CASE REPORT

Concomitant *Haemophilus influenza*e Infection and anti-N-Methyl-D-Aspartate Receptor Encephalitis in a 7-year-old Previously Healthy Girl: A Case Report

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ABSTRACT

Encephalitis is the inflammation of the brain which is usually caused by viral infections, but it can be also due to other non-infectious agents. We report an interesting case of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis with *Haemophilus influenzae* co-infection in association with severe acute respiratory syndrome coronavirus 2, without pulmonary involvement or fever.
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INTRODUCTION

Anti-N-methyl D-aspartate receptor (anti-NMDAR) encephalitis is a common autoimmune encephalitis, and it is reported to be more common among the Austronesians (1). Increasing literature has demonstrated the overlapping symptoms between neurologic and psychiatric pathology in regard to autoimmune encephalitis.

On the other hand, *Haemophilus influenzae* causes invasive diseases such as meningitis and pneumonia and has very high fatality rate of up to 60% if the patient is not properly treated. The presence of anti-NMDAR encephalitis together with *Haemophilus influenzae* co-infection in an asymptomatic COVID-19 patient is definitely interesting; a few literatures have reported that COVID-19 can trigger diseases like autoimmune or autoinflammatory conditions.

CASE REPORT

A 7-year-old previously healthy Malay girl presented to a district hospital with right-sided body weakness after a history of fall. Her mother had noticed abnormal movements of the right lower limb prior to the presentation. Contrast-enhanced computed tomography (CECT) of the brain and cervical were done and reported as normal at that time. The initial clinical impression was focal seizure or motor tics. However, the mother took 'at own risk' (AOR) discharge after four days of hospitalization as there was a positive COVID-19 case in the ward.

Two weeks later, the patient presented to a private hospital with recurrent episodes of seizures that only aborted with anti-seizure medication. Polymerase chain reaction (PCR) for SARS-CoV-2 performed there turned out to be positive. She was then referred to our hospital (COVID-19 epicentre) for further management.

Upon arrival, the child appeared dehydrated, sedated, and had developed another fitting episode which was described as generalised tonic movements of bilateral upper and lower limbs. The fits only aborted following administration of anti-seizure medication. Urgent computed tomography (CT) of the brain showed no significant abnormalities (Figure 1) and chest radiography showed unremarkable findings (Figure 2). She was empirically treated as meningoencephalitis with intravenous (IV) ceftriaxone and anti-seizure drug.

Throughout the hospital stay, she continued to develop several fitting episodes and was eventually intubated for airway protection. After discussion with a paediatric intensivist, the patient was started on intravenous immunoglobulin (IVIG). Magnetic resonance imaging

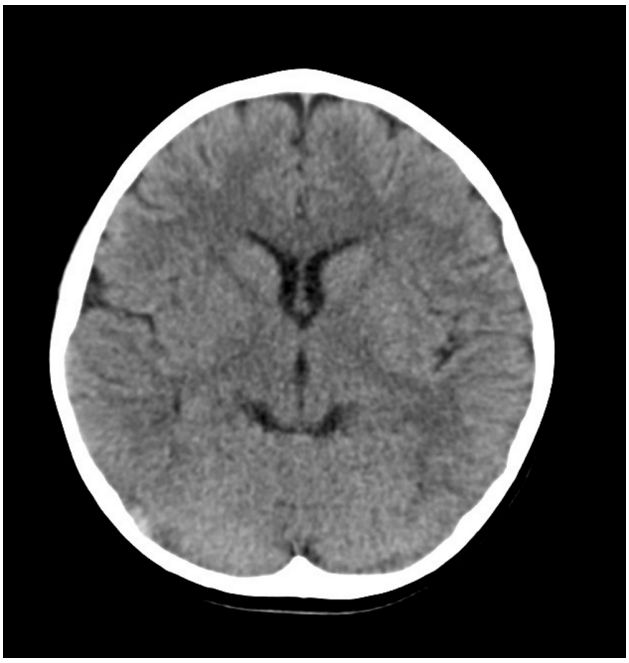

Figure 1: CT brain done on the day of admission to our centre showed no abnormality.

