Influenza A/H1N1 in Pediatric Oncology Patients

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Background: Our aim was to determine the clinical and epidemiological features of pandemic influenza A/H1N1 in immunocompromised children with solid tumors and hematological malignancies.

Patients and Methods: A prospective study was conducted during the H1N1 pandemic between August 2009 and February 2010 in a pediatric hematology-oncology unit. Demographic and clinical data were obtained from all children with suspected H1N1 infection (high fever with or without respiratory symptoms). Laboratory diagnosis of influenza A/H1N1 was performed by means of polymerase chain reaction analysis of nasopharyngeal wash specimens.

Results: We identified 57 episodes of suspected influenza A/H1N1 infection in 40 children. In all episodes, children were treated with oseltamivir and antibiotics until influenza A/H1N1 results were received. Of all episodes, 13 (22.8%) tested positive for influenza A/H1N1. Two of the H1N1-positive children (15.4%) had been previously immunized against influenza A/H1N1. No differences between H1N1-positive and H1N1-negative children were noted in terms of demographic features, clinical presentation, laboratory findings, and underlying disease. Three polymerase chain reaction-positive (23.0%) children and 1 H1N1-negative (2.3%) child were admitted to the pediatric intensive care unit and were mechanically ventilated (P = 0.03). One (7.7%) H1N1-positive patient died versus none of the H1N1-negative patients (P = 0.2). The condition of all other children in both the groups improved rapidly during hospitalization.

Conclusions: Febrile hospitalized pediatric oncology patients, with and without pandemic influenza A/H1N1, had a similar demographic and clinical presentation with a relatively good outcome. This was probably because of early antiviral treatment and possibly because of the relatively low virulence of the virus. Immunization should be encouraged in these patients.

Key Words: influenza, H1N1, oncology children

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BACKGROUND

Pandemic influenza, caused by influenza A/H1N1 virus, is a lower respiratory tract disease that emerged worldwide during the 2009-2010 winter season with increased morbidity and mortality compared with lower respiratory tract infections caused by other respiratory viruses.1

In patients with neoplastic diseases, influenza A/H1N1 infection can cause severe illness, resulting in acute respiratory distress syndrome and death.2,3 Lung tissue analysis from those patients may show diffuse alveolar damage in most of them and necrotizing bronchiolitis or extensive hemorrhage in others.4 Morbidity and mortality from pandemic H1N1 influenza in patients who underwent stem cell transplantation exceeded that of immunocompetent patients in several reports.5-7 In another study, H1N1 infection in immunocompromised hosts was characterized by a clinical picture similar to that of immunocompetent patients but with a prolonged course and higher mortality.8

Overall, in previous reports, influenza A/H1N1 infections in pediatric oncology patients were mild in most cases but was associated with substantial morbidity in a proportion of patients, especially in those who received intensive immunosuppressive therapy or when anti-influenza treatment was delayed.9-12

The influenza A/H1N1 monovalent vaccines were well tolerated by young cancer patients during chemotherapy and achieved a protective immune response in most cases.13-16 However, influenza vaccination within the first 6 months following bone marrow transplantation (BMT) was ineffective. The efficacy of the vaccine was similar to that described in nonimmunocompromised hosts initiated 2 years following BMT.17

As the clinical and radiologic findings of H1N1 infection are nonspecific in nature, a high index of suspicion is required in immunocompromised patients. Therefore, initiating empiric oseltamivir therapy while waiting for laboratory confirmation could be lifesaving.18,19

In our pediatric oncology unit, all patients who presented with fever during the H1N1 influenza pandemic season in 2009 and 2010 were treated with oseltamivir until the nasopharyngeal specimen results were reported for influenza virus.

The aims of our study were to compare the demographic, clinical, and laboratory characteristics of influenza A/H1N1-positive and influenza A/H1N1-negative oncology children who presented with fever during the influenza A/H1N1 outbreak in 2009 and 2010. In addition, we assessed the clinical outcome of influenza A/H1N1 infection in children with neoplastic diseases.

