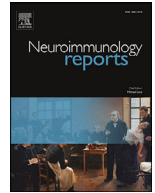




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# Possible autoimmune pediatric encephalitis following COVID-19 infection with focal cerebral dysfunction in a young female: A case report

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## ABSTRACT

**Introduction:** Post-COVID-19 autoimmune encephalitis is a rare manifestation following COVID-19. Most cases have not demonstrated solid evidence regarding their pathogenesis. Some believe it to be an immune process.

**Case presentation:** In this case report, we present a case of a young female who presented to our emergency department with visual, auditory, and olfactory hallucinations after successfully treating COVID-19 two weeks prior to this visit. On examination, her vital signs were stable, but she was agitated, distressed, and hallucinating. Neurological examinations were normal. Laboratory investigations, including autoimmune profiles, were all negative. Magnetic resonance imaging of the brain showed non-specific changes in the bilateral frontal area. Electroencephalography (EEG) showed lateralized rhythmic delta activity (LRDA) arising more from the right occipital lobes. Autoimmune psychosis was suspected due to psychosis, abnormal imaging, and abnormal EEG findings. She was given corticosteroids and antipsychotic medication. Her symptoms improved within ten days. On follow-up, she remained well without any return of psychosis.

**Conclusion:** Possible autoimmune pediatric encephalitis following COVID-19 is a rare entity that has scarcely been reported. The majority of the cases were reported to have been related to stress following the infection. To establish the correct diagnosis, an extensive workup, including an autoimmune profile, lumbar puncture, magnetic resonance imaging, and electroencephalography, is recommended.

## Introduction

SARS-CoV-2, or the COVID-19 pandemic, is one of humanity's most devastating pandemics of all time. Since its outbreak in 2019, 200 million people have been infected, resulting in 4 million deaths worldwide. Among those infected, complications including post-COVID-19 psychosis have been reported. To date, COVID-19 psychosis has been reported in several case reports and case series, but none has shown significant solid abnormalities (Troyer et al., 2020; Taquet et al., 2021; Watson et al., 2021).

Here, we present the case of a 15-year-old Thai female who experienced acute psychotic symptoms with evidence of cerebral dysfunction captured on electroencephalography (EEG).

## Case presentation

A 15-year-old Thai woman was diagnosed and admitted to a provincial hospital with a mild COVID-19 infection in mid-June 2020. Symptoms at that time of diagnosis were notable for high grade fever, rhinorrhoea, and nasal congestion without documentation of anosmia or dysgeusia. Her medications included Favipiravir and chlorpheniramine

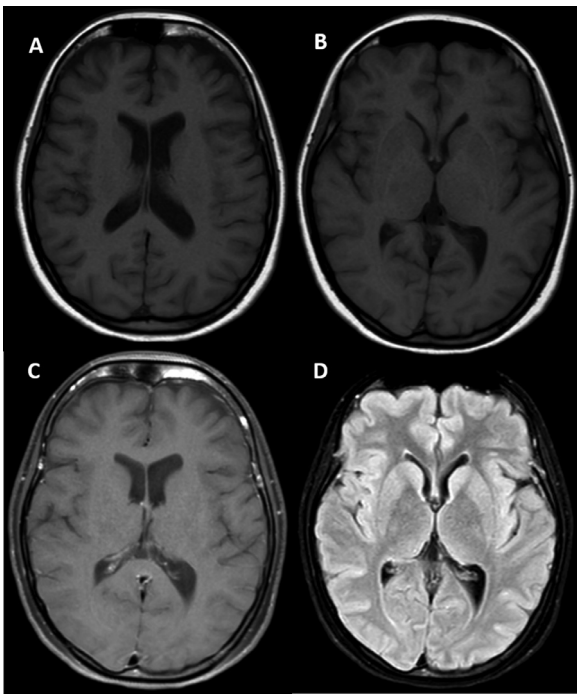
for five days. She did not need an oxygen supplement. At discharge, her symptoms subsided.

Two weeks later, she was brought to the emergency department by her mother with an abrupt onset of bizarre behavior for two days, characterized by prominent visual, olfactory, and auditory hallucinations. She began to see unknown people chasing and attempting to kill her; she witnessed an unbelievable car crash scene filled with blood and odors of blood; and she began to hear negative and malicious voices from her deceased brother. Collateral information from the patient's family revealed that she had been responding to unseen stimuli, claiming telepathic abilities and a persecutory thought pattern. Her mother denied her past medical and psychiatric history.

