Original article

Immune response to influenza vaccination in children with renal disease

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Abstract. Although immunization with influenza vaccine is recommended for children with chronic renal disease and after organ transplantation, the antibody response in these children has not been well described. We studied the response to the 1993-1994 trivalent influenza vaccine in children, aged 1-21 years, with chronic renal failure (n = 15), end-stage renal disease requiring dialysis (n = 10), and post renal transplantation (n = 17). Each group’s antibody response was compared with that of a control group (n = 7). No significant differences were found in seroconversion rates, percentage of patients achieving protective hemagglutination-inhibition titers post vaccination or change in geometric mean titers from pre to post vaccination between study groups and controls. These results suggest that pediatric patients with renal disease will respond and therefore will benefit from currently recommended influenza immunization.

Key words: Influenza – Immunization – Pediatric renal disease – Dialysis – Transplant

Introduction

Influenza infection, typically a mild illness, can be life threatening in immunosuppressed patients [1], particularly post solid organ transplant [2]. Patients with chronic renal disease requiring dialysis also carry a higher risk of serious influenza virus infection than healthy subjects [3]. Although immunization with trivalent influenza vaccine is currently recommended by the American Academy of Pediatrics (AAP) for children with chronic renal disease and in immunosuppressed transplant patients [4], the immune response to this vaccine in children with chronic renal failure, post transplant, and those requiring dialysis has not been fully described.

Patients and methods

Patients aged >1 and <21 years currently enrolled in the Johns Hopkins Hospital Harriet Lane Kidney Center with chronic renal insufficiency (CRI) defined as a creatinine clearance <75 ml/min per 1.73 m² as calculated by the Schwartz formula [5], patients with end-stage renal disease currently requiring peritoneal or hemodialysis, and patients post renal transplant were recruited as subjects. Patients from the Mount Washington Pediatric Specialty and Rehabilitation Hospital were recruited as controls. Only 3 pediatric patients without renal disease, immunosuppression, or other immunodeficiency syndrome had received influenza vaccination and had sufficient serum available to be controls for our study. Therefore, in addition, 4 healthy adult investigators had pre and post influenza vaccine titers measured.

The final comparison groups consisted of 15 patients with CRI, 10 patients requiring dialysis, 17 transplant patients, and 7 controls (4 adults, 3 children). The median age (interquartile range) of each group was: transplant 15.9 (8.4) years, CRI 7.4 (13.3) years, dialysis 13.3 (5.3) years, and control 32 (27.5) years. Of the transplant patients, 12% had been immunized previously, as had 20% of the CRI group, 10% of the dialysis group, and 88% of the control group. All transplant patients were on immunosuppression, as were 7% of the CRI group, and 30% of the dialysis group. No controls were immunosuppressed. Serum creatinine, height, gender, and age group were used to calculate an estimate of renal function via the Schwartz formula [6]. The “k” values used were 0.45 for infants ≤1 year, 0.55 for children aged 2–12 years and adolescent girls aged 13–21 years, and 0.70 for adolescent boys aged 13–21 years. Subjects were immunized per the AAP schedule for influenza with a single lot of licensed Wyeth influenza vaccine (lot no. 4938159). The 1993–1994 season vaccine contained influenza antigens A/Beijing/353/89(H3N2), A/Taiwan/1/86(H1N1), and B/Panama/45/90.

Serum for pre-immunization influenza antibody titers was obtained from patients and controls within 2 weeks prior to vaccination, and post-immunization influenza antibody titers were measured 4 weeks after vaccination (acceptable range 21–56 days). Antibody titers were measured by a standard hemagglutination-inhibition test [7] in the laboratory of Dr. Stephan Gravenstein at the University of Wisconsin.

Each group’s immune response was examined in three ways: geometric mean titers (anti-log of the means of the log-transformed values) pre and post vaccination, proportion of the group achieving protective titers (titer ≥1:40 [8]), and proportion seroconverting (defined as a fourfold rise in titer to each of three antigens).

Exploratory data analysis was performed using the SAS computer program [9]. One-way analysis of variance (ANOVA) and two-sample t-tests were used for intergroup comparisons of normally distributed continuous variables. The Kruskal-Wallis test was used for intergroup
comparisons of those continuous variables which were not normally distributed. Fisher's exact test was used to compare proportions of subjects in each group who achieved protective antibody levels.

