A Comparison between the Presentation of Confirmed Influenza A/H1N1/2009 Virus Infection and Influenza-Like Illness among Children Admitted at Queen Alia Military Hospital

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ABSTRACT

Objectives: To describe the clinical characteristics of children who were hospitalized with respiratory infections during the year 2009 at Queen Alia Military Hospital in Amman and to compare features of confirmed influenza A/H1N1/2009 virus infections with features of Influenza-like illness.

Methods: Hospitalized children under the age of 14 years with respiratory infections during the year 2009, with influenza A/H1N1/ virus infection were studied. All were tested with Real Time - Polymerase-Chain-Reaction (RT-PCR) assay for Influenza A/H1N1/2009 virus and chest radiography was done on admission. All were treated with Oseltamivir on admission till the laboratory results were available.

Results: During the study period, there were 77 admissions with respiratory infection. Only one death occurred. Forty-four (57%) were males, 44 had positive RT-PCR for influenza A/H1N1/2009 virus and 33 (43%) tested negative and were considered, to have influenza-like illness. Comparing patients who had confirmed influenza A/H1N1/2009, to those with influenza-like illness, revealed that the mean age was 51 months versus 42 months. Underlying medical conditions were present in 70% versus 48% (p<0.001). Chest radiographic findings were consistent with pneumonia in 100% versus 27% (p<0.001). All patients had fever on admission. Dyspnoea was observed in 57% versus 33% (p<0.005). Cough was seen in 91% versus 89% (p>0.05). Vomiting affected 25% versus 18% (p>0.05). Diarrhea occurred in 34% versus 21% (p>0.05). Three patients had hematuria and one had croup, all were in the positively tested group. The patient that died had neurological disability and was tested positive for the infection.

Conclusion: Influenza A/H1N1/2009 caused significant illness requiring hospitalization. When compared to patients with influenza-like illness, patients with influenza A/H1N1/2009 infections, were older, significantly more patients had dyspnoea, radiologically confirmed pneumonia and an underlying medical condition. Gastrointestinal symptoms were more common in patients with confirmed influenza A/H1N1/2009 infection, but the difference was not statistically significant.

Key words: Influenza A/H1N1/2009, Influenza like infection, Jordan.

Introduction

In late March and early April 2009, a Pandemic of influenza A/H1N1/2009 virus infection was detected in Mexico, with subsequent cases observed in many other countries. The first case of influenza A/H1N1/2009 virus infection in Jordan was documented on June 16th in two persons who were returning to Jordan from the...
USA. During the pandemic that followed, Queen Alia Military Hospital was assigned the duties of providing care to the military beneficiaries who live in Amman and the Central region. Many cases presented daily with symptoms of fever and respiratory complaints. Hundreds were seen at the purposefully allocated clinics. Only 677 were admitted from June to December 2009 of whom 77 were less than 14 years old and are the subjects of this study.

Our hospital, adopted the guidelines provided by the U.S. Centers for Disease Control (CDC) and Prevention, for diagnosis and treatment of the disease as well as the World Health Organization (WHO) guidelines and the National Committee for Epidemics.

Not all who were admitted had confirmed infection by means of a Real-Time reverse Transcriptase Polymerase Chain Reaction (RT-PCR) assay and were considered to have had influenza-like illness.

In this study, we describe the clinical, epidemiological and radiological findings in those with positive and negative RT-PCR test for influenza A/H1N1/2009.

Methods

During June and December 2009, there was a global pandemic of influenza A/H1N1/2009 viruses including Jordan. Of the hundreds of children that were seen daily at the purposefully allocated clinics, a total of 77 children, had severe respiratory infection to warrant hospital admissions and are the subjects of this study.

Eligible patients were infants and children under 14 year of age as 14 years is the age beyond which patients are treated in the adult wards in Jordanian hospitals.

