

Characterisation of winter respiratory viral infections in patients with asthma and COPD in Qatar

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Abstract Respiratory viruses in patients with chronic obstructive pulmonary disease (COPD) or asthma have not been characterised in Qatar. This study aimed to identify the most common viral strains responsible for respiratory tract infections in asthma/COPD patients (without exacerbations) in Qatar during the winter season (2008–2009). Nasal swabs from patients with asthma/COPD and respiratory symptoms were evaluated for 15 common viruses. 200 adult patients (190 with asthma and 10 with COPD) were enrolled. Viral infections were present in 36 out of 200 patients (18 %). Cough and wheezing were the most common symptoms. Rhinovirus was the most common causative agent, followed by coronaviruses. Our findings confirm previous reports of rhinovirus prevalence in respiratory tract infections in asthma/COPD. A country-wide survey to confirm our findings is warranted.

Respiratory viruses in patients with underlying lung diseases such as chronic obstructive pulmonary disease (COPD) or asthma are associated with exacerbations and excess morbidity and mortality. Murphy et al. reported that influenza in patients with asthma can cause acute exacerbations, whereas in patients with COPD, it can lead to respiratory distress [1]. Other common respiratory viruses, especially rhinoviruses, cause the majority of exacerbations in children and adults with asthma [2]. Johnston et al. carried out a study in the UK to investigate the role of viral

infections in acute exacerbations of asthma in schoolchildren, and they reported that the most commonly identified virus type in this population was rhinovirus [3].

In one of the earlier studies using PCR to detect respiratory viruses in adults, a respiratory virus was found in 44 % of exacerbations (60 % rhinoviruses) [4]. Rhinovirus infection has also been associated with nearly half of all chronic obstructive pulmonary disease (COPD) exacerbations [5]. Furthermore, the presence of two or more viral agents may contribute to the severity of exacerbations. Wilkinson et al. have reported that a total of 70 % of COPD exacerbations in the UK were associated with the bacterial pathogen *Haemophilus influenzae*, and rhinovirus was identified in 20 % of exacerbations [6]. However, higher bacterial loads were observed in exacerbations with both rhinovirus and *H. influenzae*, thus suggesting that interaction between these pathogens may contribute to exacerbation severity [6].

Other viruses have also been implicated in exacerbation of asthma and COPD symptoms. For example, Ko et al. reported that the most prevalent viruses detected during acute exacerbations of COPD in Hong Kong were influenza A virus and coronavirus [7].

Much of the morbidity, mortality, and excess health-care utilisation associated with asthma and COPD are related to exacerbations [8]. Identifying viral aetiology associated with respiratory tract infections in asthma and COPD is useful for the development of strategies for the prevention and treatment of infections leading to exacerbations in this vulnerable population.

There is little data on the frequency of respiratory viruses in the Middle East, particularly in Qatar. In this study, we sought to determine the burden of respiratory viruses in adult patients with asthma/COPD in Qatar, using real-time reverse transcription polymerase chain reaction

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(RT-PCR). The objective of this study was to identify viral strains responsible for respiratory tract infection in asthma/COPD adult patients who visited the Chest Clinic in Qatar during the winter season from October 2008 to March 2009 (corresponding to the annual peak in respiratory infections in Qatar) in order to identify the viral pathogens involved.

During October 2008–March 2009, adults with COPD or asthma, seeking care at the Chest clinic of the Hamad Medical Corporation, Qatar, with symptoms of upper respiratory tract infection were eligible for participation. All patients were outpatients at the time of recruitment. Patients with lower respiratory tract infections were excluded. All of the patients were assessed clinically by the recruiting physician to ensure the absence of other significant respiratory diseases.

All patients had at least five symptoms of respiratory tract infection (Table 1) but otherwise were stable and had no exacerbation of COPD/asthma at the time of sample collection. The most common symptoms in all patients were dry cough and wheezing. Medicines taken for asthma/COPD by the patients were not recorded in our study. Routine testing for bacteria was not performed, because the primary objective of the study was to examine the frequency of viral pathogens that cause respiratory tract infections. Nasal swabs were collected from the sample population (to detect any upper respiratory tract viruses) and sent to the Health Science Department at Qatar University for processing.

The study protocol was approved by the research committee of Hamad Medical Corporation. All study participants signed informed consent forms according to the recommendations of the Hamad Medical Corporation Research Committee, which approved the study.