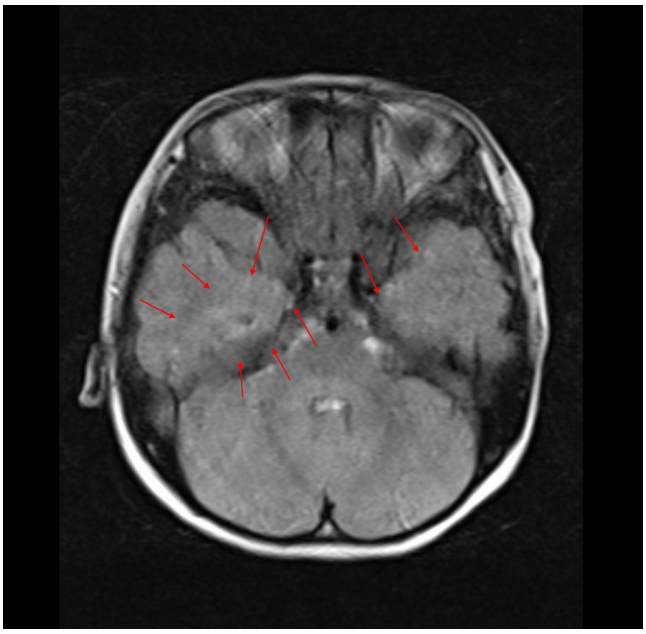

Figure 3: MRI brain showed ill-defined high signal intensity on T2 weighted image and FLAIR sequence over the medial temporal lobe. These findings may represent encephalitis.

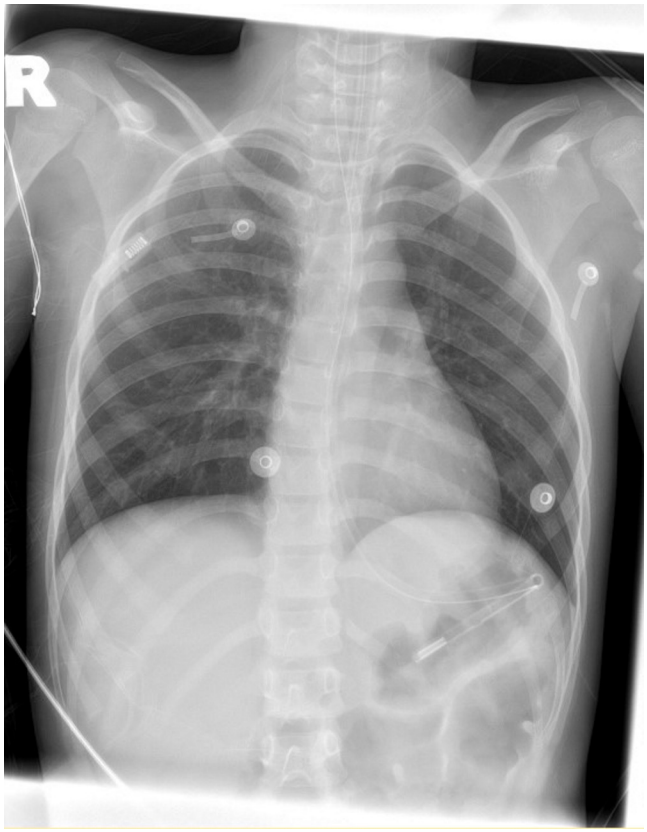

Figure 2: Chest radiography done on the day of admission was unremarkable.

(MRI) brain (Figure 3) done later showed hyperintense lesion at the left medial temporal lobe, which might represent encephalitis. The case was discussed with a paediatric neuromedical team from Women and Children's Hospital (WCH) Kuala Lumpur and the possibility of an autoimmune aetiology was suspected. Lumbar puncture and electroencephalogram (EEG) were suggested for this patient. An EEG performed the next day as the patient was having another episode of seizure showed status epilepticus pattern. She was then started on levetiracetam. Lumbar puncture was performed and the cerebrospinal fluid (CSF) sample was sent for investigations (Table I). After a week, she was finally extubated, off-tagged from COVID-19, and transferred to the general ward.

The results of anti-NMDAR for both CSF and serum turned out to be positive, and *Haemophilus influenzae* was detected via multiplex PCR. She was then transferred to WCH Kuala Lumpur for continuation of care under the paediatric neuromedical team. There, she was treated with steroids (IV methylprednisolone which was later converted to oral prednisolone) and cyclophosphamide. She had a few episodes of temperature spikes due to thrombophlebitis which was treated with antibiotics, and she was discharged two weeks later. Upon discharge, she no longer had movement issues, and generally was able to do toileting and feeding by herself. Follow up at the neurology clinic documented that the child had 90% recovered back to her normal self. She no longer had fitting episodes and the EEG showed an overall marked improvement from the previous one.