All children were tested for influenza A/H1N1/2009 virus infection by sending throat swabs to be tested with the use of an (RT-PCR) assay according to the protocol recommended by the CDC/WHO. Once collected, all specimens were placed in a sterile Virus Transport Medium (VTM) and immediately refrigerated to below 4°C for transport to the laboratory. The (RT-PCR) assay was performed at the Ministry of Health National Laboratories. Samples were collected only by specifically trained physicians and sent within 24 hours of collection with results reports back after 24-72 hours of collection. All patients had a chest radiograph on admission which was repeated as per clinical indication.

Treatment was initiated on admission before the results were received. All patients were started on Oseltamivir for at least five days if the infection is confirmed by laboratory or the illness is severe. In others, who had negative RT-PCR tests and had a mild illness, the treatment duration varied, but for mild cases, Oseltamivir was discontinued upon receiving negative RT-PCR results. All patients also received broad spectrum antibiotics; Vancomycin and Ceftriaxone, the duration of which was based on clinical improvement and the results of blood cultures. Data were tabulated in the study protocol forms after the approval of the ethical committee at the Royal Medical Services. There was a daily hospital meeting in which all who were involved with care of patients, discuss the previous day’s admissions and the progress of those still hospitalized. Data presented during these meetings were used in this study.

Results

A total of 77 children were admitted. The first child was admitted on June 20th, 2009, and the last on November 30th, 2009.

RT-PCR assays for influenza A/H1N1/2009 virus infections:

Forty-four (57%) had a positive RT-PCR. Thirty-three (43%) had negative tests.

Age and gender:

Forty-four (57%) were male; 26 (59%) and 18(54%) in the positive and negative RT-PCR groups respectively. The mean age was 47.2 months for all patients. Patients in the positive RT-PCR were significantly older than those in the negative group; 51 months versus 42.2 months (Table I). This difference was not statistically significant (p=0.224).

Most patients in both groups, were below the age of 5 years; 31(70%) and 25 (75%) in the positive and negative RT-PCR groups respectively. The age distribution of the study group is shown in Fig. 1. Twenty (26%) of all patients were less than 12 months old, 9 (20%) and 11 (33%) of the RT-PCR positive and negative groups respectively were in this age range. Thirty-six (26%) of all
patients were in the 13-60 months group, 22 (50%) and 14 (42%) of the RT-PCR positive and negative respectively. Sixteen (21%) patients were 61-108 months old, 10 (20%), 6 (20%) in the RT-PCR positive and negative respectively. Only 5 (6%) were 109-168 months old, three (23%) and 2 (18%) of the RT-PCR positive and negative respectively. There were no statistically significant differences in the age distribution among the two groups.

Duration of illness before admission:
Fifty-three (69%) of all the patients in our series, were admitted within 72 hours or less of the onset of their symptoms and antiviral therapy started on admission. Of these, 33 (75%) were in the positive RT-PCR group, as compared to 20 (61%) of the negatively tested group (Table I). This difference between these two groups was not significant (p=0.177).

Symptoms:
Symptoms at presentation are presented in Table I. The most common symptom was fever as all had fever on admission.
Cough in 91% and 88% in the positive and negative PCR groups respectively, this difference was not statistically significant. Vomiting was present in 11(25%) and 6 (18%) of the positive and negative PCR groups respectively (p=0.475). Diarrhea was present in 15(34%) and 7 (21%) of the positive and negative PCR groups respectively; this is not a statistically significant difference (p=0.216). However, four of the children in the PCR positive group, experienced severe diarrhea. Dyspnoea, which is defined as features of respiratory distress as tachypnoea and use of accessory muscles or hypoxia on admission was evident in 25(57%) and 11(33 %) of children in the positive and negative PCR groups respectively (p<0.05). Other symptoms were myalgia in three (7%) and croup in one (2%) of the RT-PCR positively tested group, but none in the RT-PCR negative group. Three (7%) had gross transient hematuria with negative urine cultures, normal kidney function tests and renal ultrasound scans, all had a positive RT-PCR tests.

