ARTICLE

Human Rhinovirus Association with Influenza-Like Illness and Symptomatic Treatment for Acute Respiratory Infection in a Brazilian Southern City

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Acute respiratory infections (ARI) are the world's leading cause of morbidity and mortality. ARI impairs children's education and have a huge impact on the economy. Human rhinovirus (HRV) is the most prevalent agent of ARI. In this study, a clinical and epidemiological surveillance in outpatients was carried to investigate the involvement of HRV in ARI cases in the city of Guarapuava, a Brazilian southern city. Attention was also given to the most common medications used for treating ARI symptoms. Samples from 135 patients were collected from Apr to Dec from 2014, HRV was identified in nearly 20% of samples, with symptoms ranging from common cold to Influenza-like Illness (ILI) and was more frequent in individuals with 10 or less years-old. Nearly two thirds of patients reported use of at least one class of drug during the ARI episodes, such as analgesics, cough and cold preparations, and NSAIDs. In some cases and with no justifiable reason, patients also reported the use of antibiotics, possibly contributing to the development of bacterial resistance. These results show a significant detection rate of HRV in ARI cases, and highlight the impact of this virus in the local population.

Key words: Human rhinovirus; Acute respiratory infection; Influenza-like illness; Antibiotics

INTRODUCTION

Acute respiratory infections (ARI) are the world's leading cause of morbidity, hospitalizations and mortality (MONTO, 2002; GILLIM-ROSS e SUBBARAO, 2006). ARI are also the most frequent cause of school and work absenteeism, impairing children's education and threatening the economic sector (BERTINO, 2002; ROELEN, KOOPMANS, et al., 2011). It is estimated that ARI costs the US economy tens of billions of dollars each year (FENDRICK, MONTO, et al., 2003; PALMER, ROUSCULP, et al., 2010).

Human Rhinovirus (HRV) is the most frequent infectious agent responsible for ARI. Although HRV can provoke common colds, it can be implicated in severe diseases as well, such as bronchiolitis, pneumonia, asthma and chronic obstructive pulmonary disease (COPD) exacerbations (MÄKELÄ, PUHAKKA, et al., 1998; TEERATAKULPISARN, PIENTONG, et al., 2014; BECKHAM, CADENA, et al., 2005). HRV can also be associated with influenza-like illness (ILI), leading to errors in the treatment of patients with ILI syndrome when based only in symptomatology (BELLEI , CARRARO, et al., 2008; WATANABE, CARRARO, et al., 2010; GARCIA, ESPEJO, et al., 2013).

Although the HRV and other respiratory viruses are responsible for most ARI cases, the use of antibiotics is high, especially in children (EBELL e RADKE, 2015; KAMIKAWA, GRANATO e BELLEI, 2015). This overuse is associated to the increase of antibiotic-resistant bacteria (AUSTIN, KRISTINSSON e ANDERSON, 1999). Moreover, patients may also be subject to unnecessary side effects, such as allergy

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reactions and diarrhea (GRIJALVA, NUORTI e GRIFFIN, 2009; KENEALY e ARROLL, 2013). Although there are some potential candidates (SHIM, SONG, et al., 2016), there is no FDA approved antiviral against HRV so far. Despite of that, the identification of HRV as an ARI causality may decrease the unnecessary use of antibiotics. The existence of many different HRV genotypes made it difficult for scientists to develop an effective vaccine, since host antibodies show little cross reactivity against those (ROHDE, 2011; JACOBS, LAMSON, et al., 2013; SIMANCAS-RACINES, GUERRA e HIDALGO, 2013).

There are several drug classes routinely used for treating ARI symptoms, such as analgesics, nonsteroidal anti-inflammatory (NSAIDs), antihistamines, corticosteroids, antitussives, adrenergic agonist inhalers and cough and cold preparations (JHAJ, BHARGAVA, et al., 2001; DAS, SARKAR e MAJUMBER, 2006; BERQUÓ, BARROS, et al., 2004). Studies on the efficacy of medications in the treatment of ARI symptomatology had indicated that analgesics and NSAIDs are effective for pain and malaise, and preparations for cold (e.g., analgesic, antihistamine and decongestant combos) can also minimize respiratory symptoms (LI, YUE, et al., 2013; DE SUTTER, VAN DRIEL, et al., 2012; KIM, CHANG, et al., 2015).

