

# Impact of the COVID-19 Outbreak on Aseptic Meningitis in Children

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## ABSTRACT

### Objectives

Viruses are the most common infectious causes of aseptic meningitis (AM). After the COVID-19 pandemic, AM following the COVID-19 disease and its different vaccines were reported. This study compares some characteristics of patients with AM before and after the COVID-19 pandemic.

### Materials & Methods

This retrospective cross-sectional study analyzed patients' demographic and laboratory data (one month to 14 years old) with AM from March 2018 to March 2022. The first period involves two years before the COVID-19 outbreak (March 2018 to March 2020). The second period starts with the COVID-19 pandemic (from March 2020 until March 2022).

### Results

A significant decrease was observed in the frequency of patients admitted with AM after the COVID-19 pandemic in the referral children's hospital in Qazvin. The incidence of AM in children older than five decreased significantly, and as a result, the average age of patients with this diagnosis decreased, too. A meaningful decline in the prevalence of AM in the summer and fall seasons has been observed.

### Conclusion

After the COVID-19 outbreak, the incidence of AM in children significantly decreased. Implementing the hygienic recommendations for inhibiting COVID-19 virus transmission also protected children from the spread of other viruses.

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## Introduction

Aseptic meningitis (AM) is the inflammation of the meningeal layers covering the brain and spinal cord without detecting a bacterial agent in the cerebrospinal fluid (CSF) culture. Different infectious and non-infectious agents can cause AM. Viral agents are the most common infectious etiology of AM (1). The most common viral agents of AM are non-polio enteroviruses (2). Other viruses, such as mumps, herpes, varicella zoster, and arboviruses, are also responsible for AM (3). Some viruses, such as herpes and varicella, cause encephalitis or meningoencephalitis in children. AM following certain vaccines, such as measles, mumps, and rubella, have been reported (4). Mortality and morbidity due to viral AM in patients with a healthy immune system are rare. Seizure and status epilepticus are serious neurologic complications of some viral AM, such as herpes virus.

Following the rapid spread of coronavirus disease 2019 (COVID-19) worldwide, which is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the World Health Organization (WHO) declared it the COVID-19 pandemic in March 2020 (5). Encephalitis, meningitis, acute cerebrovascular accident, and Guillain Barré Syndrome (GBS) are some of the known neurologic presentations of the COVID-19 disease (6). A few cases of AM in children and adults are reported with COVID-19 disease (7,8). Some cases of AM also occurred following COVID-19 vaccines, such as AZD1222 and BNT162b2 mRNA (9,10). Thus, understanding the nature of the COVID-19 disease and its different vaccines needs more time and study.

This study evaluates the impact of the COVID-19 outbreak on children (1 month – 14 years old) with AM who were admitted to the only referral

children's hospital in Qazvin province. The present study compares some characteristics of children with AM in two periods. The first period is before the COVID-19 pandemic (March 2018-March2020). The second period is from March 2020 to March 2022, after the COVID-19 outbreak.

## Materials & Methods

This retrospective cross-sectional study was conducted at the pediatric teaching hospital in Qazvin, Iran, from March 2018 until March 2022. March 2020 divides the study into two periods, before and after the COVID-19 pandemic.

The study included children from one month to 14 years old who were admitted to the hospital with AM. AM diagnosis is based on history, clinical manifestation, and more than ten white blood cells in the cerebrospinal smear without positive CSF or blood culture.

A questionnaire was filled with patient data (demographic, vaccination history, symptoms and signs, drug history before and after admission, CSF smear and culture, CSF and throat study by real-time polymerase chain reaction (PCR) for herpes, COVID-19, influenza virus detection, blood culture, duration of hospitalization and other laboratory findings). Patients with recent brain surgery or who had ventriculoperitoneal shunts and patients whose CSF smear revealed more than 10000 red blood cells with negative results for herpes virus were excluded.

## Results

The study period was divided into two parts: Before and after March 2020, when the COVID-19 outbreak began. Sixty-eight children with AM were enrolled in this study, including Forty-nine male (72%) and 19 female (28%) patients.

Before the COVID-19 outbreak, 54 of 13286 (0.4%) children were admitted to the hospital with AM. After the COVID-19 pandemic, 14 of 9406 (0.14%) patients in the pediatric age group with AM were admitted.

In this study, the male/female ratio did not differ significantly in the two study periods ( $p=.742$ ).

Living in rural or urban areas showed no meaningful difference between the two periods of the study ( $p=1$ ).