Underlying medical conditions:
As demonstrated in Table II, underlying medical conditions were present in 47 (61%) of the 77 patients. Thirty-one (70%) of those who had positive RT-PCR tests, had one or more underlying condition versus only 16 (48%) of the negatively tested patients (P=0.05).
Asthma was the most common condition, seen in 27(35%) of all children. Twenty-one (48%) of the children with confirmed infection had asthma against 6 (18%) of the negatively tested group (P<0.01). Asthma was most commonly present in those between 13-60 months old as 23(64%) had asthma. Of these, 16 (70%) had positive tests confirming infection. Neurocognitive, neuromuscular, or seizure disorders were seen in 10 (13%) of all patients and was more common in the negatively tested children as was found in 7 (21%) versus only 3 (7%) of the positively tested group. Immunodeficiency was present in 7 and all had positive RT-PCR tests. Congenital heart disease was present in 3 (4%), 2 (6%) of those who had negative RT-PCR test results. Six (8%) were diabetics; 3 (7%) and 9% in each of the RT-PCR groups.

Co-infection:
All had blood cultures taken on admission before starting treatment. None of our patients had a positive blood culture. All were treated for at least five days by intravenous antibiotics. We empirically used Vancomysin and Ceftriaxone.

Radiological Abnormalities:
All of the positively tested patients had radiological evidence of pneumonia of varying radiological appearance ranging from mild patchy consolidation to bilateral widespread opacities. Only 9 (27%) of the negatively tested cases had radiological evidence of pneumonia (p>0.001).

Outcome:
Most patients responded well to therapy and were discharged without complications. Three needed mechanical ventilation; all had positive RT-PCR tests. One was a 16 month old toddler who was healthy otherwise, the second, was a 3 years old asthmatic. The third child, who later died, was an 8 years old boy with adrenoleukodystrophy and severe disability.
**Table I**: Clinical features found in 77 patients with positive and negative RT-PCR test results for influenza A/H1N1/2009 infection

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patients with Positive RT-PCR, No. (%)</th>
<th>Patients with negative, RT-PCR, No. (%)</th>
<th>Total No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (mo)</td>
<td>51 (SD=39)</td>
<td>42 (SD=39)</td>
<td>479 (SD=39)</td>
<td>0.224</td>
</tr>
<tr>
<td>Less than 3 days of symptoms</td>
<td>33 (75)</td>
<td>20 (61)</td>
<td>53 (69)</td>
<td>0.177</td>
</tr>
<tr>
<td>Pneumonia on X-ray</td>
<td>44 (100)</td>
<td>9 (27)</td>
<td>53 (69)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>44 (100)</td>
<td>33 (100)</td>
<td>77 (100)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Cough</td>
<td>40 (91)</td>
<td>29 (88)</td>
<td>69 (90)</td>
<td>0.666</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>25 (57)</td>
<td>11 (33)</td>
<td>36 (47)</td>
<td>0.041</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (25)</td>
<td>6 (18)</td>
<td>17 (22)</td>
<td>0.475</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15 (34)</td>
<td>7 (21)</td>
<td>22 (29)</td>
<td>0.216</td>
</tr>
<tr>
<td>Haematuria</td>
<td>3 (7)</td>
<td>0</td>
<td>3 (4)</td>
<td>0.126</td>
</tr>
<tr>
<td>Croup</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (1)</td>
<td>0.383</td>
</tr>
<tr>
<td>Died</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (1)</td>
<td>0.383</td>
</tr>
</tbody>
</table>

**Fig. 1**: The age distribution among patients in our series in percentages

**Table II**: The distribution of co-morbid conditions in patients admitted with positive and negative RT-PCR tests for influenza A/H1N1/2009