Due to its continental dimensions, Brazil possesses a very wide climatic diversification. Previous studies had shown that HRV is widespread in Brazilian patients showing ARI (ALMEIDA, ZERBINATI, et al., 2010; MOREIRA, KAMIKAWA, et al., 2011; PILGER, CANTARELLI, et al., 2011; PROENÇA-MODERNA, VALERA, et al., 2012). There are relatively few studies on the HRV epidemiology in South Brazil, a humid subtropical region. In addition, there are not enough data on the ARI common symptomatic therapy practiced by outpatients in this region. This study provides information on the HRV epidemiology and clinical presentation of outpatients with ARI in a city of South Brazil, as well as the drug therapy for ARI symptoms.

MATERIAL AND METHODS

Sample Collection and ethical consent: The study was carried out in the Integrated Care Center of Vila Carli in the Brazilian city of Guarapuava, Paraná State. Guarapuava is a southern city with around 180,000 inhabitants (IBGE, 2010). Samples from 135 patients showing ARI symptoms were collected from April to December 2014. Nasal swab samples were collected from symptomatic patients who agreed to voluntary participation in the study. Inclusion criteria was the presence of any symptom of respiratory infection (coryza, cough, sore throat, fever, headache, myalgia or chills), from outpatients who attended the health center. Personal, clinical and epidemiological data were scored in a standard questionnaire, including treatment and Influenza vaccination status for the current season. The samples were transported in sterile saline, in a recipient containing ice

packs to the Virology Laboratory of the Midwest State University (UNICENTRO), and stored at -80°C until processing. According to the WHO, ILI case definition is an acute respiratory infection with measured fever of ≥ 38 C° and cough with onset within the last 10 days (WHO, 2014), while ARI is an acute respiratory infection with at least one of the following: shortness of breath, cough, sore throat or coryza (WHO, 2017).

The study protocol was reviewed and approved by the local Ethics Committees. All patients or responsible enrolled in the study had given informed consent.

RNA extraction and Rhinovirus detection: Stored samples were thawed at room temperature and the genetic material was extracted from 200μL of the samples using the RNeasy® Mini Kit (Qiagen, Valencia, CA, USA), according to the manufacturer's instructions. The presence of HRV in clinical samples was investigated by polymerase chain reaction preceded by reverse transcription technique (RT-PCR) in two steps, as previously described (WATANABE, CARRARO, et al., 2010). RNA was transcribed into cDNA with Moloney Murine Reverse Transcriptase (MMLV-RT; Invitrogen, Carlsbad, CA). PCR step was performed with Platinum® Taq DNA Polymerase (Invitrogen, Carlsbad, CA), using primers described by Savolainen and coworkers (2002), targeting part of 5'NCR and VP4/VP2 genes in HRV genome (SAVOLAINEN, MULDERS e HOVI, 2002).

All tests included positive and negative controls. Positive ones were HRV-1 strains, kindly provide by Dr. Nancy Bellei from the Federal University of Sao Paulo (UNIFESP), and negative were ultrapure water.

Statistical Analyses: Data were analyzed with SPSS version 22.0 (IBM, USA). Associations among categorical variables were examined with Qui square test (HRV, ILI, Influenza vaccination, symptoms). In all tests, p-value <0.05 was considered statistically significant.

RESULTS

Nasal swab samples of 135 patients were collected, 1 per ARI episode. Monthly inclusion was: 8 in April, 21 in May, 18 in June, 21 in July, 40 in August, 22 in September, 3 in November, 2 in October, and none in December. The average age of patients was 36 years old (1 to 82, median 33). Patients were allocated in groups divided per age, from 10 to 10 years old (yo). The number of patients in each age group was: 15 patients aged equal to or less than 10 yo, 18 in the group from 11 to 20 yo, 29 in the group from 21 to 30 yo, 19 in the group from 31 to 40 yo, 13 in the group from 41 to 50 yo, 23 in the group from 51 to 60 yo, and 18 aged 61 yo or more. Most patients were female, representing 73% of total.