Nasal swabs were collected from the patient population. An aliquot of processed samples was frozen at -80°C for subsequent RNA extraction and polymerase chain reaction

(PCR). RNA extraction from the frozen samples was performed using a standard extraction kit (QIAGEN QIAamp Viral RNA Mini Kit). Reverse transcription was performed using real-time PCR (Fast-track Diagnostics Luxembourg S.a.r.l FTD Respiratory PLUS) to detect viral DNA. The probes were specific for 15 different types of respiratory viruses; (influenza viruses A [FluA] and B [FluB]; corona viruses NL63 [Cor63], 229E [Cor229] and OC43 [Cor43], parainfluenza viruses 1, 2, 3 and 4 [para1, para2, para3, para4], human metapneumoviruses A and B [Hump A and B], rhinovirus [rhino], respiratory syncytial viruses A and B [RSVA and B] and adenovirus [AV]).

The primers and probe were used at a concentration according to the manufacturer's instructions (FTD Respiratory Pathogen 24 samples, MikrogenTM). For all PCR amplifications positive and negative controls were included. As positive controls, the positive controls provided in the kit were used. Negative controls were carried out with water instead of RNA. PCR runs were carried out according to the standard TaqMan[®] PCR profile. Amplification of target DNA and detection of PCR products were performed using an ABI machine. Amplification of the target sequence was detected as an increase in fluorescence above a baseline with no or little change in fluorescence. In order to analyse the data, the reporter (FAM) fluorescence was automatically normalised to a passive reference to avoid the measurement of non-PCR-related fluorescence. A threshold was set above the baseline, and the threshold cycle value (Ct) was defined as the cycle number at which the fluorescence passes the fixed threshold and a statistically significant increase in fluorescence is first detected.

Data analysis was performed using statistical software (SPSS version 17.0; SPSS; Chicago, IL, USA) to calculate correlations and/or significance of the data. A value of $p < 0.05$ was considered statistically significant.

Table 1 Clinical symptoms of patients at baseline:

Symptom of respiratory infection	Asthma (n = 190)	COPD (n = 10)	Total (n = 200)
Dry cough	80 (42.1 %)	3 (30 %)	83 (41.5 %)
Wheezing	69 (36.32 %)	6 (60 %)	75 (37.5 %)
Shortness of breath	69 (36.32 %)	4 (40 %)	75 (37.5 %)
Wet cough	54 (28.4 %)	4 (40 %)	58 (30.53 %)
Nasal discharge	28 (14.7 %)	2 (20 %)	30 (15 %)
Sore throat	24 (12.6 %)	2 (20 %)	26 (13 %)
Headache	17 (8.95 %)	3 (30 %)	20 (10 %)
Joint pain	16 (8.42 %)	1 (10 %)	17 (8.5 %)
Fever	14 (7.37 %)	2 (20 %)	16 (8 %)
Muscle pain	14 (7.37 %)	1 (10 %)	15 (7.5 %)
Eye discharge	12 (6.32 %)	1 (10 %)	13 (6.5 %)
Vomiting	2 (1.05 %)	1 (10 %)	3 (1.5 %)

A total of 200 adult patients (135 females and 65 males) were enrolled: 159 patients of Arab origin and 41 patients of non-Arab origin. All patients were aged ≥ 18 years (average age of asthma patients = 48 yr [ranges; n = 32 for 20–35 yr; n = 105 for 35–55 yr; n = 53 for >55 yr]; average age COPD patients = 62 yr [ranges n = 0 for 20–35 yr; n = 3 for 35–55 yr; n = 7 for >55 yr]). The majority of the patients had asthma (190 asthma patients vs. 10 patients with COPD). None of the COPD patients and 21 of the asthma patients had received an influenza vaccine over the last two years. Fourteen of the asthma patients and five of the COPD patients were smokers.

Table 2 summarises the prevalence of different respiratory viruses found in our samples. Viral nucleic acid was detected in 36 of 200 (18 %) patients (31 with asthma and 5 with COPD). Among the 36 cases with a diagnosis of viral infection, the most common agent was rhinovirus (found in 13/36 [36 %] of the cases), and the second most common viruses were coronaviruses (found in 11/36 [31 %] of patients). The 13 patients with rhinovirus infection belonged to the asthma group. Of the 11 patients with coronavirus infection, 8 had asthma and 3 had COPD.

Both groups of patients with viral infections and those without viral infections shared the same symptoms, with cough and wheezing being the most common in both groups (Table 3). However, among the patients suffering from viral infection, those infected with rhinovirus had the most severe symptoms compared with other viruses (results not shown here). Dry cough was the predominant symptom among patients with rhinovirus (n = 7) and coronavirus infections (n = 10). Chi square analysis demonstrated that the correlation between the symptoms and the presence of the virus was non-significant ($p \geq 0.05$). No significant relationship was observed between specific symptoms and age or ethnic origin.

