



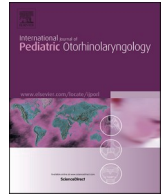
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## COVID-19 and severe ENT infections in pediatric patients. IS there a relationship?

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### ABSTRACT

**Background:** Preliminary evidence suggests that children are just as likely to become infected with SARS-CoV-2 as adults but are less prone to developing severe clinical conditions. However, there are pediatric inflammatory conditions that have also been encountered. The aim of this report is to determine whether there is a relationship between COVID-19 and severe infections in the ear, nose, throat, and deep cervical area (ENT) in pediatric populations.

**Materials and methods:** A compilation was made of all the cases of ENT area infections in the pediatric population per month attended to at the Niño Jesús University Children's Hospital from January 2010 to June 2020. Endemic channels and dispersion analysis were designed to analyze the incidence presented in the year 2020, compared to what was expected based on historical data from 2010 to 2019. Then, an epidemiological interview was conducted of the close contacts of COVID-19 of the children who presented a severe ENT infection in 2020. Finally, a serological test of IgG antibodies was performed on all of them to find out if they had overcome the COVID-19.

**Results:** 620 patients from 1022 were eligible for the study. We observed a significant outbreak in the incidence of complicated mastoiditis and deep cervical infections with complications in the year 2020 (13 patients) linked to the COVID-19 pandemic. From these patients, 54% had been confirmed or had high suspicion of close contact with COVID-19. 15.4% of children were positive in serological tests for IgG antibodies.

**Conclusion:** There has been a significant increase in mastoiditis and deep cervical infections with complications in the first four months of 2020, which constitutes an outbreak. A considerable number (54%) of these complicated infections were related to close contact with COVID-19. Still, only 15.4% were positive in serological tests for IgG antibodies, so we cannot establish a direct categorical relationship. The limitations in primary care due to a shortage of human resources in dealing with the pandemic's initial onslaught and changes in help-seeking behavior could explain increased complicated infections.

### 1. Introduction

The new coronavirus 2019 (SARS-CoV-2) is currently causing a severe disease outbreak called COVID-19, constituting a global pandemic. Preliminary evidence suggests that children became infected with SARS-CoV-2 just as easily as adults but are less likely to develop symptoms of severe clinical conditions [1]. However, other pediatric inflammatory conditions have also been described. The Royal College of Pediatrics and Child Health (RCPCH) Pediatric Multisystemic Inflammatory Syndrome Guide recognizes that the syndrome shares characteristics of other

pediatric inflammatory conditions, including Kawasaki disease, staphylococcal and streptococcal toxic shock syndromes, activation syndromes of macrophages, and bacterial sepsis [2,3].

Since there are also studies describing the presence of SARS-Cov-2 in mastoids and the middle ear in a patient with COVID-19 [4] and patients with atypical presentations of sinusitis with COVID-19 infection [5,6], it is not clear if this virus could directly be related to the severity of infectious processes that might appear at this level.

There are no publications related to an increase in the incidence of severe infections in the head and neck area and COVID-19 in children.

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The objective of the present study is to determine whether there is a relationship between COVID-19 and severe infections in the ear, nose, throat, and deep cervical area (ENT) in pediatric populations.

## 2. Material and methods

A retrospective observational analytical study was performed. A compilation was made of all patients with ENT area infections in the pediatric population per month attended to at the Niño Jesús University Children's Hospital, which required hospitalization, from January 2010 to June 2020, obtained through the registry of the coding center of our hospital. The patients included belonged to the same health area with the same accessibility to health services. This study has the approval of the Ethics Committee of the Niño Jesús University Children's Hospital.