The average sample collection time after symptoms onset was 6 days (1 to 30, median 5). In the time of sampling, 96.3%

of patients reported coryza, 73.3% cough, 54.8% sore throat, 34.8% fever, 62.2% headache, 52.6% myalgia, e 44.4% chills. A syndrome featuring Influenza-like illness (high fever plus at least one respiratory symptom and one constitutional symptom) was reported by 31.8% of patients (43/135).

A positive result for HRV presence by RT-PCR was found in 25 (18.5%), these positive samples were collected from 8 males (21.6% of the entire male population) and 17 females (17.3%). There was no statistically significant difference in HRV detection between genders. HRV detection was more frequent among patients aged 10 yo or less in comparison with the above 10 yo (40.0% vs 15.8%). This difference was statistically significant (p=0.023).

A slight tendency of fever and ILI syndrome was observed in HRV infected patients, however, with no statistically significance. The only statistically significant difference was observed in headache. This symptom was more frequent among HRV-negative patients (p=0,014). Table 1 (Table 1 was previously called Table 3, the text was reallocated to try to approach the order suggested by reviewer A, clinical data from positive and negative patients for HRV are shown in this table. Part of the clinical data appear in Tables 2 and 3, referring, respectively, to patients using medications to treat the symptomatology of ARI and patients in use of antibiotics only) shows the symptoms presentation frequency by HRV infected and non-infected patients.

From the studied population, 85 (63%) reported use of at least one class of drug for symptomatic treatment. Table 2 shows the drug classes distribution among the age groups and genders. The use of NSAIDS was more frequent among females (p=0.02), and the general use was also greater in this group (p=0.034). A statistically significant difference was observed in antibiotics use when compared under 10 yo patients against the above 10 yo. These medications were used more often amongst patients aged less than 10 (26.7% vs 8.3%, p=0.028).

In the time of sampling, some patients reported presence of underlying disease or other risk factor for ARI complication as following: Diabetes I or II 9.6%, hypertension 17.8%, pulmonary diseases 2.2%, cardiac abnormalities 11.1%, and smoking 13.3%. A special attention was given to patients who reported antibiotics use. Table 3 shows general information about these patients.

There were significantly more elderly individuals (61 yo or above) and children (10 yo or less) who reported to be vaccinated in the current season (72.2% and 60%, respectively). Brazilian vaccination campaigns recommend Influenza vaccination for these age groups, free of costs (for children, only until 5 yo). The general vaccination status was 37% (50 patients). Among vaccinated patients, 13 presented ILI in the time of sampling, 4 of them were HRV positive, the other 37 patients did not present ILI, and 3 of them were HRV positive, as shown in Cross-tab 1.

Table 1. Symptoms presentation by patients infected and non-infected with human rhinovirus (HRV).

A	B	C
Symptoms	**HRV-positive % (n/total)**	**HRV-negative % (n/total)**
Coryza	96.0 (24/25)	96.4 (106/110)
Cough	80.0 (20/25)	72.7 (80/110)
Sore throat	52.0 (13/25)	56.4 (62/110)
Fever	44.0 (11/25)	33.4 (37/110)
Headache	40.0 (10/25)	66.4 (73/110)
Myalgia	60.0 (15/25)	50.9 (56/110)
Chills	40.0 (10/25)	45.5 (50/110)
Influenza-like Illness	40.0 (10/25)	30.0 (33/110)

Column A indicates the symptom

Column B indicates the percentage ratio between the number of patients who presented the symptom and the number of patients who did not present among HRV positive patients

Column C indicates the percentage ratio between the number of patients who presented the symptom and the number of patients who did not present among HRV negative patients

Table 2. Use of drug classes for treating acute respiratory infections by each age group/gender.

