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Case Report
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Paediatric anti-GABA$_B$ receptor encephalitis associated with SARS-CoV-2 (COVID-19) infection

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ABSTRACT

Though we are approaching the end of second wave of COVID pandemic, we are still unrevealing the various presentation this viral infection can result in. There are few cases reported to have anti NMDA autoimmune encephalitis associated with COVID-19 infection or MIS-C. Here we are reporting one of its variants that was anti-GABA$_B$ receptor encephalitis associated with COVID-19 infection. We are reporting a 9 years old female child who was a known case of seizure disorder and on regular medications presented on 4th day of RT-PCR positive status for COVID-19 with complains of convulsions which was managed with antiepileptics. On day 6 of hospitalization she had autonomic instability in the form of tachyarrhythmia, repitation of speech, sudden outburst of laughter and on day 7 child landed in status epilepticus. Autoimmune encephalitis suspected secondary to COVID-19 infection and the child was started on IVIG but not much of improvement seen with this. CSF analysis showed weakly positive anti GABA$_B$ antibodies and child had persistently elevated inflammatory markers hence started on high dose corticosteroid. MIS-C ruled out. Child showed drastic improvement both clinical and biochemical after high dose corticosteroids. Prompt treatment with IVIG/corticosteroids have shown a drastic improvement in our child just like in any other autoimmune encephalitis. Though further detailed study is required to prove its exact mechanism in COVID-19 infection, it should be thought of when appropriate and prompt early initiation of therapy will help us reduce morbidity and mortality associated with it.

Keywords: Autoimmune encephalitis, Anti GABA$_B$ antibodies, IVIG, High dose corticosteroids

INTRODUCTION

With the outbreak of novel coronavirus (COVID-19), we have seen various clinical presentation in children affected with COVID-19, especially in the second wave during 2020-2021. Majority of the children affected during second wave were asymptomatic or mildly symptomatic. The viral infection showed respiratory and non-respiratory manifestations across all age groups. The non-respiratory manifestations included several neurological manifestation, the most common manifestations in children being headache, cerebellar signs, muscle weakness, autoimmune encephalitis whereas the adult population infected with SARS-CoV-2 showed neurological symptoms consistent with autoimmune epilepsy, CNS demyelination, Guillian Barre syndrome and acute necrotizing encephalopathy. Just like HSV encephalitis triggering autoimmune encephalitis noticed in children, SARS-CoV-2 was also thought to trigger autoimmune encephalitis in children infected with this virus. There were few cases of NMDA autoimmune encephalitis reported in the peri infectious period of SARS-CoV-2 in which few were tested positive for SARS-CoV-2 by PCR while few were diagnosed with MIS-C.[1,2]

Initially it was hypothesized that these neurological manifestations were due to virus binding the surface spike protein of human angiotensin converting enzyme 2 receptor (ACE 2) but this could not explain most of the

neurological symptoms which were seen. This can also be explained by the molecular mimicry between the viral epitope and the neuronal cell surface proteins, synaptic receptors involved in synaptic transmission, neuronal excitability. Majority of these autoimmune encephalitis associated with SARS-CoV-2 were diagnosed to be anti NMDA encephalitis, which showed good response to immunotherapy. Here we are reporting a rare autoimmune encephalitis secondary to SARS-CoV-2 infection anti $GABA_B$ encephalitis.

CASE REPORT

9 year old female child, who was a known case of seizure disorder, who had her first episode of convulsion at 1 and half year of age, suggestive of generalized tonic clonic convulsion which was associated with fever and was on tablet clobazam intermittent prophylaxis till the age of 5 year as she would have similar episodes associated with fever. At the age of 6, she developed right focal convulsion, associated with fever, EEG suggestive of left temporoparietal epileptiform discharges; MRI done during that time being normal, was started on sodium valproate. The child had breakthrough seizures every 5-6 months since the age of 6 years and the drug dosages adjusted. Every breakthrough seizure was consistently associated with the EEG report similar to the first one. Since last 2 months, child was started on tablet lacosamide as additional antiepileptic and the child had a good compliance with antiepileptic therapy. Child was found to be developmentally appropriate for age, with no significant birth or family history.

