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ORIGINAL ARTICLE

Association of Virus-Induced Wheezing With COVID-19

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ABSTRACT

Background: Viral respiratory tract infections are the most common triggers of wheezing illnesses in children. Though rare, COVID-19 infection in children may trigger a viral-induced wheeze that requires distinguishing from other viral and asthma triggers. **Objectives**: The current study aimed to assess the role of COVID- 19 in causation of viral induced wheeze in pediatrics age group in our locality. **Methods**: The study included 30 pediatrics cases ≥ 2 months attending the Emergency Room and Department of Pediatrics, Faculty of Medicine, Zagazig University Hospital. According to the inclusion criteria for the study, patients were aged from 2 – 144 months with mean age (21.1±35.3 month). They were 13 females (43.3%) and 17 males (56.7%). Twelve patients had positive family history of asthma (40.0%). The standard technique for confirming COVID-19 is the real-time polymerase chain reaction (RT-PCR). **Results**: 30 children hospitalized with wheezing, 24 patients (80%) presented with difficult breathing, 18 patients (60%) were feverish, and 17 patients (56.7%) had cough. Running nose was noted in 9 patients (30%), grunting was observed in only one patient (3.3%). The mean O2 saturation of all patients was 91.8±2.6 and ranged from (92-95%). GIT manifestation was reported in 13.3%. The two confirmed cases has positive PCR test for Covid-19, a 7 year old male and a 5 year old female. Positive family history of COVID-19 was reported in both cases, neither of them has blood eosinophilia, they were on regular controller medication. Patients presented with wheeze, cough, difficult breathing, with no grunting or GIT manifestation. They were treated for 2 to 3 days by O2, inhaled B agonists plus short course of systemic steroids. **Conclusion**: Covid-19 is uncommon cause of viral induced wheeze among our patients. Only two cases of covid-19 related asthma exacerbation were reported in our study.

Key words: Viral-induced wheezing, Children, Allergic Asthma, COVID-19 disease, RT-PCR

INTRODUCTION

Wheezing in children is a common problem encountered by family physicians. Approximately 30 to 50 percent of infants will have at least one wheezing episode, and nearly one half of children have a history of wheezing by six years of age. It is usually caused by a virus and is usually called Viral-Induced Wheeze**[1]**.

The COVID-19 pandemic has predominantly affected the adult population. The disease is less well-defined in children (≤18 years) **[2]**. With the virus being so easily transmitted, effects on the pediatric community were inevitable, and the very first reported case was encountered in January 2020 in a 10-year-old boy who contracted the virus in Wuhan-China**[3]**. Since then, a multitude of pediatric cases have been reported globally.

Asthma is the most common chronic disease seen in children, and its prevalence is increasing **[4]**. According to CDC, those with moderate and severe asthma are in the risk group for coronavirus infection. COVID-19 can affect the nose, throat, and lungs, causing asthma attack, pneumonia, and acute respiratory disease **[5]**. It is

known that viral infections especially rhinovirus, RSV, and influenza can cause asthma attack **[6]**, however, it not yet clear whether asthma is a risk factor for COVID-19. In the previous coronavirus pandemics (SARS-CoV and MERS-CoV), asthma was not a risk factor for these infections **[7]**. There are limited studies on the prevalence, clinical symptoms, severity of COVID-19, and findings after improvement of infection in COVID-19 pediatric patients with asthma. The prevalence of asthma in adults and children diagnosed with COVID-19 was between 0.3–17.9 and 0–14%, respectively **[8-10]**.

COVID-19 associated asthma exacerbation is rare; although there is a theoretical risk of COVID-19 causing a virus triggered asthma exacerbation. Previous epidemics of the coronavirus also did not report significant numbers of asthma exacerbations **[4]**.

Literature on pediatric asthma and COVID-19 is sparse and limited to case reports highlighting mild disease mostly not requiring hospitalizations and ICU care**[6,7,9,11]**.

The Global initiative for asthma guidelines suggest that asthma exacerbations due to COVID-19 should be treated with corticosteroids as appropriate **[12]**. However, there is no research on the choice of corticosteroid. No adverse effects attributable to the use of steroids were noted in these children.

A systematic review and meta-analysis of the prevalence of common respiratory viruses in children younger than 2 years with bronchiolitis in the pre-COVID pandemic era has been published recently **[13].** It included 50 articles published between October 1999 and December 2017, RSV was largely the most commonly detected virus (59.2%), both as the only virus involved and in co-infections **[13]**.

