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Original Article

Paediatrics Section

Clinical and Laboratory Characteristics associated with Adenovirus, H3N2, H1N1, and RSV in Children: A Cross-sectional Study from a Tertiary Care Hospital, Chennai, India

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ABSTRACT

Introduction: The seasonal recurrence of influenza and adenovirus is a significant public health concern among children worldwide. Without definitive real-time Reverse Transcriptase Polymerase Chain Reaction (rRT-PCR) results, the differentiation between an infection caused by the influenza virus or adenovirus is difficult, given its non specific clinical presentation. Hence, clinical and laboratory predictors for diagnosing influenza and adenovirus could help in optimal management of these infections.

Aim: To assess various demographic, clinical and laboratory characteristics associated with H3N2, H1N1 and Human Adenovirus (HAdv) and Respiratory Syncytial Virus (RSV) in paediatric population.

Materials and Methods: This cross-sectional study was carried out at Paediatrics department of Government Omandurar Medical College and Hospital, Chennai, Tamil Nadu, India for about 10 months from April 2023 to February 2024. A total of 114 children satisfying inclusion criteria aged between one month to 12 years and whose nasopharyngeal swab for RT-PCR analysis tested positive for adenovirus, H3N2, H1N1 and RSV were included. The demographic, clinical and laboratory results were analysed between various viral infection groups using independent t-test and Chi-square test. A p-value <0.05 was considered statistically significant.

Results: The mean age group of children infected with RSV was 1.156±0.92 years. Abdominal pain 7 (9.4%), diarrhoea 4 (5.4%), pharyngeal congestion with tonsillar exudates 23 (31%) and skin rashes 6 (8%) were the significant clinical features seen in children with HAdv when compared with other groups, whereas severe respiratory distress was seen in H1N1 and RSV infections. Neutrophilia 40 (54%) and thrombocytopenia 14 (18.9%) with elevated C-Reactive Protein (CRP) (mean 47.99 mg/L) values were associated with HAdv infections. Among those infected with HAdv, children with CRP >50 mg/L had a significantly higher occurrence of diarrhoea, severe respiratory distress, tonsillar exudates and low platelet counts compared with the low CRP group (<50 mg/L).

Conclusion: Present study concluded that predominant Gastrointestinal (GI) symptoms, skin rashes, tonsillopharyngitis, neutrophilic leucocytosis, thrombocytopenia and elevated CRP can be used as predictors for diagnosing HAdv earlier in children.

Keywords: C-reactive protein, Neutrophilic leucocytosis, Respiratory syncytial virus, Skin rashes, Thrombocytopenia

INTRODUCTION

Influenza, adenovirus, parainfluenza virus, human metapneumovirus, RSV are common viruses affecting children worldwide, causing absenteeism from school and work, economic disruption and other problems [1,2]. Recent worldwide epidemics of respiratory infections due to HAdV have resulted in renewed interest in this virus. The HAdV infections are associated with a wide range of respiratory and GI tract symptoms and can cause fatal infections in healthy and immunocompromised patients [3]. In case of H1N1 and seasonal influenza infections, antiviral therapy has to be initiated as early as possible to prevent the progression of disease [4,5]. Accurate and prompt clinical diagnosis will benefit both the individual patient and the society because the patients can be isolated quickly and control measures can be initiated. But differentiation between an infection caused by the influenza virus or adenovirus and an infection caused by other respiratory pathogens can be made accurately only with rRT-PCR, which is expensive to be done in all patients in resource-limited settings [6].

Adenovirus-infected children who present to emergency facilities often undergo evaluation for serious bacterial infections, including the determination of inflammatory markers because of the sustained febrile response associated with the infection. Among the inflammatory markers, serum CRP has become an increasingly popular adjunct to the differentiated White Blood Cells (WBC) [7]. For accurate prediction, cut-off CRP levels offering clinically useful likelihood ratios have been proposed and vary between 40 and 90 mg/L [8,9]. These values exceed the upper limit of the normal range (i.e., 10 mg/L) [10]. Hence, the CRP concentrations in children with adenovirus infections and those with influenza infections were analysed. Also, the clinical features in children with adenovirus infections between those with high (>50 mg/L) and low (<50 mg/L) CRP values were analysed.