Table 1: Laboratory investigations showing inflammatory markers.

Parameters	Values
CRP (in mg/dl)	80
ESR (in mm)	128 in first hour
LDH (in mg/dl)	1299
D-dimer (in ng/dl)	1660.9

This child presented to us on day 4 after being tested positive for SARS-CoV-2 by PCR with complaints of fever, 1 episode of convulsions, described as right focal convulsion, altered sensorium since 1 day. The child was already started on low molecular weight heparin, tablet dabigatran elsewhere as the child had high D-dimer values. On admission child had normal temperature (98.7 ^{o}F), vitals stable, GCS-11/15 ($E_3V_3M_5$), increased tone in right upper and lower limbs with extensor plantar response on left side and treated as acute encephalitis syndrome. Relevant blood investigations done and child had elevated inflammatory markers as in Table 1.

Thus low molecular weight heparin continued. Child had right focal convulsions on day 2 of hospitalization, IV anticonvulsants given for appropriate control of convulsions. CT head was done and was found normal. Repeat RT-PCR was negative. On day 6 of admission child noticed to have autonomic instability in the form of tachyarrhythmia, repetition of speech, sudden outburst of laughter and on day 7 of hospitalization child landed in status epilepticus when the child was managed accordingly and was supported with mechanical ventilation and midazolam infusion. Repeat EEG showed diffuse slowing of background activity with delta brush pattern- encephalopathy pattern.

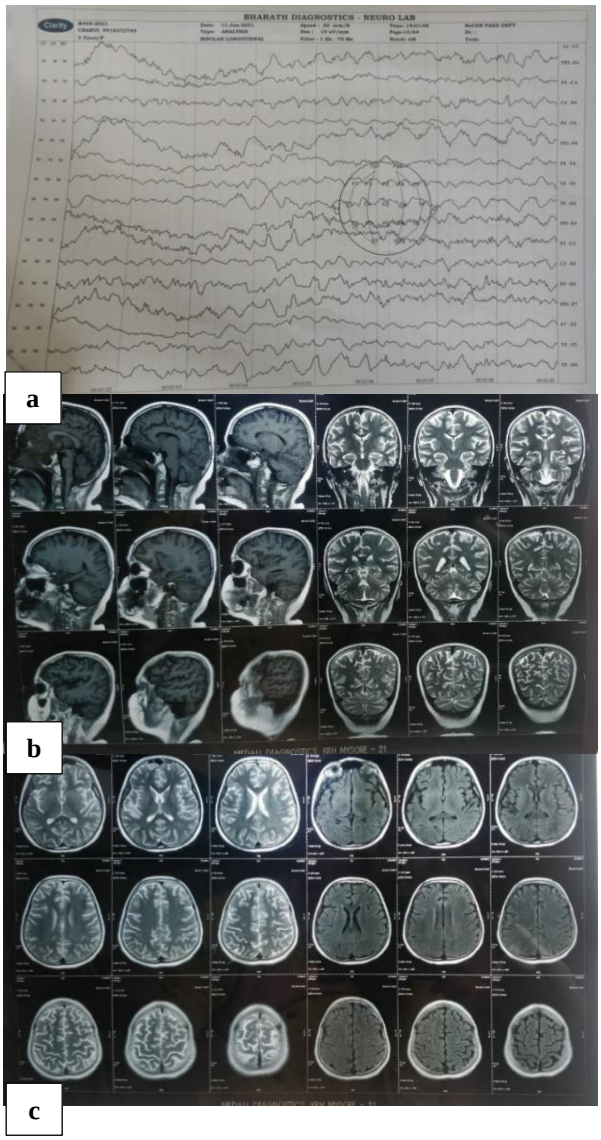

Figure 1: Neuroimaging of our child; (a) bedside EEG: delta brush pattern; (b and c) MRI brain of the child: showing normal brain parenchyma.

MIS-C was ruled out. COVID antibodies were negative. Child continued to have further right focal convulsions inspite of multiple anticonvulsants at their maximum doses, SARS-CoV-2 induced autoimmune encephalitis was suspected as child had autonomic instability, status epilepticus and CSF and serum samples sent for autoimmune antibody testing along with viral serology

for HSV 1 and 2, Japanese encephalitis. CSF analysis was normal (Table 2).

