Original Paper

Adenovirus infections that require hospital admission: epidemiology, laboratory findings and approach

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Abstract

Introduction: adenovirus infections have a variable clinical presentation and are an important cause of childhood morbidity. They are frequently and unnecessarily treated with antibiotics. This study analyses the characteristic of patients with adenovirus infections in order to determine if they differ from those with bacterial infection.

Patients and methods: 174 patients admitted in a tertiary hospital with positive adenovirus detection from January 2009 to August 2017 were studied. Laboratory and clinical findings were analyzed and compared with those of a sample of patients with bacterial infection, confirmed in the same center, in 2016.

Results: adenovirus infection rate was 1.58/100 admissions. 64% were males, with an average age of 17 months. Those with only gastrointestinal symptoms were younger and presented more favourable laboratory results than those with only respiratory symptoms. 24.5% were coinfected by another virus and were admitted for a longer time (7.93 versus 6.17 days, $p = 0{,}006$). Bacterial infection criteria did not show significant differences when adenovirus-infected patients and bacteria-infected patients were compared, except for a significant though minimal difference in C reactive protein levels.

Conclusions: laboratory and clinical variables studied were not sufficient for discriminating between bacterial and adenovirus infection. Systematic adenovirus infection rule out would be adequate before antibiotic treatment was initiated.

Key words:
- Acute phase proteins
- Adenovirus infections, human
- Coinfection
- Respiratory tract infections

Infección por adenovirus que requiere ingreso hospitalario: epidemiología, datos analíticos y manejo

Introducción: las infecciones por adenovirus tienen una presentación clínica variable y son una importante causa de morbilidad en la infancia. Frecuentemente reciben tratamiento antibiótico de forma innecesaria. Este estudio busca analizar las características de los pacientes con infección por adenovirus y ver si difieren de aquellos con infección bacteriana.

Pacientes y métodos: se estudiaron 174 pacientes ingresados en un hospital terciario desde enero de 2009 hasta agosto de 2017 a los que se les detectó adenovirus. Se analizaron las variables clínicas y analíticas y se compararon con las de una muestra de pacientes diagnosticados de infección bacteriana confirmada en el mismo centro en 2016.

Resultados: la tasa de pacientes con infección por adenovirus fue de 1,58/100 ingresos. El 64% eran varones, siendo la edad media de 17 meses. Los que solo presentaban síntomas gastrointestinales tenían una menor edad y resultados analíticos más favorables que los que solo mostraban síntomas respiratorios. Un 24,5% presentaban coinfección por otro virus, observándose en este grupo una mayor estancia hospitalaria (7,93 versus 6,17 días, $p = 0{,}006$). Los criterios analíticos de infección bacteriana grave no mostraron diferencias significativas al comparar entre los pacientes infectados por adenovirus y los que tenían una infección bacteriana confirmada, excepto una diferencia mínima, aunque estadísticamente significativa, al comparar las cifras de proteína C reactiva.

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Palabras clave:
- Coinfección
- Infecciones del sistema respiratorio
- Infecciones por adenovirus humanos
- Reactantes de fase aguda

Resumen

Conclusiones: las variables analíticas y clínicas estudiadas no son suficientes para discriminar entre infección bacteriana y por adenovirus. Sería adecuado descartar infección por adenovirus sistemáticamente antes de instaurar tratamiento antibiótico., sospechado inicialmente como una patología psiquiátrica pero posteriormente diagnosticado con mononucleosis infecciosa e infección por VEB confirmada serológicamente. Este caso refleja la importancia de reconocer este síndrome por parte de los médicos de urgencias y evitar derivaciones inadecuadas al servicio psiquiátrico.

INTRODUCTION

Infection by adenovirus is a frequent cause of fever in children. Upper respiratory tract infections, such as pharyngitis or rhinitis, and lower respiratory tract infections, such as pneumonia, are the most frequent clinical presentations. Adenovirus infection can cause gastrointestinal, genital, urinary tract, ophthalmologic and neurologic illness less frequently.

Adenoviruses are a group of nonenveloped double-stranded DNA viruses. Seven species have been described this far (A-G). The species that are clinically relevant include B, C and E (associated with respiratory infection), D (which causes conjunctivitis) and F (associated with gastroenteritis).[1]

More than 80% of cases of confirmed adenovirus infection occur in children aged less than 4 years, probably due to the immaturity of their humoral immunity. Although most cases are self-limited, disseminated infection and pneumonia due to adenovirus may be life-threatening, especially in immunocompromised patients.

