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Short Communication

Cerebrospinal fluid analysis of pregnant women at early stages of COVID-19

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ABSTRACT

Objective: To determine the presence or absence of SARS-CoV-2 in the cerebrospinal fluid of pregnant women at early stages of COVID-19.
Materials and methods: We conducted a prospective observational study with pregnant women undergoing cesarean section and real-time polymerase chain reaction to SARS-CoV-2 was performed in the cerebrospinal fluid in the early stages of COVID-19.
Results: Fourteen pregnant women, whose COVID-19 symptoms started between four to 18 days prior to delivery, were included. Eleven of the women reported anosmia, dysgeusia, and headaches and there were two fatal cases. SARS-Cov-2 was not present in the cerebrospinal fluid of these COVID-19 patients with early neurological symptoms, even in severe cases.
Conclusion: Our study suggests that peripheric cell damage and parainfectious phenomena may predominate over direct central nervous system injury in the pathophysiology of COVID-19 related early neurological symptoms on pregnant women.
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Introduction

Several neurological signs and symptoms have been described in patients with coronavirus disease (COVID-19), but it is unknown whether they are due to direct nervous system invasion by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or are secondary to inflammatory and immunological processes. Typically, headaches, anosmia, and dysgeusia occur in the initial disease stages, while more severe neurological conditions such as encephalitis, stroke, and seizures may appear later [1].

As most studies have not detected SARS-CoV-2 in the cerebrospinal fluid (CSF) of patients with severe neurological disorders [2,3], Panciani et al. proposed the interesting hypothesis that early symptoms are caused by direct neurological injury when the viruses are present in the CSF, whereas later symptoms are due to immune-mediated damage upon SARS-CoV-2 clearance from the CSF [4]. However, as CSF analysis is usually reserved for patients with more severe neurological symptoms, it is currently unknown whether SARS-CoV-2 is actually present or not in the CSF in the early stages of COVID-19.

In pregnant women, hospitalizations due to COVID-19 occur mainly in the third trimester [5]; therefore, spinal anesthesia for those undergoing cesarean section is a great opportunity to assess the presence of SARS-CoV-2 in the CSF. We performed a study to determine the presence or absence of SARS-CoV-2 in the CSF of pregnant women at early stages of COVID-19.

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Materials and methods

This study is part of a larger project - PROUDEST: Effects of COVID-19 on pregnancy, childbirth, puerperium, neonatal period and child development: prospective, multicenter cohort study registered on the Brazilian Register of Clinical Trials (REBEC), RBR65QXS2, https://ensaiosclinicos.gov.br/rg/RBR-65qxs2/and approved by the Research Ethics Committee of the University of Brasilia School of Medicine (http://www.fm.unb.br/cep-fm - CAAE 32359620.0.0000.5558) [6]. All participants provided written, informed consent.

In this segment, we conducted a prospective observational study in women undergoing cesarean section at a COVID-19 referral hospital in Brasília, Brazil, from June 20 to August 18, 2020. COVID-19 was diagnosed based on the following criteria: (a) positive SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) on a nasopharyngeal swab specimen, (b) identification of serum antibodies to SARS-CoV-2 concomitantly with a chest computed tomography (CT) compatible with COVID-19, or (c) clinical symptoms suggestive of COVID-19 and a chest CT compatible with COVID-19.

We reserved a CSF sample from each woman when a lumbar puncture for spinal anesthesia was performed during the cesarean section. RT-PCR was performed with Molecular Research Institute of Paraná (Paraná, Brazil) or VIASURE SARS-CoV-2 (CerTest Biotech, Zaragoza, Spain) kits, whose detection limit is 4 copies per reaction.

Results

Fourteen pregnant women, whose COVID-19 symptoms started 4–18 days prior to delivery, were included. Among them, ten, three, and one had mild, severe, and critical diseases, respectively. Eleven reported anosmia, dysgeusia or headaches (Table 1).

There were two fatal cases, a critical disease patient who died 18 days postpartum due to respiratory failure and a severe disease patient whose respiratory condition was improving when she suddenly developed recurrent generalized tonic-clonic seizures and died 13 days postpartum. Angiotomography findings indicated posterior reversible encephalopathy syndrome, with no signs of thrombosis or hemorrhage. The CSF was SARS-CoV-2 RNA negative in all patients.