PATIENTS AND METHODS

Study Design

A prospective study was conducted between August 2009 and February 2010 at the Pediatric Hematology-Oncoogy unit in Soroka University Medical Center, Beer-Sheva. The study was approved by the Helsinki committee.

The study population included all children (0 to 18 y) with neoplastic disease who were admitted to the Pediatric...
Hematology-Oncology unit with fever with or without other symptoms suggestive of influenza A/H1N1 infection. Vaccinated patients received Pandemrix— influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) before hospitalization.

All patients were treated with oseltamivir and antibiotics until the results for influenza A (H1N1) were received.

We excluded suspected influenza A/H1N1 episodes in children with a nasopharyngeal wash, with an interval of ≤ 10 days between washes, with identical H1N1 results in the same patient.

Disease and treatment staging was performed according to the intensity of the pediatric cancer treatment protocols.29

**Data Collection**

The following data were obtained from all patients’ medical files: demographic data, the nature of the underlying neoplastic disease and the therapy received, clinical presentation (body temperature, upper and lower respiratory infection symptoms, gastrointestinal symptoms, etc.), and laboratory data, including complete blood count, C-reactive protein, and blood culture.

**Laboratory Test**

Nasopharyngeal wash specimens were obtained by the pediatric oncology residents from all patients. Only the nasopharyngeal wash obtained immediately before or within the first 48 hours of hospitalization was included to exclude hospital-acquired cases. Only 1 specimen was obtained from each patient. The specimens were processed as described elsewhere.22 Detection of influenza A/H1N1 was performed using a polymerase chain reaction (PCR).22

**Statistical Analysis**

Data were recorded using Access Microsoft office software. Statistical analysis was performed using SPSS 18.0 software. Children with PCR-confirmed influenza A/H1N1 infection were compared with children with negative PCR-confirmed H1N1. The clinical course of children infected with H1N1 was also documented and compared with that of children not infected with influenza A/H1N1. The null hypothesis for the outcome analysis was that the number of influenza A/H1N1-infected patients will be equal to that of noninfluenza A/H1N1-infected patients.

Contingency table analyses for comparing the rates between unmatched samples were performed using the 2-tailed χ² test or the Fisher exact test, as appropriate. The Student independent sample t test was used to compare continuous variables.

**RESULTS**

During the study period, 40 pediatric oncology patients with 57 episodes were hospitalized with a diagnosis of suspected influenza A/H1N1. Among the 40 children with malignancy, 16 suffered from leukemia, 10 from lymphoma, 4 from neuroblastoma, and 10 from other malignancies.

All cases were treated with oseltamivir until the result for influenza A/H1N1 was received. In addition, all patients were treated empirically with pipracillin or tazobactam and amikacin.

Of all 57 episodes, 13 (22.8%) were influenza A/H1N1 positive. In the H1N1-positive episodes, 2 of the 13 (15%) were previously immunized with H1N1 vaccine versus 14 (32%) of the 44 in H1N1-negative episodes (P = 0.3). Two children were found positive twice for influenza A/H1N1, one of them after immunization.

There were no significant differences in demographic characteristics between the groups of children with and without A/H1N1 infection (Table 1).

The underlying disease and its treatment intensity were not significantly different between the 2 study groups; there was no significant difference in the stage of the underlying disease. Similarly, no difference was noted in the proportion of children who received chemotherapy in the influenza A/H1N1-positive group when compared with the H1N1-negative group (69.2% vs. 65.1%, respectively, P = 0.8). The proportion of children who underwent BMT was similar in the 2 study groups: 7.7% and 4.8% among influenza A/H1N1-positive and influenza A/H1N1-negative children, respectively (Table 1).

The clinical presentation of the 2 study groups was similar (Table 2). The mean levels of body temperature were 38.05 ± 0.96 and 38.02 ± 1.01 among influenza A/H1N1-positive and influenza A/H1N1-negative children, respectively (P = 0.93). Upper respiratory tract infection (URI) symptoms (including cough, rhinorrhea, and respiratory distress) were noted in 9 of 13 (69.2%) and 22 of 44 (50.0%) influenza A/H1N1-positive and influenza A/H1N1-negative children, respectively (P = 0.34). All 4 influenza A/H1N1-positive episodes presented at admission without URI symptoms remained asymptomatic (URI-wise) through hospitalization. The positive and negative predictive values for URI symptoms and H1N1 infection were 29% and 85%, respectively.