Several studies analysing the clinical characteristics of pandemic influenza (H1N1) 2009 in children have been performed [11,12], and clinical prediction rules for diagnosing seasonal influenza have been carried out [12]. However, almost all of the studies [11-13] have concentrated on clinical predictors of the pandemic (H1N1) 2009 and have not included those of contemporary seasonal influenza (H3N2). Also, these studies are mainly based on the clinical characteristics of patients in acute care settings [11], patients in military settings [12], in-patients [13] or students from a university campus [13]. Until now, no comprehensive studies into the accuracy of the clinical diagnosis of pandemic (H1N1) 2009 and seasonal influenza in the outpatient paediatric population has been done.

Hence; present study was conducted to assess the various demographic, clinical and laboratory characteristics associated with H3N2, H1N1 and HAdv and other Influenza-Like Illness (ILI) and their prediction to diagnose the same in paediatric population.

MATERIALS AND METHODS

This was a hospital based cross-sectional study, which was done in Paediatrics department of Government Omandurar Medical College and Hospital, Chennai, Tamil Nadu, India, from April 2023 to February 2024. Study was commenced after obtaining Institutional Ethical Committee (IEC) approval. (28/IEC/GOMC/2023).

Inclusion criteria: Children aged between 1 month to 12 years, presenting with clinical features suggestive of influenza or ILI, that is, generalised prodromal symptoms, upper respiratory infection, fever, GI symptoms, sore throat, cough, and conjunctivitis with/without features suggestive of pneumonia, who were tested with nasopharyngeal swab RT-PCR, were included in the study.

Exclusion criteria: Children less than one month and more than 12 years, children with chronic lung diseases like cystic fibrosis and bronchiectasis, children with infections of skin or skin structures, bacterial pathogens in nasopharyngeal swabs, non sterile cultures from blood or any other normally sterile site, urine culture yielding significant bacteriuria, respiratory viral panels showing bacterial infections coexisting with other viral infections and children on immunosuppressants or chemotherapy were excluded from the study.

Sample size: A total of 114 children who were tested positive for either H3N2/H1N1/HAdv/RSV within the study duration were included in the study, and data were analysed.

Data collection: The children who met the inclusion criteria were screened for H3N2, HAdv (adenovirus), H1N1, and RSV by RT-PCR analysis. RT-PCR testing was done at King's Institute of Virology, Guindy, Chennai, Tamil Nadu, India.

Study Procedure

All patients were managed either symptomatically or with antibiotics/antivirals/oxygen supplementation as required. The Paediatric Respiratory Severity Score (PRESS score) is one of the scores used for triaging and assessment of respiratory status [14]. PRESS score was done for all children during the time of admission into the hospital. PRESS includes five components namely, respiratory rate, wheezing, accessory muscle use, SpO_2, and feeding difficulties. Respiratory rate was evaluated based on the World Health Organisation (WHO) guidelines [15]. Wheezing was defined by auscultation performed by experienced paediatricians. Accessory muscle use was defined as visible retraction of one or more of the supraclavicular/suprasternal, intercostal, and subcostal muscles. SpO_2 was evaluated as above or below 95% at room air. Feeding difficulties were assessed using information provided by the parents. Each component was given 0 or 1 point and the PRESS total score was calculated. The total score value (scale of 1-5) was used for analysis between the groups.

The data were collected based on the demographic, history, clinical features, and examination findings. Complete Blood Count (CBC), differential count (neutrophil, lymphocyte, monocyte percentages), Liver function tests (Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), Serum bilirubin), renal function tests (serum urea, creatinine), CRP levels, blood culture [Table/Fig-1] and chest X-ray were done for each patient. CBC was analysed using three part haematology analyser. Neutrophils more than 60% were considered as neutrophilia and lymphocytes more than 40% as lymphocytosis [16]. CRP was analysed by turbidimetric method using an in-vitro diagnostic reagent in serum sample and values more than 6 mg/L were considered positive [16]. The outcomes were entered in a predesigned case recording form.