Discussion

Brain invasion by SARS-COV-2 has been reported on humans and animal models but remains unclear whether and how the virus crosses the blood–brain barrier (BBB) [7–9]. Since severe neurological manifestations of COVID-19 typically occur after the acute phase, microbiological examination of the CSF was rarely performed in the early stages of the disease [10]. However, during the first wave of the COVID-19 we had the opportunity to analyze the CSF of pregnant women whose symptoms had started between four and eighteen days.

Our results indicate that SARS-CoV-2 is not present in the CSF of COVID-19 patients with early neurological symptoms and therefore these symptoms may be not attributable to direct viral injury to the central nervous system.

As headache is a ubiquitous, non-specific symptom frequently seen in other infectious diseases, it can be a systemic effect of the SARS-CoV-2 infection. On the other hand, anosmia and dysgeusia are recognized as cardinal symptoms of early stages of the disease and have been used as diagnostic markers. They are most often transient, with a regaining of smell and taste after several days to weeks. This sudden onset, followed by a rapid recovery, is a strong argument against neuronal damage as a cause, given the time course of neuronal regeneration. Additionally, there is currently no evidence that the SARSCoV-2 virus itself can reach the brain in the acute phase of anosmia [11]. Therefore, since SARS-CoV-2 enters human cells via the angiotensin-converting enzyme 2 (ACE 2) receptor that is expressed in the sustentacular cells of the olfactory epithelium but not in the olfactory sensory neurons, it has been proposed that anosmia and dysgeusia are secondary to olfactory epithelium damage [11].

Our data are in line with the growing evidence suggesting that parainfectious immune-mediated mechanism predominate over direct neurological injury in the pathophysiology of COVID-19 related neurological symptoms [1,12,13].However, more studies are needed to determine the real entry routes of SARS-CoV-2 into the central nervous system, which pathogenic responses are triggered in infected cells and whether these mechanisms are influenced by pregnancy.

Table 1
Clinical features of pregnant women with COVID-19 and results of SARS-CoV-2 RNA testing of the cerebrospinal fluid.

Nº	Diagnostic criteria	Severity	Neurological symptoms (at any time)	Days from first symptoms to delivery and CSF[a] analysis	Interval between the nasopharyngeal and CSF[a] PCR[b] tests	CSF[a] PCR[b] results
1	PCR[b]	Severe	None	4	Same day	Negative
2	PCR[b]	Mild	Anosmia, dysgeusia	5	Same day	Negative
3	PCR[b]	Mild	Headaches	6	3 days	Negative
4	PCR[b]	Mild	Headaches, anosmia, dysgeusia	6	3 days	Negative
5	PCR[b]	Mild	Headaches	7	1 day	Negative
6	PCR[b]	Severe	Headaches, anosmia, dysgeusia	7	Same day	Negative
7	Ab[c] and CT[d]	Critical[e]	None	7	NA[g]	Negative
8	CT[d]	Mild	Headaches, anosmia, dysgeusia	8	NA[g]	Negative
9	CT[d]	Mild	None	9	NA[g]	Negative
10	PCR[b]	Severe[f]	Anosmia. Generalized tonic-clonic seizures. Brain CT: Posterior reversible encephalopathy syndrome	12	Same day	Negative
11	CT[d]	Mild	Anosmia, dysgeusia	13	NA[g]	Negative
12	PCR[b]	Mild	Headaches	13	11 days	Negative
13	Ab[c] and CT[d]	Mild	Headaches, anosmia, dysgeusia	14	NA[g]	Negative
14	PCR[b]	Mild	Anosmia, dysgeusia	18	18 days	Negative

Abbreviations: [a] CSF, cerebrospinal fluid; [b] PCR, polymerase chain reaction; [c] Ab, antibodies; [d] CT, computed tomography; [e] Death on the 18th day postpartum due to respiratory failure; [f] Death on the 13th day postpartum due to multiple organ failure, [g] NA, not applicable.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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