As for bronchiolitis due to SARS-CoV-2, coronaviruses other than SARS-CoV-2 are also sometimes detected in respiratory samples, often presenting as co-infections. However, in contrast to **Milani PG et al.**[14] who reported that SARS-CoV-2 might case bronchiolitis requiring hospitalization**, Andina-Martinez et al. [15]** did not find any cases of bronchiolitis due to SARS-CoV-2 during the 2019-2020 seasons. The current study aimed to assess the pediatric age group with viral induced wheeze suspected COVID-19 infection. The first objective of this study was to guide the pediatrician to answer the question whether COVID-19 can present with viral induced wheeze in pediatric age group or not?, Secondly to asses relationship between COVID-19 infection and viral induce wheeze, and to assess the effect of COVID-19 infection in known asthmatic patient with acute exacerbation and upper respiratory tract infection (URTI).

METHODS

This analytical case-control study included children diagnosed with wheezing admitted in the Emergency Room and Department of Pediatrics, Faculty of Medicine, Zagazig University Hospital (ZUH). Evaluation and Enhanced Surveillance of COVID-19 were performed during the period study (year 2021). The study included 30 pediatric patients ≥ 2 months, According to the inclusion criteria for the study, patients were aged from 2 – 144 months with mean age of 21.1±35.3 month. They were 13 females (43.3%) and 17 males (56.7%). Twelve patients had positive family history of asthma (40.0%).

History taking and clinical evaluation included specific information on: wheeze, features of respiratory distress, history of similar illness, history of contact with suspected case of COVID-19, family history of asthma and atopy, and a detailed history of presenting complaints.

CBC, ESR, CRP, LDH, S. Ferritin, D. Dimer, Liver function test, kidney function test was ordered whenever indicated.

The standard technique for confirming COVID-19 is the real-time polymerase chain reaction (RT-PCR). Radiological imaging, especially thin slice CT, has important roles in the diagnosis, management, and follow-up of patients with COVID-19 pneumonia. Chest CT can detect early phases of infection and enable early isolation of patients.

Written Informed consent was taken from the patient parents and/or their caregivers. The permission for the study was received from the Pediatrics Departments of Zagazig University Hospitals after the permission of the Institutional Review Board (IRB). The research was carried out in compliance with the Code of Ethics of the World Medical Association (Decleration of Helsinki) for studies involving humans

Statistical analysis:

All data were collected, tabulated and statistically analyzed using IBM Corp. Released 2015. IBM SPSS (Statistics for Windows, Version 23.0). Armonk, NY: IBM Corp. Quantitative data were expressed as the mean ± SD &median (range), and qualitative data were expressed as number & (percentage).

RESULTS

The study included 30 children attending the emergency room and Department of Pediatrics, Faculty of Medicine at Zagazig University Hospital, according to the inclusion criteria for the study. They were 17 boys (56.7%) and 12 girls (43.3%). The mean age of all patients were

21.1±35.3 months and ranged from (2-144) months. Twelve patients reported positive family history of asthma (40.0%) (Table 1).

Table 2; showed the clinical presentation of the studied children. All children had wheeze, 24 patients (80%) presented with difficult breathing, 18 patients (60%) were feverish, and 17 patients (56.7%) had cough. Running nose was reported in 9 patients (30%), whereas grunting was observed in only one patient (3.3%), The mean O_2 saturation of all patients was 91.8±2.6 and ranged from (92-95%), GIT manifestation) were seen in 13.3% .

Table 3; showed the laboratory findings of our studied children. Hb%, S. ferritin and D. dimer of all patients were almost within normal values. The two Covid-19 confirmed cases were lymphopenic.

Chest X-ray finding of studied children are shown in (Table 4), 36.6% showed no abnormalities. Hyperinflation was noted in 40% and prehiler congestion in 16.7%. Only two cases show complicating bronchopneumonia

Clinical, laboratory and Radiological characters of **Covid-19** PCR positive: Case 1: a 7 years old male, had positive family history of COVID19. Patient presented with wheeze, cough, difficult breathing, and dyspnea, with no grunting or GIT manifestation. The patient suffered from fever 38.5 °C, heart rate was 125p/m, and respiratory rate 35 p/min. Case 2: a 5 years old female with positive family history of COVID19, presenting with wheeze, cough, difficult breathing, and dyspnea with no grunting or GIT manifestation as well. The patient was febrile (38.3 °C), heart rate was120 /m, and respiratory rate was 37/min. Both cases were lymphopenic with normal S. ferritin and D. dimer. C.T chest of both cases was unremarkable. The O2 saturation did not drop below 92%. They were on regular controller medications (fluticasone –salmetrol combination).Their hospital course was short and smooth. They were treated by supplementary O2, inhaled short-acting B2 agonists plus short course of systemic steroids with no need for ICU admission or mechanical ventilation.
(Table 5).