AGE (years old)	NSAID (%)	ANALG (%)	ANTIB (%)	CCP (%)	ANTIHIS(%)	ANTIT/EX (%)	BRONC %	CORT (%)	DECO (%)	ALT (%)	ANY (%)
≤10	26.7	33.3	26.7	6.7	6.7	13.3	0.0	0.0	0.0	6.7	73.3
11-20	11.1	22.2	16.7	16.7	5.6	22.2	0.0	0.0	0.0	0.0	61.1
21-30	20.0	30.0	3.3	23.3	3.3	6.7	3.3	13.3	6.7	0.0	53.3
31-40	5.6	33.3	22.2	5.6	16.7	11.1	5.6	5.6	0.0	0.0	66.7
41-50	7.7	58.8	0.0	23.1	7.7	0.0	0.0	0.0	0.0	0.0	84.6
51-60	13.0	30.4	4.3	13.0	0.0	8.7	0.0	0.0	4.3	8.7	52.2
≥61	11.1	11.1	5.6	33.3	5.6	11.1	0.0	5.6	0.0	5.6	67.7
GENDER											
Females	18.4*	33.7	11.2	17.3	6.1	11.2	2.0	6.1	3.1	3.1	68.4*
Males	2.7*	18.9	8.1	18.9	5.4	8.1	0.0	0.0	0.0	2.7	48.6*
GENERAL	14.1	29.6	10.4	17.8	5.9	10.4	1.5	4.4	2.2	3.0	63.0

NSAID = nonsteroidal anti-inflammatory drug; ANALG = analgesic; ANTIB = antibiotic; CCP = cough and cold preparation; ANTIHIS = antihistamine; ANTIT/EX = antitussive/expectorant; BRONC = broncodilator; DECO = decongestant; ALT = alternative therapy; ANY = at least one type of medicine. *statistically significant difference.

Table 3. General information of patients in antibiotics use.

Age	Gender	Symptoms	Underlying diseases/risk factors	Vaccinated
6	Female	Common cold	-	No
6	Female	Common cold	-	No
28	Female	Influenza-like Illness	Cardiac abnormality	Yes
58	Female	Coryza + cough + sore throat	Hypertension	No
16	Female	Influenza-like Illness	-	No
39	Female	Coryza + cough + sore throat	Pulmonary disease	Yes
5	Male	Coryza + cough + sore throat	-	No
38	Male	Influenza-like Illness	-	No
62	Female	Influenza-like Illness	Diabetes + hypertension	Yes
14	Female	Influenza-like Illness	-	Yes
19	Female	Influenza-like Illness	-	No
31	Female	Influenza-like Illness	Smoking	No
36	Female	Coryza + cough + sore throat		No
8	Male	Influenza-like Illness		No

Cross-tab 1. Frequency of ILI presentation and HRV detection among patients vaccinated against Influenza.

Vaccinated patients	HRV negative	HRV positive	Total
ILI present	9	4	13
ILI absent	34	3	37

DISCUSSION

HRV was detected in 18.5% of patients showing ARI. This found was similar to the detection rate of previous studies carried in Brazil (BEZERRA, BRITO, et al., 2011; CAMARA, SILVA, et al., 2004; FAWKNER-CORBETT, DUARTE, et al., 2012; SILVA, PITREZ, et al., 2013; WATANABE, CARRARO, et al., 2011). There was no significant difference in HRV detection between genders. The detection was higher in children aged 10 or less in comparison to older patients. It is estimated that children experience ARI at least twice as often as adults (MONTO, FENDRICK e SARNES , 2001). Along with RSV, HRV is a major cause of infections in this age group, raising a concern about this virus. Despite of that, the data do not exclude a co-infection with other respiratory viruses, such as coronavirus.

The symptom profiles presented by HRV-positive patients were inconstant, from common cold to ILI. Among HRV infected patients, 40% showed ILI in the time of sampling. Similar results were reported in previous studies (BELLEI , CARRARO, et al., 2008; SILVA, MENDES, et al., 2015; WATANABE, CARRARO, et al., 2010). Some vaccinated against Influenza showed ILI, and among them some were positive for the HRV presence. Although this can be attributed to the lack of efficacy of the vaccine (nearly 80%) (MARTÍNEZ-BAZ, NAVASCUÉS , et al., 2015) or other viruses, a possible etiological role of HRV should not be discarded.

Nearly two thirds of the patients reported the use of at least one class of drug for symptomatic treatment of ARI. The

majority of patients reported the use of analgesics, combinatory preparations for cold, and NSAIDs (see Table 2). Similar results about drug classes and its frequency of use were found in previous studies (BERQUÓ, BARROS, et al., 2004; CRUZ, DOURADO, et al., 2014). According to the current literature, the best results for symptoms relief are obtained when focusing in pain and moderate fever, with analgesics and NSAIDs. Combinatory preparations for cold can also relief respiratory symptoms (DE SUTTER, VAN DRIEL, et al., 2012; LI, YUE, et al., 2013; KIM, CHANG, et al., 2015). Antitussives and expectorants show a slight reduction in cough frequency (SMITH, SCHROEDER e FAHEY, 2014), while bronchodilators are effective only in cases of obstruction (BECKER, HOM, et al., 2015).