<table>
<thead>
<tr>
<th>Underlying Medical Condition</th>
<th>Positive RT-PCR Number (%)</th>
<th>Negative RT-PCR Number (%)</th>
<th>Total Number (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>31 (70)</td>
<td>16 (48)</td>
<td>47 (61)</td>
<td>0.0500</td>
</tr>
<tr>
<td>Asthma</td>
<td>21 (48)</td>
<td>6 (18)</td>
<td>27 (35)</td>
<td>0.0071</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (7)</td>
<td>3 (9)</td>
<td>6 (8)</td>
<td>0.7122</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>7 (16)</td>
<td>0</td>
<td>0</td>
<td>0.0162</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1 (2)</td>
<td>2 (6)</td>
<td>3 (4)</td>
<td>0.395</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>3 (7)</td>
<td>7 (21)</td>
<td>10 (13)</td>
<td>0.062</td>
</tr>
</tbody>
</table>

**Discussion**

Influenza A/H1N1/2009 virus strain represents a quadruple reassortment of two swine strains, one human strain, and one avian strain of influenza. Influenza A/H1N1/2009 virus in animal model, was found to be more pathogenic than a seasonal influenza A/H1N1 virus, with more extensive virus replication occurring in the respiratory tract. Many cases were seen daily at our specifically allocated clinics at Queen Alia Military Hospital. Only 77 children were admitted. Previous studies, estimated that less than 1% of patients with H1N1 infection are admitted to hospital. The majority of children and adults with H1N1 had mild symptoms that resembled infections with other winter viruses. We admitted only severe cases of the disease. Rates of hospitalization and death have varied widely according to country. Tests available for influenza A/H1N1/2009 virus infection, include the rapid influenza diagnostic test (RIDT), RT–PCR, viral culture, and Direct Immunofluorescence Assay (DFA). We used the RT–PCR tests in our patients as a...
confirmation of influenza A/H1N1/2009 virus infections can only be made with RT–PCR or viral culture. Specimens need to be collected on a swab with a synthetic tip on a plastic or aluminium shaft. Ideal specimens are nasopharyngeal swabs or nasal aspirate. The time from illness onset to specimen collection, the site and quality of the specimen swab, and the time elapsed between specimens collection and testing can all contribute to a lower sensitivity for tests to detect influenza A/H1N1/2009 viruses infection.

Many reasons could account for the high negative results in the settings of an outbreak of influenza A/H1N1/2009 viruses in our cohort. These patients could have had other viral illnesses not tested for. Some others may be false negative cases of influenza A/H1N1/2009 virus infections due to sampling and samples processing errors. All attempts were made to avoid delay in sampling and samples processing. Samples were only collected by physicians trained in the procedure. Thus we considered these patients as having influenza-like illnesses other than the influenza A/H1N1/2009 and this consideration is supported by the significant differences in the clinical and radiological features in each group.

Most patients in both groups were less than 5 years old. The WHO, reported global hospitalization rates to be highest for children under the age of five. This is contrary to ages reported in many countries elsewhere. The majority of the children in the initial series in the United States were between 10 and 18 years old; similarly, in a series in Chicago, the attack rate was higher in the group aged 5–14 years than in the group less than five years old. Data from Canada, found that 65% of the children admitted were above five years old. Our study population is different in many ways. Firstly it is for children up to the age of 14 years. Secondly; Jordanian population is significantly younger than that in the United States and Canada. Also many older children may had had the disease and not admitted because of milder clinical disease.

Time elapsed between the onset of symptoms and initiation of treatment was found to be important for improved outcome. A Chinese Study showed that starting treatment with Oseltamivir therapy within 48 hours after the onset of symptoms can reduce the duration of viral shedding.

In our series, 75% and 61% of RT-PCR positive and negative groups respectively, presented within three days of the onset of symptoms. This is also the time of Oseltamivir administration. In a previous study in Argentina, the median time of presentation was four days in 156 children. In Mexico, the time between the onset of symptoms and admission to the hospital ranged from four to 25 days (median=6).