Of all episodes in vaccinated patients, 7 of 16 (44%) presented with fever and URI symptoms compared with 24 of the 41 (59%) in nonvaccinated children (P = 0.38). Gastrointestinal symptoms, including diarrhea and abdominal pain, were equally observed in both groups (Table 2).

No adverse effects related to oseltamivir treatment were observed.

Mean leukocyte counts were 3230 ± 3515 and 4755 ± 6234 cells/mm³ in influenza A/H1N1-positive and

| Table 1. Demographic and Underlying Disease Characteristics of Pediatric Oncology Patients With and Without Influenza A/H1N1 |
|-----------------|-----------------|-----------------|-----------------|
| Influenza A/H1N1 Positive | N = 13 | Influenza A/H1N1 Negative | N = 44 |
| Mean age (n ± SD) (y) | 11.8 ± 3.5 | 10.4 ± 5.1 | 0.29 |
| Sex (n [%]) | 75 (53.8) | 34 (77.2) | 0.099 |
| Male | | |
| Origin (n [%]) | 3 (9.2) | 20 (45.5) | 0.38 |
| Jewish | 4 (3.0) | 24 (54.5) | |
| Stage of disease (n [%]) | | | |
| 1 | 5 (41.7) | 9 (20.9) | |
| 2 | 5 (41.7) | 14 (32.5) | 0.23 |
| 3 | 0 | 6 (14) | |
| 4 | 2 (15.4) | 14 (31.8) | 0.31 |
| Under chemotherapy treatment (n [%]) | 9 (69.2) | 28 (63.6) | 1.0 |
| Bone marrow transplantation (n [%]) | 1 (7.7) | 2/42 (4.5) | 0.6 |
TABLE 2. Clinical Presentation and Treatment of Pediatric Oncology Patients With and Without Influenza A/H1N1

<table>
<thead>
<tr>
<th>N = 13</th>
<th>N = 44</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C) (n ± SD)</td>
<td>38.02 ± 1.01</td>
<td>38.05 ± 0.96</td>
</tr>
<tr>
<td>URI symptoms (n [%])</td>
<td>22 (50.0)</td>
<td>9 (69.2)</td>
</tr>
<tr>
<td>GI symptoms (n [%])</td>
<td>30/38 (78.9)</td>
<td>8/10 (80.0)</td>
</tr>
<tr>
<td>Antibiotics treatment (n [%])</td>
<td>44 (100)</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Oseltamivir treatment (n [%])</td>
<td>44 (100)</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Duration of hospitalization (n ± SD) (d)</td>
<td>5.4 ± 4.4</td>
<td>5.7 ± 5.8</td>
</tr>
<tr>
<td>Mechanical ventilation (n [%])</td>
<td>1 (2.3)</td>
<td>3 (23.0)</td>
</tr>
</tbody>
</table>

GI indicates gastrointestinal; URI, upper respiratory tract infection.

influenza A/H1N1-negative children, respectively (P = 0.27). The respective mean absolute neutrophil counts were 2055 ± 2832 versus 3286 ± 5149 cells/mm³ (P = 0.28), the mean absolute lymphocyte counts were 709 ± 845 versus 788 ± 1101 cells/mm³ (P = 0.79), and mean platelet counts were 130,000 ± 98,000 versus 148,000 ± 116,000 cells/mm³ (P = 0.59). C-reactive protein levels (µg/dL) were 7.77 ± 8.94 versus 4.86 ± 4.85 in influenza A/H1N1-positive versus influenza A/H1N1-negative children, respectively (P = 0.79) (Table 3).

Three (6.8%) and zero (0%) of the nasopharyngeal wash specimens obtained from influenza A/H1N1-negative and influenza A/H1N1-positive patients, respectively, tested positive for respiratory syncytial virus. All children tested negative for influenza B.

