Original Article

Respiratory Infections in Children Associated to Parainfluenza Virus Type 4

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Abstract

Little is known about the role of certain viruses, such as parainfluenza virus type 4 (HPIV-4) in the etiology of respiratory infections. The objective of this study is to present preliminary data on respiratory infections associated with HPIV-4 in children living in the city of Fortaleza capital of the state of Ceará, Brazil. A set of 846 samples of nasopharyngeal aspirates collected during four years from children with acute respiratory infections were submitted to direct immunofluorescence for the detection of HPIV-4. Fifteen HPIV-4 were detected. Cases of the upper respiratory infections, bronchiolitis and pneumonia were associated to this virus. Further studies are needed to clarify the clinical significance of HPIV-4 infections.

Key words: Acute respiratory infections; Human parainfluenza virus type 4; Direct immunofluorescence assay.

Introduction

Human parainfluenza viruses (HPIV) are important human respiratory pathogens of upper or lower respiratory infections in children previously healthy or not [1-3]. It is estimated that 6.8% to 10% of hospitalizations for acute respiratory infections in children are due to HPIV overall [1]. They belong to the family Paramyxoviridae, genera Respirovirus (HPIV-1 and HPIV-3) and Rubulavirus (HPIV-2 and HPIV-4) [4]. There are two HPIV-4 subtypes: HPIV-4a and HPIV-4b.

Studies on HPIV have primarily focused on HPIV-1 to 3 and little is known about HPIV-4. Monoclonal antibody specific for this virus is not included in the commercially available immunofluorescence kits generally used in research or for respiratory virus surveillance systems. In addition, another possible explanation for the limited information on HPIV-4 is its difficulty in isolation in cell culture. The use of molecular biology methods for the detection of HPIV-4 in human respiratory infections has brought more information on the participation of this virus [3,5-15].

HPIV-4 has been frequently associated with cases of mild respiratory infections, which has limited knowledge about the pathogenic potential of this virus. More recently, however, HPIV-4 has been detected in cases of croup, bronchiolitis and pneumonias in hospitalized patients [12-15].

The aim of this study was to show preliminary epidemiology and clinical data of HPIV-4 infections in children living in the city of Fortaleza, Northeast Brazil.

Methods

From January 2008 to December 2011 a total of 3,534 nasopharyngeal aspirates were collected from children who attended Hospital Infantil Albert Sabin (HIAS) with complaints of respiratory tract infections. The HIAS is a teaching, public care, tertiary-level and reference hospital for children and adolescents. This health facility is located in the city of Fortaleza, the capital of Ceará state (northeast Brazil), at 3o 43'S, 38o 32' W, at sea level. The localization of Fortaleza in the Brazilian territory is showed in the Figure 1.

All samples were submitted beforehand to indirect immunofluorescence assay (IFA) for respiratory syncytial virus, influenza A and B, adenovirus and parainfluenza virus 1, 2 and 3, as described previously.16 For this study, only samples with a negative IFA result were used. A set of 846 samples randomly selected were submitted to a direct immuofluorescence assay (DFA) using a fluorescein isothiocyanate-conjugated monoclonal antibody against HPIV-4 (Millipore, Light DiagnosticsTM ®, Temecula, California, US) following manufacturer's instruction.

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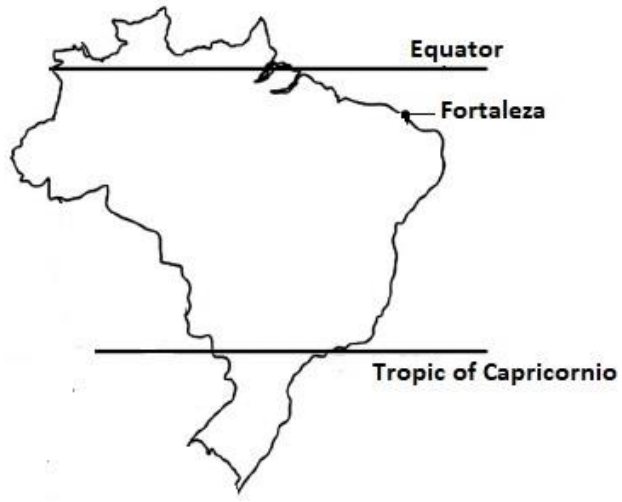
Figure 1. Location of Fortaleza, city where the study was carried out, in the Brazilian territory.



A database of the study population was created with information obtained during child care in emergence room or from their medical records when they were hospitalized. This study was approved by the Institutional Review Board of the HIAS. Written informed consent was obtained from all participants in the study (024/2013).