The patient was initially admitted to the general medicine service, whereupon a psychiatrist was consulted for further evaluation and management. At the time of her initial interview, her body temperature was 37.5 °C, her heart rate was 110 beats per minute, oxygen saturation was 97%, and her blood pressure was 126/83 mmHg. She was agitated, distressed and hallucinating. She was unattended but had good eye contact. Her speech was observed to be accelerating, irrelevant, and incoherent. She had a labile mood and an inappropriate affect. She exhibited a tangential thought process and persecutory delusions. At the time of her

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**Fig. 1.** Brain MRI: (A-B) T1 imaging shows mild volume loss with asymmetrical lateral ventricle. (C) T1 with gadolinium imaging shows no significant enhancement. (D) T2/FLAIR imaging shows non-specific hypersignal intensity foci in the white matter of the right frontal lobe.

initial assessment, she denied any suicidality or homicidality. Orientation was intact during bedside testing. However, she was lethargy in which more effort has to be put into examination. Other neurological examinations were normal.

Laboratory investigations included SARS-Cov-2 RNA on admission from a nasopharyngeal swab was negative. Blood test showed mild leukocytosis (white cell count  $10.1 \times 10^9/L$  62% neutrophils), mild elevated D-dimer (769 mg/mL fibrinogen equivalent units) but otherwise normal electrolyte, renal function, liver function, urine analysis, and C-reactive protein. Drug and toxin screening were all negative. Interleukin levels were not measured. She underwent magnetic resonance imaging (MRI) of the brain showing non-specific small T2/FLAIR hyperintense foci in the white matter of bilateral frontal lobes with mild brain volume loss on the left (Fig. 1). A lumbar puncture revealed a clear cerebrospinal fluid. Cell count shows 1 mononuclear cell. Protein was 24 mg/dL and glucose was 70 mg/d. Bacterial cultures, meningoencephalitis panel, cell based assay autoimmune panels (including N-methyl-D-aspartate (NMDA) receptor antibody), unclassified neuronal antibody and oligoclonal bands were all negative. SARS-CoV-2 RT-PCR was not performed on the cerebrospinal fluid due to laboratory limitations.

Electroencephalography showed focal cerebral dysfunction with abnormal awake EEG. The EEG shows an abnormally awake pattern with an intermix of alpha-theta-delta background. Continuous lateralized rhythmic delta activity (LRDA) was noted in the occipital area, more prominent on the right (Fig. 2).

The patient was given 10 mg of dexamethasone intravenously every 6 h for 3 days, then changed to 1 g of methylprednisolone for 5 days due to the ongoing hallucinations. Olanzapine (titrated to a total daily dose of 10 mg) was used because of the uncontrolled psychosis and agitation. After 10 days of treatment, she was notably more organized, and denied perceptual disturbances. She was discharged with olanzapine 5 mg twice daily.

Upon 2 weeks' telephone interview, she was coping well at home with no lingering psychosis. Upon follow-up one month later, the patient's psychosis resolved. The antipsychotic medication was tapered off

without a return of her hallucinations. A repeated EEG showed resolution of the LRDA.

## Discussion

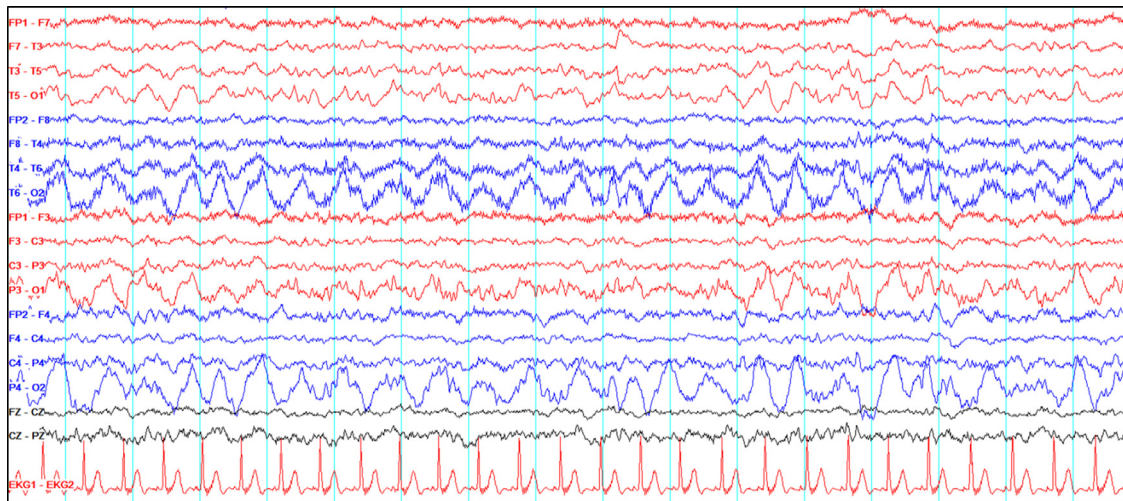
Regarding our case, given a new presentation and short history of psychotic symptoms after COVID-19 infection with no other plausible psychiatric or medical explanations, the diagnosis was first believed to be "brief psychotic disorder" according to the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (*American Psychiatric Association, 2013*). However, autoimmune encephalitis along with autoimmune psychosis must also be considered in the differential diagnosis. Our patient's abrupt onset of psychotic manifestations with the presence of disproportionate cognitive dysfunction, and decreased level of consciousness qualified her for possible autoimmune psychosis (*Pollak et al., 2020*). On the other hand, possible autoimmune encephalitis should also be considered but further investigation is needed (*Graus et al., 2016*). Therefore, serum and CSF antibodies should be tested for neuronal surface antibodies, paraneoplastic, unclassified neuronal antibodies, and oligoclonal bands. All the results turned negative. Hence, MRI and EEG are critical for further evaluation.