Infections were classified as complicated and uncomplicated. We consider mastoiditis with complications if intracranial or extracranial, such as intracranial abscess, jugular thrombosis, venous sinus thrombosis, subperiosteal abscess, facial paralysis, or labyrinthitis. Complicated sinusitis was assumed if an intracranial abscess or orbital complications such as intraorbital abscess, subperiosteal abscess, pre or post septal orbital cellulitis. Besides, we include retropharyngeal, parapharyngeal, submandibular, parotid, and multi-space abscesses as deep cervical infections. Peritonsillar abscess, adenophlegmon or cervical lymphadenitis without abscess, abnormalities of the branchial cleft, and infections due to embryonic development abnormalities were excluded from this group.

Likewise, a stratified analysis was carried out according to whether the infection was complicated and if the patients had been referred from another hospital.

Endemic channels graphically show the current incidence against the historical incidence to detect abnormally high disease cases [7]. Hence, we designed endemic channels to analyze the incidence presented in the year 2020 regarding what was expected based on historical data from 2010 to 2019.

The methodology for elaborating the endemic channels was through quartiles and monthly cumulative incidence, which is recommended as there is a low annual incidence of cases [7]. In the endemic channels, four areas were designed, determined by the quartiles of the cases observed in the previous years from 2010 to 2019: success (green area), security (yellow area), alarm (red area), and outbreak.

Similarly, a dispersion analysis of the number of new patients presented in the first four months of each year from 2010 to 2020 was carried out, calculating the median and standard deviation. Likewise, a comparative analysis of the mean number of patients with complicated infections per month in the first four months of 2020 was carried out for previous years using the non-parametric Mann-Whitney test. A telephone interview was then conducted with all the parents of the children who presented a severe ENT infection in the year 2020 to determine whether they had epidemiological contact with COVID-19 and its statistical significance. Finally, a serological test for IgG antibodies was carried out on all the children to know if they had overcome COVID-19. The statistical significance level was  $p < 0.05$ , and statistical analysis was carried out through Microsoft Excel v. 16.31 and SPSS Statistic v. 22.

## 3. Results

We reviewed 1022 clinical histories; 376 were not included due to insufficient data or because they were not within the period of interest studied. Sixteen patients were excluded due to infections originating from embryonic development abnormalities, and ten patients were excluded due to coding errors. Thus, the analysis was carried out on 620 patients eligible for the study. Table 1 describes the number of patients with pediatric infections by location and is stratified for the presence of complications and whether or not they have been referred from another hospital.

**Table 1**

Number of patients analyzed classified by infection location, complications, and if the patients had been referred from another hospital.

Number of patients	Total patients		Infections with complications	
	Total	No referrals from other hospitals	Total	No referrals from other hospitals
Deep cervical infections	96	88	49	44
Retropharyngeal and/or parapharyngeal abscess	58	42	58	42
Sinusitis	104	97	50	46
Mastoiditis	225	215	54	46
Peritonsillar abscess	137	133		
Total	620	575	211	178

Endemic channels were designed according to the cumulative incidence per month. A full analysis was performed, which can be seen in Fig. 1, stratified by complications.

An individualized analysis was also carried out, shown in Fig. 2, for each type of severe infection stratified by the referred patients: mastoiditis, sinusitis, and deep cervical infections with complications.

It is observed that there are no increased incidences in the total of ENT infections, regardless of their severity. Nevertheless, there is a significant outbreak in the incidence of complicated mastoiditis and also, to a lesser extent, an outbreak of deep cervical infections with complications in the year 2020 linked to the COVID-19 pandemic.

In a pooled analysis of severe mastoiditis and deep cervical infections with complications is evident that this year's number of cases invade the outbreak area, which becomes even more evident if we exclude the cases referred from other hospitals (Figures 3A and B). None of the mastoiditis of the 2020 year was secondary to cholesteatoma.

