

DO SEVERE PEDIATRIC ASTHMA PATIENTS HAVE AN INCREASED SUSCEPTIBILITY OF BEING INFECTED BY COVID-19?

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Abstract

Background: The Coronavirus disease 2019 caused by SARS-CoV2 virus has rapidly spread worldwide becoming one of the most important challenges humans are facing nowadays. Risk factors for severe outcomes have been identified, but asthma seems not to be one of them. **Objectives:** To analyze lifestyle before the pandemic in severe pediatric asthma patients in treatment with a monoclonal antibody, belonging to Castellon's University General Hospital Health's Department, and investigate the prevalence of COVID-19 in these patients in order to see if their lifestyle may have influenced the probability of being infected by COVID-19. **Methods:** A questionnaire was developed asking about: their lifestyle before the pandemic; suggestive COVID-19 symptoms and exposition to the disease; and patients' behavior, asthma control and treatment during the pandemic. Total SARS-Cov-2 antibody tests were performed to all patients. **Results:** A total of 15 patients were included. All patients had a high social exposure before the pandemic. 2 patients had direct contact with positive COVID-19 patients. Both experienced mild symptoms that could be attributed to the disease, but neither of them had a positive serological test. Most patients followed asthma treatment correctly before and during the pandemic. 13 patients referred good asthma control. Most patients continued monthly monoclonal antibody administration. Serological tests were negative for all patients. **Conclusion:** Severe asthma pediatric patients in treatment with MAB, do not have an increased susceptibility for being infected by the virus, but in the case that they contracted the disease, evidence says they would have shown very weak symptoms.

Key words: Severe pediatric asthma patients. Monoclonal antibodies (MAB). COVID-19.

INTRODUCTION

Since the coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in December 2019, the disease caused by SARS-CoV2 virus has rapidly spread worldwide resulting in declaration of a pandemic by the World Health Organization (WHO) on March 2020, becoming one of the most important challenges humans are facing nowadays. [1,2] Its clinical manifestations characteristically vary from asymptomatic cases, to mild and severe cases, mainly affecting the respiratory tract.

People with asthma are usually at greater risk of more severe outcomes due to virus infections. However, recent reports reveal that the prevalence of COVID-19 in asthma patients is lower than expected. [3]

It seems that COVID-19 has less direct impact on children and adolescents than on adults. Only about 1% of the entire COVID-19 population are children, being pediatric asthma patients underrepresented in this population. [4] Symptoms tend to be less severe, varying from asymptomatic, to mild-moderate cases. There is no gender difference, and all ages appear to be susceptible to the disease. [5]

Several hypotheses have been proposed to explain this fact: reduced angiotensin converting enzyme 2 (ACE2) gene expression, less often comorbidities associated, less potent PAMP activation, suboptimal and Th2-skewed cytokine production, resulting in a hypo-inflammatory immune response, and an extensive vaccination program, leading all to a beneficial immune response towards SARS-CoV-2 infection. [1,5]

Until now, no one has considered if both individual and social behavior of patients before the pandemic could have influenced this low prevalence.

The main purpose of this study is to analyze lifestyle before the pandemic in severe pediatric asthma patients in treatment with monoclonal antibody (MAB), belonging to Castellon's University General Hospital Health's Department (Castellon, Spain), and investigate the prevalence of COVID-19 in these patients in order to see if their lifestyle may have influenced the probability of being infected by COVID-19 or not. Secondly, we wanted to study the behavioral of these patients, and determine the level of asthma control during the pandemic.

METHODS

Data source

This is an observational, cross-sectional study designed by the Allergy Department of Castellon's University General Hospital, Spain. Subjects recruited were pediatric patients with severe asthma in treatment with MAB, pertaining to the Pediatric Allergy Department in our hospital. Inclusion criteria: patients with severe asthma, in treatment with MAB (omalizumab, mepolizumab, benralizumab, reslizumab or dupilumab), for 6 months or more and with a positive complementary study for asthma diagnosis (spirometry with positive bronchial dilatation, or positive methacholine test). Exclusion criteria: patients who had recently started biological treatment (\leq 6 months), or patients who did not compliment treatment correctly. Analysis dates went from 1^o March to 31^o July 2020.

