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POST COVID ANTI-NMDAR ENCEPHALITIS IN AN ADOLESCENT GIRL

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ABSTRACT

Anti-N-Methyl D-aspartate receptor (NMDAR) encephalitis is a neuro-inflammatory disorder caused by antibodies targeting neurons in the central nervous system. Certain viruses break immune tolerance of neuronal proteins and increase the permeability of blood brain barrier (BBB) to antibodies resulting in post infectious autoimmunity. We report a case about a 13 years old girl diagnosed as a case of anti-NMDAR encephalitis, who presented with psychiatric symptoms followed by abnormal movements and encephalopathy, with later development of autonomic instability with tachycardia and blood pressure at 98th centile. Her thyroid profile initially showed hyperthyroidism with negative anti-thyroid antibodies with subsequent normalization without anti-thyroid drug. Her SARS-CoV-2 antibody was positive despite being asymptomatic that had induced autoimmunity in central nervous system and caused transient thyroiditis. She poorly responded to first tier immune therapy (methylprednisolone pulse & plasmapheresis) but there was remarkable response to second tier immune therapy with Rituximab, with prompt attainment of ambulation and self care.

KEY WORDS: Anti-NMDAR encephalitis, Abnormal movements, Encephalopathy, SARS-CoV-2 Ig.

INTRODUCTION:

Anti-N-Methyl D-aspartate receptor (NMDAR) encephalitis is not rare. First described in 2007, it is the most frequent autoimmine encephalitis (AE) after Acute Disseminated Encephalomyelitis (ADEM).[1] It frequently affects young adults, with a strong female preponderance (4:1).[2] Non-paraneoplastic AE is triggered by infection or environmental factors resulting in autoantibodies production against cell surface neuronal antigens. Certain viruses break the immune tolerance of neuronal proteins and increase permeability of blood brain barrier to antibodies. There has been several neurological presentations reported with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, both infectious and post-infectious. Asymptomatic and mildly symptomatic children with SARS-CoV-2 infection may not be identified during the acute illness but later may present with para-infectious autoimmune phenomenon.[2] We present a case with anti-NMDAR encephalitis as a para-infectious complication of SARS-CoV-2 confirmed by SARS-CoV-2antibody.

CASE REPORT:

13 years old girl, 2nd in order of 5 siblings, product of non-consanguineous marriage, presented with behavioral issues for 1 week in terms of intermittent aggression and irritability with disturbed sleep wake cycle. Later she developed irrelevant talk and memory loss. In the 2nd week of illness, she had three episodes of generalized tonic clonic seizures with worsened conscious level. There was no preceding history of any fever, flu like or gastrointestinal symptoms. She was not vaccinated for COVID. Examination showed an encephalopathic girl with sustained muscle contraction causing abnormal dystonic posture, oro-facial dyskinesia and dystonia of ocular muscles with generalized upper motor neuron signs. Fundus examination was normal. She was tachycardiac and blood pressure was at 98th centile. There was no rash, joint swelling, alopecia or significant systemic finding. Family history revealed mother being hypothyroid.

She was thoroughly investigated with cerebrospinal fluid (CSF) examination showing less than 3 cells, normal protein and glucose. Her ceruloplasmin and urinary copper levels were normal and Kaiser-Fleischer (KF) rings were absent on slit lamp examination. Considering family history, high blood pressure and tachycardia, thyroid profile was reviewed and it was consistent with hyperthyroidism, which later became normal without any anti-thyroid drug. Thyroid antibodies (anti-thyroid peroxidase antibody and thyrotropin receptor antibody) were negative excluding the possibility of Hashimoto's encephalopathy. Repeat CSF for anti NMDAR antibody came out to be positive.

Extensive imaging including MRI brain was normal and MRI of abdomen and pelvis also excluded the possibility of any neoplasm. EEG showed slow background with delta brush pattern (Figure 1). Since there was multi-system involvement including encephalitis, thyroiditis and transaminitis, possible viral trigger was thought of. Viral serologies were sent and only SARS-CoV-2 antibody came positive, though there was no history of SARS-CoV-2 infection in past neither any contact. This ascertained the para-infectious etiology for the triggered immune response. The investigations are shown in Table 1.