Outbreaks of adenovirus-related illness are most frequent in winter and spring. The virus may be transmitted by close contact (inhalation of saliva droplets, contact with conjunctival secretion or faecal-oral transmission) or through fomites. In addition, the virus may remain in lymphoid tissue or the renal parenchyma and undergo subsequent reactivation, a situation that is particularly likely in immunocompromised patients.

Acute respiratory tract infections are a significant cause of morbidity and mortality in early childhood worldwide. In addition, they are the most frequent form of infectious illness in the paediatric population in Spain.[2-6]

Although most cases are caused by viruses, there is an excessively frequent prescription of antibiotics, which are unnecessary in this type of infection. Their use does not achieve clinical improvement and may even be harmful, as it exposes patients to potential adverse events while increasing the prevalence of drug-resistant bacteria and thus decreasing the likelihood of an invasive bacterial infection responding to standard antibiotherapy.[3,7-12]

However, several studies have found that most physicians choose not to change the antibiotherapy regimen once a viral pathogen is detected in collected samples, partly due to the short age of the patients and also due to the customary practice of completing antibiotherapy regimens to decrease the likelihood of bacteria developing drug resistance. Nevertheless, ordering tests for detection of viral pathogens may be useful for the individual management of patients, to reduce the number of unnecessary diagnostic tests performed and to implement necessary isolation measures to decrease the incidence of nosocomial infection, thus reducing lengths of stay and the associated health care costs.[5]

The objectives of our study were to describe the clinical and laboratory characteristics associated with adenovirus infection, compare these variables in patients with coinfection by more than one viral pathogen, and analyse the differences between patients with adenovirus infection and patients with confirmed bacterial infections.

PATIENTS AND METHODS

Inclusion criteria

We included patients admitted to a tertiary care hospital in whom adenovirus was detected. The period under study ranged from January 2009 to August 2017 (a total of 8 years and 8 months). Tests for detection of adenovirus were ordered for all patients admitted with clinical manifestations suggestive of respiratory or gastrointestinal infection of unknown aetiology at admission.

We also analysed data for patients with a confirmed diagnosis of bacterial infection, which served as a control group for the purpose of comparing the laboratory characteristics associated with infection.

Detection methods

The assessment for adenovirus infection of the respiratory tract was made by collection a nasopharyngeal secretion aspirate sample either in the emergency department or in the first day of hospitalization followed by use of a commercial panel (Allplex Respiratory RP3, Seegene, Taewon Building, 91 Ogeum-ro, Songpa-gu, Seoul, South Korea) for detection of 19 respiratory viruses by means of real-time qualitative polymerase chain reaction: adenovirus, bocavirus, coronavirus NL63, 229E and OC43, enterovirus, influenza A (with specific differentiation of A-H1, A-H1pdm09 and A-H3) and B, metapneumovirus, parainfluenza 1 to 4, respiratory syncytial virus A and B and rhinovirus. Detection of adenovirus in the gastrointestinal tract consisted of collection of a sample of stool from a spontaneous bowel movement that was later subjected to a commercial assay for detection of adenovirus by real-time qualitative polymerase chain reaction.

Data collection

SWe collected data on the following variables: age, sex, date of admission, length of stay in days, duration of symptoms from onset to admission in days, number of siblings, presence of smokers in the household, history of illness in the household prior to admission, fever at admission, baseline oxygen saturation at admission, general health (good, fair, poor), counts/proportions of white blood cells (WBCs), neutrophils, band cells and platelets, serum levels of C-reactive protein (CRP) and procalcitonin (PCT), infection by other respiratory viruses, interpretation by radiologist of the chest radiograph (normal, abnormal), antibiotherapy and oxygen therapy during hospitalization.

Statistical analysis

We performed all the statistical analyses using the software IBM SPSS Statistics, version 15.0. We set the level of statistical significance at 0.05. We have expressed the results with as 95% confidence intervals.

We used the χ^2 and the Fisher exact tests to compare qualitative variables. We used the Kolmogorov-Smirnov test to determine whether quantitative data followed a normal distribution and based on the results we used the Student *t* test to compare normally distributed variables and the Mann-Whitney U test otherwise.