To answer the objectives proposed, a questionnaire was developed with a total of 19 questions (Table 1) divided in 3 blocks. Block one: (questions 1 to 4) patients were asked about their lifestyle before the pandemic. Block two: (questions 5 to 9) referred to COVID-19 symptoms and possible exposition to the disease. Block Three: (questions 10 to 19) analyzed patients' behavior, asthma control and treatment during the pandemic.

When analyzing their daily activity before the pandemic (question 1), an active level of activity was defined as going out 7 days a week (school, sport activities, social meetings, shopping, etc.); a normal level 5 days a week, a moderate level less than 5 days a week, and a low level of activity less than 2 days a week. When referring to therapeutic adherence to base treatment (question 10), Test of Adherence to Inhalers (TAI – 10 items) [6] was used. A result of 50 meant good adherence, between 46-49 meant intermedia adherence, and 45 or below, meant bad adherence. Subsequently, to analyze patients' asthma control (question 15), the Asthma control test (ACT) [7] was used. A result of 20 or more meant good asthma control, meanwhile, 19 or less, meant poor asthma control. Questionnaires were filled out with a face-to-face interview with prior authorization from their parents. Approval from the ethics committee was obtained.

Clinical data was also collected for each patient (Table 2), using the hospital's clinical network. Clinical values were chosen based on risk and protective factors described for coronavirus disease. [8,9] Data registered included, sex, age, type of asthma, inhaled corticosteroid doses, and comorbidities. Significant clinical values for asthma syndrome were recorded: FEV1, association of nasal polyps, Samter's Triad, Allergic bronchopulmonary Aspergillosis (ABPA), and the need of medical attention or hospitalization in the last year, due to uncontrolled asthma.

Finally, in order to study COVID-19 prevalence in our patients, serological tests were performed at the hospital's laboratory, to all patients, by using total SARS-Cov-2 antibody test by immunochromatography (Wondfo®), Guangzhou Wondfo Biotech Co., Ltd. P.R. China), being its sensitivity (86.43%) and its specificity (99.57%).

RESULTS

A total of 19 patients were enrolled, of whom only 15 were included in the study. Due to exclusion criteria, 4 patients were excluded: the 4 of them due to bad adherence to MAB treatment.

Patients' responses to the questionnaire are shown in Table 1.

When analyzing patients' responses, about their lifestyle before the pandemic, (questions 1-4), it is worth outlining that all patients had an active or normal level of activity, and lived with three or more people at home, meaning that their personal risk of being infected by SARS-Cov-2 was not only conditioned by their own public exposure, but also by the social exposure of their relatives. It can be highlighted that 86.7% of the patients studied had assisted to crowded meetings weeks before the pandemic reached Spain.

In reference to possible exposition to the disease (questions 5-6), 2 patients had a known contact with positive COVID-19 subjects. The first patient is a 14 year old boy. He had been in a social meeting, just before the beginning of the pandemic, where several people got infected. Also, his father and twin sister, with whom he lived at home, experienced symptoms, having both a positive serological test for COVID-19. His father started with symptoms at the beginning of March, having high fever, chills, body ache and loss of taste and smell. His sister, instead, started with symptoms at the beginning of April. In her case, symptoms were limited to the skin, presenting erythema, pruritus, and vesicles on acral areas. In the patient's case, at the beginning of March, he experience a mild asthma exacerbation, which resolved in 4 days, without needing oral corticoid therapy or medical intervention, and at mid-April, he experienced abdominal pain, reflux, and diarrhea, with no fever of respiratory symptoms, which resolved in 5 days. Curiously, the serological test performed to him in June, was negative.

The second patient is a 13 year old boy, whose parents started with fever, cough, headache, and body ache at mid-March, having both a positive test for COVID-19. In the patient's case, he started with slight fever, on the 23 of March, which he controlled with acetaminophen at home. He did not course with other symptoms, and fever resolved in 48 hours. Curiously, the serological test performed to him in June, was negative too.

Regarding suggestive COVID-19 symptoms (question 7), only 3 patients referred symptoms. Two of them had fever, and cold symptoms, and one of them had fever and asthma exacerbation. Serological test performed to the three of them were negative.