Table (1): Demographic and family history of studied children (n=30):

Variable	**(n = 30)**	
Age per months		
Mean ±SD (Range)	21.1±35.3 (2-144)	
	N	**%**
Sex		
Females Males	13 17	43.3 56.7
Family history of asthma		
Positive Negative	12 18	40.0 60.0

Table (2): Clinical presentation of studied children (n= 30):

Clinical characteristics	**N**	**%**
Wheeze	30	100
Difficult breathing	24	80
Fever	18	60.0
Cough	18	60.0
Running nose	9	30.0
Tachypnea	6	20.0
Granting	1	3.3
GIT manifestation	4	13.3

Clinical characteristics	N	%
O2 saturation	91.8±2.6	92 (92-95)

***Patients may have more than one symptom**

Table (3): Laboratory finding of studied children (n= 30):

Laboratory Finding	Mean ±SD	Median (Range)
WBC (x 10^9/L)	10.8±5.5	10.7(2.6-22.7)
HGB	10.7±2.03	10(7.6-14.7)
PLT	3465±106	351.5(165-586)
CRP (mg/L)	13.3±12.4	9.7(0.18-47.54)
S. ferritin	204.6± 102.7	197(26-430)
D. dimer	0.323±0.12	0.3(0.1-0.7)
PCR (COVID-19)		
Negative	28	93.3
Positive	2	6.7

Table (4): X-ray finding of studied children (n= 30):

X-ray findings	N	%
Complicating Bronchopneumonia	2	6.7
Hyper inflation	12	40
Prehiler congestion	5	16.7
FREE	11	36.6

Table (5): Clinical, laboratory and Radiological characters of Covid19 PCR positive:

	Case 1	Case 2
Age	**7y**	5y
Sex	**Male**	Female
Family history of contact	**Positive (+ve)**	positive**(+ve)**
Clinical presentation	**Wheeze**	Wheeze
Temperature	**38.5C**	38.3C
Heart rate	**125 p/m**	120p/m
Respiratory rate	**35**	37
Cough	**YES**	YES
Difficult breathing	**YES**	YES
Dyspnea	**YES**	YES
Granting	**NO**	NO
GIT manifestation	**NO**	NO
CRP	**27mg/l**	15mg/l
Lymphopenia	**Yes**	Yes
S. Ferritin	**Normal**	Normal
D. dimer	**Normal**	Normal

	Case 1	Case 2
C.T Finding	**Hyperinflation**	Hyperinflation
O2 saturation	**92%**	92%
Controller medication	**Fluticasone-salmetrol combination**	Fluticasone-salmetrol combination
Supplement O_2	**Yes**	Yes
Inhaled short acting B agonist	**Yes**	Yes
Short course systemic steroid	**Yes**	Yes
Days of admission	**2days**	3days
Need for mechanical ventilation	**NO**	NO

DISCUSSION

This study included 30 pediatrics cases. According to the inclusion criteria for the study, patients were aged from 2 – 144 months with mean age was a 21.1±35.3 month. They were 13 females (43.3%) and 17 males (56.7%). Twelve patients had positive family history of bronchial asthma (40.0%). By defining all bronchiolitis patient were less than 2 years, the remaining children are pre-school wheezers and asthmatic children. In agreement with our results, many other studies also reported the male sex as a risk factor for pediatric asthma. **Mummidi et al.** [16] reported higher (75%) proportion of males admitted with wheezing [17].

Regarding the clinical presentation of our studied group, all patients suffered from chest wheeze (100%). the second most common presentation was difficult breathing (80%) followed by fever and cough (each 60%). The O2 saturation of our patients ranged from (92-95%). According to GINA guideline 2021, coughs, dyspnea, difficult of breathing are commonest presentation of pediatric asthma [18]. According to the national institute for health and care excellence (NICS), tachypnea, tachycardia, and difficult breathing are among the common presenting symptoms of acute bronchiolitis[18].