DISCUSSION

This is a case of a fully immunised 7-year-old child, who initially presented with right sided body weakness following a fall. She became a close contact to a COVID-19 patient during initial hospital admission and later was positive herself but remained asymptomatic. Her condition worsened when she started to develop status epilepticus two weeks later, which could only be

Table I: Summary of patient's blood and cerebrospinal fluid (CSF) findings

Indices	Values
CSF biochemistry	Appearance: Clear Glucose: 5.1mmol/L Protein: 0.29g/L
CSF culture and sensitivity (C&S)	No growth
CSF Meningoencephalitis Panel (Multiplex PCR)	*Haemophilus influenzae* Detected
CSF for SARS-CoV-2 RT-PCR	Not Detected
Anti-NMDAR (CSF & Serum)	Positive
CSF Japanese Encephalitis PCR	Not Detected

aborted by administration of anti-epileptic drugs. It was later known that she had concomitant *Haemophilus influenzae* infection and anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis through analysis of the CSF. Her serum was also positive for the anti-NMDAR antibody. Extensive search in the existing database showed there is no published case report of concomitant *Haemophilus influenzae* infection and anti-NMDAR encephalitis. However, according to a study by Erickson et al., among 231 patients who were diagnosed with encephalitis at their centre in 2010-2017, only 58% had the causes identified (2). The most common cause was viral infection which was about 22% (51/231 patients). Eight percent was caused by bacterial infection and anti-NMDAR encephalitis was the most common autoimmune cause identified, at 13% (31/231 patients) (2). This study agreed with the earlier California Encephalitis Project that was conducted in 1998-2000 which found almost similar results (3).

NMDA receptors, which are present within the hippocampus and the cerebral cortex, is a family of glutamate receptors and play important role in learning and memory. NMDAR encephalitis mainly occurs in women with ovarian teratoma and is associated with antibodies against NR1 or NR2 subunit of the NMDA receptors. The affected patients mainly presented with psychotic symptoms (4). However, the pathogenesis of ovarian-teratoma-associated anti-NMDAR encephalitis remains poorly understood. On the other hand, *Haemophilus influenzae* – a small fastidious Gram-negative coccobacillus with its capsular type B (Hib) – used to be a common cause of meningitis during pre-vaccination era. It colonises the upper respiratory tract of humans, and the presence of polysaccharide capsules in addition to adhesins-like fimbriae, IgA proteases, and outer-membrane proteins helps to facilitates invasion. The age of patients infected with *Haemophilus influenzae* are usually less than five years old. COVID-19 infection has been reported in several case reports as possible triggering factor to several conditions, especially those related to autoimmune diseases. It is postulated that when a patient is infected by SARS-CoV-2, antibodies towards viral particles such as non-structural protein 8 (NSP8) and 9 (NSP9) are formed. The blood brain barrier (BBB) may be disrupted in COVID-19 patients due to IL-17 production and SARS-CoV-2 associated endothelitis. These events could lead to the entry of the antibodies into the central nervous system, which may then cross-react with NMDAR subunit GluN1 and cause anti-NMDAR encephalitis (5).

It is believed that this child's presentation was initially leaning more towards anti-NMDAR encephalitis until she started to have seizure, because both causes could have instigated it. Other differential diagnosis would include schizophrenia. Therefore, it is very important to also perform mini mental state examination (MMSE) when patients presented with such features to exclude psychiatric disorders. Differential diagnoses also include other viral causes of encephalitis such as herpes simplex virus, Epstein-Barr virus, varicella zoster virus, and other autoimmune causes such as systemic lupus erythematosus.

Cerebrospinal (CSF) analysis between *Haemophilus influenzae* infection and anti-NMDAR encephalitis also differs. According to a study conducted in China, from a total of 43 patients who was diagnosed with anti-NMDAR encephalitis, 100% had positive antibody detected in their CSF but only 62.8% (27/43) had positive antibody in their serum. Increased intracranial pressure was observed in 39.5% of patients, elevated total cell counts were observed in 58.1% and 18.6% exhibited raised total protein counts in CSF. Sugar and chlorine levels were normal in 93% of the cases (4). Meanwhile, *Haemophilus influenzae* infections are usually associated with reduced CSF glucose level, increased white cell count (with predominant neutrophils) and protein level, and bacterial PCR positivity is over 90%. Our patient's CSF analysis was clear in colour, had elevated glucose level, with normal protein level. Cell count and white blood cells were not elevated. No similar CSF findings were found after an exhaustive literature search. These results were puzzling as the sample was taken at the same time with the samples sent for PCR and anti-NMDAR antibodies tests which turned out to be positive. However, it is possible that the patient had a resolved recent *Haemophilus influenzae* infection which was still detected by PCR because it only provides limited information on the physiological states of the microorganisms.

According to the literature, brain MRI in patients with autoimmune antibodies could either be normal, or may exhibit increased T2 signal, especially at the region of

the medial temporal lobes. These findings are similar with MRI findings of other viral encephalitis. Infection with tuberculosis, syphilis, or other infections may have also the same MRI findings. In conclusion, brain MRI is unable to distinguish between infectious and autoimmune causes, and having a normal MRI does not totally rule out the possibility of encephalitis.

CONCLUSION

Diagnosing autoimmune encephalitis is challenging due to the many similarities shared in terms of clinical, imaging, and laboratory findings with other causes such as infectious encephalitis. Hence, a broad investigation approach towards identifying the potential aetiologies in patients presented with neurological symptoms could point to a correct diagnosis.

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