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Original Research Article

Clinical and laboratory profile of acute adenoviral infections in children in a tertiary care centre in India

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ABSTRACT

Background: Adenoviral infections have very dramatic presentation with high grade fever, prolonged course and high inflammatory markers, causing much alarm among caretakers and health care workers. Being very common in pediatric age group, it leads to rampant use of antibiotics and hospitalization. This study attempts to characterize acute adenoviral infections and those related to swimming pools.
Methods: A study was conducted among children, aged 2 months to 14 years, who presented with fever and clinical features of adenoviral infection. Diagnosis was confirmed by nasopharyngeal swab and clinical and laboratory data were analyzed statistically.
Results: Fever was the commonest presentation (100%), with >80% experiencing high-grade fever and 7.3% lasting≥10 days. Respiratory symptoms were most common (75%), followed by gastrointestinal (51%), ophthalmic (41%) and neurological (19%). Multisystem involvement occurred in 78%. Elevated inflammatory markers were frequent: CRP>50 mg/L in 70%, ESR>50 mm/hour in 53% and leukocyte count>15,000/mm³ in 65%. Neither higher inflammatory markers nor fever severity correlated with longer fever duration or hospital stay. Swimming pool-related cases showed a higher incidence of conjunctivitis. Post COVID era saw in surge of adenoviral infections.
Conclusions: Adenoviral infections cause prolonged fever, multisystem involvement and high inflammatory markers despite being viral. Elevated inflammatory markers do not predict prolonged illness or hospitalization and should not alone guide antibiotic use in clinically stable children. Early diagnosis can prevent unnecessary antibiotics. A global surge in adenoviral infections has been observed post-COVID.

Keywords: Adenovirus, High inflammatory markers, Multisystem involvement

INTRODUCTION

Adenoviruses are non-enveloped, double-stranded DNA viruses classified under the Mastadenovirus genus of the Adenoviridae family. Being first isolated from human adenoids and thus gained the name, adenoviruses not only have a myriad of clinical manifestations, but also have proved as tools for vaccine vector and gene replacement therapy.[1] Literature describes over 100 human adenovirus types, which have been categorized into seven species (A–G), with new variants emerging due to genomic arrangements.[2,3] Adenoviral infections occur worldwide throughout the year, with no clear seasonality. They present both sporadically and in epidemic outbreaks. While infections can affect individuals of all ages, they are most prevalent in children under five years, who lack prior immunity.[1,3] Most adenoviral infections are asymptomatic or mild and self-limiting.[4] However, severe cases are more common during outbreaks, particularly in immunocompromised individuals and those with underlying conditions. Adenoviral infections spreads through fomites, the fecal-oral route, respiratory droplets and contaminated medical equipment.[1] Notably, adenoviral infections are frequently

associated with contaminated swimming pools.[5] Swimming pool related adenoviral infections present with pharyngitis, conjunctivitis and fever, also known as Pharyngoconjunctival Fever (PCF).

While Adenoviruses can survive up to weeks on surfaces and is resistant to many disinfectants thanks to its non-enveloped structure, it can be inactivated by heat, formaldehyde and bleach. The incubation period is from 2 to 14 days.[1] The spectrum of adenovirus infections can involve various systems including respiratory, gastrointestinal, nervous, ophthalmic, cardiac and urinary systems. Most common system involved is the respiratory system with symptoms anywhere between rhinitis, pharyngotonsillitis, bronchitis, bronchiolitis, pneumonia and even ARDS.[6] Other system manifestations of adenovirus infection include conjunctivitis, gastroenteritis, cystitis, myocarditis, cardiomyopathy and meningoencephalitis.[7]

Various adenovirus serotypes also demonstrate tissue tropism. HAdV-3, HAdV-2 and HAdV-7 serotypes were known to cause respiratory illnesses, whereas types 40 and 41 are responsible for gastroenteritis. HAdV-3, HAdV-7 and HAdV-8 were found to cause conjunctivitis, whereas HAdV-1, HAdV-2 and HAdV-3 caused encephalitis, thereby exhibiting tissue tropism.[6,7] Certain strains like HAdV-7 are known to cause more severe infections, resulting in mortality and morbidity.[8]

Limited literature is available on adenoviral infections in the southwestern region of India. Respiratory manifestation of adenoviral infections was the most studied, whereas limited literature is available regarding non respiratory manifestations of adenoviral infections. During our study period, we observed a notable increase in adenoviral infections with varied manifestations in this region. The aim of our study was to study the clinical and laboratory profile of acute adenoviral infections in pediatric population in our region.