Two of the influenza A/H1N1-positive patients had a positive blood culture (1 with Pseudomonas aeruginosa and 1 with Klebsiella pneumoniae) and one of the influenza A/H1N1-negative patients had a positive blood culture for Candida albicans.

Three (23.0%) children infected with influenza A/H1N1 were admitted to the Pediatric intensive care unit versus 1 (2.3%) patient in the influenza A/H1N1-negative group (P = 0.03). All 4 patients were mechanically ventilated. Of the influenza A/H1N1-positive patients, 1 (7.7%) died with a diagnosis of influenza infection and secondary sepsis due to P. aeruginosa. All other children in both groups fully recovered during hospitalization (mean 5.5 ± 4.7 d), including the single patient in the influenza A/H1N1-negative group who was admitted to the Pediatric intensive care unit and had sepsis due to C. albicans.

DISCUSSION

In this prospective study conducted during the influenza A/H1N1 outbreak, we aimed to determine specific characteristics in background medical history (such as underlying oncology diseases) and demographic, clinical, laboratory, and outcome features of pediatric oncology patients with influenza influenza A/H1N1 infection.

In our study, 22.8% of all febrile episodes in pediatric oncology patients tested positive for influenza A/H1N1. Our only requirement for H1N1 testing was fever. It was previously suggested that fever and cough occur in > 90% of oncology patients infected with H1N1 influenza, whereas lower respiratory tract involvement was seen in only 27% of those patients.23,24

As H1N1 infection in oncology patients can cause severe illness,2,3 the index of suspicion in our hospital was very high during the influenza season and favored enhanced testing for influenza, as suggested before.23

We did not find any statistically significant difference between children with and without H1N1 infection in terms of demographic features, staging of the underlying disease and its treatment, clinical presentation, and laboratory findings. However, in children with PCR-confirmed influenza A/H1N1 infection, we noted a trend for a higher rate of URI symptoms.

The relatively mild clinical presentation found in our study is in accordance with the mild H1N1 clinical manifestation found in other studies.9–11 This could be related, at least partially, to the relatively low virulence of influenza A/H1N1 virus, which mainly replicates (at least in the early stages of infection) in the upper respiratory tract.25 Early treatment with oseltamivir allows rapid termination of the virus spread23 and leads to a mild form of the disease.

The outcome of children with and without H1N1 infection was similar in terms of hospitalization duration and low case fatality rates in both groups. These results can be attributed to the early treatment with oseltamivir and antibiotics received by all children and to the fact that medical care is readily accessible for most of them.

However, a higher admission rate to the pediatric intensive care unit and a higher frequency for mechanical ventilation were observed in H1N1-positive children.

A similar Lebanese study12 concluded that children infected with pandemic influenza may respond very well when the diagnosis and treatment are rapid. However, the underlying disease severity was found to be associated with prognosis.12 Thus, it is not surprising that in our study the outcome was generally favorable in both groups, as the underlying disease severity was similar.

As other serious and potentially life-threatening viral, bacterial, and fungal infections were observed in both H1N1-positive and H1N1-negative patients, we believe that the antibiotic treatment protocols for fever in oncology patients should not be altered in the presence of a known or suspected H1N1 infection.

We observed a trend (probably not reaching statistical significance because of the small study population) for less severe H1N1 disease, fewer upper respiratory symptoms, and better outcome in children previously immunized with
H1N1 vaccine compared with nonvaccinated children. This emphasizes the need to encourage influenza vaccination, especially in a highly susceptible population.

Our study has some limitations. First, this is a study with a relatively small number of patients, and some parameters may not have reached statistical significance because of these small numbers. Second, this is a single-center study, and the results in other centers can be potentially different as most of our patients were only treated with chemotherapy and a relatively small number of patients received BMT. Additional studies should be conducted on this population to support these study results.

In conclusion, febrile hospitalized pediatric oncology patients with and without pandemic influenza A/H1N1 had a similar demographic and clinical presentation with a relatively good outcome. This was probably because of early treatment and possibly because of the relatively low virulence of the virus. Early treatment for influenza and potential bacterial complications may reduce mortality in these high-risk patients. Immunization should be encouraged in these patients.

REFERENCES