Parameters	Normal range	Method of estimation	Reference
SGOT (U/L)	1 to 36 months - 20-63 3 to 15 years- 10-50	UV-Kinetic Methods	[16]
SGPT (U/L)	1 to 12 months – 12-45 1 to 15 years- 5-45	UV-Kinetic Methods	[16]
Serum bilirubin (mg/dL)	>1 month -<1	Jendrassik-Grof Method – based on Diazo reaction	[16]
Serum urea (mg/dL)	>1 month – 5-18	Enzymatic Method (Urease-Glutamate dehydrogenase method)	[16]
Serum creatinine (mg/dL)	0-4 year- 0.03-0.50 4-7 year- 0.03-0.59 7-10 year- 0.22-0.59 10-14 year- 0.31-0.88	Jaffé Method (Alkaline Picrate Method)	[16]
CRP (mg/L)	<6	Immunoturbidimetry	[16]

[Table/Fig-1]: Method of estimation and cut-off range for the parameters [16].

STATISTICAL ANALYSIS

The data was entered in a Microsoft Excel sheet and analysed with Statistical Package for the Social Sciences (SPSS) software version 22.0. Descriptive analysis was done. Categorical variables were expressed in frequency and percentages. Quantitative variables were expressed in mean and standard deviation. Inferential analysis was done. The demographic, clinical and laboratory parameters were compared using Chi-square test and Fisher's exact test between the groups (HAdv, H1N1, H3N2, RSV). The mean±SD were compared using ANOVA between the groups. Independent t-test was used to compare the mean±SD between the two groups (based on CRP levels) and Chi-square test was used to compare the clinical and biochemical parameters between the two groups. An appropriate, two-tailed level of significance was set at 0.05.

RESULTS

Out of the total 114 samples, 74 samples tested positive for adenovirus, H1N1 was positive in 10, H3N2 positive in 17, RSV positive in nine and H3N1 was positive in one child (was not included in analysis). Two children had co-infection with adenovirus and H3N2, and one child had co-infection with adenovirus and H1N1 (children with co-infections were also not included in analysis).

Out of the 114 children, 62 (54.4%) were male and 52 (45.6%) were female. The mean age of children in the RSV group was 1.156, which was statistically significant when compared with other groups. The most common complaint was fever in all viruses isolated. Abdominal pain was present in 7 (9.4%) children and diarrhoea in 4 (5.4%) with adenovirus, which was statistically significant when compared with other groups. Pharyngeal congestion and tonsillar exudates were seen in 23 (31%) children and skin rashes in the form of maculopapular eruptions were seen in 6 (8%) with HAdv, which was also statistically significant when compared with other groups [Table/Fig-2].

With respect to nutritional status, 73 (66.3%) children had normal nutritional status, 3 (2.7%) had Severe Acute Malnutrition (SAM), 9 (8.18%) had moderate acute malnutrition, 9 (8.18%) underweight, 4 (3.6%) thinness, 5 (4.4%) had severe thinness, and 6 (5.4%) were overweight, 1 (0.9%) child was obese. Out of the study group, 6 (5.3%) children had co-morbid illnesses such as asthma, 2 (1.8%) children had seizure disorder and 1 (0.9%) had associated congenital heart disease.

The PRESS score was compared between the various groups, revealing that the RSV and H1N1 infected children had more respiratory distress compared to others [Table/Fig-3].

In present study, mean CRP at the time of presentation was substantially elevated (47.99 mg/L) in adenoviral infections. While in other infections, mean CRP levels were at 18.40 mg/L in H1N1, 20.71 mg/L in H3N2 and 20.56 mg/L in RSV infections. On comparing CRP values between the groups, it showed that