METHODS

This study was a case series of 41 patients, who had acute adenoviral infections and whose clinical and laboratory profile were studied.

This study was conducted amongst children aged 2 months to 14 years admitted in a tertiary care hospital, Sree Gokulam Medical College, Trivandrum, Kerala, India from March 2023 to November 2024.

Those children with fever and clinical features suggestive of adenoviral infection were subjected to nasopharyngeal swab PCR for human adenovirus at the Institute of Advanced Virology, Attingal, Trivandrum, Kerala. Out of the 138 swabs sent, total of 41 (29%) patients turned positive for adenovirus in the nasopharyngeal swab PCR. All those children from the study population who turned positive for Adenovirus in the nasopharyngeal swab was included in the study. Consecutive sampling technique was followed and all children who had confirmed acute adenoviral infections during the study period were included in the study. The clinical details, investigation reports and examination findings were collected.

Those patients from the sample population whose nasopharyngeal swab was negative was excluded from the study.

Since this study was a case series, which retrospectively collected and analysed data and used no personal details or identity of the patient, no formal consent was taken.

Statistical tests used

Categorical and quantitative variables were expressed as frequency (percentage) and mean±SD respectively. Karl Pearson Correlation Coefficient was used to find out relationship of quantitative parameters. Chi-square test was used to find association between categorical variables. For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance. Statistical analyses were performed by using a statistical software package SPSS, version 20.0.

RESULTS

Out of the 41 patients, 12 patients (29%) were found to have adenoviral infection following the use of a few common swimming pools during a specific time period. The rest of the cases did not have any association with swimming pool use. No definite seasonality was seen in this study and adenoviral infections were seen in clusters as well as isolated cases throughout the year. However, some studies have demonstrated seasonality in adenoviral infections with increased incidence during late winter and early spring.[9]

The mean age of patients in our study was 6 years, a little higher than expected. Out of the 41 patients, 48% of the patients were of age 5 years or younger. Minimum age was 1 year and maximum age was 12 years. Infants were not affected in our study, probably due to passive immunity from breast feeding. We found that mean age among the swimming pool related infection was higher 8.9 years, compared to 5 years in non-swimming pool related cases. Susceptibility to adenoviral infections decreases with age, but the inclusion of swimming pool related infections might have contributed to the slightly increased proportion of older children in this group.[10-12]

The male to female ratio was 1.157, with slight male predominance as demonstrated by other studies.[13,14] Callaway et al speculated that since boys have smaller airway diameters relative to lung volume, this gender difference in lung structure may make them more susceptible to severe morbidity because of pulmonary infection.[14] The most common symptom of adenoviral infection in our study was fever, which was present in all

of the patients. Majority of fever was moderate grade (100.5 to 102.2 F) in 61% (21) to high grade (102.4-105.8) in 22% (9). The fever lasted for long duration (>/= 7 days) in 53% of the patients. The mean duration of fever was 6 days. The next most common presentation in our study was pharyngitis, which was present in 75% (31) of the patients, followed by rhinitis in 65% (27), cough in 53% (22) of the patients. Crepitations on auscultation as part of lower respiratory tract infection due to adenovirus was present in 22% (9) of the patients.

Gastrointestinal symptoms like vomiting were seen in 51% (21) of the patients; abdominal pain was seen in 23% (11) of the patients; diarrhea in 21% (9) of the patients. Conjunctivitis was seen in 41% (17) of the patients. Headache was seen in 17% (7) of the patients. Febrile seizure was seen in one patient (2%).

High inflammatory markers are characteristic of adenoviral infections.[15] In our study of 41 patients, high CRP values more than 50 mg/l were seen in 70 % (29) of the cases, out of which 29 % (12) had a CRP>100 mg/l. The mean value of CRP was 84.5 mg/L, with a highest value of 190 mg/l.

ESR values more than 50 were seen in 53% (22) of the patients. The mean value of ESR was 51.9 mm/hour. The maximum value of ESR was 100 mm/hour. Total count was elevated with values>15000 in 65% (27) of the cases. The mean total count was 16112. The maximum total count was 27870. The counts were polymorphic in 92% (38) of the cases. A prolonged duration of hospital stay was observed with 36% (15) of patients requiring hospital stay of more than >5 days. The mean duration of hospital stay was 5 days. The longest duration of hospital stay was for 11 days in the study. Analysis was also done to see if longer duration of fever was associated with high CRP, ESR and high total count values. However, no statistically significant association was seen between higher inflammatory markers and longer duration of fever. Also, analysis was also done to see if longer duration of fever was associated with high ESR, CRP and Total count values. However, no statistically significant association was seen between higher inflammatory markers and longer duration of hospitalization. Attempt was also made to see if high grades of fever were associated with higher values of inflammatory markers. In the study, we also found that higher grades of fever were not associated with higher inflammatory markers.

