.4	4.6	6400	2800	1.8	50	41 / 49	65 / 69	46 / 67
Case 5			2700	2200		12.2	87 / 60	90 / 65	176 / 100
Case 6	8.4	8.9	11100	4700		8.8	18 / 54	16 / 48	34 / 54
Case 7	4.6	4.8	5000	4820	0.5	157.5	68 /48	60 / 60	57 / 48

PRE: Before H1N1 infection. PERI: During H1N1 infection. POST: Immediately after H1N1 infection. TAC: Tacrolimus (ng/ml). WBC: Leukocyte level (X/mm^3). CRP: C-reactive protein (mg/dl). ALT/AST: Alanine/aspartate aminotransferase (IU/ml).

days after his PCR result was found positive for H1N1 virus infection. He did not have any concomitant antibiotic treatment and was discharged on the 6th day of hospitalization without any complications.

Case 3:

A 2.5-year-old boy with hepatoblastoma had been transplanted when he was 18 months old. He was admitted to the hospital because of ongoing fever, cough and rhinorrhea for two days. Oseltamivir treatment was given for five days for PCR-proven H1N1 infection. This patient was also commenced on intravenous ampicillin/sulbactam treatment due to chest X-ray (CXR) findings consistent with lobar pneumonia. He was discharged on the 6th day of his admission. Ampicillin/sulbactam treatment was discontinued on the 10th day. One month after his discharge, this patient developed respiratory failure and was admitted to the intensive care unit (ICU) with the diagnosis of pneumonia complicated with acute respiratory distress syndrome (ARDS). Fifteen days after ICU admission, he was transferred to the infectious diseases (ID) clinic to complete his antibiotic treatment. During these two episodes, he never had any signs of organ rejection. This patient had been on TAC for 12 months since the liver transplant. His immunosuppression was discontinued in his ICU admission but not in the first admission as per our recommendation. He was discharged from the hospital without any sequelae. After six months of follow-up for the respiratory failure event, he had had no signs or symptoms of respiratory disease or organ rejection. It is unclear to us whether this patient's second admission with respiratory failure was connected to H1N1 infection. However, he still had residual recurrent respiratory symptoms six months after the 2009 H1N1 influenza incident. He was admitted to the hospital again with the diagnosis of pneumonia, and was investigated for other underlying conditions responsible for the recurrent pneumonia. His work-up for recurrent pneumonia did not reveal any underlying pathology. His immunosuppressive treatment was commenced again after he became completely asymptomatic 10 days after discharge. He did not show any graft dysfunction or signs of another episode of infection during the follow-up.

Case 4:

An eight-year-old boy, who had cryptogenic cirrhosis, was transplanted when he was seven years, four months old. Six months after liver transplantation, he was seen in the clinic with fever (38.9°C), rhinorrhea and cough, which started the day before he was seen in the clinic. He was admitted to the ID ward and commenced on oseltamivir and ampicillin/sulbactam treatment because of CXR findings consistent with pneumonia. He was found positive for H1N1 virus infection with PCR. He was on TAC only at the time he was seen in the clinic. He was admitted for six days in the hospital and was discharged afterwards without any complications.

Case 5:

A 13-year-old boy was transplanted four years before with the diagnosis of cryptogenic cirrhosis. He was off immunosuppression due to a previous history of suspected posttransplant lymphoproliferative disease and multiple attacks of cholangitis due to bile duct anastomosis dysfunction. He was admitted to the ID ward after a positive H1N1 viral PCR result, as he had fever (40°C) and cough lasting for two days. He was discharged home after two days of hospitalization, while he was on oseltamivir treatment, as he refused to stay in the hospital. Oseltamivir treatment was completed to five days and he did not have signs of rejection or any complication following H1N1 virus infection.

Case 6:

A male patient, 58 months old, transplanted at the age of almost four years after fulminant hepatitis A infection, was admitted to the hospital after the H1N1 PCR result was reported as positive. He had complaints of fever (38.5°C), cough and rhinorrhea for three days. He had findings consistent with pneumonia on his CXR, and was commenced on both oseltamivir for five days and ampicillin/sulbactam for 10 days. He was discharged from the hospital on day 3 after he was afebrile and stabilized. He completed his treatment at home and did not experience any complications.

Case 7:

A 26-month-old boy, transplanted when he was seven months old with the diagnosis of extrahepatic biliary atresia, was seen in the clinic with fever (39.5°C), cough and rhinorrhea. He was admitted to the hospital and was commenced on oseltamivir and ampicillin/sulbactam treatment. He had pleural effusion and consolidation on his CXR. He has been on TAC for 19 months. TAC was not discontinued; the patient was discharged from the hospital on the 7th day of his hospitalization without any complications. He completed the ampicillin/sulbactam treatment course at home.