Analyzing patients' behavior, asthma control and treatment during the pandemic (questions 10-19), most patients (86.6%) followed asthma treatment correctly, and did not change their adherence due to the pandemic (93.4%). When asked about their mood, stable mood, and anxiety, were the most relevant answers. No one had depressive mood.

In reference to the need of medical ambulatory assistance during the lockdown, 3 patients needed medical attention, corresponding with the 3 patients who referred suggestible COVID-19 symptoms. The two patients who had fever, and cold symptoms, received telephone assistance, and did not need to attend a medical center, and the one who had fever and asthma exacerbation had to attend the medical center in 3 occasions, due to persistence of symptoms.

When analyzing asthma control, only 2 patients referred not to be controlled during the pandemic, while the other 13 patients referred good asthma control.

Drawing the attention to the period of lockdown declared in Spain, from the 15 of March 2020, until the end of May, most patients did not discontinue MAB administration. In March only 4 patients did not go for MAB dose administration. In April, 3 patients, and in May, 1 patient.

During the months of June and July, serological tests were performed by using total SARS-Cov-2 antibody test, to study the real prevalence of the disease in all patients, being negative for all of them.

DISCUSSION

Coronavirus disease 2019 (COVID-19), has become in a short period of time, one of the worst infection diseases ever known around the world, declaring a Public Health Emergency of International Concern. Spain

has been one of the most severely affected countries in Europe. Data dated on the 12 of August 2020, declares 3.350.547 confirmed cases in all of Europe, 329.784 of which correspond to Spain.

When studying severe pediatric asthma patients in treatment with MAB, corresponding to our Medical Department, two important observations can be drawn. Firstly, 2 patients had direct and continuous contact with the virus, as several members of their family got infected, but although both experienced mild symptoms that could be attributed to the disease, neither of them had a positive serological test. This could be because, they really did not get infected by COVID-19, or because they did not acquire immunity to the virus. Secondly, in case they had suffered the disease, although they did not acquire immunity, this study suggests they would have shown mild symptoms. Reasoning for this include a series of factors recently studied in the wake of COVID -19 pandemic. Theoretically, asthmatic patients should have increased susceptibility and severity for SARS-CoV-2 infection due to a deficient antiviral immune response and the tendency for exacerbation caused by common respiratory viruses. However, certain aspects of type 2 immune response, might provide potential protective effects against COVID-19. Allergy seems not to be a risk factor, nor influence the course and severity of the disease. [2] Furthermore, conventional therapeutics used for asthma control, including inhaled corticosteroids, [10] and anti-IgE monoclonal antibody, seem to provide beneficial effects, reducing the risk of COVID-19 infection. [3,11] Recent studies have shown that blocking IgE could reduce susceptibility to respiratory virus infection. Taken together, these observations suggest a potential effect of omalizumab on antiviral responses.

Uncontrolled asthma may be included as a risk factor for severe COVID-19. [4] A sufficient control of symptoms in children with asthma is key in the current pandemic. [12] It is therefore recommended that asthmatic patients continue with prescribed medications during the pandemic [11] to optimize asthma controls.

The conclusions drawn from this study, underline that pediatric patients with severe asthma, in treatment with MAB have a societal behavior comparable to the general population, and their lifestyle before the pandemic did not influence the probability of being affected by the disease. Therefore, they do not have an increased susceptibility for being infected by the virus, but in the case that they contracted the disease, they would have shown very weak to no symptoms. The fact that they may not acquire immunity to the disease, needs to be corroborated with further investigation.