Table 1: Clinical and lab parameters and in paediatric adenoviral infections.

S. no.	Parameter	Percentage of patients affected
1	Fever	100
2	Moderate to high grade fever	83
3	Duration of fever >7 days	53
4	Duration of hospital stay >5 days	36
5	Conjunctivitis	41
6	Pharyngitis	75
7	Rhinitis	65
8	Cough	53
9	Vomiting	51
10	Diarrhoea	21
11	Abdominal pain	23
12	Headache	17
13	Seizures	2
14	Crepitation on auscultation	22
15	ESR>50 mm/hour	53
16	CRP>50mm/hour	70
17	TC>15000cells/mm^3	65
18	Polymorphic total counts	92

Table 2: Comparison of conjunctivitis in swimming pool and non-swimming pool related infections.

		Swimming pool		Non swimming pool		χ^2	P value
		Count	**Percent**	**Count**	**Percent**		
Conjunctivitis	Absent	3	25.0	21	72.4	7.86*	0.005
	Present	9	75.0	8	27.6		

*Significant at 0.01.

Comparison of various parameters was done between swimming pool and non-swimming pool related infections. Swimming pool related infections were more associated with conjunctivitis (p=0.005). However, the comparison of CRP, ESR and Total count values between swimming pool and non-swimming pool infections did

not reveal any predilection for any group. Also, no significant difference could be appreciated between the duration of fever and duration of hospital stay between swimming pool and non-swimming pool related infections.

DISCUSSION

This study presents the clinical and laboratory profile of adenoviral infections in children from southwestern India (Kerala). The prevalence of adenoviral infections in this region was 29%. The age of the children ranged from 1 to 12 years, with a mean age of 6 years.

Clinical presentation

The most prevalent presentation observed in our cohort were fever (100%), pharyngitis (75%), rhinitis (65%), cough (53%), vomiting (51%), conjunctivitis (41%), abdominal pain (23%), crepitations (22%), diarrhea (21%) and headache (17%). System-wise, respiratory symptoms were the most common (75%), followed by gastrointestinal (51%), ophthalmic (41%) and neurological manifestations (19%). Literature reviews confirm that respiratory system is the most commonly affected among adenoviral infections worldwide.[15,16]

Multisystem involvement was observed in up to 78% (32) of patients, consistent with previous studies, "adenoviral infections affecting multiple systems are also associated with increased mortality".[17,18]

Fever profile

Fever was the most common symptom, occurring in all cases, as demonstrated in other studies.[15,19] Adenoviral infections are known to cause high-grade fever of prolonged duration.[1,15] Fever lasting ≥10 days was observed in 7.3% of cases, with a maximum duration of 13 days; comparable to findings by Hyo Jin Kwon et al where 6.8% of patients experienced fever ≥10 days.[16] Additionally, >80% of cases presented with moderate to high-grade fever.

Prolonged high-grade fever is often a major source of parental concern and leads to unnecessary antibiotic use. Studies have shown that early diagnosis of adenoviral infections in case of prolonged fever, have significantly altered treatment in many cases, helping in antibiotic stewardship and avoiding many unnecessary interventions.[20] Our study emphasizes that early diagnosis and exclusion of other coinfections can help prevent unnecessary antibiotic use.

Respiratory manifestations

Pharyngitis was the most common respiratory presentation, affecting 75% of patients. Lower respiratory tract involvement was less frequent (22%), with only one patient requiring antibiotics for persistent chest signs lasting over 10 days.[10,19] Adenoviral respiratory infections can manifest as upper respiratory tract infection (URTI), tonsillitis, bronchitis and pneumonia. Adenoviral infection is the leading cause of post-infectious bronchiolitis obliterans in children.[11]

Ophthalmic manifestations

A notable finding was the higher prevalence of ophthalmic involvement (41%) compared to previous reports.[17] This increased prevalence may be linked to direct exposure to contaminated swimming pool water and inclusion of many swimming pool related cases in our study. Our study established a clear association between adenoviral conjunctivitis and swimming pool exposure.

Ophthalmic manifestations ranged from mild conjunctival congestion to severe keratitis in one patient, leading to blurred vision. Occular manifestations of adenoviral infections is well documented with acute nonspecific conjunctivitis to chronic conjunctivitis and keratitis.[21] Many of our patients fitted the description of Pharyngoconjunctival fever (PCF), which is characteristic of adenoviral infection with conjunctivitis, pharyngitis and fever.

