

Ataxia and Seizure as a Manifestation in a Pediatric Case of SARS-CoV-2

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Authors' contributions

This work was carried out in collaboration among all authors. Author Farzad Ahmadabadi designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AA and NN managed the analyses of the study. Author Faramarz Ajri managed the literature searches. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Background: SARS-CoV-2 infection is an ongoing pandemic with more than seven million cases worldwide and a wide range of presenting symptoms in various ages. Neurological symptoms as mildly as a light headache and as severe as an acute encephalitis are reported.

Objective: We aim to report the clinical course of pediatric patient infected with SARS-CoV-2 whom also presented ataxia and seizures as her neurological manifestation.

Case: Patient was a 16 month old baby girl with clinical presentations of ataxia, focal myoclonic seizures, fever and diarrhea and no significant medical history. Her seizures were controlled with sodium valproate along with carnitine. She developed respiratory symptoms after her RT-PCR test from her nasopharyngeal sample swap returned with positive results. We ruled out a wide range of

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disease such as paraneoplastic and metabolic disorders. Patient was discharged with full recovery after receiving IVIG.

Discussion: We believe there is a post infectious mechanism involved that has lead the patient to have such neurological manifestations because of a significant response to IVIG while she also presented typical finds in children infected with SARS-CoV-2. Patients with SARS-CoV-2 infection can have neurological manifestations despite their negative RT-PCR test for SARS-CoV-2 in their cerebrospinal fluid.

Conclusion: During the pandemic, every practitioner should have SARS-CoV-2 infection in mind when it comes to neurological manifestations without a strongly-associated explanation.

Keywords: SARS-CoV-2; pediatrics; seizure; ataxia; case report.

1. INTRODUCTION

Beginning at the end of 2019 and identified in patients with pneumonia of unknown origin at Wuhan, China, novel coronavirus (CoV) [1] started its journey to endanger all human beings. World Health Organization issued a standard format of Coronavirus Disease-2019 (COVID-19) On February 11,2020 and the novel coronavirus causing it was named Severe Acute Respiratory Syndrome Coronavirus 2(SARS-COV-2) at the same day [1]. As of July 2nd, 2020, 10 533 779 cases and 176 102 deaths by SARS-CoV-2 were reported worldwide [2].

Similar to previously known SARS-COV, SARS-COV-2 also enters the cell via angiotensin-converting enzyme 2 (ACE2) that is expressed in lung, kidney, heart, intestine [1] cerebral cortex, gallbladder, testis and adrenal gland [3] and cells such as neurons and glial cells which can act as targets for SARS-COV-2 [4].

Most common symptoms findings are fever and cough [4-6] and findings show a favorable clinical course in children and adolescents compared to adults [6].

Neurological manifestations are reported as frequent as in 36% of cases [4]. Some patients have experienced mild neurological symptoms such as headache, dizziness, hypotension, hyposmia and hypopsia while the others have had concurrent severe neurological manifestations such as acute Cerebrovascular Diseases (acute ischemic stroke, cerebral venous sinus thrombosis, cerebral hemorrhage, subarachnoid hemorrhage), meningitis / encephalitis, acute necrotizing hemorrhagic encephalopathy, acute disseminated encephalomyelitis and acute Guillain-Barré syndrome while being infected with SARS-CoV-2 [3,4] ataxia, seizure, muscle injury are also

reported [3,4] Interestingly, there could be a positive correlation between presence of neurological symptoms and severity of the SARS-CoV-2 infection [3,4].

With the main reason remaining yet to be established, SARS-CoV-2 could possibly effect the Central Nervous System(CNS) via direct(hematogenous and neuronal retrograde disseminations) and/or indirect(severe systemic manifestations such as hypoxia, viremia, cytokine storm, coagulopathy and immune-mediated routes) mechanisms [3,4].

The first case of meningitis/encephalitis associated with SARS-CoV-2 was reported by Takeshi et al. and provided direct evidence for this virus to be neuroinvasive [7].