Our final sample size yielded 80% power to detect a difference of 40% in the proportions of transplant or renal failure patients seroconverting to vaccine compared with controls, and 30% power to detect a 40% difference in the proportion of dialysis patients seroconverting when compared with controls. The study protocol was reviewed by the Johns Hopkins Institutional Review Board (IRB) and verbal consent was obtained, as approved by the IRB.

Results

The proportions of subjects with protective antibody titers pre and post vaccination to each of the three antigens are shown in Table 1. There were no statistically significant differences between groups (P > 0.45 for the 3 antigens, Fisher's exact test). The proportion of subjects in each group who seroconverted after vaccination did not differ significantly between groups. Seven of 17 (41.2%) transplant subjects, 9 of 15 (60.0%) CRI subjects, 6 of 10 (60.0%) dialysis subjects, and 3 of 7 (42.9%) controls responded to the A/H3N2 antigen (P = 0.65, Kruskal-Wallis). For the A/H1N1 antigen, 11 of 17 (64.7%) transplant subjects, 11 of 15 (73.3%) CRI subjects, 8 of 10 (80.0%) dialysis subjects, and 5 of 7 (71.4%) controls responded serologically (P = 0.86, Kruskal-Wallis). For the influenza B antigen, 14 of 17 (82.3%) transplant subjects, 14 of 15 (93.3%) CRI subjects, 8 of 10 (80.0%) dialysis subjects, and 4 of 7 (57.1%) controls seroconverted (P = 0.25, Kruskal-Wallis).

Pre and post vaccination geometric mean antibody titers ranged from 1:8 to 1:36 (pre) and 1:38 to 1:320 (post) for the three antigens contained in the influenza vaccine. They did not differ significantly between the four subject groups (P > 0.38 for each antigen, F-tests, one-way ANOVA). Geometric mean fold antibody rises also did not differ between subject groups and controls (P > 0.12 for each antigen, F-tests, one-way ANOVA).

Discussion

The burden of influenza disease in patients with renal disease is uncertain, but its morbidity is likely to be greater than that of the healthy pediatric population, whose influenza infection rates average 42 per 100 children per year [10]. Influenza B can be life threatening in the immunocompromised host [2]. Serious neurological involvement, respiratory failure, and death from influenza B infection have been reported in pediatric solid organ transplant recipients [2].

Previous reports have suggested that immunization against influenza in adults with renal disease may not result in seroconversion or in protective antibody titers, particularly in patients requiring dialysis who had never been vaccinated previously [11, 12]. Our evaluation of a pediatric population with renal insufficiency, post transplant, or requiring dialysis suggests a different result.

Table 1. Percentage of subjects per group with protective titers pre and post vaccination

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Group</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A/H3N2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant (n = 17)</td>
<td>12%</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>CRI (n = 15)</td>
<td>20%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>Dialysis  (n = 10)</td>
<td>30%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Control (n = 7)</td>
<td>29%</td>
<td>71%</td>
<td></td>
</tr>
</tbody>
</table>

CRI, Chronic renal insufficiency  * Protective titers defined as titer ≥ 1:40 by hemagglutination-inhibition assay

Conclusions from this study are limited by small sample size, and differences between study groups and controls in median age, prior immunization status, and immunosuppression. Despite these factors, which would be expected to introduce bias in favor of our controls’ response, patients with renal insufficiency, on dialysis, and post transplant responded as well as controls to influenza vaccination in seroconversion, achievement of protective antibody titers, and geometric mean titers achieved. In addition, their antibody response rates were well within the range reported as normal for response to influenza vaccine [13]. There were no differences observed between child and adult controls or between patients with mild or severe renal insufficiency. There were no episodes of acute rejection in the 17 immunized transplant patients within a 3-month period following vaccination. In the light of these findings, vaccination against influenza is likely to produce a reasonable immune response in patients with chronic renal disease, who may be at high risk for serious sequelae of influenza infection. Further study of the clinical protection against influenza afforded by influenza vaccination in patients with pediatric renal disease is warranted.

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References