Laboratory findings

Elevated inflammatory markers are a hallmark of adenoviral infections.[22] A similar picture was seen in this study with CRP levels exceeded 50 mg/l in 70% of patients, ESR was >50 mm/hour in 53% and total leukocyte count exceeded 15,000/mm^3 in 65%.

We analyzed the correlation between CRP, ESR and total leukocyte counts with fever duration, hospital stay and fever severity. The findings indicate that elevated inflammatory markers do not necessarily predict prolonged fever, longer hospital stay or more severe fever, as shown by other studies.[23,24]

Buonsenso et al in their analysis of antibiotic prescription in adenoviral infections among children found that high CRP is often relied upon as an indication for initiation of antibiotics.[25] Our study clearly demonstrates that inflammatory marker levels alone should not be used to determine disease severity and antibiotic initiation in otherwise stable children. A study by Biserni et al demonstrated that IL-6 and IL-10 maybe a better indicator of disease severity and progression in adenoviral infections.[3] More research regarding the feasibility of use of these biomarkers can help in early identification of severe adenoviral infections.

Swimming pool-associated infections

A unique aspect of our study was the inclusion of a subset of adenoviral infections linked to swimming pool exposure, accounting for 29% of cases. Comparative

analysis between swimming pool-associated and non-swimming pool-associated infections revealed a higher incidence of conjunctivitis in the former, whereas other parameters were similar in both groups. Swimming pool related outbreaks of adenoviral infections have been reported elsewhere' with Pharyngoconjunctival Fever like presentation.[5]

Hospitalization and mortality

The mean hospital stay was 5 days, with 36% of patients requiring hospitalization for more than 5 days. As all enrolled children were immunocompetent, no mortality was observed. However, adenoviral infections are known to cause higher mortality in immunocompromised individuals and those with comorbidities.[26-29]

Post-COVID-19 trends

The post-COVID-19 pandemic period (2022–2024) saw a surge in adenoviral infections in various parts of India and globally, with an increased incidence of severe complications such as acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS).[4,8,9,13,17,18] The rise in cases may be attributed to the lifting of COVID-19 related restrictions. We concur with Varadarajan et al that the heightened severity of adenoviral infections could reflect immune dysregulation as a sequela of prior COVID-19 infections.[17] This study holds the distinction of being one of the few investigations from southwest India that analyze adenoviral infections in the region. While the majority of existing literature has emphasized the respiratory manifestations of adenoviral infections, our study successfully characterizes the non-respiratory presentations as well. Notably, we identified outbreaks linked to contaminated swimming pools, which allowed us to alert public health authorities. In response, chlorination and decontamination measures were implemented, effectively curbing the outbreak and contributing to improved public health outcomes.

A limitation of our study is the relatively small number of cases, which constrains the depth of insights that can be drawn. Additionally, further analysis of adenovirus genotypes and strains could enhance our understanding of tissue tropism and the clinical features specific to each strain.

CONCLUSION

Fever was the most predominant symptom of adenoviral infections in our study, followed by pharyngitis and conjunctivitis, with the majority of cases exhibiting multisystem involvement. Notably, swimming pool-associated infections were more frequently linked to ophthalmic manifestations. Adenoviral infections contribute significantly to morbidity, often leading to prolonged hospitalization as seen in the study. Although adenoviral infections are viral in nature, elevated inflammatory markers are a characteristic finding. However, our study demonstrates that higher inflammatory marker levels do not necessarily correlate with prolonged fever duration, extended hospitalization or increased fever severity. It has to be born in mind that while adenoviral infections have dramatic clinical manifestations and high inflammatory markers, most adenoviral infections are self-limiting.

A significant rise in adenoviral infections has been observed in the post-COVID-19 period, highlighting the need for continued surveillance and further research to understand the potential role of immune dysregulation in disease severity.

Clinical significance

Adenoviral infections produce a dramatic clinical picture with prolonged, high-grade fever, multisystem involvement and high inflammatory markers with CRP and ESR in 100s. With a high index of suspicion in such cases, prompt isolation of Adenovirus can help in antibiotic stewardship by avoiding unnecessary antibiotic use. Contrary to the popular belief that high inflammatory markers indicate bacterial infections, it is evident from our study that high inflammatory markers are also a feature of certain viral infections. High inflammatory markers should not alone dictate antibiotic initiation. Proper maintenance of swimming pools is important to prevent swimming related adenoviral infections, which can cause significant morbidity in children.

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