Peer reviewed article

Serum C-reactive protein in children with adenovirus infection

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Summary

Objectives: (1) To evaluate serum C-reactive protein (CRP) concentrations in children with adenovirus infection, and (2) to compare CRP concentrations in adenovirus and influenza virus infection.

Patients and Methods: Retrospective, comparative single-center study conducted in Emergency Department patients of a paediatric tertiary care center. Comparison of CRP in adenovirus infection and influenza was performed in patient groups stratified according to age and duration of fever.

Results: In 87 children with adenovirus infection (median age, 1.5 years; interquartile range, 0.9–3.0), CRP levels of <2 mg/L, <10 mg/L, and <100 mg/L were found in 4 (4%), 12 (13%), and 66 (76%) patients, respectively. Median CRP in the children with adenovirus infection and in 130 children with influenza was 49 mg/L (21–96) and 9 mg/L (3–20), respectively (p = 0.001). A statistically significant difference remained when these 2 patient groups were stratified according to age (≤ 2 vs. >2 years) and duration of fever (≤3 vs. >3 days) (p <0.001). In adenovirus infection CRP concentrations were unrelated to age, duration of fever and severity of illness, as judged by the extent of mucosal involvement and by the frequency and duration of hospitalisation.

Conclusion: Paediatric adenovirus infection is associated with substantially elevated CRP concentrations in the absence of secondary bacterial infection. CRP levels were independent of the duration of illness, indicating that adenoviruses trigger an immediate inflammatory host response resembling invasive bacterial infection.

Key words: adenovirus; C-reactive protein; acute-phase protein; cytokine; influenza; fever

Introduction

Adenoviruses are major aetiologic agents of respiratory and intestinal tract infections in children less than 5 years of age, accounting for 1–6% [1] and 5–15% [2–4] of all cases, respectively. Mainly in immunocompromised individuals and in neonates, adenoviruses also cause renal, central nervous system, cardiac, hepatic or disseminated infection, and inflict high rates of adverse outcome [5, 6]. The clinical presentation of adenovirus infection usually is nonspecific. However, a vigorous and often sustained febrile response, matched only by influenza virus infection, sets it apart from other common respiratory viruses such as RSV, parainfluenza virus or rhinovirus [7, 8]. Hence, adenovirus-infected children who present to emergency facilities often undergo evaluation for serious bacterial infection, including the determination of inflammatory markers. Among these, serum CRP has become an increasingly popular adjunct to the differentiated WBC [9]. CRP performs better in predicting serious bacterial infection in febrile young children than WBC, ANC, or ABC [10, 11]. For accurate prediction, cut-off CRP levels offering clinically useful likelihood ratios have been proposed, and vary between 40 and 90 mg/L [10, 11]. These values exceed the upper limit of the normal range (i.e. 10 mg/L [12]) be-

Abbreviations

ABC	absolute band count
ANC	absolute neutrophil count
CRP	C-reactive protein
IL-6	Interleukin 6
LRTI	lower respiratory tract infection
RSV	respiratory syncytial virus
TNF-α	tumor necrosis factor alpha
WBC	white blood cell count

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cause CRP levels in serious bacterial infections and in viral infections overlap. In the 1980s, two studies conducted in Finland indicated that among the common viral infections of young children, adenovirus infections stand out for being associated with elevated CRP levels [13, 14]. If clinical decision making strongly relies on CRP values, many adenovirus infections are thus misclassified as bacterial infections and managed accordingly.

The aim of this study was to analyse CRP concentrations in a group of children with adenovirus infection presenting to a tertiary care emergency facility, and to compare the findings with groups of patients with influenza virus infection, matched for age and duration of fever. Influenza was chosen for comparison because its presentation resembles adenovirus infection with respect to clinical manifestations and duration of fever [8], and because of its propensity to cause secondary bacterial infections [15].

Patients and methods

Study design

A retrospective, comparative study was conducted at the Department of Paediatrics and the Institute for Infectious Diseases of the University of Bern.

