CASE REPORT

# Co-infection of Coronavirus Omicron variant and Salmonella Meningoencephalitis

*Efraim Culminas, Lucy Kathrina Banta- Banzali, Jay Ron Padua*

**ABSTRACT** *:* It has been considered that viral infections predispose patients to bacterial infections due to immunosuppression.[3] However, it is still unclear what exact roles co-infections play in patients with COVID-19 infection[1]. Centers for Disease Control and Prevention defines co -infection as an infection concurrent with the initial infection. This report discusses a case of meningoencephalitis presenting with seizures. Notable in this case was the detection of SARS-CoV-2 RNA and Salmonella in the CSF.

## CASE REPORT

A previously well three-month-old Filipino girl presented with one-day history of fever. A day prior to admission, the patient had difficulty of breathing and seizures described as persistent upward gaze which lasted for two minutes. Pertinent neurologic findings were irritability and nuchal rigidity. Initial work up including a complete blood count, showed elevated white blood cell count (WBC) with segmenter-predominance. C-reactive protein and procalcitonin were also elevated. Chest x-ray showed pneumonia for which she was treated with Ceftriaxone at 100 milligram per kilogram per day (mkd). Bedside cranial ultrasound showed bacterial meningitis with ependymitis. Blood culture showed presumptive gram-negative bacilli, hence, Amikacin was started.

The patient was then noted to have myoclonic jerks of upper and lower extremities. Levetiracetam at 20mkd was started with resolution of seizure. The nasopharyngeal SARS-CoV-2 RT-PCR revealed positive and she was started on Dexamethasone.

Lumbar CSF analysis showed a slightly turbid CSF, elevated WBC with lymphocytic-predominance, elevated protein and hypoglycorrhachia. The CSF co-agglutination test, Acid Fast Bacilli, and gram stains were all negative. The CSF SARS-CoV-2 RT-PCR result was positive and on gene sequencing revealed Omicron variant. The blood culture yielded growth of Salmonella group hence antibiotics were shifted to Amikacin, Cefepime and Ciprofloxacin. Patient was also started on Remdesivir.

On the fifth hospital day, she had four episodes of seizure described as right versive gaze, tonic flexion of left upper extremity, and tonic extension of the right upper extremity. Levetiracetam was increased to 60mkd and Phenobarbital at 5mkd was added. The patient was then hooked to non-invasive positive pressure ventilation due to episodes of tight air entry and respiratory distress.

On the sixth hospital day, the CSF culture grew Salmonella group with the same susceptibility pattern as the blood isolate. Baseline work-up for COVID-19 severe infection showed slightly elevated ferritin, D-dimer, and Creatine Kinase-MB.

After twenty-one days of antibiotic treatment, cranial magnetic resonance imaging (MRI) showed pachymeningitis with minimal communicating hydrocephalus (Figure). A repeat lumbar CSF analysis showed normal WBC with lymphocytic predominance, an improved protein and hypoglycorrhachia. The repeat CSF culture and SARS-CoV-2 RT-PCR were negative. Intravenous Cefepime and Ciprofloxacin were completed for 28 days. Before discharge, a repeat COVID ECLIA was reactive for IgG and nonreactive for IgM. The immunodeficiency panel were within normal for age. On discharge, the patient had no seizure recurrence with no neurologic deficits. On follow-up, neurologic examination was normal with developmental milestones at par with age.

## Discussion

Co-infection is the simultaneous infection of a host by multiple pathogens resulting in a delay in diagnosis and poor prognosis. Currently, coronavirus infection is a global health concern. In children, coronavirus with concomitant infections is rarely reported. During this pandemic, acute illnesses in children may be associated with coronavirus infection. An acute illness non-responding to conventional treatment, or that which presents atypically or leads to further deterioration, might be associated with coronavirus infection. COVID-19 symptoms may mimic various other diseases. The febrile phase of dengue, typhoid, malaria, and many other diseases may overlap with the coronavirus infection which may lead to substantial misdiagnosis.[2] Based on the available literatures, there is one case report of a 5-year-old girl diagnosed with acute SARS-CoV-2-associated meningoencephalitis based on the detection of its RNA on a nasopharyngeal swab and CSF, and on cerebellar biopsy, *Mycobacterium tuberculosis* complex DNA was detected by PCR.[5]

Salmonella meningitis accounts for <1% of confirmed cases in infantile age group. Despite being an uncommon it is associated with higher rates of complications when compared to other forms of gram-negative rods meningitis.

Its mode of transmission is mainly fecal-oral.[6] The first COVID-19 and enteric fever co-infection was a case of a 56-year-old male who was admitted due to fever, shortness of breath, and myalgia with positive nasopharyngeal SARS-CoV-2 RT-PCR and blood culture for salmonella.[7]

SARS-CoV-2 involves multiple organs including the central and peripheral nervous system. Since the outbreak of the COVID-19, there have been reports of neurologic manifestations of COVID-19 mostly seen in adults, with a few cases described in children which include encephalopathy, encephalitis, stroke, hemorrhage, acute disseminated encephalomyelitis, and Guillain-Barré syndrome.[8]

Both viral and autoimmune meningoencephalitis have been reported in COVID-19 but these complications are rare.[9] Currently, most of the patients with SARS-CoV-2 infection with neurological complications are elderly.[10] In a systematic review by Liang Huo, the incidence of SARS-CoV-2-associated encephalitis/ meningitis is relatively low in children, which may be related to the relatively mild illness of COVID-19.[8]

The underlying mechanisms of neurologic complications in patients with COVID-19 are diverse and multifactorial. Neurologic complications arise most frequently from systemic response to the infection. Distinct mechanisms include: neurologic injury from systemic dysfunction, renin-angiotensin system dysfunction, immune dysfunction and direct viral invasion of the nervous system. Recent evidence suggest that disruption of the blood brain barrier might be one of the potential routes for viral transport and entry to the brain regions. Overall, huge research work is still needed to investigate these processes and mechanisms as no convincing evidence is available that could prove these proposed mechanisms.[11]