Variables	Adenovirus (n=74)	H1N1 (n=10)	H3N2 (n=17)	RSV (n=9)	p-value
M:F	1.2:1	1:1	0.8:1	3.5:1	0.841
Number of male children	41 (55.4)	33 (44.6)	8 (47.1)	7 (77.8)	-
Number of female children	33 (44.6)	5 (50)	9 (52.9)	2 (22.2)	-
Age in years (Mean)	4.345±2.56	2.960±2.97	4.382±3.05	1.156±0.92	0.004*
Nutritional status (Normal)	47 (63.5)	7 (70)	11 (64.7)	8 (88.9)	0.721
Malnutrition (undernourished)	23 (31)	1 (10)	5 (29.4)	1 (11.1)	0.561
Overweight and obesity	4 (5.4)	2 (20)	1 (5.8)	0	0.742
Co-morbid illness	6 (8.1)	0	3 (17.6)	0	0.571
Fever (Yes)	70 (94.5)	9 (90)	17 (100)	9 (100)	0.562
Vomiting (Yes)	18 (24.3)	1 (10)	4 (23.5)	0	0.297
Abdominal pain (Yes)	7 (9.4)	0	0	0	0
Diarrhoea (Yes)	4 (5.4)	3 (30)	2 (11.7)	0	0.042*
Cough (Yes)	65 (87.8)	7 (70)	17 (100)	7 (77.8)	0.116
Coryza (Yes)	23 (31)	1 (10)	7 (41)	0	0.075
Sore throat (Yes)	25 (33.78)	2 (20)	4 (23.5)	0	0.158
Temperature (100.4-102°F)	55 (74.3)	5 (50)	15 (88.2)	5 (55.6)	0.121
Per abdomen examination (Normal)	62 (83.78)	8 (80)	15 (88.2)	9 (100)	0.744
Throat exudates and congestion	23 (31)	1 (10)	2 (11.7)	1 (11.1)	0.045*
Tragal tenderness and ear discharge	11 (14.86)	2 (20)	3 (17.6)	0	0.204
Rashes	6 (8)	(30) 3	0	0	0.034*
Lymphadenopathy	13 (17.56)	2 (20)	2 (11.7)	0	0.525
Haemoglobin (Mild anaemia)	23 (31)	1 (10)	2 (11.7)	4 (44.4)	0.010
Platelet count Thrombocytopenia	14 (18.9)	0	0	1 (11.1)	0.002*
Lymphopenia	9 (12.1)	1 (10)	2 (11.7)	1 (11.1)	0.304
Neutrophilia	40 (54)	8 (80)	4 (23.5)	5 (55.6)	0.010*
Neutropenia	1 (1.35)	0	2 (11.7)	0	0.402
Chest X-ray findings	Bilateral infiltrates 18 (24.3)	Bilateral infiltrates 4 (40)	Patchy opacity 2 (11.7)	Bilateral infiltrates 3 (33.3)	0.160
Duration of hospital stay – mean	5±1.2	4.1±1.4	5.6±1.8	5.2±1.4	0.310

[Table/Fig-2]: Comparison of demographic parameters, clinical features and laboratory parameters between HAdv, H1N1, H3N2, and RSV.
F: Female; M: Male; RSV: Respiratory syncytial virus

Infection	PRESS score						Total	p-value
	0	1	2	3	4	5		
HAdv	30	35	4	4	0	1	74	<0.001**
H1N1	4	1	3	2	0	0	10	
H3N2	8	4	2	3	0	0	17	
RSV	0	3	1	3	2	0	9	
Total	42	43	10	12	2	1	110	

[Table/Fig-3]: Comparison of PRESS score between different viral infections.
PRESS: Paediatric respiratory severity score; RSV: Respiratory syncytial virus

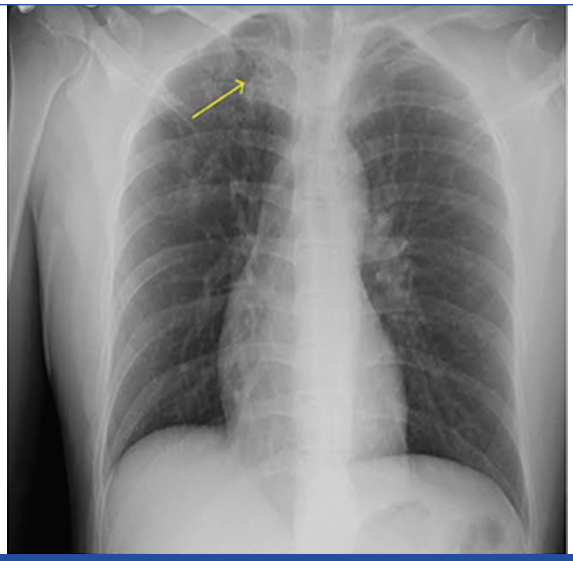
adenovirus infection was associated with higher concentrations of CRP than other respiratory viruses (p-value <0.05) [Table/Fig-4].