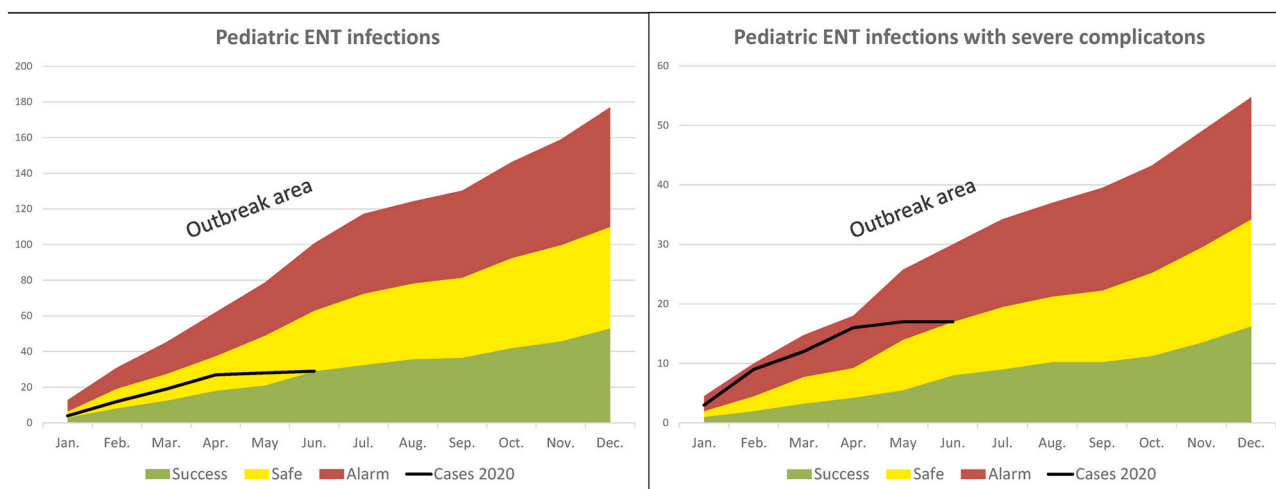
In the dispersion analysis, we observe that the number of cases of the first four months of 2020 of complicated deep cervical infections and complicated mastoiditis is significantly higher than in previous years, exceeding 1.25 of the standard deviation (SD) plus the mean of the observed cases during the same time in the years 2010–2019. These differences were statistically significant (Mann-Whitney non-parametric test  $p = 0.03$ ), so we can conclude that they are not due to chance.

Thirteen patients with complicated deep cervical infections and complicated mastoiditis were observed from January to May 2020. Of these, a PCR test for COVID-19 was only performed on six children because the remaining 7 were patients that appeared before establishing the protocol for performing PCR tests on all children requiring hospital admission. Of these six children, only one was positive. A PCR or serological test for COVID-19 was not performed on parents during hospital admission due to the policy of resource rationing caused by the pandemic.

Afterward, a telephone survey was conducted with all the parents of the children with these pathologies. Our objective was to identify if they were suspected of having been infected by COVID-19. Six of them (46%) affirmed that they had not had compatible symptoms or close contact with confirmed COVID-19 patients. Four of the parents (31%) had had the infection confirmed by a test: Two mothers had been PCR positive at the same time that their children developed a severe infection. One mother was PCR positive within a few weeks of the appearance of the infectious process of her son, and a father was IgG + for COVID-19 in the serological test, without knowing exactly when the disease had transpired. Likewise, three parents (23%) stated that they had a high suspicion of having suffered the infection due to having compatible symptoms, but without confirmation by any test.

Furthermore, a serological test for IgG antibodies against COVID-19 was performed. We observed that of the total number of cases of severe infections with complications of mastoiditis and deep cervical infections, 15.4% were positive.

In summary, only two patients were positive for IgG antibodies to



**Fig. 1. Pediatric ENT Infections. Stratified by Presence of Complications.** The image contrasts the cumulative incidence of pediatric ENT infections with/without complications of the 2020 year (black line) in the endemic channels where four areas were determined by the quartiles of the cases observed in the previous years from 2010 to 2019: success (green area), security (yellow area), alarm (red area), and outbreak. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

COVID-19, one of them confirmed by PCR test at the time of infection. Both patients were adolescent women aged 14 and 15 years old, presented deep cervical infection with abscess, and only one of them with a positive close contact confirmed by PCR test. The rest of the patients were under six years old; three of them had close contact confirmed by serologic or PCR test but were negative for PCR and IgG antibody tests. The remaining eight patients were negative for both tests and did not have close contact with COVID-19.