2. CASE PRESENTATION

2.1 Patient Description

A 16 month old baby girl with no significant medical history presented with her parents complaining from her intermittent episodes of gait disturbance and involvement of her left lower extremity, inability of bearing her weigh and not being able to keep her neck straight with her head falling to her left side. It is worth mentioning that there was no medical history regarding a previously reported seizures and none of her first degree relatives had epilepsy.

She was an otherwise healthy child with normal gestational and birth histories.

Because of the existing relativity between her parents and a similar condition reported a year ago in her cousin ,inborn errors of metabolism were suspected and a metabolic screening and urine organic acid tests were requested.Her cousin is under treatment in our hospital with

similar symptoms (Intermittent Ataxia and refractory seizure) and based on investigations on her, we diagnosed autoimmune (Glutamic acid decarboxylase-GAD) antibody encephalitis (38.3 degrees Celsius) and diarrhea upon her admission.

3. RESULTS OF INVESTIGATIONS

An electroencephalogram record just before her admission showed random paroxysmal epileptic discharges in right Centro temporal region and made tracing mild abnormal (Fig. 1).

Due to the current coronavirus pandemic and a suspicious contact with an infected person, a possible SARS-CoV-2 infection was considered and *reverse transcription polymerase chain reaction* (RT-PCR) test from her nasopharyngeal swap was requested. Initial laboratory data showed slightly increased white blood cells count ($12.9 \times 10^9/L$) with a dominancy in lymphocyte count (66%) and thrombocytopenia ($110 \times 10^9/L$). Non-quantitative C-reactive protein levels were increased to 3 plus.

Paraneoplastic syndromes as Opsclonus myoclonus ataxic syndrome (OMAS) were also considered because she had more than 3 days of truncal ataxia and eye-rolling. Chest computed tomography (CT) and a sonography of the abdomen and genitourinary tract were requested. Both of them showed normal results. and normal levels of Vanillyl mandelic acid (VMA) proved it to be less likely.

A brain magnetic resonance imaging (MRI) was obtained which showed mild degrees of periventricular leukomalacia. An autoimmune and post infectious conditions as acute disseminated encephalomyelitis (ADEM) was also considered because lack of any insults when she was born such as asphyxia and also because she was a full-term baby. But her imaging were not strongly suggestive for ADEM, we did not consider it as a possible explanation for her condition (Fig. 2).

On second day at the hospital, her temperature rose higher and a lumbar puncture was performed. The resulted laboratory data showed a colorless, clear cerebrospinal fluid (CSF) with no white blood cells and normal levels of glucose and protein. The CSF pressure was normal. RT-PCR test for SARS-CoV-2 and herpes simplex virus-1 was also requested for the obtained CSF.

Ataxia was still present and patient couldn't sit without falling.

Her condition was improved relatively as we checked and ruled out the possible differential diagnosis and she was then discharged after four days of admission while we waited for her metabolic screening test results. We strongly suggested that she should be quarantined at home because her RT-PCR results were not ready at the time of her discharge. She was under close observation afterwards.

Her RT-PCR test results for SARS-CoV-2 and herpes simplex virus-1 were reported negative just before three days later, when she was hospitalized again due to a focal myoclonic seizure seen at her left extremities. However; laboratory assistant mentioned the results can be false-negative possibly because of technical failure in nasopharyngeal sampling. The quality of the swap used was also questionable because of the rapidly increasing outbreak and lack of enough supplements.

She was febrile again at the beginning of her hospitalization. A second lumbar puncture was performed and the resulted CSF analysis again showed a colorless, clear cerebrospinal fluid (CSF) with no white blood cells and normal levels of glucose and protein. The CSF pressure was again, normal. Another two RT-PCR tests for nasopharyngeal swap and CSF fluid for SARS-CoV-2 were requested.

Because of the existing relativity between her parents and a similar condition reported a year ago in her cousin, inborn errors of metabolism were suspected and a metabolic screening and urine organic acid tests were requested and all results were normal. The results are listed in Table 1.