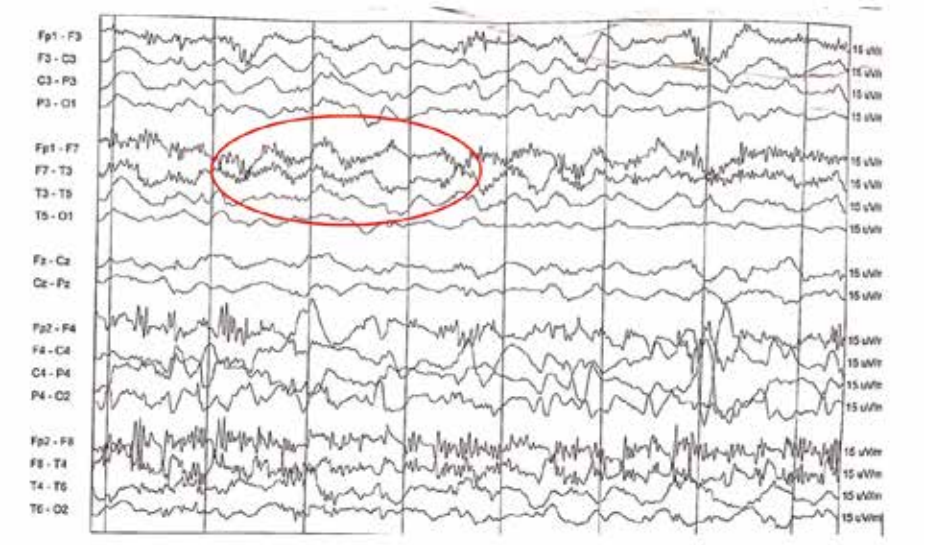

Figure 1: EEG with delta brush pattern

Table 1: Important investigations

INVESTIGATION	RESULTS		
Cerebrospinal fluid examination	1ST CSF: WBC- 3 Lymphos-90% Polys-10% RBC- 4 Sugar- 69 mg/dL (50-80mg/dL) Protein- 27.6 mg/dL (15-45mg/dL)	2ND CSF: WBC <5 Lymphocytes-100% Protein-20 mg/dl Sugar-102 mg/dl Anti-NMDAR positive ++	
Thyroid profile: T3 T4 TSH Anti-thyroid Peroxidase antibody Thyrotropin receptor antibody	 2.0 (0.69-2.15 ng/ml) 140 (52-127 ng/ml) 0.2 (0.3-4.50 ng/ml) < 10 IU/ml (Normal) <0.800 IU/L (Normal)	 1.09 (1.26-3.28 nmol/L) 17 (5.6-11.7 ug/dl) 0.6 (0.7-6.4 uIU/ml)	 1.26ng/ml (N) 6.56ug/dl (N) 1.03 uIU/ml (N)
S.Bilirubin Alanine transaminase Ceruloplasmin	0.8mg/dl 259 U/L 30 (14-40mg/dl)		
Anti-nuclear antibody	Negative		
Complement levels C3 C4	 101.2 mg/dl (90-180) 16.5 mg/dl (10-40)		

Immune-therapy was given with intravenous methylprednisolone (IVMP) pulses (30mg/kg/day) over 5 days with strict control of blood pressure and seizures alongside neuroprotective measures. After 2 days of IVMP completion, there was no clinical response, so therapy was quickly escalated to plasmapheresis; 5 cycles in 10 days, but she showed no significant benefit with 1st line therapy. She had persistent dystonia, dyskinesia and encephalopathy; though autonomic instability was well controlled with medications. 2nd line immune-therapy with rituximab was given; 375mg/m2: 4 doses: 1 week apart. After the second dose of rituximab, child significantly showed improvement in her conscious level from Glascow Coma Scale of 8/15 pre- rituximab to 12/15 post-rituximab and abnormal movements also settled, though she was still not ambulatory. After 4th dose, she became ambulatory with support and was able to self-feed. She was discharged on oral steroids, anti seizure medication including levetiracetam at 30mg/kg/day, muscle relaxants and vitamin supplementation as she was on gavage feeding for a prolong period, she was given multivitamins in order to suffice the vitamin need until she was on regular meals. On follow up at 8 weeks, she was ambulatory unsupported, with no abnormal movements and good control of seizures. At 16 weeks follow up, she was ambulatory in all settings, able to self care, feed and perform daily activities with ease. However residual deficit in executive function was still present. The clinical course with respect to treatment is graphically depicted in figure 2.