Results

In the 3534 samples analyzed by the IFA 755 viruses were detected, considering both, single and multiple infections. The detected viruses were 339 RSV, 180 HPIV: 42 HPIV-1, 24 HPIV-2 and 114 HPIV-3, 151 influenza: 143 influenza A and 8 influenza B, and 85 adenovirus.

Samples in which HPIV-4 was tested represented 24% of all samples submitted to IFA and 30.4% of those that presented negative results by this method. HPIV-4 was detected in 15 samples, representing 1.7% of the samples analyzed. Table 1 shows the total of samples analyzed by IFA and DFA in the four years of study, as well as viruses detected by each method.

HPIV-4 positive samples were predominantly from male children (66.6%), aged 2 to 24 months (80%), who were not hospitalized (93.3%). Patients treated for upper respiratory tract infections (URTI) accounted for 77.3% of the positive cases for HPIV-4. Three of these patients were admitted to the hospital emergency department during an asthmatic crisis after the onset of URTI.

Bronchiolitis was the most prevalent diagnosis of the lower respiratory tract infections, followed by pneumonia. Although most patients infected with HPIV-4 did not have underlying diseases, three of them were asthmatic and one had congenital heart disease. The latter presented bronchiolitis, being the only admitted.

Table 1. Viruses detected in the study.

Years of study	2008	2009	2010	2011	Total
Number of samples (IFA)	706	679	1119	1030	3534
Detected viruses	157	228	105	265	755
Negative samples	550	445	1017	770	2782
HPIV-1	13	3	18	8	42
HPIV2	4	6	4	10	24
HPIV-3	20	31	25	38	114
RSV	89	93	26	131	339
Influenza A	14	75	16	38	143
Influenza B	1	2	3	2	8
Adenovirus	16	18	13	38	85
Number of samples (DFA)	330	208	195	113	846
HPIV-4	4	3	3	5	15

IFA= indirect immunofluorescence assay; DFA= direct immunofluorescence assay; HPIV= human parainfluenza virus; RSV= respiratory syncytial virus.

Table 2. Clinical and epidemiological aspects of acute respiratory infections caused by human parainfluenza virus type 4.

Patient	Hospitalization	Month/Year	Gender/Age (in months)	Co-morbidity	Diagnostic
1	No	May/2008	Male/76	--------	URTI*
2	Yes	July/2008	Male/5	Congenital cardiopathy	Bronchiolitis
3	No	September/2008	Male/22	--------	Pneumonia
4	No	November/2008	Female/8	Asthma	URTI + Asmathic crisis
5	No	January/2009	Female/9	------	URTI
6	No	November/2009	Female/2	------	URTI
7	No	November/2009	Male/11	------	Bronchiolitis
8	No	September/2010	Male/20	-------	URTI
9	No	September/2010	Male/15	-------	URTI
10	No	November/2010	Male/59	-------	URTI
11	No	February/2011	Female/24	------	URTI
12	No	February/2011	Male/29	Asthma	URTI + Asmathic crisis
13	No	February/2011	Male/23	Asthma	URTI + Asmathic crisis
14	No	September/2011	Male/10	------	Bronchiolitis
15	No	November/2011	Female/7	------	URTI

URTI: upper respiratory tract infections.

All patients who presented positive respiratory infection for HPIV-4 evolved without complications, even the hospitalized one. The table 2 shows the epidemiological and clinical characteristics of children with respiratory infections positive for HPIV-4.

Discussion

The use of DFA in the present study resulted in an HPIV-4 detection rate of 1.7%. This technique has been used to detect HPIV-4 directly in clinical samples or as a

method of confirming isolation of this virus in cell culture. The use of IFA in the identification of respiratory viruses has been greatly reduced with the introduction of molecular diagnostic methods, however it is still used by respiratory virus surveillance systems in several countries, including Brazil [17,18]. However, HPIV-4 is not comprised in the pool of viruses screened in the commercially available immunofluorescence kits. Laboratory surveillance for HPIV infections in England and Wales from 1975 to 1997 detected 88 HPIV-4, however the HPIV identification method only became available after 1988 when DFA accounted for 51 of the 70 HPIV- 4 reports [19]. HPIV-4 was the only virus detected in a respiratory infection outbreak that occurred in a facility for children with developmental disabilities [20]. All forty-one cases investigated were detected by RT-PCR whereas DFA detected only 29 of 39 tested cases. The sensitivity of immunofluorescence varies substantially among HPIV that are routinely screened by it.

Among HPIV overall, there is wide range of the type detected; however, most studies report a predominance of HPIV-3 and HPIV-1 [5,7,8,13] HPIV-4 has been detected in rates that ranged from less than 1% to 3%.3,6,8,10,11,12,14,15 In two studies HPIV-4 was the most detected HPIV [3,11]. One of these studies was conducted with adults patients [11].