To analyse diagnostic tests, we calculated odds ratios and the area under the curve (AUC) of receiver operating characteristics (ROC) curves.

RESULTS

During the period under study, there were a total of 174 admissions to the general paediatrics ward of our hospital of patients with infection by adenovirus out of a total of 10 990 admissions, which corresponds to an incidence of adenovirus infection of 1.58 cases per 100 admissions, with a high interannual variability (range, 0.41-2.18). When it came to the distribution by month of the year, we found that more than half of the cases were distributed between March (17.2%), April (12,6%), May (10.9%) and December (10.9%), while August was the month with the fewest admissions for this reason (1.7%). In our sample, 64.4% of patients were male and the mean age was 17 months. We

found considerable variation in laboratory parameters, as a substantial number of patients had values suggestive of severe bacterial infection (WBC count >15 000 cells/µl, CRP >3 mg/dl, PCT >1 ng/ml), even though blood tests were not done in 24% of the patients. Table 1 presents the general characteristics of the overall sample.

Of all participants that answered the epidemiologic questions, 20 had a parent that smoked (11.5%) and 8 had a recent history of illness in the household (4.6%).

We found 54 cases presenting with gastrointestinal symptoms, associated with respiratory symptoms in 44.4%. Table 2 compares the characteristics of patients that presented only with gastrointestinal symptoms and those that presented only with respiratory symptoms. We found that patients with gastrointestinal symptoms alone were younger and had more favourable laboratory test results compared to patients with isolated respiratory symptoms.

A total of 92 (52.9%) patients received antibiotics in the emergency department or at some point during their hospital stay.

Nearly one-third of patients (51) had a viral coinfection: 11% by RSV, 8.2% by rhinovirus, 5.5% by rotavirus, 2.2% by bocavirus and 1% by influenzavirus.

Table 3 compares the characteristics of patients based on the presence or absence of coinfection. Patients with coinfection had longer lengths of stay, a difference that was statistically significant. They also tended to have a higher body temperature and increased elevation of laboratory parameters, with the exception of a WBC count above 15 000 cells/µl. Last of all, we ought to note that there was barely a difference in age between the two subsets of patients.

When we compared the selected patients with adenovirus with the controls that had a bacterial infection confirmed by culture, we found no significant differences in the 3 laboratory criteria suggestive of severe bacterial infection (WBC count >15 000 cells/µl, CRP >3 mg/dl, PCT >1 ng/ml), as

Table 1. Characteristics of patients with adenovirus

Age (years), mean ± SD (minimum; maximum)	1.39 ± 1.32 (0.8; 7.8)
Male, n (%)	112 (64.4)
Fever at admission, n (%)	119 (68.4)
Time from onset to admission (days), mean ± SD (minimum; maximum)	4.16 ± 4.28 (0.1;30)
White blood cells ×1000/µl, mean ± SD (minimum; maximum)	15.1 ± 8.24 (2.32; 56.4)
Neutrophils ×1000/µl, mean ± SD (minimum; maximum)	8.93 ± 6.95 (0.39; 50.41)
C-reactive protein (mg/dl), mean ± SD (minimum; maximum)	4.88 ± 5.32 (0.06; 29.3)
Procalcitonin (ng/ml) mean ± SD (minimum; maximum)	1.65 ± 2.11 (0.1; 15)
White blood cells >15 000/µl, n (%)	61 (35.1)
C-reactive protein >3 (mg/dl), n (%)	63 (36.2)
Procalcitonin >1 (ng/ml), n (%)	23 (13.2)

SD: standard deviation.

Table 2. Comparison of gastrointestinal infections and respiratory infections by adenovirus

	GI	Respiratory	*p*-value
Length of stay (days_, mean ± SD	6 ± 3	7 ± 4	> 0.05
Age (years), mean ± SD	0.77 ± 0.59	1.54 ± 1.50	0.006
White blood cells × 1000/µl, mean ± SD	13.16 ± 8.54	16.01 ± 8.83	0.036
Neutrophils ×1000/µl, mean ± SD	6.21 ± 4.91	9.94 ± 8.18	0.005
C-reactive protein (mg/dl), mean ± SD	2.98 ± 4.83	5.26 ± 5.57	0.01
Procalcitonin (ng/ml), mean ± SD	1.01 ± 1.86	1.25 ± 2.47	> 0.05

GI: gastrointestinal infection; **SD:** standard deviation.