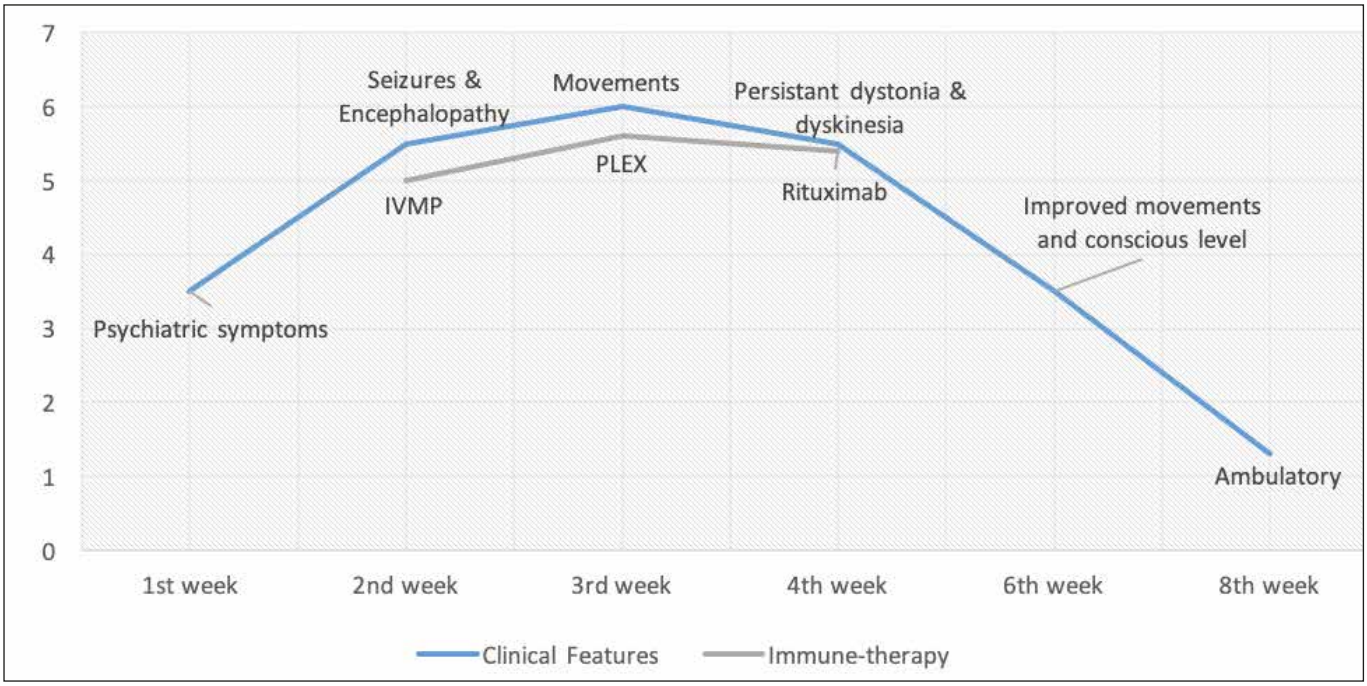

Figure 2: Clinical features and response to treatment.

DISCUSSION

Autoimmune encephalitis is an increasingly recognized neuro-inflammatory disorder in children and adolescents with anti-NMDAR encephalitis being the most common type.[3] It usually is associated with autoantibodies against the cell surface or intracellular neuronal antigens. Possible triggers are viral infection, environmental factors or teratomas. Previously there have been numerous studies on post-herpes NMDAR encephalitis.[4]After novel coronavirus pandemic that arose from Wuhan, China in December 2019 and the subsequent discovery of multisystem inflammatory syndrome in children (MIS-C) in April 2020, numerous cases of infectious and para-infectious immune-mediated disorders have been reported, triggered by SARS-CoV-2 infection.[5] Possible pathogenesis accounts for dysregulated inflammatory reaction and production of antibodies that break the immune tolerance of neuronal proteins and increase permeability of BBB to these antibodies.[6] The most commonly reported neurological disorders across all age groups are cerebrovascular accidents, splenial lesions, Guillain-barre syndrome (GBS), benign intracranial hypertension, meningo-encephalitis and ADEM.[7]

Morales S et al studied 10 pediatric patients with neurological symptoms having confirmed SARS-CoV-2

infection and found 3 patients with GBS, 2 patients with optic neuritis, 2 acute ischemic stroke, 1 myositis, and only 1 patient to be anti-NMDAR positive signifying that high index of suspicion is needed in cases where movements complicate encephalopathy.[8] Another study done on 27 patients of pediatric multisystem inflammatory syndrome, four patients had neurological manifestations with encephalopathy, headache, brainstem and cerebellar signs, muscle weakness, and reduced reflexes but none had NMDAR antibody positive highlighting the rarity of autoimmune encephalitis associated with SARS-CoV-2 infection.[9]

Age at which children presented in previous case reports had been variable from as young as 23 months reported by Burr et al[10] to adolescent male 17 years (Moideen et al)[11] and female 18 years (Allahyari F et al).[12]Children with autoimmune encephalitis presents with polysymptoms including behavioral issues, psychiatric symptoms, disturbed sleep wake cycle, mutism, seizures, abnormal movements and neurocognitive deficits like our index case.[3] Considering the polysymptoms, the diagnosis of autoimmune encephalitis was considered in this case and investigation for possible triggers were carried out which only revealed SARS-CoV-2 antibody.Our patient also had other systems involvements that has not been reported previously in which she initially had high thyroid hormones with negative thyroid antibodies which subsequently became normal, highlighting the possibility of immune mediated cytokine storm affecting various other systems. Our patient did not respond to 1st line immune therapy and was escalated to 2nd line with rituximab which showed promising results without significant side effects. There has been studies on anti-NMDAR encephalitis being refractory to 1st line treatment but responded well to 2nd line immune therapy with minimal side effects like in our case.[13]

The neurological presentation of SARS-CoV2 in the pediatric age group is still surfacing. We need to brace ourselves up with newer presentations as we are still in the middle of this pandemic situation which seems to linger on for some time. We believe this case report will further broaden the horizon of immune mediated neurological disorder associated with post-SARS-CoV2 infection.

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Author's contribution:
Javeria Raza Alvi; data collection, data analysis, manuscript writing, manuscript review
Muhammad Haider Sultan; data collection, data analysis, manuscript writing, manuscript review
Tipu Sultan; data collection, data analysis, manuscript writing, manuscript review