Our results suggest the possibility of HPIV-4 be more frequently detected than other viruses. Comparing the number of HPIV-4 and influenza B detected in three years (2008, 2009, 2011), HPIV-4 exceeded the number of influenza B. In relation to other types of HPIV, the circulation of HPIV-2 was similar to that of HPIV-4 in two years (2008, 2010). The most frequent detection of HPIV-4 in relation to HPIV-2 has been reported in several studies [3,6,8,10,11,12,14]. In addition to the small number of analyzed samples, another factor that may have determined the small number of HPIV-4 detected was the fact that we used only negative samples for the other viruses analyzed by IFA.

Other reports have shown that HPIV-4 has been frequently detected in co-infection with other respiratory viruses [5,6,8,10].

These are preliminary data on clinical and epidemiological features of HPIV-4 infections in children living in a city of northeast Brazil. However, HPIV-4 was included among the viruses investigated in some Brazilian studies [14,21, 22]. The rate of detection of HPIV-4 detection was not reported in one of them [22]. The frequency order of HPIVs in the present study was similar to that reported in one of the studies carried out in the city of São Paulo [14].

The data presented here showed that this virus can be detected in patients diagnosed with different syndromes, including bronchiolitis and pneumonia, although the majority of cases were considered mild, and managed as outpatient. Three patients in whom HPIV-4 was detected were admitted to the emergency room due to asthmatic crisis-related symptoms following the onset of upper airway infection. In this way, this is another virus whose infection by it may be associated with an asthma exacerbation in children, which is well known with other viruses [23].

HPIV have been pointed out as second leading cause of hospitalization due to viral respiratory infections in young children in the United States of America [1]. Bronchiolitis was diagnosed in three patients positive for HPIV-4, one of them required hospitalization. This case occurred in a patient who had a congenital heart disease as the underlying disease. The detection of HPIV-4 in two patients with congenital heart disease was also reported in a study carried out in another Brazilian city [21]. In a previous study performed with children living in Fortaleza, 12% of the children positive for HPIV (1, 2 and 3) were hospitalized [16]. There is increasing publication of studies showing the association of HPIV-4 to cases of severe respiratory infections in previously healthy or immunocompromised patients, which contradicts the previous idea that this virus was associated only with cases of mild infections [8, 10,14,15,24,25].

Considering that the set of samples submitted to DFA were not representative of a continuous collection over the four years, it was not possible to establish a pattern of seasonality to the HPIV-4 in Fortaleza, as previously described for other HPIV [16].

Despite its limitations, this study contributes to a better understanding of viral respiratory infections by adding the first information about of HPIV-4 in respiratory infections in children living in the Brazilian Northeast. Further studies are needed to expand our understanding of the epidemiology and clinical impact of HPIV-4 infections in patients of higher ages.