Patient identification and selection

The electronic microbiology laboratory database was searched for patients 0 to 16 years of age who had been seen at the Emergency Department between October 1, 1997 and September 30, 2001, and in whom adenovirus infection had been established. For each patient a defined set of data was extracted from the medical record. Patients were excluded if at least one of the following criteria were met. (1) Signs of an infection of skin or skin structures, (2) detection of *S. pyogenes* in a throat swab (Strep A OIA Max®, Thermo BioStar, Boulder, CO), (3) detection of a respiratory virus other than adenovirus in nasopharyngeal secretions, (4) a nonsterile culture from blood or from any other normally sterile site, and (5) a urine culture yielding significant bacteriuria [16]. Acute otitis media was not an exclusion criterion. Standard emergency room procedures for evaluation of children with fever without a clinically evident source of infection and/or toxic appearance included a differentiated WBC, CRP and, if the patient was expected to require admission, sampling of nasopharyngeal secretions for direct immunofluorescence assays (see below).

Definitions

Fever was defined as a rectal temperature ≥ 38.0 °C or an axillary temperature ≥37.5 °C. The following categories were applied to describe the clinical presentation of adenovirus infection. (1) Upper respiratory tract infection only (including conjunctivitis, rhinitis, pharyngitis, tonsillitis and laryngitis), (2) LRTI (bronchitis, bronchiolitis and pneumonia), (3) diarrhea, (4) fever without source, and (5) other.

Laboratory methods

Serum CRP was determined from the initial blood sample obtained at presentation by automated immunoturbidimetry using a Roche/Hitachi 917 immunochemistry analyser (Hitachi Corp., Tokyo, Japan). The lower limit of detection was 2 mg/L. A value of 1 was assigned to levels <2 mg/L. Detection of adenovirus, RSV, influenza A and B viruses, and parainfluenza virus types 1–3 in nasopharyngeal secretions aspirated using a mucus trap (Vygon® infant mucus aspirator, Ecouen, France) was performed by direct immunofluorescence assays (Light Diagnostics® Respiratory Panel DFA, Chemicon International, Inc., Temecula, CA). Adenovirus culture of respiratory, stool and urine specimens was performed using either the shell vial technique (HEp-2 cells) or conventional viral culture (Vero, MRC5, and A549 cells), with subsequent identification using a monoclonal antibody (Chemicon).

Comparison of adenovirus and influenza virus infections

Patients seen at the Emergency Department between January 1, 1999 and April 30, 2001, and in whom the diagnosis of influenza virus infection had been made, were identified and selected as described. A limited set of data was collected from these patients. For comparison of CRP concentrations, patients were grouped according to age (≤2 vs. >2 years) and duration of fever (≤3 vs. >3 days).

Statistical analysis

The StatXact® software package, version 5.0.2 (Cytel Corp., Cambridge, MA) was used. Nonparametric tests were used throughout (i.e. Mann-Whitney U-test, stratified Mann-Whitney U test, Spearman rank correlation test). Proportions were compared using Fisher's Exact test. Results were considered significant if the p-value was <0.05.

Results

Patients

Adenovirus infection was identified in 123 patients. Exclusion criteria were present in 36 patients (missing CRP value in 19, viral coinfection in 8, bacterial infection in 7, Henoch-Schönlein purpura and Kawasaki disease each in 1). The clinical, laboratory, and outcome data of the 87 study patients are listed in table 1. Fifty-six (64%) and 76 patients (87%) were ≤2 years and ≤5 years old, respectively.

Clinical presentation

A history of fever could be elicited in 72 patients (83%), with a median duration of 3 days (interquartile range, 2–5) (table 1). On examination, fever was recorded in 71 patients (82%), upper res-

piratory tract illness in 76 patients (87%), LRTI in 19 (22%), a history of diarrhea in 39 (45%), fever without source in 5 (6%), and other manifestations in 7 (seizure in 6, glomerulonephritis in 1). The most common combination was upper respiratory tract illness and diarrhea in 36 cases (41%). Otitis media was diagnosed in 6 patients (7%). Of these, 5 were receiving antimicrobial therapy at the time of presentation. Overall, antimicrobial therapy initiated before presentation at the Emergency Department was recorded in 29 patients (33%; median duration, 2 days; interquartile range, 2–6 days). Emergency room evaluation led to antimicrobial therapy in 37 patients (43%), in 28 of whom antibiotics were given parenterally (median duration, 5 days; interquartile range, 3–10).