#### 4. Discussion

How COVID-19 affects the pediatric population is not fully understood. Oligosymptomatic or asymptomatic involvement has been widely described in most of this age group; however, associated inflammatory hyperresponsiveness processes have also been described.

Initially, it was believed that the viral infection was located in the airways only, but in postmortem studies, it has been isolated in the mastoids and middle ear [4].

Some published case series call attention to atypical presentations of complicated sinusitis infections associated with SARS-CoV-2 infection. An article describes two adolescents who suffered sinusitis and hemorrhage with intracranial abscess and COVID-19 infection [6]. Another report describes a young man with sinusitis with intracranial complications in the context of bilateral nasal polyposis, meaning SARS-CoV-2 infection could have masked the other infection [5].

In our daily activity in a national pediatric tertiary hospital, we were struck by why we saw more complicated patients with infections in our pediatric otolaryngology service, regardless of whether we were a referral hospital for pediatric emergencies during the strict confinement that began in March in Madrid city.

During the pandemic, especially in the beginning, many human resources diverted from primary care and hospitals [8]. Thus, access to local pediatricians or general physicians and primary care compromised due to a workforce shortage in dealing with the pandemic's initial onslaught. The medicine's accessibility was not significantly affected.

For this reason, we decided to carry out this study to find out whether or not there is a direct or indirect relationship between COVID-19 and the striking increase in the incidence of severe infections in the ENT area in children.

According to the results, we have observed a noticeable increase in incidence in 2020, which constitutes an outbreak if we compare it with the cases observed in previous years, since 2010.

We observe no difference in the incidence of total cases of ENT infections that required hospitalization (Fig. 1). However, if we consider those severe ENT infections with complications, we see that the curve of the cases that appeared in 2020 was located in the alarm zone at the upper limit, although without invading the outbreak zone. For this reason, we performed an individualized analysis by type and location of severe infection.