Rhinoviruses and coronaviruses usually cause self-limited and harmless upper respiratory illnesses. However, these viruses have been associated with exacerbations in patients with asthma and COPD. Our study is the first in Qatar to analyse the clinical aetiology of respiratory tract viral infections in adult patients from all age groups with asthma or COPD. However, it is important to note that our study did not investigate the viral aetiology in patients with exacerbations. All patients were stable at time of recruitment and sample collection. To our knowledge, there are no other studies in which the frequency of respiratory viruses in adults with asthma/COPD in the Middle East has been reported. Rhinovirus was the most common viruses identified, followed by coronaviruses. The COPD sample was too small to allow any specific conclusions regarding viral aetiology. However, in the COPD population, the corona viruses were the most common viral infectious agents.

Viral infections in our sample population were identified in 36 out of 200 patients. The low detection rate could reflect lower sensitivity of detection in older age groups or with nasal swabs compared with paediatric groups or with nasopharyngeal samples. It may also be that other pathogens are involved in respiratory tract infections affecting Middle Eastern populations. For example, metapneumovirus has been shown to affect adults with respiratory tract infections and wheezing in this region [10–12].

Cough and wheezing were the most predominant clinical manifestations in the present study in patients at baseline, with and without viral infections. We found that the distribution of viral infections did not correlate with the age and ethnic background of the patient. However, the effects of smoking were difficult to evaluate due to the small number of smokers in the population. In the last several years, respiratory virus infections have been identified in >50 % of wheezing episodes in adults [1, 3, 9]. Furthermore, in several

Table 2 The frequency of respiratory viruses in the patient population

Virus type	Asthma (n = 31/190)	COPD (n = 5/10)	Total (n = 36/200)
Rhino	13	0	13
Cor229	4	1	5
Cor43	3	1	4
Cor63	1	1	2
Para3	2	0	2
RSVAB	2	1	3
Adeno	2	1	3
Influenza B	1	0	1
Para2	1	0	1
Para1	1	0	1
HumpAB	1	0	1
Influenza A	0	0	0
Para4	0	0	0

Rhinovirus (n = 13) was the most prevalent virus, followed by coronaviruses (n = 11), in patients with viral respiratory infections

Table 3 Analysis of symptoms of patients affected by viruses vs. patients not affected by viruses

Symptoms	No virus (164)	Viruses (36)
Dry cough	72	11
Wheezing	67	8
Shortness of breath	67	8
Wet cough	55	3
Nasal discharge	82	2
Sore throat	26	0
Headache	18	2
Joint pain	17	0
Fever	15	1
Muscle pain	14	1
Eye discharge	13	0
Vomiting	3	0

In patients with and without viral infections, dry cough and wheezing were the most common symptoms

studies, rhinovirus has been identified as the most common respiratory virus associated with asthma exacerbations, and coronavirus is the second most frequent [3, 4]. Our findings in the Qatari population corroborate data from previous studies and present the first of such studies in Qatar, albeit in adult asthma and a minority of COPD patients with no exacerbations [1–8]. It is possible that the aetiology of viral infection would differ if samples were analysed during an exacerbation. Furthermore, while most studies have focused on the paediatric population, this is one of the few studies that examines viral aetiology in adults.

There are several potential shortcomings of the current study. The sample size is quite small and may not be an accurate representation of the Qatari asthmatic population. Larger studies are needed to verify the current data. The number of COPD patients was markedly smaller than that of asthma patients. This was mainly because patients with asthma may be more concerned for their health, especially when they suffer from upper respiratory tract infections (URTIs), and go to the hospital, while COPD patients may not consider their symptoms very serious. Indeed, there is very poor education and awareness of COPD in Qatar among physicians and patients. In addition, there is a large population of COPD smoker patients in Qatar who are not aware of their disease status. Larger numbers of COPD patients must be enrolled in order to determine viral aetiology more accurately in this population. Furthermore, an equal number of females and males also need to be included in future studies.

Another potential shortcoming is that a control population was not included in the study; therefore, the frequency of rhinovirus or coronavirus infections in populations hospitalised with non-respiratory conditions or in asymptomatic

populations or non-asthmatic or non-COPD populations with respiratory tract infections cannot be determined. Finally, this study was limited to the “winter season” in Qatar, and it may be that the infection pattern changes throughout the year. Longer-term studies are needed to determine this.

The morbidity associated with rhinovirus and coronavirus infections, especially in high-risk populations such as patients with asthma or COPD, suggest that these infections should be a target for prevention or treatment strategies. In addition, the relatively low number of viruses found in our sample population may point towards other pathogens (viral or bacterial pathogens not investigated here) that may be implicated in causing URTIs in patients in Qatar.

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