NP swab	CRP (Mean mg/L±SD)	n	CRP values in HAdv swab positive	CRP values in other viral infections	p-value
ADENO+	47.99±28.1	74	Adenovirus	H1N1+	0.008*
H1N1+	18.40±17.4	10	Adenovirus	H3N2+	0.001*
H3N2+	20.71±24.9	17	Adenovirus	RSV+	0.025*
RSV+	20.56±22.08	9			

[Table/Fig-4]: Mean CRP concentrations and comparison of CRP between HAdv and other viruses.
CRP: C-reactive protein; NP Swab: Nasopharyngeal swab; RSV: Respiratory syncytial virus

As HAdv infections were associated with a significantly high CRP (mimicking a serious bacterial infection), they were compared in two groups as CRP <50 mg/L and CRP >50 mg/L, to analyse if there are differences in the clinical manifestations and laboratory characteristics in those with high CRP. To assess if treatment with antibiotics started early in the course of illness affects the CRP levels. Analysis revealed that those with a CRP >50 mg/L had significantly higher occurrences of diarrhoea, severe respiratory distress (elevated PRESS score), tonsillopharyngitis and low platelet counts. In contrast, Total Leucocyte Count (TLC), Absolute Neutrophil Count (ANC), Absolute Lymphocyte Counts (ALC), other clinical presentations, chest X-ray findings [Table/Fig-5,6] and outcomes assessed by frequency and duration of hospitalisation

[Table/Fig-5]: Chest X-ray showing bilateral infiltrates in H1N1 infection.



[Table/Fig-6]: Chest X-ray showing patchy opacity of right upper lobe in H3N2 infection.

were non significant among the groups. Among children who have been started on antibiotics early in the course of illness also had elevated CRP [Table/Fig-7].

Variables	CRP in adenovirus		p-value
	<50 mg/dL n=36	>50 mg/dL n=38	
Age (Mean)	4.075	4.600	0.382
Antibiotics prescribed outside	4 (11)	4 (10.5)	0.512
Clinical features			
Fever with chills	(30.5) 11	9 (23.68)	0.506
Myalgia	(27.77) 10	5 (13.15)	0.118
Sore throat	(33) 12	13 (34)	0.936
Vomiting	(25) 9	9 (23.68)	0.895
Abdominal pain	(5.5) 2	5 (13.16)	0.264
Diarrhoea	0	4 (10.5)	0.045*
PRESS score			
0-1	(92) 33	32 (84)	0.045*
2-5	(8) 3	6 (16)	
Lower chest in drawing	(16.6) 6	4 (10.5)	0.440
Crepitations	(5.5) 2	3 (7.8)	0.689
Throat exudates	(19.4) 7	18 (47.36)	0.040*
Tragal tenderness and ear discharge	(19.4) 7	4 (10.5)	0.281
Lymphadenopathy	(13.8) 5	8 (21)	0.418
Rashes	(5.5) 2	4 (10.5)	0.434
TLC (Mean)	12094.56	13805.26	0.125
Platelets (Mean)	3.33 lakhs	2.70 lakhs	0.028*
ANC (Mean)	7408.55	8686	0.144
ALC (Mean)	3810	3602	0.726
Chest X-ray findings	Bilateral infiltrates 9 (25%)	Bilateral infiltrates 9 (23.68%)	0.809
Duration of hospital stay			
<5 days	8 (22)	11 (29)	0.903
>5 days	13 (36)	12 (31.5)	