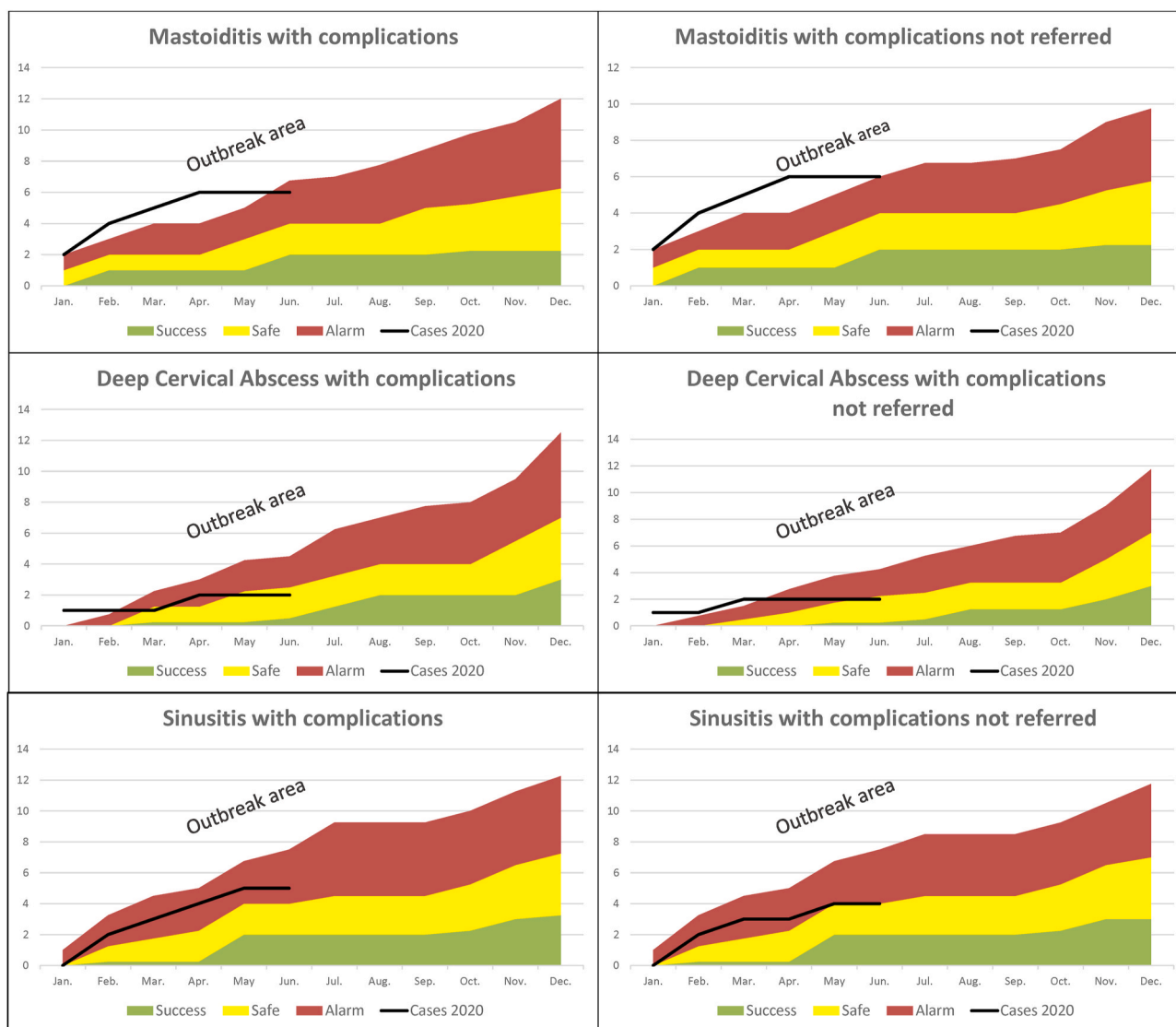
In the first place, we have a significant number of complicated mastoiditis patients that remain above the alarm zone until June and then begin to decrease (Fig. 2). These findings coincide precisely with the pandemic's better control, thanks to the lockdown that began in March in Spain. Secondly, we note that the incidence of deep cervical infections also enters the outbreak area, especially between January and March. Moreover, in the third place, we observe that although complicated sinusitis does not enter the outbreak area, it is in the alarm zone, meaning that it has an increased incidence, but not enough to be considered an outbreak. Therefore, we could say that during this first four-month period of 2020 in which we lived in a pandemic context, we had a significant increase in the incidence, constituting an outbreak of complicated mastoid and deep cervical infections. The next question would be whether this is a direct or indirect effect of the pandemic.

From the total number of patients with complicated mastoiditis and deep cervical infections with complications in the first four months of the year, 54% had been confirmed or had high suspicion of close contact with COVID-19. 31% of the parents of the patients had the infection confirmed by a test, 23% stated that they had a high suspicion without confirmation of having suffered the infection due to compatible symptoms, and only 46% affirmed that they had not had compatible symptoms or close contact with confirmed COVID-19 patients.

Two patients particularly stood out to us. One of them was a nursing baby girl who presented severe mastoiditis with intracranial abscess and a high inflammatory component in the middle ear and mastoid with mastoid bone and ossicular chain destruction. The mother was COVID-19 positive, confirmed by a PCR test, but the result of the PCR test in the patient was negative despite too close contact.

Another patient was a 14-year-old girl diagnosed with a retropharyngeal abscess and adenophlegmon with multi-space abscess without a history of foreign bodies or bones in the throat. It is an uncommon, aggressive, and atypical clinical presentation for this age [9, 10]. She and her mother were positive for COVID-19, confirmed by a PCR test.