Adenovirus detection

In 66 patients (76%), adenovirus antigen was detected by direct immunofluorescence in nasopharyngeal specimens. In 12 of these patients an additional culture was performed and found to be positive in 11 (92%). Adenovirus was isolated by culture in 32 cases (37%; stool, 23 patients; respiratory tract secretions, 8; urine, 3). Immunofluorescence assays from respiratory specimens were

Table 1

Clinical and laboratory parameters in children with adenovirus or influenza virus infection at the time of presentation in the Emergency Department.

	adenovirus* (n = 87)	influenza virus* (n = 130)	p-value**
Female gender (%)	42 (48)	55 (42)	0.406
Age (years)	1.5 [0.9–3.0]	1.5 [0.8–4.8]	0.535
Findings at presentation			
Duration of illness (d)	4 [3–6]	2 [2–5]	<0.001
Duration of fever (d)	3 [2–5]	2 [1–4]	0.121
Antimicrobial therapy (%)***	29 (33)	NA****	
Rectal temperature (°C)	39.0 [38.3–39.7]	NA	
White blood cell count (G/L)	16.0 [10.8–21.2]	8.5 [5.7–11.6]	<0.001
Absolute band count (G/L)	1.6 [0.8–2.6]	0.7 [0.3–1.6]	<0.001
Absolute neutrophil count (G/L)	9.6 [5.4–13.9]	4.3 [2.6–6.8]	<0.001
CRP (mg/L)	49 [21–96]	9 [3–20]	0.001
No. of patients hospitalised (%)	69 (79)	93 (72)	0.203
Duration of hospitalisation (d)	5 [3–6]	4 [3–6]	0.226

* Continuous variables are given as median [interquartile range]
** Fisher's Exact test or Mann-Whitney U test
*** Ongoing, i.e. previously initiated, oral antimicrobial therapy at the time of presentation. In 25 of 29 patients (86%), the duration of therapy was known (median, 2 days; interquartile range, 2–6)
**** NA, not assessed

Table 2

Findings in patients with adenovirus infection, grouped according to serum CRP concentration (cut-off value, 50 mg/L).

	CRP (mg/L)*		p-value*
	≤50 (n = 44)	>50 (n = 43)	
Age (years)	1.4 [0.9–2.9]	1.8 [0.9–3.0]	0.516
Clinical findings			
Temperature (°C)	38.8 [37.9–39.4]	39.5 [38.7–39.8]	0.009
Duration of fever (days)	3.0 [1–5]	3.0 [2–4]	0.529
Upper respiratory tract findings only (%)	15 (34)	15 (35)	1.000
Any lower respiratory tract findings (%)	11 (25)	8 (19)	0.605
Any gastrointestinal findings (%)	19 (43)	20 (47)	0.831
Fever without source (%)	1 (2)	4 (9)	0.202
Inflammatory markers			
White blood cell count (G/L)	13.5 [9.1–20.6]	18.1 [13.0–21.9]	0.035
Absolute band count (G/L)	1.6 [0.7–2.4]	1.7 [1.1–2.7]	0.258
Absolute neutrophil count (G/L)	8.1 [5.0–12.3]	11.5 [7.0–14.9]	0.010
Ongoing antimicrobial therapy (%)**	15 (34)	14 (33)	1.000
No. of patients hospitalised (%)	36 (82)	33 (77)	0.605
Antimicrobial therapy ordered (%)	11 (25)	26 (60)	0.001
Duration of hospitalisation (days)	4 [3–6]	5 [4–6]	0.667

* Continuous variables are given as median [interquartile range]. Mann-Whitney U test or Fisher's Exact test were used for statistical analysis
** Previously initiated oral antimicrobial therapy at the time of presentation

Table 3

Serum CRP in children with adenovirus or influenza virus infection, stratified according to age and duration of fever.