[Table/Fig-7]: Comparison of clinical and laboratory characteristics in HAdv infections grouped according to serum CRP concentration (cut-off value 50 mg/L).
ALC: Absolute lymphocyte count; ANC: Absolute neutrophil count; CRP: C-reactive protein; HAdv: Human adenovirus; PRESS: Paediatric respiratory severity score; TLC: Total leucocyte count

DISCUSSION

HAdV and influenza viruses are one of the most common causes of fever requiring hospital admission when it occurs in younger age groups (less than 10-year-old). RSV infections predominantly affect children under one year of age. The characteristics exhibited by adenovirus are slightly different from those of other viral infections. The present study was conducted during the seasonal peak reveals some prominent clinical features and laboratory parameters of proven adenoviral infection. More GI symptoms (diarrhoea, abdominal pain) and tonsillar exudates with pharyngeal congestion were present in the adenovirus-infected group than in other viral infections. The findings correlate with study by Farng KT et al., which concluded that chest retraction and extrapulmonary manifestations like conjunctivitis, gastroenteritis, lymphadenopathy, bleeding diathesis, and exanthem were significantly more common in adenovirus infections [17].

In the present study, adenovirus-infected children had significantly elevated total leucocyte count, higher neutrophil levels and low platelet count, which was in contrast with the findings of a study by Zheng L et al., where cases with adenovirus infection had lower leucocyte levels and higher neutrophil levels than cases without adenovirus infection [18].

Children infected with RSV and H1N1 viruses had more severe respiratory distress, as observed by the elevated PRESS score in these groups, compared with HAdv, which is also in contrast with the study by Farng KT et al., [17]. Bilateral infiltrates in chest X-ray [Table/Fig-4] were the finding frequently observed in all the viruses studied here [17], whereas the study by Rao L et al., reported that the characteristic of chest radiography in the early stage of adenovirus type 55 infection was unilateral infiltrates [Table/Fig-5], and later as pneumonia worsens, multilobar or bilateral lung infiltration progresses [19].

This study confirms that adenovirus infections are associated with markedly elevated CRP concentrations when compared with influenza and RSV infections. This finding was consistent with previous reports. Although an elevated CRP is generally considered to reflect bacterial infection, Putto A et al., 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 [20]. Ruuskanen O et al., 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) [21].

Thus, in contrast to other common viruses, HAdv induces a prominent acute phase response. The underlying inflammatory process was examined in two paediatric studies. Mistchenko AS et al., measured serum cytokine levels in adenovirus Lower Respiratory Tract Infection (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 [22]. Interleukin-1β was not detectable. Serum concentrations of IL-6 were one to two orders of magnitude greater than those measured in influenza [23]. Kawasaki Y et al., confirmed these results and found a strong positive correlation between CRP and interleukin-6 [24]. Thus, the elevated CRP levels in adenovirus infection are attributed to this cytokine storm.

When adenovirus infected children were divided into two groups based on the CRP concentration and compared, the group with higher CRP levels had more cases of diarrhoea, tonsillopharyngitis, severe respiratory distress and significant thrombocytopenia compared to the group with CRP levels of <50 mg/L. This too is explained by the more robust cytokine storm response in severely infected children causing worsening of clinical condition along with raised CRP levels.

Limitation(s)

A PCR test was used; hence, serotypes could not be diagnosed; hence, individual characteristics of HAdv infections could not be assessed. Other inflammatory marker levels like IL-6 and procalcitonin were not assessed, which would have given a better correlation with CRP levels. Future studies can incorporate multicentre, longitudinal surveillance to better define the epidemiology, seasonality, and clinical outcomes of adenovirus and other ILI in children. There is also a need for molecular characterisation and viral load assessment to elucidate strain-specific pathogenicity and its association with disease severity.

CONCLUSION(S)

The RSV infection was predominantly seen in children younger than one year of age. H1N1 and RSV infections were associated with severe respiratory distress compared to other respiratory viruses like adenovirus and H3N2. Adenoviral infections in children are associated with more GI symptoms, tonsillitis, pharyngitis, elevated TLC, neutrophilia and thrombocytopenia when compared with other viruses. CRP levels are significantly elevated in HAdv, which can be used as a predictor for early diagnosis of adenoviral infections in children.

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