The sensitivity of RT-PCR nasopharyngeal swabs of SARS-CoV-2 to detect acute COVID-19 is high, but current data are limited to evaluate the sensitivity of this technique in CSF in patients with neurological disease. Due to the time limit of transmission of COVID-19, its CSF titer may be extremely low which makes it difficult to diagnose SARS-CoV-2-related encephalitis.[12]

By definition, SARS-CoV-2-associated encephalitis/meningitis is an inflammatory process. Supporting evidence includes the presence of COVID-19 with CSF pleocytosis and elevated protein.[13] Definitive evidence about direct neuro-invasiveness of SARS-CoV-2 would include SARS-CoV-2 RNA PCR positive tests in CSF, SARS-CoV-2-specific antibodies positive tests in CSF, or SARS-CoV-2 RNA or antigen positive tests in brain tissue obtained at autopsy or biopsy. Although SARS-associated encephalitis have been reported, few actually meet the strict

criteria for direct SARS-CoV-2-associated encephalitis. In the majority of reported patients with COVID-19-associated encephalopathy, CSF was reported as normal. Thus, detailed nervous system physical examination, ancillary examination, and positive rate of SARS-CoV-2 detection in CSF are very important to provide direct neurotropic evidence of SARSCoV-2.[8]

In SARS-CoV-2-associated encephalitis may involve any part of the brain, especially the temporal lobe, white matter, frontal lobe, and corpus callosum. Neuroimaging abnormalities usually present with high T2/FLAIR signal hyperintensity in the subcortical white matter or other parts of brain injury. There are a myriad of patients without neuroimaging changes. On the other hand, EEG findings of monomorphic biphasic high amplitude delta waves with occasional myoclonic has been suggested as a direct effect of COVID-19 infection.[8]

Patients with encephalitis generally need intensive care and mechanical ventilation. In most of the patients with SARS -CoV-2-associated encephalitis/meningitis were treated with antibiotics and antiviral drugs. Some patients were also treated with IVIg and corticosteroids. Anticonvulsant medications were used in the patients with seizure.[8]

In general, the presence of neurological disease in COVID-19 patients is associated with higher mortality, disturbance of consciousness, refractory epilepsy, and severe physical disability. However, in a review of published case reports by Liang Huo and colleagues found that most COVID-19 patients with encephalitis/ meningitis improved after systematic treatment. Although the literatures available are mostly in adults.[8]

Currently there is no recommended vaccine in children less than 5years old. Vaccination reduced a significant number of infections in the pediatric population, including symptomatic and severe COVID-19. Vaccination of family members and household members may also contribute in achieving herd immunity. At present, there are no published studies showing the effectiveness of COVID vaccine on covid infection with neurologic manifestation.

Locally, there is only one case report of a 12-year male diagnosed with focal encephalitis with documented SARS-CoV-2 in the CSF.[14] However there have been no reports of meningoencephalitis co-infection with SARS-CoV-2.

## CONCLUSIONS

COVID-19 co-infections with bacterial pathogens are not well documented.[15] Signs and symptoms of COVID-19 in children may mimic or may overlap with other diseases. Moreover, due to overburden in health services, the diagnosis of co-infections becomes difficult and treatment may be delayed.

Therefore, infection accompanying COVID-19 may lead to misdiagnosis and sudden deterioration of the patient's general condition that leads to increase in morbidity and mortality.[7] Hence, not only bacterial pathogens, but also COVID-19 infection should be considered in patients with presenting with meningitis. In this view, a high index of suspicion, careful attention to the clinical course, and RT-PCR are necessary to identify the coronavirus infection with recent illnesses. Delay in diagnosis of associated COVID-19 results in poor prognosis.[2]

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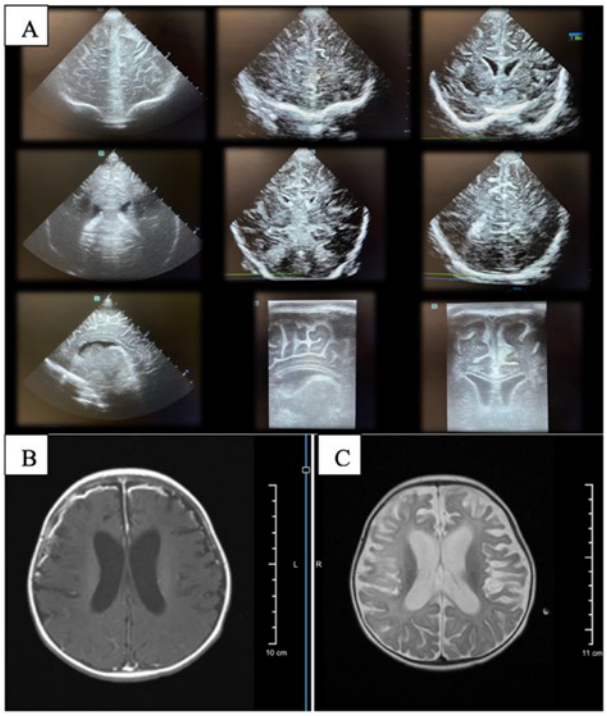


**Figure. A. Cranial Ultrasound.** The sulci are thick, irregular and hyperechoic, within the interhemispheric fissure and bilateral convexity consistent with Bacterial meningitis with ependymitis. **Cranial MRI plain with contrast (T1 with contrast (B) and T2(C)).** There is abnormal enhancement of the dura overlying both anterior frontal and left medial frontal lobes suggestive of Pachymeningitis.