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Influenza A H1N1/2009 Infection in Pediatric Solid Organ Transplant Recipients

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Annex 1

CERTIFICAT DEL DIRECTOR O CO-DIRECTOR DEL TREBALL DE RECERCA

Joan Gavaldà i Santapau, metge especialista adjunt del Servei de Malalties Infeccioses del Departament de Medicina Interna de l'Hospital Universitari de la Vall d'Hebron,

FA CONSTAR,

que el treball titulat "Influenza A H1N1/2009 Infection in Pediatric Solid Organ Transplant Recipients" ha estat realitzat sota la meva direcció per la llicenciada Evelyn Cabral Galeano, trobant-se en condicions de poder ser presentat com a treball d'investigació de 12 crèdits, dins el programa de doctorat en Medicina Interna/Diagnòstic per la Imatge (curs 2011-2012), a la convocatòria de juny.

A Barcelona, 25 de maig de dos mil dotze.

ÍNDEX

Abstract ..... Pag 4

Introduction ..... Pag. 5

Material and methods..... Pag. 6

Results ..... Pag. 8

Discusion ..... Pag. 10

Conclusions ..... Pag. 11

References ..... Pag. 12

Tables ..... Pag. 15

Abstract

Objective:

The aim of this study was to describe the clinical characteristics of pandemic influenza A H1N1 infection.

Material and Methods:

A retrospective study was performed to describe the clinical characteristics of pediatric patients with SOT and confirmed influenza A H1N1/2009 infection from June to December 2009, diagnosed in two Spanish teaching.

Results:

Forty-nine patients were included. Pneumonia was diagnosed in 4 patients (8.2%), and 3 of them required respiratory support. There were no related deaths. Antiviral treatment within 48 hours was associated with a lower likelihood of pneumonia (0/38, 0%) than treatment started after 48 hours (4/11, 36.3%) ($p<0.01$).

Conclusion:

Infection by pandemic influenza A H1N1/2009 had in most patients a benign course in this pediatric SOT cohort. The incidence of pneumonia was low (8%), but the clinical course was severe.

Introduction

Influenza virus is an important respiratory pathogen in young children, with the highest associated morbidity and hospitalization rates being in young infants (1, 2). A new influenza A strain, H1N1, was first recognized in early 2009 and resulted in a worldwide pandemic (3). Some recently published epidemiological studies have shown an incidence of about 20 to 30% of H1N1 infection in general population under 25 years old (4, 5). To date, there are limited reports of pandemic influenza A infection in pediatric solid organ transplant (SOT) recipients (6, 7).

In this study, we report our experience with inpatient and outpatient pediatric SOT patients with 2009 pandemic influenza A H1N1 infection.

Ours aims were to assess the clinical characteristics and outcome of the infection.

Material and methods

This retrospective study included all pediatric patients (<18 years) who underwent liver, kidney, or liver-kidney transplantation in Hospital Universitari Vall d´Hebron (Barcelona) or Hospital Universitario La Paz (Madrid), and had microbiologically confirmed influenza A H1N1 infection between June and December 2009. Institutional review board approval was obtained at each participating center.

A single transplant infectious disease physician performed a chart review and recorded the data on a standardized form.

Upper respiratory tract infection (URTI) was defined as the presence of at least one of the following: fever (>38ºC), cough, sore throat, myalgia, rhinorrhea, bronchospasm.

Pneumonia was diagnosed in a patient when an abnormal finding was documented on chest radiography or computed tomography study. The radiological images were analyzed by a pediatric radiologist according to the current practice of each centre.

The diagnosis of pandemic influenza A (H1N1) infection was made by real-time polymerase chain reaction (RT-PCR) assay (ProFlu+, PRODESS; Waukesha, Wisconsin USA) that detects influenza A, B, and respiratory syncitial virus (RSV) from a single specimen.

The pediatric transplant population followed in the participating hospitals, in late 2009 was approximately 835 children.

All of our pediatric transplant population was allowed to contact with the medical staff by phone whenever they had a medical consultation and, during 2009 pandemic's period, they had the instruction to come to the Outpatient Clinic of the Children's Transplant Unit or the Emergency Room if they had some incipient respiratory symptoms. This policy was carried out in 2009 because the vaccine arrived after the onset of the pandemic.

Analysis of swab samples was performed in all SOT patients (outpatient, inpatient, and patients in emergency department) with clinically suspected disease who coming at institutions involved in the study period.

Additional tests were performed according to the protocol of each center and the treating physician's discretion.

Statistical analysis

A descriptive analysis was performed. Continuous variables were expressed as the median and range. All proportions were calculated as percentages of patients with available data. Bivariate analysis was applied to identify factors leading to pneumonia and the need for intensive care unit (ICU) admission. For bivariate analysis, the chi-square test or the Fisher's exact test was used for categorical variables.

Data analysis was performed with SPSS Statistics 16 (IBM SPSS, Chicago, Illinois USA).