Table 3. Comparison of patients with and without coinfection			
	Coinfection	No coinfection	*p*-value
Length of stay (days), mean ± SD	7.93 ± 4.45	6.17 ± 4.25	<0.006
Age (years), mean ± SD	1.20 ± 1.32	1.45 ± 1.30	>0.05
Temperature (°C)	37.61 ± 1.05	37.40 ± 1.04	>0.05
White blood cells × 1000/µl, mean ± SD	16.18 ± 10.03	14.51 ± 7.28	>0.05
Neutrophils ×1000/µl, mean ± SD	9.37 ± 9.17	8.67 ± 5.76	>0.05
C-reactive protein (mg/dl), mean ± SD	5.92 ± 6.12	4.48 ± 5.03	>0.05
Procalcitonin (ng/ml), mean ± SD	1.27 ± 1.78	1.14 ± 2.31	>0.05
White blood cells > 15 000, n (%)	16 (40)	45 (48.9)	>0.05
C-reactive protein > 3 (mg/dl), n (%)	21 (58.3)	43 (47.2)	>0.05
Procalcitonin > 1 (ng/ml), n (%)	10 (34.4)	14 (24.1)	>0.05
Platelets > 400 000/µl, n (%)	22 (51.1)	46 (35.3)	>0.05
Antibiotherapy, n (%)	26 (59)	66 (48.5)	>0.05
ICU admission, n (%)	5 (11.1)	11 (8.2)	>0.05
Positive blood culture, n (%)	2 (4.6)	1 (0.7)	>0.05
Oxygen therapy, n (%)	23 (56.1)	64 (50)	>0.05

SD: standard deviation.

can be seen in **Table 4**. These findings were corroborated by the ROC curve shown in **Figure 1**. Our findings demonstrated that laboratory parameters were of little use to distinguish between bacterial infections and adenovirus infection. As can be seen in **Table 5**, the only AUC that was statistically significant was the one corresponding to the CPR level, although it showed that it had a negligible power to discriminate between bacterial and viral infection.

DISCUSSION

The incidence of adenovirus infection in our study was of 1.58/100 admissions to the General Paediatrics Ward of our hospital, with a wide annual variability that was most likely the result of detection bias.

Spring was the season in which there were the most admissions due to adenovirus infection. Of all patients with this diagnosis, 64.4% were male. Both findings were consistent with the existing medical literature.[5]

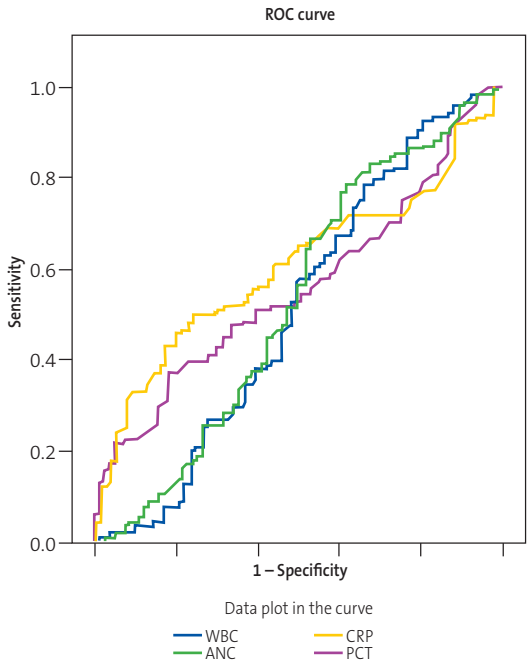
There was coinfection with another virus in 24.5% of the patients, a proportion that was similar to those reported by other authors.[5,13] In the subset of patients with coinfection, 11% had infection by respiratory syncytial virus (RSV) and 8.2% by rhinovirus. These 2 viruses are the viruses detected most frequently in patients with acute upper respiratory tract infections in most of the studies we reviewed, which would explain why they were the viruses found most frequently in association with adenovirus in our study.[5]

As for the age of patients, we found significant differences based on the presence or absence of coinfection, as the latter was more frequent with decreasing age. This was consistent with the findings of previous studies, where the authors reported a lower rate of coinfection in older children[5,14]; this

Table 4. Comparison of patients with bacterial infection and adenovirus infection				
	Bacterial infection	Adenovirus	OR	CI
At least 1 criterion	92	62	1.30	(0.66-2.77)
At least 2 criteria	58	33	1.54	(0.84-2.84)
All 3 criteria	23	12	1.48	(0.65-3.41)

CI: confidence interval; **OR:** odds ratio.
Criteria: 1) White blood cells > 15 000/µl; 2) C-reactive protein > 3 mg/dl; 3) procalcitonin > 1 ng/ml.