	CRP (mg/L)		p-value*
	adenovirus median (n)	influenza virus median (n)	
Total	49 (85)**	9 (123)**	<0.001***
Age ≤2 years	45 (56)	7 (68)	
Fever <3 days	42 (24)	3 (44)	<0.001
Fever ≥3 days	48 (32)	11 (24)	0.001
Age >2 years	66 (29)	15 (55)	
Fever <3 days	45 (15)	12 (24)	0.034
Fever ≥3 days	68 (14)	15 (31)	0.003

* Mann-Whitney U test

** Two and 7 of the total of 87 and 130 cases, respectively, were excluded because the duration fever could not be determined

*** stratified Mann-Whitney U test

performed in 19 of these culture-proven cases, and reported positive in 11 (58%).

CRP

Median CRP at the time of presentation to the Emergency Department was substantially elevated (49 mg/L; interquartile range, 21–96) (table 1, figure 1). CRP concentrations of <2 mg/L, <10 mg/L, and <100 mg/L were found in 4 (4%), 12 (13%), and 66 (76%) patients, respectively. When patients were grouped according to a cut-off value of 50 mg/L (table 2) it was found that those with a CRP >50 mg/L had significantly higher body temperature, WBC and ANC. In contrast, duration of fever, clinical presentation, and outcome assessed by frequency and duration of hospitalisation were similar. A cut-off value of 100 mg/L yielded similar results (data not shown). Antimicrobial therapy initiated before presentation did not affect CRP concentrations when comparison was made with untreated patients (median CRP, 46 vs. 51 mg/L; p = 0.682). In contrast, patients receiving antimicrobial therapy based on the emergency room evaluation had higher CRP concentrations than untreated patients (median CRP, 74 mg/L vs. 33 mg/L, p <0.001).

Other laboratory findings

The distribution of peripheral WBC in patients with adenovirus infection is given in table 1 and figure 1. Blood cultures had been obtained in 38 patients (44%), cerebrospinal fluid cultures in 15 (17%), urine cultures in 65 (75%), and throat antigen tests for detection of group A streptococci in 16 (18%). Chest radiographs obtained in 47 patients were reported normal in 21 (45%), consistent with bronchial or bronchiolar disease in 21 (45%) and with pulmonary parenchymal involvement in 5 (10%).

Inflammatory markers in adenovirus vs. influenza virus infection

Influenza was identified in 130 patients. Of these, 124 (95%) harboured type A. Clinical characteristics are summarized in table 1. Comparative data on inflammatory markers are given in figure 1. Comparison made after stratification for age and duration of fever demonstrated a consistent significant difference in CRP between adenovirus infection and influenza (table 3).

Discussion

This study confirms that adenovirus infections are associated with markedly elevated CRP concentrations. This finding is consistent with previous reports. Although an elevated CRP is generally considered to reflect bacterial infection, Putto et al. [13] found that mean CRP levels in tonsillitis caused by adenovirus (64 ± 51 mg/L), Epstein-Barr virus (36 ± 38 mg/L) and group A streptococcus (65 ± 49 mg/L) were similar. Ruuskanen et al. [14] investigated CRP levels in respiratory viral infections and found that those caused by adenovirus were associated with significantly higher levels (41 ± 48 mg/L) compared to those caused by parainfluenza virus (10 ± 10 mg/L) and RSV (17 ± 25 mg/L), but not in the case of influenza virus (23 ± 24 mg/L). However, the number of influenza-infected patients was too small to rule out a type 2 error. Nakayama et al. [17] observed that adenovirus LRTIs were accompanied by higher CRP levels compared to influenza (19 ± 4 vs. 6 ± 4 mg/L), but statistical analysis was not presented. In the present study, we were able to establish that a highly significant difference in CRP between adenovirus infection and influenza was independent of age and duration of illness (table 3).