3.1 Treatment Plan

Initially, levetiracetam syrup was prescribed for her, because we suspected that main reported complains could have possibly been pseudo ataxia but it wasn't effective.

Sodium valproate was prescribed for her due to the myoclonic nature of her seizure and because she was under 2 years of age, carnitine was also prescribed. We requested carnitine levels before we started this prescription so her normal reported levels cannot be due to this prescription.

She was under observation for the next six days when she had a repeated episode of seizure similar to the first one she had before at the beginning of her second admission. Her condition was stable for the next two days when she developed weakness in her left extremities. She also had a noticeable weakness in her neck and she couldn't sit or walk. Also considered as a possible differential diagnosis was the post infectious central nervous system involvement. A second brain MRI was obtained. It showed

patchy signal changes at T2 and FLAIR near the left sylvian fissure which could indicate a post ictal or ischemic process.

Because her ataxia wasn't resolved and we suspected a possible post infectious mechanism and due to the SARS-CoV-2 outbreak we could not have prescribed a high dose corticosteroid and intravenous immunoglobulin (IVIG) was used instead. Her condition was improved significantly within next two days.

Table 1. Metabolic screening and urine organic acid test results of the patient; all values are based on Germany Wegner laboratory that our samples had sent there

Metabolic screening	
Hemoglobin	Unremarkable
Tyrosine stimulating hormone	<5
17-OH-Progesterone	Normal
Galactose	Normal
Gal-1-P-Uridyltransferase	Normal
Succinylacetone	Normal
Biotinidase	Normal
Disorders of amino acids metabolism	
Amino acids	Unremarkable
Argininosuccinic acid	Normal
Leucine+ Isoleucine	Normal
Valine	Normal
Citrulline	Normal
Methionine	Normal
Phenylalanine	Normal
Tyrosine	Normal
Disorders of beta-oxidation of fatty acids	
MCADD, VL CADD, LCHADD	Unremarkable
Disorders of carnitine metabolism	
Free carnitines (TMS)	Within normal limit
Disorders of organic acids	
Isovalerylcarnitine	Unremarkable
Glutaric acid	Unremarkable
Defects of urea cycle	
Citrulline	Unremarkable
Argininosuccinate	Unremarkable
Acylcarnitine profile	
Showed normal pattern	
Urine organic acid test reports	
Showed normal pattern with no evidence for organic aciduria.	