While the reports were awaited the child was started on IVIG 0.4 g/kg for 5 days. The child was noted to have persistent fever spikes, increased inflammatory markers, found to have nosocomial urinary tract infection and was appropriately managed. CSF analysis (autoimmune panel) results showed weakly positive anti-$GABA_B$ antibodies; CSF and serum samples for HSV1 and 2, JE were negative, CSF SARS-CoV-2 not obtained and thus child started on IV methylprednisolone 30 mg/kg for 5 days and the child improved dramatically and we could withdraw ventilator support, IV anticonvulsants tapered and shifted to oral medications. MRI brain found to be normal. Inflammatory markers were monitored and showed a declining trend. USG abdomen and pelvis done to look for any teratomas, found to be normal. Following IV methylprednisolone, child started on oral prednisolone and was monitored for any further complications. With immunotherapy the child improved dramatically and was discharged and is doing well.

Table 2: CSF analysis.

CSF parameters	Values
Cell count	2 cells
Sugar (in mg/dl)	63
Protein (in mg/dl)	21
Chloride (in mmol/l)	727

DISCUSSION

Autoimmune encephalitis incidence has seen an increase in its incidence because of increased availability of investigation and prompt early diagnosis. Autoimmune process can be triggered by infection, vaccine or occult neoplasm.[3] Neurotrophic behavior of SARS-CoV-2 has been observed more frequently especially in the second wave. Anti-NMDA autoimmune encephalitis remained the commonly seen autoimmune encephalitis among few COVID positive children as well. The exact prevalence of individual type of autoimmune encephalitis was unknown.[3] The multiple mechanisms by which neurological manifestations occur are depicted in Figure 1.[4]