The inflammatory events leading to increased CRP concentrations in adenoviral infections are incompletely understood. An obvious explanation would be bacterial coinfection. Indeed, Korppi et al. [18] found serologic evidence for bacterial coinfection in 9 of 20 children with adenovirus infection, but none were associated with an elevated CRP. In contrast, Ruuskanen et al. [15] found that adenovirus infection was less frequently complicated by bacterial otitis media than RSV, influenza A, and parainfluenza type 3. Our data provide circumstantial evidence refuting the hypothesis that bacterial coinfection is responsible for elevated CRP levels in adenovirus infection. (1) There was no correlation between CRP and the duration of illness. Secondary bacterial infection following virus-induced mucosal damage [19] would be expected to induce a delayed increase of CRP. (2) Antimicrobial therapy initiated before presentation had no effect on CRP levels. (3) CRP concentrations in influenza, known for its propensity to

cause bacterial superinfection [15], were significantly lower, irrespective of the duration of fever. (4) The wide range of CRP concentrations (figure 1) was unrelated to the severity of disease, as judged by the site of mucosal involvement, and the frequency and duration of hospitalisation (table 2).

Thus, in contrast to other common viruses, adenoviruses induce a prominent acute-phase response in some individuals. The underlying inflammatory process was examined in 2 paediatric studies. Mistchenko et al. [20] measured serum cytokine levels in adenovirus LRTI and found that IL-6 and TNF-α, both being major inducers of hepatic synthesis of CRP, were elevated in cases of severe infection but not in LRTI of moderate severity. Interleukin-1β was not detectable. Serum concentrations of IL-6 were one to two orders of magnitude greater than those measured in influenza [21]. Kawasaki et al. [22] confirmed these results and found a strong positive correlation between CRP and IL-6. The possibility of bacterial coinfection was not addressed. In experimental gene therapy, the host response elicited by exposure to adenovirus has become a focus of interest because dose-limiting inflammatory responses had been observed in trials using adenoviral vectors. *In vitro* studies indicate that exposure to intact adenovirus virions or empty capsid induces a prominent release of IL-6 by peripheral blood mononuclear cells [23]. Experimental adenovirus infection of mice demonstrates that within minutes of exposure, alveolar macrophages internalise adenovirus virions and begin expressing mRNA of IL-6 and TNF-α. Within 6 hours IL-6 and TNF-α levels are significantly increased in bronchoalveolar lavage fluid [24]. Available evidence thus indicates that exposure to adenovirus can result in an immediate innate host response inducing the release of acute-phase proteins. Such a scenario could explain that CRP levels in our study were independent of the duration of illness.

The study has important limitations. (1) Detailed characterization of clinical manifestations and their correlation with CRP levels were hampered by the retrospective collection of data. Potential bias arises from the fact that patients referred to the Emergency Department are likely to be more ill-appearing than adenovirus-infected patients cared for in an outpatient practice or those who do not seek medical attention. (2) Some adenovirus-infected patients undoubtedly were missed because adenovirus detection by immunofluorescence is relatively insensitive. (3) Prolonged faecal shedding after a recent adenovirus infection may have caused erroneous attribution of the current illness to adenovirus infection in patients with positive stool culture only. (4) Coinfection with some respiratory viruses (e.g., rhinovirus or coronavirus) was not studied comprehensively.

Nevertheless, the major study findings are robust and confirm that paediatric adenovirus infection is associated with elevated CRP levels. Future studies will need to address the large and currently unexplained interindividual variability of CRP values, and the performance of new generations of inflammatory markers such as procalcitonin in differentiating adenovirus infection from serious bacterial infections.