Some characteristic data of patients in this study are shown in Table 1.

A meaningful decrease in the incidence of AM in children older than five years was noted after the COVID-19 outbreak ( $p<.001$ ). The mean age of the patients significantly declined after the outbreak ( $51.23\pm46.19$  months v/s  $13.01\pm3.73$  months) ( $p=.006$ ).

No COVID-19 virus, influenza virus, or herpes virus were detected during the study.

The length of hospitalization in the first period was  $8.35\pm3.95$  days (1-19 days). It did not differ significantly ( $p=.792$ ) from the second period, about  $8.64\pm2.06$  (4-23) days.

Figure 1 shows the seasonal distribution of AM in two periods (before and after the COVID-19 pandemic).

No significant difference in white blood cells, red blood cells, percentage of lymphocyte and polymorphonuclear cells, or the glucose contents of patients' CSF were noted in the two parts of the study.

Some CSF characteristics are shown in Table 2.

Acyclovir treatment started in seven out of fifty-four cases (13%) in the first period and seven out of 14 (50%) cases in the second period of the study.

**Table 1.** Demographic data of children with AM before and after the COVID-19 outbreak

Demographic characteristics	March2018-2020	March 2020-2022	P value
male	38	11	0.742
female	16	3	
Living in rural areas	21	6	1
Living in urban areas	33	8	
1-11 months	5	1	<0.001
12-60 months	27	13	
More than 60 months	22	0	
Age(months)	$51.23\pm46.19$ months (3-162 months)	$13.01\pm3.73$ months (4-23 months)	0.006
Length of hospital stay (days)	$8.35\pm3.95$ (1- 19 days)	$8.64\pm2.06$ (5- 12 days)	0.792

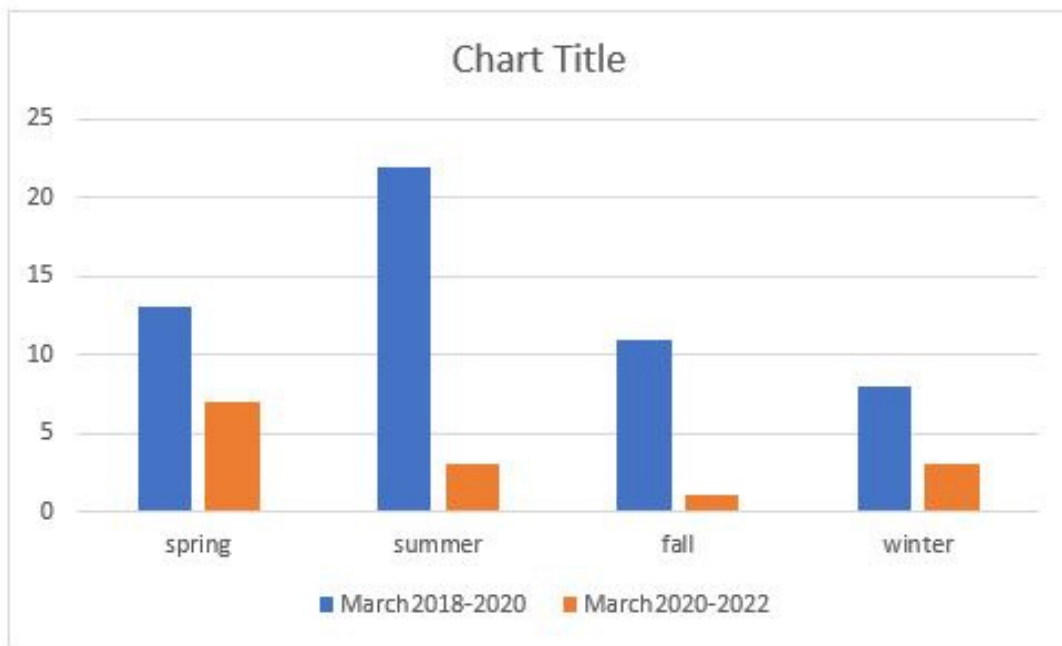


Fig 1. The seasonal distribution of AM before and after COVID-19 outbreaks

Table 2. CSF characteristic of patients with AM before and after COVID-19 outbreak

tests	March2018- 2020	March2020-2022	P value
WBC count (cells/ mm <sup>3</sup> )	515±570 (19- 2943)	735±606 (20-1855)	0.124
% Lymphocyte	81±15	73±26	0.514
% PMN	18±15	26±10	0.666
RBC count (cells/ mm <sup>3</sup> )	52±31	14±40	0.087
Protein (mg/dL)	37.22±23.06	52.57±32.11	0.013
Glucose, (mg/dL)	59±14	55±27	0.177
CRP of CSF (mg/L)	1.50±1.59	.52±.9	0.016