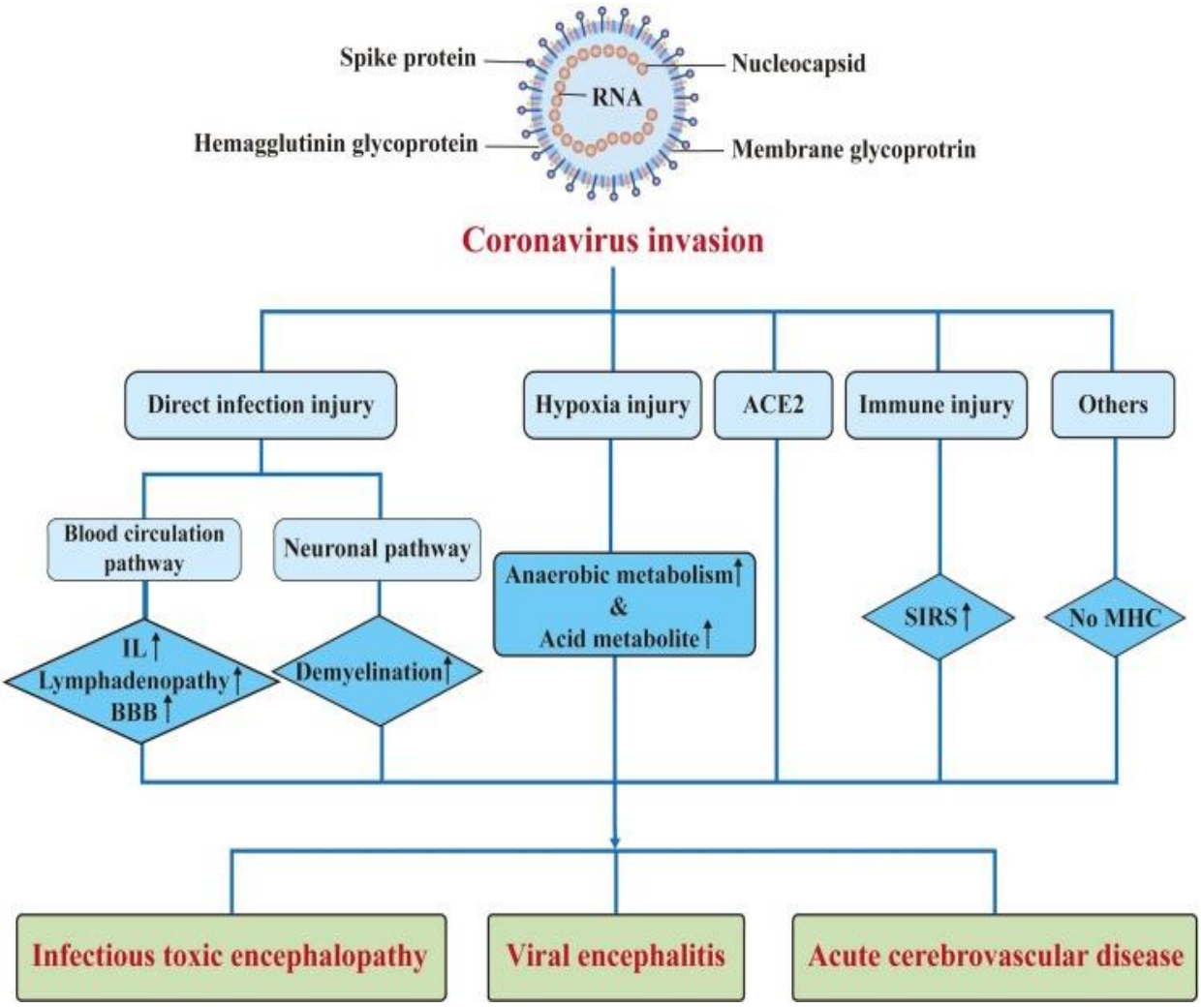

Figure 3: Multiple mechanisms of neuronal injury by COVID-19 infection.[4]