These results might make us think that there could be a relationship



**Fig. 2. Types of severe infections.** Location of pediatric ENT severe infections stratified by the referred cases. The image contrasts the cumulative incidence of mastoiditis, deep cervical abscess, and sinusitis with complications from the 2020 year (black line) in the endemic channels where four areas were determined by the quartiles of the cases observed in the previous years from 2010 to 2019: success (green area), security (yellow area), alarm (red area), and outbreak. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

between COVID-19 and the appearance of complications at these levels. However, when performing the serological tests for IgG antibodies, we only found that only 15.4% were positive; curiously, they were adolescents. Therefore, we cannot establish a direct relationship between these findings and COVID-19.

The exact pathophysiology of severe COVID-19 disease is still unclear. This infection has been associated, as previously described, with an inflammatory hyper-response in some children, and cases that significantly compromise life have been described. It has also been linked to myocarditis.

A consistent observation reported is the presence of a proinflammatory surge, the so-called “cytokine storm.” Higher plasma concentrations of cytokines and chemokines have been described, as has the elevation of interleukin IL-2R, IL-6, IL-10, and tumor necrosis factor  $\alpha$  among the cohort of severe COVID-19 patients [11–13]. This phenomenon is thought to be a contributory factor in the development of myocarditis [14]. It is currently unknown whether this response is purely related to inflammation, autoimmunity, or a combination of both, as seen in other types of viral myocarditis [15–17].

Something similar we can think could be happening in mastoids and

deep neck infections, especially those children who have been exposed to an intimate environment with at least one PCR-confirmed COVID-19 case. The exposure to the virus could generate a more intense inflammatory response that aggravates their infectious process, leading to more complicated and atypical forms that we usually do not see. However, it is hard to demonstrate how exposure to a virus without infection would alter disease outcomes.

It is unclear whether the rise in complicated infections is due to access to healthcare or whether it is a result of the virus. Patients with complicated mastoiditis as a result of AOM which would be more suggestive of viral etiology.

Given the findings, we cannot establish a direct categorical relationship due to the small number of confirmed cases, the limited number of PCR tests performed (only 53% of admitted patients received a test), and the variability of the sensitivity of IgG antibodies serologic test ranging from 69.9% to 98.9% [18].

Thus, a plausible hypothesis is that the shortage of human resources in dealing with the initial onslaught of the pandemic and limitations in the primary care facility could have led to a delay in diagnosis and treatment and lead to an increase of several referrals to our tertiary care

hospital because of complications. Likewise, many parents, for fear of they or their children getting infected, could have avoided going to the emergency room, allowing the infectious process to develop until it worsens to the point that they are forced to go. Both factors have probably come together, explaining these findings.

Since it is completely unclear whether the rise in complicated infections is due to access to healthcare or the result of the virus, extensive epidemiological studies must address the questions raised by this report. It is advisable to carry out multicenter studies with a large number of patients to determine with higher statistical power and reliability whether there is a relationship between COVID-19 and severe clinical presentations of ENT infections in pediatrics.

## 5. Conclusion

There has been a significant increase in mastoiditis and deep cervical infections with complications in the year 2020, which constitutes an outbreak. A significant number (54%) of these complicated infections were related to close contact with COVID-19. However, we only found that only 15.4% were positive in serological tests for IgG antibodies, all of them adolescents, so we cannot establish a direct categorical relationship.

The shortage of human resources in dealing with the initial onslaught of the pandemic and limitations in the primary care facility could have led to a delay in diagnosis and treatment, cause increased complicated infections.

Likewise, changes in help-seeking behavior because of fear of getting contagious could have negatively impacted the infectious process.

Consequently, these outcomes show how COVID-19 pandemic could negatively impact other disease processes because of resource reallocation or public perception.

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## Declaration of competing interest

The authors have no conflicts of interest to disclose.

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