In our study x-ray finding ranged from hyperinflation (40%), minor finding as prehiler congestion (16.7%) or completely free x-ray in (63.6%), which is comparable to the study from Boston by **Mathews et al.[10]** and the study of **Muthukrishnan and Raman** [19], who reported that hyperinflation is the commonest radiological finding in bronchiolitis. Definite clinical criteria should be defined to avoid unwarranted chest radiography in children with acute wheeze [19].

In **2017**, **Vella and Muscat** reported that, chest X-rays are regularly requested for wheezy children, as there are no clear guidelines as to when imaging should be performed. The commonest indication for performing a chest radiograph was a fever associated with the episode of wheezing. No abnormality was noted in (75%) of chest X-rays taken. The remaining (25%) had a chest X-ray finding ranging from mild peri-bronchial cuffing to collapse or consolidation [20].

The two COVID-19 PCR positive cases in our study give positive history of contact with family member with covid-19. Our results goes in agreement with **Xia et al. [21]** who reported that 65% of COVID-19 pediatric patient had positive family history of close contact with COVID-19 diagnosed family members. The majority (85%) of all reported pediatric cases have had exposure to a household positive contact or been within a family cluster outbreak [22]. A study that identified all patients aged less than 16 years with confirmed COVID-19 in Switzerland found that in 79% of family cluster cases an adult household contact developed suspected or confirmed COVID-19 before the child [23].

The hospital course of the two Covid-19 positive cases was short and smooth. Their O2 saturation did not drop below 92%, they were on regular controller medications (fluticasone–salmetrol combination). They were treated by supplementary O2, inhaled short-acting B2 agonists plus short course of systemic steroids with no need for ICU admission or mechanical ventilation. Recent large studies focusing on the course of asthmatic children during the pandemic revealed that they are not disproportionately affected by the virus, and surprisingly, they appear to have improved outcomes. This was attributed to reduced exposure to asthma triggers, increased steroid prescriptions, and better treatment adherence during the pandemic. Another possible contributing factor is the timely adaptation of the clinical services to the pandemic by replacing physical appointments with virtual ones [7].

One study reported that asthma with allergic sensitization is characterized by lower ACE2

expression in children's nasal epithelia, but not in non-allergic asthmatic children [24] .

Literature on pediatric wheezing and COVID-19 is sparse and limited to case reports highlighting mild disease mostly not requiring hospitalizations and ICU care [7,9].

Survey exploring data from 147 centers, **Moeller et al.[25]** found 49 asthmatic children who tested positive for SARS-CoV-2. All children were admitted, but 29 required no treatment, 19 received supplemental oxygen, and only 4 required mechanical ventilation and admission to the pediatric intensive care unit (PICU). They speculated that the 29 untreated children were admitted purely for safety reasons. Regarding the 4 PICU admissions, the seasonal factors might have played a role.

Severe disease was reported in only 3% of cases. The symptom prevalence is like that of the adult population, with fever and cough being the most reported symptoms. Still, they are reported to a lesser degree, with only half of the patients reporting fever or cough.

The incidence of symptomatic severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) infection in children is relatively low, and the disease causes lower symptom severity compared to adults. There is little information about the role of SARS-CoV-2 in bronchiolitis, although experimental studies performed in ferrets have shown lung lesions compatible with bronchiolitis [26].

Our study did not detect any bronchiolitis PCR positive cases for COVID-19 As for bronchiolitis due to SARS-CoV-2, coronaviruses other than SARS-CoV-2 are also sometimes detected in respiratory samples, often presenting as co-infections. However, in contrast to what was reported by **Milani PG et al** who reported that SARS-CoV-2 might case bronchiolitis requiring hospitalization [14]**, Andina-Martinez et al. [15]** did not find any cases of bronchiolitis due to SARS-CoV-2 during the 2019–2020 seasons.

As for the laboratory findings of the two Covid- 19 positive cases, both of them were lymphopenic with mildly elevated CRP and normal values for serum ferritine and D Diamer. **Wang et al** reported that WBCs may be normal or low or high (lymphocytopenia is present in > 80% in patients). Other findings may include low platelet count and decreased hemoglobin [27]. This findings also agree with **Xia et al.**[21] **Habibzadeh and Stoneman** [28] who reported low white blood cells, lymphopenia, thrombocytopenia, high serum C reactive protein, and elevated serum ferritin in pediatric patients.

CONCLUSION

Covid-19 is uncommon cause of viral induced wheeze among our patients. Only two cases of covid-19 related asthma exacerbation were reported in our study. No cases of bronchiolitis related covid-19 was reported in our study.

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