Female patients reported more frequent use of medications than males. Previous studies about general use of medications in Brazil found this difference as well (DAL PIZZOL, PONS, et al., 2012; LOYOLA FILHO, UCHOA e LIMA-COSTA, 2006; MORAES, DELAPORTE, et al., 2011). There is some evidence that women put more attention to their health problems. This could be a possible explanation for their higher use of medicines (BERTOLDI, DE BARROS, et al., 2009; LAUKKANEN, HEIKKINEN, et al., 1992). Among age groups, antibiotics were the only drug with significant difference of use, and were used more often by children aged 10 or less (the comparison was made against the total number of patients older than 10 years old, not only the group aged between 31-40 y. Although this group presented a higher antibiotics use in comparison to the others, it still lower than the rate presented by the group aged 10 years old or less. When compared against all patients older than 10 years old, the difference was statistically significant), some of them showing only common cold symptoms. Previous studies with exclusively pediatric population reported an antibiotic usage rate of about 40% (KAMIKAWA, GRANATO e BELLEI, 2015; ZHANG, MENDOZA, et al., 2005), higher than what was found in the studied population, but similar to pediatrics usage rate. Pediatric population is an important focus in the fight against antibiotics overuse. They attend propitious environments for infectious diseases propagation, such as daycares and schools. Once a child acquires an infection caused by resistant bacteria, it can be easily transmitted to other children (CHERIAN, STEINHOFF, et al., 1994; SOUZA, RAMOS, et al., 2003).

Some patients in antibiotics use reported to be carrier of chronic conditions or risk factors (see Table 3). A study found that diabetic patients experience more infections of the lower respiratory tract than healthy individuals (MULLER, GORTER, et al., 2005). In addition, diabetes carriers have reduced immunity to fight infections (ZHONG, QIN, et al., 2015). Patients with cardiovascular abnormalities, hypertension

and smokers are more likely to suffer from acute myocardial infarction (AMI). ARI can significantly increase the risk for AMI in those patients (CLAYTON, THOMPSON e MEADE, 2008). Antibiotics do not have proven benefit to minimize the risk of AMI (VU, FARISH, et al., 2002). Pulmonary diseases (PD) are a major risk factor for severe and occasionally life threatening complications arising from an ARI, regardless of the causative agent (MIRAVITLLES, 2002; SAPEY e STOCKLEY, 2006; WALSH, FALSEY e HENNESSEY, 1999). Influenza vaccination is highly recommended in these patients.

More than half of patients in antibiotics use had ILI. The suspicion of influenza infection raises the possibility of secondary bacterial infections. This could justify the antibiotics prescription in some cases, such elderly person, young children and individuals with PD (SMITH, SCHROEDER e FAHEY, 2014). Nonetheless, the diagnosis of influenza infection based only in symptoms is not accurate. Although there is no current antiviral for treating HRV infection, the identification of this virus can avoid the wrong treatment based on other ARI etiologies. We identified two HRV infected patients using antibiotics (14.3% of all patients in antibiotics use). Although antibiotics are not effective against viral infections, its inappropriate use is the main cause of microbial resistance (FREDERICKS, HOLLINGWORTH, et al., 2015; ROQUE, HERDEIRO, et al., 2014).

This was the first study about HRV and to evaluate the use of drugs for treating ARI symptoms in the region. The viral detection among patients of all ages with ARI showing variable symptoms was high. The general use of drugs for ARI symptoms was in according with the current literature. On the other hand, antibiotics overuse was observed in some cases. Notably, using a simple monoplex RT-PCR technique it was possible to identify a high HRV prevalence among Guarapuava patients. Although we cannot affirm that the virus detected by this method is causing the infection, it is a strong indication, especially in certain circumstances. The improvement of quantitative molecular techniques and its better interpretation may clarify the difference between viral infection and passive colonization.

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