CSF, cerebrospinal fluid, WBC, white blood cells. PMN, polymorphonuclear, L, lymphocyte, RBC, red blood cell, CRP, c-reactive protein

### Discussion

This study showed a significant reduction in the incidence of AM in children after the COVID-19 pandemic in this hospital. The most notable decline occurred in children older than five years old. The average age of patients with AM significantly decreased. These changes are partly due to the increased emphasis on implementing hygienic measures (IHM) in

practice, such as social distancing, face mask-wearing, hand washing, school closures, and tele-education. Consequently, community exposure to transmission of respiratory droplets was mitigated, thereby limiting the spread of COVID-19 and other airborne viruses responsible for AM.

After the COVID-19 outbreak, children’s hospital admission rate was reduced by 30%. In children with AM, the admission rate decreased by 70%.

However, this decline was not observed in hospital admissions with other neurologic diagnoses, such as seizures, during the same period.

Lee et al. showed a decrease in the incidence of meningitis, including viral meningitis, in children younger than 18 years old in Korea after the COVID-19 pandemic. This decline was more notable in children older than five (11). In their study, the decrement of AM incidence in children older than five years old after the COVID-19 outbreak was compatible with the present study's results. They attributed these changes to implementing non-pharmaceutical intervention protocols during COVID-19 outbreaks.

Another study reported a positive impact of the COVID-19 outbreak on the reduction of bacterial meningitis incidence in children in Morocco (12). They proposed that these changes in bacterial meningitis frequency are related to implementing hygienic measures which prevent the COVID-19 virus from spreading in the community.

Volk et al. reported a decrease in hospital admission rates for viral meningitis in children and adults compared with the period before the COVID-19 outbreak. However, they did not find any changes in pneumococcal meningitis frequency in children after the COVID-19 pandemic despite a reduction of pneumococcal meningitis in adults (13). This decrease in pneumococcal meningitis in adults was partly attributed to the influence of emphasis on vaccination (more than 30%) against *Streptococcus pneumoniae* in people older than sixty after the COVID-19 outbreak. In that study, the children's vaccination rate against *S. pneumoniae* was up by 80%. Vaccination against *S. pneumoniae* in pediatric age did not differ after the COVID-19 outbreak in that region.

In the present study, the real-time PCR test did not detect herpes simplex, influenza, and the

COVID-19 virus as responsible agents for AM. This finding is due to the paucity of these viruses as responsible agents for AM in children and the low frequency of patients in the study.

However, acyclovir, as the drug of choice in treating AM due to the herpes virus, was started in 14 (20%) patients in this study. This drug was discontinued with negative real-time PCR results for herpes virus in patients' CSF.

Despite all diagnostic advancements, the exact viral etiology of AM can be identified in less than 70% of cases (14). Enteroviruses are the most common recognizable viral pathogen for AM (14,15). In this study period, no PCR tests were positive for enterovirus. However, a meaningful decline in the frequency of AM was observed in summer and fall. AM before COVID-19 outbreaks were more frequently reported in summer and fall (15,16). School and daycare closures (partially or totally) and mitigation of respiratory droplet transmission significantly decreased the frequency of even fecally-orally transmitted agents like enteroviruses.

The present study revealed that the average length of hospitalization in children with AM did not differ significantly before or after the COVID-19 outbreak. Another study in the Islamic Republic of Iran (IRI) reported a similar length of hospitalization in patients with AM and a negative PCR test in their CSF before the COVID-19 outbreak (15). Rapid and sensitive diagnostic molecular tests such as multiplex real-time PCR are useful in identifying the responsible agent for AM, especially in patients who received prior antibiotic therapy before hospital admission. Routine use of this test in patients with AM helps to shorten the length of hospitalization and decreases the cost of AM management. In one study in Korea, the length of patient hospitalization

significantly increased from five to seven days after the COVID-19 pandemic (11). The reason for the increase in hospitalization length was not reported. However, the length of hospitalization was less than that of our study.

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### Authors' Contribution

Banafsheh Arad, Hossein Farshad, Zahra Pirzadeh conducted the analysis of the data, wrote the analysis, plan, drafted and revised the paper; Mehri Jamshidand Zahra Pirzadeh conducted analysis and revised the paper.

### Conflict of interest

None.

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