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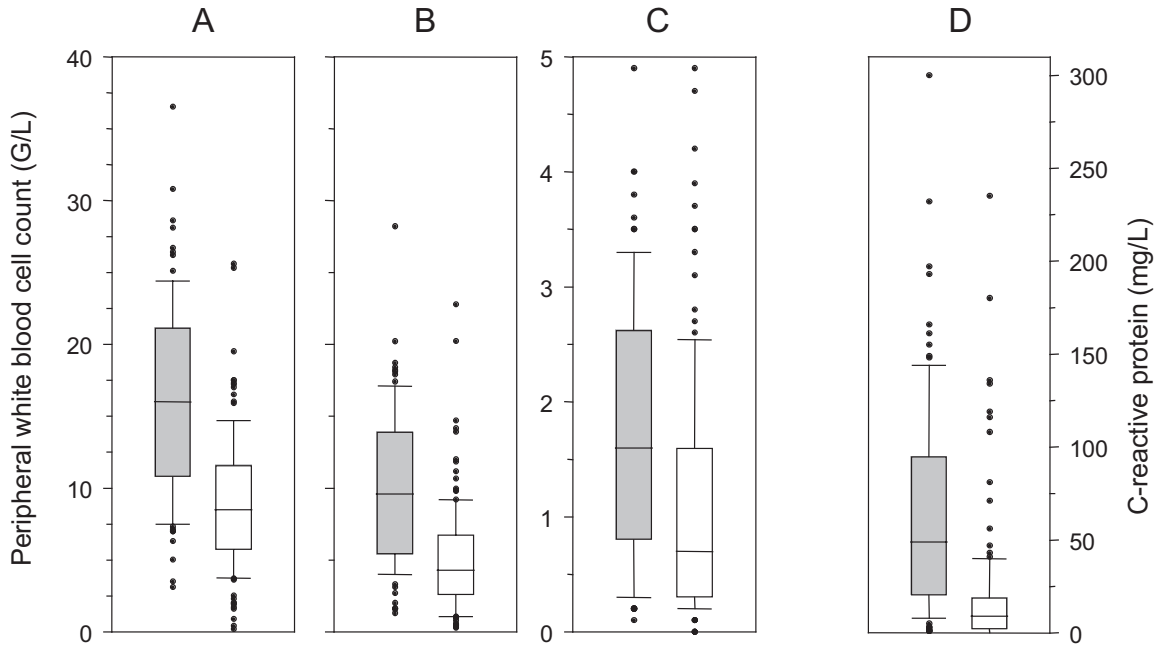

Figure 1

Boxplot presentation of inflammatory markers in 87 children with adenovirus infection (shaded boxes) and 130 children with influenza virus infection (open boxes). A, total white blood cell count; B, absolute neutrophil count (ANC); C, absolute band count (ABC); D, C-reactive protein (CRP). The boxes define the 25th, 50th, and 75th percentiles, error bars define the 10th and 90th percentile, and dots define individual outliers.

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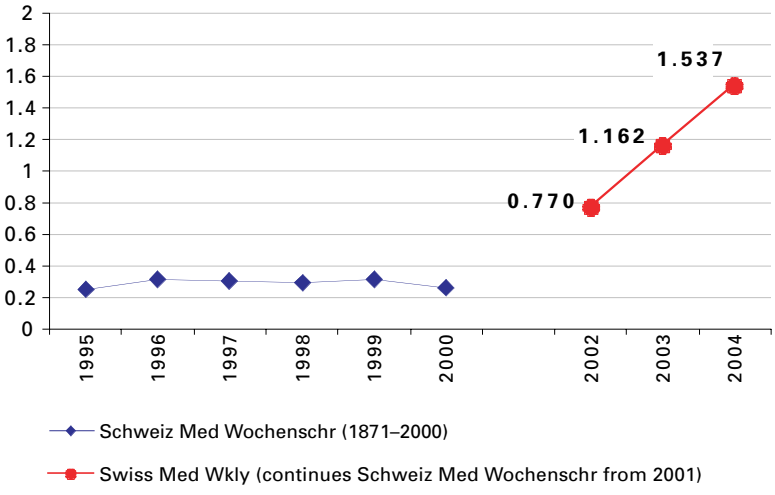

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