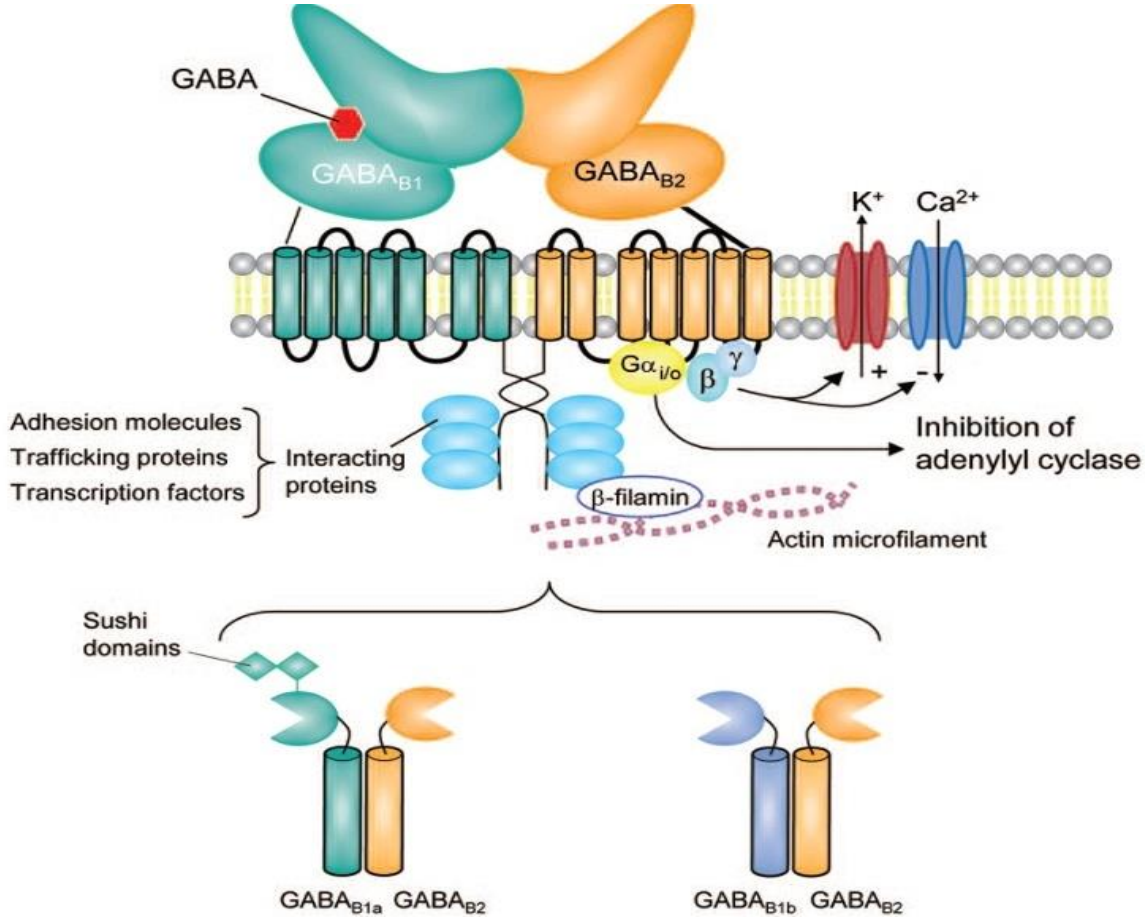

Figure 4: Structure of $GABA_B$ receptor.[5]

$GABA_B$ receptors are G protein coupled receptors that are linked via these G proteins to potassium channels. $GABA_B$ receptors modulate synaptic excitability and plasticity in the cerebral cortex, generating rhythmic activity in cortical and thalamic circuits, affecting the activity of dopaminergic and other monoaminergic neurons. These receptors were recently identified to be involved in limbic encephalitis and were previously known to be associated with neurological and psychiatric disorder like absence seizures.[5]

Unlike NMDA receptor antibodies, $GABA_B$ antibodies altered the synaptic function.[6]

There are evidences that etiological agents like HSV, HHV-6 and Japanese encephalitis trigger autoimmune encephalitis, especially anti-NMDA autoimmune encephalitis.[7,8] We hypothesise that similar trigger was shown by COVID-19 virus and thus our child was thought to have autoimmune encephalitis. Initially it was hypothesized the at these neurological manifestations seen in COVID-19 were due to virus binding the surface spike protein of ACE 2 receptor. Another mechanism could be the release of brain specific neoantigens caused by viral toxicity that trigger the production of pathogenic antibodies.[3]

These children usually presented with impairment in recent memory, mental and behavioral disorders (stereotypical behaviors, irritability, hyperactivity, hyper sexuality) and epileptic seizures. Neurocognitive assessment may identify deficits in memory, attention, problem solving, language, processing speed.[9] Though psychosis was rare in children, few psychiatric disturbances like mood swings can be seen.

Diagnosis is based on clinical features suggestive of autoimmune encephalitis, ruling out other causes of encephalitis, demonstration of autoantibodies in CSF, neuroimaging. CSF analysis can show lymphocytic pleocytosis. Though EEG and radiological changes are not commonly seen in pediatric age group, MRI FLAIR and T2 signal abnormalities can be seen in a few cases.

As the etiology is immunologic, the mainstay of treatment includes remained steroids, IV immunoglobulin and plasma exchange. if any child does not respond to these agents, second line agents like rituximab/cyclophosphamide can be considered. Third

line agents were include bortezomib, tocilizumab which are rarely used in pediatric age group. Corticosteroids have a good penetrance across blood brain barrier and are usually given at a high dose methylprednisolone 30 mg/kg/day for 3-5 days, followed by oral steroids (prednisolone 1-2 mg/kg/day) which can then be tapered over 6-12 months depending on the individual case. Other alternative being IVIG 2g/kg given over 5 days. These therapies were to be followed by maintenance therapy with either oral steroids, monthly pulse steroid or monthly pulse IVIG. The duration of maintenance therapy is individualized.[3]

The early diagnosis and early prompt immunotherapy has shown a good outcome than those not receiving immunotherapy. The NMDA autoimmune encephalitis reported to be associated with COVID-19 has shown good improvement with immunotherapy. Even our child with anti $GABA_B$ autoimmune encephalitis associated with COVID-19 has shown improvement with IVIG and pulse steroid therapy.

CONCLUSION

Just like any other viral infection triggering autoimmune process, COVID-19 can be a trigger for any autoimmune encephalitis. High suspicion with subtle signs and symptoms of autoimmune encephalitis, early diagnosis and prompt treatment with corticosteroids/IVIG will help reduce the morbidity and mortality associated with it.

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