The majority of influenza A/H1N1/2009 cases are not hospitalized and only have been mild influenza-like illnesses that resembles many winter viruses. Gastrointestinal manifestations appear to be more common with influenza A/H1N1/2009 than seasonal influenza.

Among 268 patients, adults and children, in the United States requiring hospitalization for influenza A/H1N1/2009 infection, clinical findings included fever (93 %), cough (83 %), shortness of breath (54 %), fatigue or weakness (40 %), chills (37 %), myalgias (36 %), rhinorrhea (36 %), sore throat (31 %), headache (31 %), vomiting (29 %), wheezing (24 %), and diarrhea (24 %). The presenting features of influenza A/H1N1/2009 in the children in our series reveal similar trends. Fever was present in all our patients. In the United States, fever was present in 93% of patients. Respiratory symptoms were present in the majority of our patients; cough in 40 (91%) and 29 (88%) of the RT-PCR positive and negative groups respectively. Dyspnea was found in 25 (57%) and 11 (33%) of the RT-PCR positive and negative groups respectively. A study on Argentinean children, found cough in 70%, rhinorrhea in 32%, and hypoxemia in 82%.

In our study, gastrointestinal symptoms were common. Vomiting was present in 25% and diarrhea in 34%. For patients with negative RT-PCR tests results, vomiting and diarrhea were less common, found in 18% and 21% of cases respectively. In the United States, 25-29% of those reported had vomiting or diarrhea, which is comparable to our findings.

Three of our patients had gross haematuria suggestive of cystitis. All had positive tests for
influenza A/H1N1/ 2009 and other investigations, revealed no other explanation for the haematuria than the H1N1 infection.

Asthma was a risk factor in 48% of the RT-PCR positive cases and only 18% of the RT-PCR negative cases. Asthma had been identified as a significant risk factor for influenza A/H1N1/2009 requiring hospital admissions. A study of 272 patients infected with influenza A/H1N1/2009 hospitalized in the USA found that 73% of the patients had a single co-morbidity on admission, of which asthma was the most common. A previous study(16) suggested that asthma was a more significant risk factor for influenza A/H1N1/2009 requiring hospital admission than for seasonal influenza and that children with mild asthma were also at risk. Other risk factors include immunodeficency state such as malignancies and its therapy and primary immunodeficiency.

All patients had chest radiographs on admission. All patients (100%) with RT-PCR positive tests for influenza A/H1N1/ 2009 infection had radiological evidence of pneumonia. This is higher than previously reported. In a large series of patients in California, 833 (66%) patients who underwent chest radiography had opacities suggestive of pneumonia. A study in Argentinean(18) children, found pneumonia in 78% of their patients.

None of our patients had a proven bacterial infection. However, all were treated with antibiotics soon after admission. An American post-mortem study of patients with H1N1 infection found co-infection with Streptococcus pneumonia, Streptococcus pyogenes, Staphylococcus aureus, Staphylococcus mitis, or Haemophilus influenza in 29%24.

Antiviral neuraminidase inhibitor drugs Oseltamivir (Tamiflu) and Zanamivir (Relenza) are used in the treatment of influenza A/H1N1/2009.25 We used Oseltamivir upon admission. This is in accordance with the WHO recommendation that treatment with Oseltamivir, had to be started as soon as possible after onset of symptoms.26 Many studies, suggested that there might be a reduction in morbidity and mortality with this approach.5

Oseltamivir should be commenced within 24–48 hours of onset of symptoms but might be of benefit in those with severe illness within seven days of onset.26

Conclusion

Influenza A/H1N1/ 2009 caused significant illness requiring hospitalization. When compared to patients with influenza like illness, patients with influenza A/H1N1/2009 infections, were older, significantly more patients had dyspnoea, radiologically confirmed pneumonia and an underlying medical condition. Gastrointestinal symptoms were more common in patients with confirmed influenza A/H1N1/ 2009 infection, but the difference was not statistically significant.

References