Figure 1. Receiver operating characteristic (ROC) curve of laboratory parameters used to compare bacterial infection and adenovirus infection



CRP: reactive protein C; **PCT:** procalcitonin.

could be attributed to a lower clearance of the virus in younger children due to the immaturity of their immunity against viral pathogens.[5]

When it came to the need for oxygen therapy, we did not find significant differences between patients with viral coinfection and patients without, which was similar to the findings of most previous studies we reviewed, although some authors found that coinfection was associated with a lower frequency of oxygen therapy.[5,13]

In addition, the length of stay was longer in patients with coinfection by other respiratory viruses compared to patients with isolated infection by adenovirus. This finding diverged from the findings of other studies where patients with infection by a single pathogen had a longer mean length of stay compared to patients with coinfection by other respiratory viruses.[5]

Different authors have presented contradictory results on the association between coinfection and the severity of acute illness. Some have found that illness is more severe if the infection involved several viral pathogens,[15-21] while others did not find any differences in severity between cases with and without infection by multiple viruses.[18,22-31] There are even studies that have reported that patients with viral coinfection required admission to intensive care units less frequently compared to patients infected by a single virus, which could be due to undetected viral-bacterial coinfections, which evinces that in the future it would be advisable to research the different types of coinfection present in these patients.[5,13,30,32-37]

In regard to the laboratory parameters, CPR is an acute-phase protein indicative of tissue damage due processes such as infection, trauma or inflammation, so it is essential to take into account the clinical context of the patient in the interpretation of its values and to remember that it cannot effectively discriminate between viral and bacterial infection,[3] although some authors have found that a serum CPR greater than 40 to 60 mg/l was significantly more frequent in patients with bacterial infection.[38]

In our sample, CRP levels above 3 mg/dL were more frequent in the coinfection group (58.3%) compared to the isolated adenovirus infection group (47.2%). We also found a higher mean CPR level in

Table 5. Area under the curve of laboratory parameters used to compare bacterial infection and adenovirus infection

Outcome variables	AUC	*p*	95% confidence interval	
			Upper limit	Lower limit
White blood cells	0.508	0.850	0.423	0.593
Total neutrophils	0.527	0.514	0.442	0.612
C-reactive protein	0.609	0.009	0.531	0.687
Procalcitonin	0.559	0.159	0.479	0.638

the former group. In both cases, the difference was not statistically significant.

The comparison of some of the findings of blood tests suggestive of severe bacterial infection in the patients included in our sample to those in patients with a confirmed bacterial infection (WBC count >15 000 cells/µL, CRP > 3 mg/dL, PCT > 1 ng/mL) revealed no significant differences, which illustrates the limited usefulness of blood tests when it comes to differentiating between a viral and a bacterial aetiology, which was further corroborated by the AUC found for the laboratory parameters included in our analysis, which did not exceed 0.609 in any case (the value for the CPR AUC, which was the highest). Some authors have noted that viral respiratory tract infections increase susceptibility to bacterial infection due to their effects on physical barriers and the immune system.[39]

The main limitations of our study are those intrinsic to retrospective studies and that since the sample was exclusively of inpatients, we did not include any data on cases managed at the outpatient level. In addition, there may be a mild elevation of CRP after infection has resolved,[5,14,40] although bacteriological tests were negative in all such cases.

In conclusion, adenovirus infection is a frequent cause of hospital admission in the paediatric age group, especially in male individuals and in the spring. It is frequently associated to infection by other viruses, which increases the length of stay and serum CPR levels. The laboratory parameters that are usually indicative of infection do not allow differentiation between a viral and a bacterial aetiology, so it would be reasonable to rule out infection by adenovirus prior to initiation of antibiotherapy. Further studies are required to better define the characteristics and associated factors of adenovirus infection in paediatric patients.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare in relation to the preparation and publication of this article.

ABBREVIATIONS

CPR: C-reactive protein • **PCT:** procalcitonin • **RSV:** respiratory syncytial virus.

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