MRI is both essential to look for signs of inflammation and to fulfill the criteria for the diagnosis of autoimmune encephalitis and autoimmune psychosis. Even though bilateral medial temporal lobes are areas of great significance in giving a diagnosis of autoimmune encephalitis/psychosis (*Troyer et al., 2020; Graus et al., 2016*), it is possible to show non-specific changes, or even no changes at all. (*Antony and Haneef, 2020*). Apart from the usual findings on MRI, reversible cerebral atrophy has also been reported (*Iizuka et al., 2010; 2016*). Studies have postulated that it is due to the immune process involving areas that are densely populated with the affected receptors.

EEG is essential to identify the presence of temporal neocortical or limbic epileptiform discharges, as well as slow wave activity associated with psychosis (*Pollak et al., 2020*). To date, there has been no pathological EEG finding proposed in autoimmune neuropsychiatric disorders related to COVID-19 infection (*Antony and Haneef, 2020; Kubota et al., 2021*). However, none of the cases have reported lateralized rhythmic discharge presented in the occipital area. Our case presented herein remarks the first case of focal cerebral dysfunction with frequent LRDA activities at occipital area and an abnormal awake EEG pattern characterized by poorly sustained posterior alpha rhythm in non-sedated – fully conscious patient. LRDA is a unilateral repetitive waveform that occurs at a rate of up to 3 Hz. Regarding previous reports, LRDA has highly localizing values and points to focal cerebral dysfunctions. The causes include stroke, tumors, traumatic brain injuries, and infection (*Gaspard et al., 2013*). Since the emergence of autoimmunity, accumulative data has found that LRDA could be one of the findings of autoimmune encephalitis (*Moise et al., 2021*). Therefore, interpreting that our case could be related to autoimmune process.

Autoimmune psychosis was established in order to identify mild and atypical forms of autoimmune encephalitis. However, disagreement has been made due to the uncertain term of the diagnosis. One group suggest that the study used to established the criteria was a small cohort based study. Therefore, might not differentiate autoimmune psychosis from autoimmune encephalitis. But still, condition once known as a *formes frustes* autoimmune encephalopathy like autoimmune dementia and autoimmune epilepsy have been proven to response to treatment (*McKeon et al., 2020*). Another group suggest that the criteria might not be necessary if we understand the existing criteria and red flags. In other words, establishing a new criteria based on symptom is unnecessary (*Martinez-Martinez P and Titulaer., 2020*). In our opinion, we believed that the criteria described by Pollak et al. might be useful in the consideration of an autoimmune continuum. However, cautious should be considered for the ambiguity of this entity as stated above.

To make the diagnosis clearer. A set of diagnosis criteria proposed by Cellucci et al. was established for pediatric patients



**Fig. 2.** EEG shows an abnormal awake pattern with intermix of alpha-theta-delta background. Continuous lateralized rhythmic delta activity (LRDA) was noted in the occipital area more prominent from the right.

(Cellucci et al., 2020). These criteria composed of five main categorical features – acute onset, neurological dysfunction, paraclinical evidences, serology and exclusion of other etiologies. Thereafter, the diagnosis certainty is categorized into possible, probable and definite. For our case, the diagnosis certainty was possible pediatric encephalitis. The pros of using this criterion is that it is established for pediatric patients and has less ambiguity.

Considering our treatment strategy, it is hard to conclude that the patient respond to immunotherapy or antipsychotic. We believed that treatment is based on the clinical manifestations and paraclinical findings. Therefore, our main treatment was on the immunotherapy, while antipsychotic was given at a low dose for symptom control.

## Conclusion

Regarding autoimmune encephalitis, our case satisfies the criteria for possible autoimmune pediatric encephalitis. We emphasized the importance of multimodal investigation, including autoimmune profiles, lumbar puncture, MRI, and EEG, in order to make the correct diagnosis. In addition, the correct diagnosis could lead to reasonable treatment and better outcome of the patient.

## Declarations

### Consent for publication

The patient provided written informed consent for publication of this case report and any accompanying images.

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### Author contribution

WW and WR: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis and interpretation of data

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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