Results

Between April and December 2009, 49 pediatric SOT recipients (32 liver, 14 kidney, and 3 combined liver-kidney) were diagnosed with pandemic influenza A H1N1 virus infection. There was one case acquired in the hospital. No patient received the pandemic vaccine prior to diagnosis.

The patients' demographic, clinical features and outcome data are shown in Table 1.

At diagnosis, 17 (34.7%) patients were receiving triple maintenance immunosuppressive regimens, 27 (55.1%) on double regimens, and 5 on single therapy (Table 1).

The median delay between the onset of symptoms and influenza diagnosis was 2 days (interquartile percentile 25-75 [IQ $_{25\text{-}75}$] 1-3).

The most common presenting symptoms were fever in 47 patients (95.9%), rhinorrhea in 36 (73.5%), and cough in 36 (73.5%).Other signs and symptoms are reported in Table 1.

Imaging data were available for 23 (47%) patients.

In 4 patients (8.2%), imaging findings were consistent with pneumonia, and 45 had URTI (91.8%).

All patients received oseltamivir treatment, dosed according to weight and adjusted for renal function, and the treatment was well tolerated. Patients with URTI received oseltamivir for 5 days.

Hospitalization decision was made according to the attending physician. Fifteen patients required hospitalization (30.6%) due to fever plus malaise in 5 (33.3%), pneumonia in 4 (26.6%), neutropenia in 4 (26.6%), and bronchospasm in 2 (13.3%). The median hospital stay was 5 days (IQ $_{25\text{-}75}$ 3-15)

There was no respiratory syncytial virus coinfection. Leukopenia was documented in 10 patients (19.7%), of whom 6 (11.7%), had neutropenia (<1000/μL).

Patients with URTI had a favorable evolution, with total clinical resolution in a median of 4.1 days (IQ $_{25\text{-}75}$ 2.7-5). Three out of four patients with pneumonia needed ICU admission and respiratory support for respiratory failure.

Bronchoalveolar lavage (BAL) samples were taken for microbiological study in patients requiring tracheal intubation (2 patients). In addition to the Influenza virus, *Streptococcus pneumoniae* was isolated in one of them, and *Aspergillus fumigatus* in the other one. This patient with Influenza A/H1N1 infection and concomitant pulmonary aspergillosis with images suggestive of fungal infection in thoracic scanner, was treated with oseltamivir and liposomal amphotericin B, at day +8 of admission has decreased level of consciousness, brain CT showed focal lesions. Voriconazole was added to the antifungal treatment and two weeks later the patient had massive bleeding at the focal brain lesions that caused her death.

In patients with pneumonia and mechanical ventilation, the period to negative PCR testing for pandemic influenza A (H1N1) in nasal swab samples was 11, 14, and 21 days; antiviral treatment was maintained until PCR study confirmed negative status.
Median duration of ICU hospitalization was 36 days (26, 36, and 46 days per patient, respectively).No follow-up nasal swabs were done in those patients that were not admitted to ICU.
There were no deaths related to influenza infection.

The start of antiviral treatment was within 48 h of symptoms onset in 38 (77.5%) patients.
Early antiviral treatment was associated with a lower likelihood of pneumonia (no pneumonia in the group of patients treated within 48 h (0%) vs. 4/11 (36.3%) pneumonia cases in patients treated after 48 h ($p<0.01$).
Prompt treatment was also associated with a lower likelihood of ICU admission: 0/38 patients treated within 48 h versus 3/11 (27%) treated after 48 h ($p<0.01$).
We did not find any statistical association between the type of immunosuppressive therapy administered and the development of pneumonia.
In our cohort the median time from transplantation to infection was 6.5 years (IQ_{25-75} 2-9). The median time post-transplantation did not have any impact on the patient outcomes (pneumonia, ICU) (median of 6.6 years vs. 6.5 years).
No patients experienced allograft rejection in the 6 months following the pandemic influenza A (H1N1) diagnosis.

Discussion

Infection with influenza virus and especially with pandemic influenza A H1N1 virus infection can result in a wide spectrum of clinical disease in SOT recipients, ranging from URTI to severe illness requiring ICU hospitalization (6-13).

In this study, we describe the clinical characteristics and prognosis of pandemic influenza A H1N1 infection in pediatric liver and/or kidney recipients. Morbidity was substantial in our cohort (hospital admission in 30.6% and ICU admission in 6.1%). Nearly 10% of patients had pneumonia. The most important finding was that starting antiviral treatment within 48 h of symptoms onset was associated with a lower likelihood of developing pneumonia and needing ICU admission.

In our experience, pediatric liver and kidney transplant recipients were mainly affected with URTI (91.8%). This is likely because the degree of awareness was very high at the time, and patients came to the daycare clinic or emergency room soon after the onset of symptoms. The clinical signs and symptoms present in our cohort were similar to those described in other cohort series for seasonal influenza(8, 13-15) and pandemic influenza A H1N1 infection(11, 12, 16-18) , although there were fewer gastrointestinal symptoms (less than 7% of patients). This difference was also seen when comparing our results to those of a multicenter study of pandemic influenza A H1N1 infection in 82 pediatric SOT recipients, in which 47% had gastrointestinal symptoms (6).

