

Respiratory Tract Infection and Diarrhea as Risk Factors for Relapsing Nephrotic Syndrome

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Abstract

While infections are known to precipitate disease relapses in childhood nephrotic syndrome, it is unclear whether diarrheal illnesses carry the same risk for relapses as acute respiratory tract infections. This paired case–control study included age- and sex-matched episodes of relapses (cases) and remission (controls). Records were reviewed retrospectively for the presence of acute respiratory tract infections and diarrhea in the two weeks preceding the clinic visit. McNemar test was used to examine associations between these infections and relapse. In 17 patients with 38 paired episodes of relapses and remission, the odds ratio for relapse compared to remission, associated with acute respiratory tract infections, was 3.25 (95% confidence interval: 1.06, 9.97; $P = 0.03$), while that for acute diarrhea was 3.5 (95% confidence interval: 0.73, 16.85; $P = 0.10$). Acute respiratory tract infections are a risk factor for relapses in pediatric nephrotic syndrome, while acute diarrhea does not predispose to disease relapses.

Keywords: Frequent relapses, minimal change disease, triggers

INTRODUCTION

Idiopathic nephrotic syndrome of childhood, characterized by massive proteinuria, hypoalbuminemia, edema, and hypercholesterolemia,^[1,2] is a relapsing illness that responds to corticosteroids. Relapses may be triggered by infections, poor compliance to therapy, allergy or stress^[2,3] and are associated with complications of disease or therapy, decreased quality of life, altered behavior and stress on caretakers.^[4,5] Since acute respiratory tract infections may initiate such relapses,^[6] presumably through aberrant leukocyte release of cytokine(s), it is speculated that acute diarrhea may likewise trigger relapses.^[3] This study was planned to evaluate whether respiratory tract infections and diarrhea precipitate relapses of nephrotic syndrome.

in the Nephrology clinic at the Child Health Department of the Cipto Mangunkusumo Hospital, Jakarta, during May–December 2015. We selected pairs of case–controls from children with nephrotic syndrome, such that cases were visits during episodes of relapses, while controls were visits during remission. Controls were matched to cases for age and sex, and consecutive sampling was performed to enroll 38 matched episodes of relapses and remission. For each case and control (episodes of relapse and matched remission), records were reviewed for the occurrence of respiratory or diarrheal infections in the preceding two weeks. We excluded patients with incomplete medical records, cases without matched controls, episodes with concurrent respiratory and diarrheal infections, and those with infections other than respiratory or diarrheal infections.

METHODS

Patients

This retrospective review of medical records included patients with nephrotic syndrome, aged 1–18 years, seen

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Definitions

Remission of nephrotic syndrome was defined as proteinuria <4 mg/m²/hr or trace or negative result on urine dipstick for 3 consecutive days.^[2] Relapse was the recurrence of proteinuria at 2+ or more on urine dipstick or >40 mg/m²/hr for three consecutive days, after having attained remission previously.^[2] Acute respiratory tract infection was defined as the presence of at least three of the following symptoms for <3 weeks: fever $>38^{\circ}\text{C}$, rhinitis, dysphagia, earache, myalgia or malaise.^[6,7] Acute diarrhea was defined as passage of three or more stools a day for <2 weeks, with a recent change in consistency and with or without blood in stools.^[8]

Analysis

The proportions of cases with preceding acute respiratory infection and diarrhea were compared between pairs of cases and controls using McNemar test on the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, version 20.0; IBM Corp, Armonk, NY).

RESULTS

Patients

We included 38 cases (relapses) in 17 patients (10 boys) with nephrotic syndrome associated with acute respiratory tract infections and 38 controls (remission) in 17 patients (9 boys) associated with acute diarrhea. The median age of patients was 3 (range 1–16) years.

Comparison of exposure to infections

Cases associated with acute respiratory tract infections included one relapse in each of 9 patients, and more than one relapse per patient, up to 8 relapses in one patient. Table 1 shows that acute respiratory tract infections more often preceded episodes of relapse (cases) than remission (controls) ($P = 0.03$). The odds ratio for relapse compared to remission, associated with acute respiratory tract infections, was 3.25 (95% confidence interval: 1.06, 9.97; McNemar $P = 0.03$).

Cases associated with acute diarrhea included one relapse in each of 10 patients, and more than one relapse per patient, up to 7 relapses in one patient. Table 2 shows that acute diarrhea more often preceded episodes of relapse (cases) than remission (controls) ($P = 0.09$). The odds ratio for relapse compared to remission, associated with acute diarrhea, was 3.5 (95% confidence interval: 0.73, 16.85; $P = 0.10$).

DISCUSSION

This paired case–control study included 17 subjects with nephrotic syndrome with 38 episodes each of relapse and remission, such that each subject had at least one relapse or remission episode as their match; some episodes had

Table 1: Acute respiratory tract infections preceding episodes of relapse or remission

	Respiratory tract infection		n	P
	Present (%)	Absent (%)		
Relapse (cases)	16 (42.1)	22 (57.9)	38	0.03
Remission (controls)	7 (18.4)	31 (81.6)	38	

Table 2: Acute diarrhea preceding episodes of relapse or remission

	Acute diarrhea		n	P
	Present (%)	Absent (%)		
Relapse (cases)	7 (18.4)	31 (81.6)	38	0.09
Remission (controls)	2 (5.3)	36 (94.7)	38	

more than one match. The predominance of boys among included subjects is comparable to previous reports that suggest the disease is more common in boys.^[9–13] Our patients were usually younger than 5-years, an age group in which infections are common.^[14] We included patients with infrequent as well as frequent relapses,^[2] as indicated by the frequency of relapses per enrolled subject. Relapses in nephrotic syndrome may be initiated by infections, potentially through release of inflammatory cytokine (s).^[2,15] Infections reported to trigger relapses include acute respiratory infections, diarrhea, fever, urinary tract infection, empyema, pneumonia, tuberculosis, cellulitis, enteric fever, and hepatitis.^[2,9–11] Children <5 years old usually have 6–8 episodes of acute respiratory infections each year.^[7,16] A study each from Pakistan^[17] and India^[11] found that respiratory infections are common in children with nephrotic syndrome. Our results suggest that acute respiratory infections are associated with disease relapses, confirming findings by MacDonald *et al.*, who reported 41 relapses and 61 episodes of respiratory infections in 40 patients.^[6] Moorani *et al.* found that 63% relapses are precipitated by infections, chiefly acute respiratory (55%) or diarrheal (22%) illnesses.^[9,10] While the prevalence of diarrhea in developing countries is quite high,^[8] diarrhea was a trigger for nephrotic syndrome relapses in only 6% cases in a report from India^[6] and 14% of cases in Pakistan.^[10] Our findings suggest that acute diarrhea is not a robust risk factor for relapse in nephrotic syndrome. It is possible that diarrheal illnesses may not induce the systemic pro-inflammatory response essential to precipitate relapses, but this requires detailed study of cytokine profiles.

Our study has limitations inherent to its retrospective case–control design, including potential for incomplete recording of infection events. We did not look for additional triggering events, whether infectious or stress related. Overall, our findings confirm that acute respiratory tract

infections are a risk factor for relapses in pediatric nephrotic syndrome, while acute diarrhea does not appear to have an association with disease relapses.

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Conflicts of interest

There are no conflicts of interest.

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