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References

1. Weinberg GA, Hall CB, Iwane MK, Poehling KA, Edwards KM, Griffin MR, et al. Parainfluenza virus infection of young children: estimates of the population-based burden of hospitalization. J Pediatr. 2009; 154:694-9.
2. Maeng SH, Yoo HS, Choi SH, Yoo KH, Kim Y-J, Sung KW, et al. Impact of parainfluenza virus infection in pediatric cancer patients. Pediatr Blood Cancer. 2012; 59:708-710.
3. Frost HM, Robinson CC, Dominguez SR. Epidemiology and clinical presentation of parainfluenza type 4 in children: a 3-year comparative study to parainfluenza types 1–3 2014. J Infect Dis. 2014; 209: 695-702.
4. Amarasinghe GK, Ceballos NGA, Banyard AC, Basler CF, Bavari S, Bennett AJ, et al. Taxonomy of the order Mononegavirales: update 2018. Arch Virol. 2018; 2283-2294.
5. Liu WK, Liu Q, Chen DH, Liang HX, Chen XK, Huang WB, et al. Epidemiology and clinical presentation of the four human parainfluenza virus types. BMC Infect Dis.2013; 13:28-35.
6. Fairchock MP, Martin ET, Kuypers J, Englund JA. A prospective study of parainfluenza virus type 4 infections in children attending daycare. Pediatr Infect Dis J. 2011;30:713-716.
7. Steffens A, Finelli L, Whitaker B, Fowlkes A. Population-based surveillance for medically attended human parainfluenza viruses from the influenza incidence surveillance project, 2010-2014. Pediatr Infect Dis J. 2016; 35:717-722.
8. Ren L, Gonzalez R, Xie Z, Xiong Z, Liu C, Xiang Z, et al. Human parainfluenza virus type 4 infections in Chinese children with lower respiratory tract infections: A comparison study. J Clin Virol.2011; 51(3): 209-212.
9. Kumar P, Medigeshi GR, Mishra VS, Islam M, Randev S, Mukherje A, et al. Etiology of acute respiratory infections in infants: A prospective birth cohort study. Pediatr Infect Dis J. 2017; 36(1): 25-30.
10. Xiao NG, Duan ZJ, Xie ZP, Zhang LL, Zeng SZ, Huang H, et al. Human parainfluenza virus types 1-4 in hospitalized children with acute lower respiratory infections in China. J Med Virol. 2016; 88(12):2085-2091.
11. Dia N, Richard V, Kion D, Cisse EHAK, Sarr FDM, Faye A, et al. Respiratory viruses associated with patients older than 50 years presenting with ILI in Senegal, 2009 to 2011. BMC Infect Dis. 2014; 14:189-194.
12. Swamy MA, Malhotra B, Reddy PVJ, Kumar N, Tiwari JK, Gupta ML. Distribution and trends of human parainfluenza viruses in hospitalized children.Indian J Pedriatr 2016; 83:1109-1113
13. Fathima S, Simmonds K, Invik J, Scott AN, Drews S. Use of laboratory and administrative data to understand the potencial impact of human parainfluenza virus 4 on cases of bronchiolitis, croup, and pneumonia in Alberta, Canada. BMC Infectious Diseases 2016; 16: 402-409.
14. Thomazelli LM, Oliveira DBL, Durigon GS, Brett W, Kamili S, Bezerin EN, Durigon EL. Human parainfluenza virus surveillance in pediatric patients with lower respiratory tract infections: a special view of parainfluenza type 4. J Pediatr (Rio J) 2017 doi: 10.1016/J.Jped.2017.07.017.
15. Pan Y, Zhang Y, Shi W, Peng X, Cui S, Zhang D et al. Human parainfluenza virus infection in severe acute respiratory infection cases in Beijing, 2014-2016: A molecular epidemiological study. Influenza Other Respir Viruses 2017; 11: 564-568.
16. Fé MMM, Monteiro AJ, Moura FEA. Parainfluenza virus infections in a tropical city: clinical and epidemiological aspects. Braz J Infec Dis 2008; 12(6):192-197.
17. WHO. Virus identification by immunofluorescence antibody staining. In: WHO Global Influenza Surveillance Network Manual for the Laboratory Diagnosis and Virological Surveillance of Influenza. Geneva. 2011. 151p. Accessed 17 May 2017. Available in: http://apps.who.int/bookorders.
18. Ministério da Saúde. Secretaria de Vigilância em Saúde. Situação epidemiológica de Influenza no Brasil até a semana epidemiológica 32 de 2017. Boletim Epidemiológico 2017; 48(25).
19. Laurichesse H, Dedman D, Watson JM, Zambon MC. Epidemiological features of parainfluenza virus infections: laboratory surveillance in England and Wales, 1975-1997. Eur J Epidemiology. 1999;15(5):475-484.
20. Abiko C, Mizuta K, Aoki Y, Ikeda T, Itagaki T, Noda M, et al. An outbreak of parainfluenza virus type 4 infections among children with acute respiratory infections during the 2011-2012 winter season in Yamagata, Japan. Jpn J Infect Dis. 2013; 66(1):76-78.
21. Parmezan SN, Camargo C, Watanabe A, Godoy-Martínez, Granato C, Belley N. Detection of parainfluenza virus in immunocompromised and immunocompetent patients in a terciary hospital in São Paulo, Brazil. Rev Chilena Infectol. 2016; 33(5):501-504.
22. Bezerra PGM, Britto MCA, Correia JB, Duarte MCMB, Fonceca AM, Rose K, et al. Viral and atypical bacteria detection in acute respiratory infections in children under five years. PlosOne. 2011; 6(4):e18928.
23. Fu LS, Tsai MC. Asthma exacerbation in children: a practical review. Pediatrics and Neonatology. 2014; 55 (2):83-91.
24. Ozkaya-Parlakay A, Cetin II, Tezer H, Guiklhan B, Sayli TR. Parainfluenza virus 4 presenting with pericardial effusion in an immunocompetent child. J Infect Dev Ctries 2014; 8:1079-1080.
25. Mcfarlane HJ, MacDonald J, Collins TC, Molyneaux PJ, Carman WF. Severe pneumonia after cardiac surgery as a result of infection with parainfluenza virus type 4. J Cardiothoracic Vasc Anesth 2009; 23:84-86.

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