DISCUSSION

Various organizations declared the 2009 H1N1 influenza as a significant threat for humans. The Centers for Disease Control (CDC) has recently published data concerning the extensiveness of H1N1 infection among pediatric patients (1). In our institution, 103 patients are followed in the pediatric liver transplant clinic. Overall survival in our cohort is approximately 90%. We report here seven liver transplant patients with documented H1N1 viral infection. Although we recommend routinely getting the commercial vaccine shot for seasonal influenza, none of them had been vaccinated against seasonal influenza virus or the 2009 H1N1 influenza virus. Financial problems may have contributed to this, as families provide the vaccine by themselves. All patients presented here had fever, cough and rhinorrhea ongoing for one to three days. Six patients were admitted to the hospital and were discharged without any complications. One patient (Case 3), four weeks after being discharged from the hospital, developed pneumonia and subsequently ARDS. However, it is not clear whether this incident was due to the 2009 H1N1 influenza infection, or if this was an isolated nosocomial infection. Case 3 was discharged from the ICU eventually without any complications. All patients but one were on immunosuppressive treatment. We followed patients with close monitoring of physical examination findings, liver function tests and TAC levels during their admission. Immunosuppressive treatment was continued at the same dose during the H1N1 infection as used before to avoid the risk of graft rejection, except in Case 3. None of the patients showed signs of rejection during the 2009 H1N1 influenza infection. All patients were treated with oseltamivir, and we did not observe any side effects. Oseltamivir treatment was given to all patients empirically, and continued for five days, as PCR results were returned as positive. Four patients received antibiotics (Cases 3, 4, 6, 7) during their admission. Ampicillin/sulbactam had been commenced for all four patients as per ID consult. All but one patient survived the 2009 H1N1 influenza pandemic without any complications. Case 3 showed signs of respiratory disease, which resolved without any sequelae during his clinical follow-up. He was investigated further for the possible underlying conditions for the recurrent pneumonia, and no underlying pathology was found.

Libster et al. (2) reported 251 cases from Argentina with 2009 H1N1 influenza. In that series, 16 cases were reported to be under immunosuppression. Out of 251 cases, 13 patients died. None of the patients in the group taking immunosuppressive died. However, it is not clear from the article whether patients continued taking immunosuppression or not. In our cohort, continuation of immunosuppressive treatment at the usual dose neither deteriorated the patient's condition, nor caused morbidity or mortality. In Libster's cohort, 49 patients were admitted to the ICU, and 42 of them were mechanically ventilated. ICU admission and mechanical ventilation were highest among patients with asthmatic conditions. Our patient with ICU admission and subsequent ARDS did not have any signs of asthma prior to the incident. In Libster's cohort, 25 patients were diagnosed with either documented or presumptive pneumonia, and 186 cases were treated with antibiotics. In our cohort, we diagnosed four out of seven patients with pneumonia and commenced antibiotics in all four patients.

Perez-Padilla (3) reported 18 mixed pediatric and adult cases from Mexico with pneumonia and respiratory failure. Five out of 18 cases had underlying conditions, none with immunosuppression. Seventeen cases were treated with several antibiotics. Seven patients died due to respiratory failure and related complications. Of seven patients, none was less than five years old, one was between 5-10 years old and another was 10-15 years old. The major risk factor for mortality for children under five years of age was neurodevelopmental delay or pulmonary conditions.

Lister (4) reported 32 pediatric influenza A infection cases admitted to the ICU with or without comorbidities. Of 32 patients reported, nine died.

Hackett (5) reported 78 cases with positive H1N1 influenza from the United Kingdom (UK). The median hospital stay was 24 hours. Six patients required ICU admission. The most commonly observed symptoms were fever, cough, rhinorrhea, vomiting, and sore throat. In our cohort, all patients had fever, cough and rhinorrhea. None of the patients followed had additional findings. An interesting point in this article is that 29 patients out of 71 did not fulfill the criteria defined by the UK's Health Protection Agency.

In our report of seven cases, there are some weak points. This is a retrospective analysis of seven patients with 2009 influenza A infection. We included in this report only PCR-positive H1N1 influ-

enza A infection patients with liver transplant. In the clinic, we sent specimens from patients only with fever higher than 38.5ºC and cough and rhinorrhea. It is possible that we missed some patients with H1N1 influenza A infection with vague symptoms and not fulfilling the criteria mentioned above, as Hackett et al.5 described in their cohort. Supporting the argument, Meyer et al. (6) reported an asymptomatic heart transplant recipient patient. On the other hand, we do not have any other patient in our transplant cohort who died or was admitted to the hospital with respiratory failure or pneumonia. Even if there are patients, who were not investigated for 2009 influenza A infection, they must have had a mild enough disease that did not cause any morbidity or mortality.

Kumar et al. (7) reported the outcome of 237 solid organ transplant patients, both adults and children, with influenza A infection from 26 transplant centers. In this cohort, 48 patients had liver transplant. Unfortunately, it is not mentioned in the article how many of the 48 patients were children. In this cohort, 70% (n=167) of the total patients were hospitalized, 16% (n=37) were admitted to the ICU, and 4% of the patients (n=10) died at a median of 15 days after symptom onset. They found out that early introduction of oseltamivir treatment, 48 hours after the onset of symptoms, was associated with lower risk of hospital and ICU admissions, need for mechanical ventilation and death. However, one of the problems with this study, as they mentioned, is that the influenza A diagnosed in their cohort was not necessarily H1N1 influenza and might have also included patients with seasonal influenza A.

Because this is a retrospective analysis of patients, some data are missing for different reasons. We do not have data on one patient, just prior to infection, because this patient was followed every six months, as five years had passed since the transplant. The missing laboratory data in four patients was erythrocyte sedimentation rate (ESR), which is only ordered when there is suspicion of bacterial infection or post-transplant complications like post-transplant lymphoproliferative disease (PTLD).

Despite these studies, there is a paucity of data regarding the outcome in pediatric patients with liver transplant and 2009 influenza A pandemic. There is only one case report regarding zanamivir treatment efficiency and complications in a pediatric liver transplant patient with severe influenza A H1N1 infection (8). As Green and Allen (9) mentioned, multicenter studies and collaboration of centers providing liver transplantation for their patients are needed.

In conclusion, the 2009 influenza A infection was well tolerated in our cohort, with no mortality. We think oseltamivir treatment and close monitoring of patients can prevent significant morbidity and mortality among influenza A H1N1-infected transplant patients under immunosuppression. Larger series or multicenter studies are needed to strengthen our conclusions.

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