DATA SHARING: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TABLES

Table 1. Questionnaire and patients answers to the questionnaire

QUESTIONNAIRE		ANSWERS Variable N= 15 (100%)
What was your level of activity before the state of alarm+ began?	Active Normal Moderate Low	<i>14 (93.3%) 1 (6.7%) 0 (0%) 0 (0%)</i>
With how many people do you live at home?	One Two Three Four Five or more	<i>0 (0%) 0 (0%) 2 (13.3%) 9 (60%) 4 (26.7%)</i>
Where you in any meeting or social event with more than 10 people, before the state of alarm began?	Yes No	<i>13 (86.7%) 2 (13.3%)</i>
Do your parents smoke?	Yes No	<i>6 (40%) 9 (60%)</i>
4.1. If responded yes: did your parents stop smoking in the wake of the pandemic?	Yes No	<i>0 (0%) 6 (100%)</i>
Do you know any person who has given positive for covid-19 test?	Yes No	<i>3 (20%) 12 (80%)</i>
Have you been in contact with someone positive for covid-19?	Yes No	<i>2 (13.3%) 13 (86.7%)</i>
Have you had symptoms compatible with Covid-19?	Yes No	<i>3 (20%) 12 (80%)</i>
Have you had a covid-19 RT-PCR test done?	Yes No	<i>1 (6.6%) 14 (93.4%)</i>
If responded yes: what was the result?	Positive Negative	<i>0 (0%) 1 (100%)</i>
Have you been hospitalized do to covid-19?	Yes No	<i>0 (0%) 15 (100%)</i>
What has been your therapeutic adherence to your base treatment during the state of alarm?	TAI result++ Good Intermedia Bad	<i>13(86.6%) 1(6.7%) 1(6.7%)</i>

QUESTIONNAIRE		ANSWERS Variable N= 15 (100%)
Have you followed treatment the same way as before the pandemic?	Yes No	14 (93.4%) 1 (6.6%)
How did you feel animically during the first months of the state of alarm?	Good Anxious Depressive	8 (53.3%) 7 (46.7%) 0 (0%)
Have you needed medical assistance during the state of alarm?	Yes No	3 (20%) 12 (80%)
13.1. If responded yes: what was the reason why?	Open answer	See text
13.2. If responded yes: did you attend a medical centre?	Yes No	1 (33.3%) 2 (66.7%)
13.3. Did doctors resolve the problem?	Yes No	3 (100 %) 0 (0 %)
13.4. Where you satisfied with the attention given?	Yes No	3 (100 %) 0 (0%)
Did you need to use your short-acting bronchodilator during the state of alarm?	Yes No	3 (20%) 12 (80%)
How controlled has your asthma been during this month?	ACT result§ No control Control	2 (13.3%) 13 (86.7%)
Have you left your home during the state of alarm?	Yes No	0 (0%) 15 (100%)
Did you go to administer your biological treatment in March?	Yes No	11 (73.3%) 4 (26.7%)
Did you go to administer your biological treatment in April?	Yes No	12 (80%) 3 (20%)
Did you go to administer your biological treatment in May?	Yes No	14 (93.4%) 1 (6.6%)

+State of alarm declared by the Spanish Government the 15th of March of 2020, in response to COVID-19 pandemic, in order to try to restore the order within the country, adopting strict measures of social distance and lockdown.

++ TAI: Test of adherence to inhalators. § ACT: Asthma control test.

Table 2. Patients clinical characteristics description

Variable	Categories	N= 15 (100%)
Gender	Male Female	10 (66.7%) 5 (33.3%)
Age (Years)	5 6-10 11-14	0 (0%) 3 (20%) 12 (80%)
Samter´s Triad, nasal polyps and/or ABPA¶	Yes No	0 (0%) 15 (100%)

Variable	Categories	N= 15 (100%)
Type of Asthma	Allergic Asthma Nonallergic asthma	13 (86.7%) 2 (13.3%)
Inhaled corticosteroid dose¥	Low Medium High	7 (46.6%) 4 (26.7%) 4 (26.7%)
Last FEV1 registered	[?] 50% 51-59% 60-80% 81-89% [?]90%	0 (0%) 0 (0%) 4 (26.7%) 3 (20%) 8 (53.3%)
Comorbidities	None One Two or more	13 (86.7%) 2 (13.3%) 0 (0%)
Need of medical assistance due to asthma symptoms during the last year	Yes No	9 (60%) 6 (40%)
Need of medical hospitalization due to asthma symptoms during the last year	Yes No	0 (0%) 15 (100%)

¶ ABPA: Allergic bronchopulmonary Aspergillosis; ¥ GEMA 5.0 (<http://gemasma.com>)

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2. TABLES.docx available at <https://authorea.com/users/348278/articles/476626-do-severe-pediatric-asthma-patients-have-an-increased-susceptibility-of-being-infected-by-covid-19>