Nonetheless, the severity of the infection in our patients seems similar to that presented in the study of Kumar et al. (6), regarding the incidence of pneumonia (16% vs. 8.2%, although imaging study was performed in less than 50%), mechanical ventilation (4% vs. 6.2%), and ICU admission (12% vs. 6.2%), with no deaths in either series.

We have had one patient, recently renal transplanted (45 days) that presented invasive aspergillosis complicating influenza A (H1N1) infection, there are some reports that suggest that infection with influenza A (H1N1) may predispose in immunocompromised patients to develop invasive aspergillosis(19-21).

There are few data on the use of antiviral treatment in recipients of organ transplants. Previous studies in SOT cohorts with pandemic influenza A H1N1 infection (6, 11, 12)

have not reported any adverse effects. In our experience the oseltamivir treatment was well tolerated.

Low et al. (11) reported that early initiation of oseltamivir by day 2 of the illness shortened the duration of symptoms by a mean of 1.6 days and PCR positive viral shedding by 0.6 days in adult SOT recipients infected with pandemic influenza A H1N1.

One of the most outstanding findings in the American Society of Transplantation Influenza Collaborative Study Group cohort was that starting antiviral treatment within 48 h of symptoms onset was associated with a decrease in hospital and ICU admissions, need for mechanical ventilation, and death(6). In the present study, most patients received antiviral therapy within 48 h after symptoms onset (38 of 49, 77.6%), and delayed antiviral treatment (more than 48 h after onset) was associated with a higher risk of pneumonia and ICU admission.

In recent studies in SOT recipients, concomitant pandemic influenza A H1N1 infection and moderate-severe acute rejection have been reported (10, 12, 22). Three out of 51 (5.9%; one of the loss his graft) SOT with H1N1 infection in the Spanish cohort had allograft rejection in the month following the influenza diagnosis(12). Activation of the immunologic mechanism by influenza leading to allograft rejection is felt to be related to production of interleukin (IL)-1, tumor necrosis factor, IL-6, and IL-8 during viral replication (23). In the present study, no acute rejections were detected at the time of the flu episode or in the following 6 months.

An important limitation of our study is the small size of the cohort.

Conclusions

A high index of clinical suspicion plus initiation of antiviral treatment within 48 h of the clinical symptoms seems crucial to decrease the severity of disease resulting from pandemic influenza A H1N1 infection in children undergoing SOT.

Although the infection followed a benign course in most patients, more than one-third of this population required hospital admission. The pneumonia rate was 8% and the course was severe in patients with this condition. Three out of 4 patients with pneumonia required ICU admission and respiratory support.

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Table 1. Demographics, clinical features, and outcomes of the 49 pediatric SOT recipients with pandemic influenza A H1N1

Features	N (%)
Age, (years)	10 (IQ_{25-75} 7-14)
Female/ Male	30 (61)/19 (39)
Type of transplant	
Kidney	14 (28.6)
Liver	32 (65.3)
Kidney-liver	3 (6.1)
Immunosuppression	
Tacrolimus	35 (71.4)
Cyclosporin	8 (16.3)
6-methylprednisolone	39 (79.6)
Mycophenolate	25 (51)
Everolimus	6 (12.3)
PTLD	2 (4.1)
Chronic Epstein Barr virus replication	13 (26.5)
Acute rejection *	0
Chronic rejection	12 (24.5)
Antilymphocyte globulin in preceding 6 months	1 (2)
Interleukin-2 receptor antagonists in preceding 6 months	2 (4)
Symptoms	
Fever >38°	47 (95.9)
Cough	36 (73.5)
Rhinorrhea	36 (73.5)
Expectoration	16 (32.7)
Sore throat	10 (20.4)
Headache	5 (10.2)
Myalgia	16 (32.6)
Gastrointestinal symptoms	3 (6.1)
Site of Infection URTI / Pneumonia	45 (92) / 4 (8)
Hospital admission	15 (30.6)
URTI admitted / URTI total	11/45
Pneumonia admitted/Pneumonia total	4/4
Median duration of antiviral treatment (days)	
URTI	5
Pneumonia	16.55 (IQ_{25-75}7.5-20.5)
Median time (years) from transplant to infection	6.5 (IQ_{25-75} 2-9)
Graft rejection at 6 months of follow-up	0
Influenza H1N1 infection related mortality	0

Abreviations: IQ_{25-75} , interquartile percentile 25-75; PTLD, post-transplant lymphoproliferative disease; URTI, upper respiratory tract infection; SOT, solid organ transplant; ICU, intensive care unit.
Data show the number (%) of patients, unless otherwise indicated
Notes: * diagnosed in the previous 3 months to influenza infection