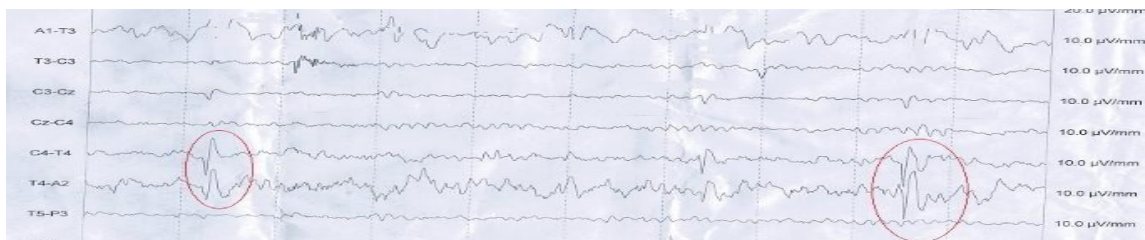


Fig. 1. Random spikes mostly in right temporal region

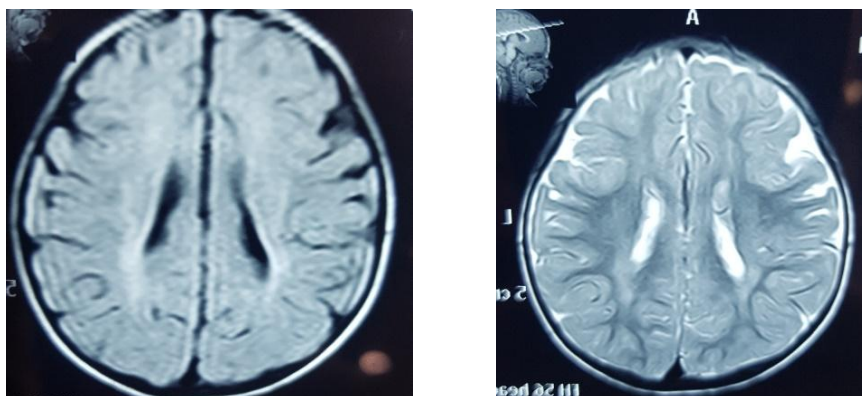


Fig. 2. FLAIR and T2W Sequences of our patients MRI showed hypersignal changes in occipital white matter

Table 2. Showed normal pattern with no evidence for a metabolic disease

Serum amino acid HPLC	Normal pattern
CSF lactate	9 mg/dl
Plasma lactate	16 mg/dl

Three days later, on her 12th admission day, she presented signs of abdominal distention and diarrhea. She developed respiratory distress after she aspirated while thriving from her mother's breast milk and her pulse oximetry showed an oxygen saturation level of 85%. She was then transferred to the pediatric intensive care unit for a day and was transferred back to the neurology ward with normal blood oxygen saturation levels. A prescription of topiramate was added to her treatment plan. Three days later, on her 16th admission day, positive and negative RT-PCR results for her nasopharyngeal swap and CSF analysis were reported, respectively. Treatment for the SARS-CoV-2 infection began with hydroxychloroquine added to her medications. Her chest X-ray was however, normal. She developed signs of respiratory distress with decreased blood oxygen saturation levels was transferred to PICU. She was carried to the infectious disease department after 3 days and Lopinavir was also started then. Eight days after the patient was discharged with resolved condition. After two month follow up she had not any symptoms as ataxia or seizure.

4. DISCUSSION

Data regarding the epidemiologic characteristics and clinical features of infected children SARS-CoV-2 are limited [6,8,9] and fever, coughing, sore throat, nasal congestion, rhinorrhea, diarrhea are mostly the reported symptoms in

children [6,8-10] SARS associated with coronaviruses seems to have a favorable disease course in children, without a clear reason. However; suggested mechanisms included vaccination associated unspecific enhancement of immunological activity, difference between tissue distribution of ACE2 (angiotensin-converting enzyme 2) with adults, inability to start a cytokine storm due to still developing immune system and last but not least, due to a possible underestimation and unrecognition [11]. Our patient showed lesser respiratory symptoms which we believe can be due to some these mentioned causes. We didn't have a full compatibility with certain criteria to justify our patient's symptoms as an encephalitis associated with SARS-CoV-2 [3]. We've previously reported cases of ANEC due to a possible viral infection, [12] which was one of the reason we also considered a post-infectious mechanism as a possible explanation for the child's neurological manifestations. Altered consciousness seems more consistent with encephalopathy, [3,13] and even though the patient didn't have such presentation at her disease course, with no behavioral changes, she presented seizures. Ataxia and seizures can lead us to believe there was an autoimmune process. We believe her condition was mostly resolved after a prescription of IVIG, which can strongly correlate with a possible post infectious CNS involvement in our patient. We don't whether there is a cause and effect relation between our patient's neurological manifestations and her SARS-CoV-2 infection or it's simply a co-existence however; due to favorable response to IVIG and ruling out other possible causes, we think it's best to consider SARS-CoV-2 infection as the causative agent.

5. CONCLUSION

Due to the ongoing COVID-19 pandemic, wide range of reported symptoms and correlation between previously reported viral infections (Influenza, SARS-CoV, etc.) and nervous system involvement, it's best to consider SARS-CoV-2 infection in the differential diagnosis of children with acute neurological manifestations without a clear explanation for their disease.

CONSENT

As per international standard, parental written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist

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