Published Ahead of Print on January 4, 2021 as 10.1212/WNL.0000000000011476

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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000011476

Pediatric Parainfectious Encephalitis Associated With COVID-19

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Number of characters in title: 62
Abstract Word count:
Word count of main text: 1012
References: 7
Figures: 1
Tables: 1

Search Terms: [360] COVID-19, [145] Post-infectious, [227] All Pediatric

Study Funding:
The authors report no targeted funding

Disclosure:
M.G reports no disclosures relevant to the manuscript. S.C. reports no disclosures relevant to the manuscript. S.O'R. reports no disclosures relevant to the manuscript. N.T. reports no disclosures relevant to the manuscript. C.McG. reports no

disclosures relevant to the manuscript. J.K. reports no disclosures relevant to the manuscript.

Neurological presentations in children with COVID-19 infection are rare. Reports of pediatric multi-inflammatory syndrome have dominated the literature, although cases of pure neurological manifestations have been described. [1-3] Akinetic mutism has previously been reported in steroid responsive COVID-19 related encephalitis. [4] We present the case of a 16-year-old female who presented with visual hallucinations and ritualistic behaviours. She subsequently developed a severe encephalopathy with akinetic mutism in the context of COVID-19 infection.

Methods

Consent was obtained to report this case. SARS-CoV-2 was tested via RT-PCR amplification of virus nucleic acid from a nasopharyngeal swab. SARS-COV-2 was tested in the CSF using RealStar ® Altona (E and S gene) RT-PCR assay. MRI Brain was performed using axial T1, T2, FLAIR and DWI and T1 post contrast sequences.

Case

Prior to presentation the patient was medically very well, but did have mild learning needs, requiring minor assistance in a mainstream school. In mid-March 2020, she complained of a sore throat. Three days later, she became very anxious, before developing insomnia, anorexia, paranoia and ritualistic behaviours. Visual hallucinations prompted referral to the emergency department for urgent psychiatric review. On attendance, temperature was elevated at 38.6°C. SARS-CoV-2 was detected, and remained detectable on six nasopharyngeal swabs over subsequent weeks. She was persistently pyrexial and tachycardic for the first 10 days of admission. She was not hypoxic and had no respiratory symptoms throughout her

clinical course.

Examination on admission was limited as the patient was unable to co-operate fully with commands. She was awake and tracked movement within the room. Tone, power and reflexes appeared initially normal. She described visual and auditory hallucinations, including lions in the room leaping towards her, in a whispered manner. She feared that she had harmed members of her family. Five days post admission she developed mutism. She exhibited little to no voluntary motor activity. She was fed via nasogastric tube and had faecal and urinary incontinence. She demonstrated motor perseveration with repetitive scissoring movements involving her legs and circular movements involving her arms, which persisted for hours at a time and were a constant feature for the first two weeks of her clinical course.

Ten days following admission, bilateral limb rigidity with subtle high frequency tremor were noted, however at this point she had been treated with Olanzapine and Haloperidol, raising the possibility of an iatrogenic response.

Investigations

Laboratory investigations on admission showed normal white cell and lymphocyte count, but elevated transaminases and ferritin levels. Chest X Ray was normal. CSF examination showed 2 white cells with normal protein (0.43 g/L) and glucose (2.9 mmol/L). CSF analysis for SARS-CoV-2 virus was negative. Brain MRI demonstrated 2 tiny, punctate T2/FLAIR hyper-intensities in the centrum semiovale bilaterally, with no diffisuion restriction or contrast enhancement. They were felt to non-specific based on consensus review. Autoimmune antibody panel including anti-NMDA receptor antibody, anti-GAD, anti-DPPX, anti-AMPA1,2, anti-GABAb, anti-VGKC antibody, anti-LGI1, anti-CASPR and anti-glycine antibody were negative in

CSF and serum. Infectious screen in the CSF, including HSV and VZV PCR were negative. Two weeks later, following therapeutic intravenous immunoglobulin (IVIG) anti-GAD antibody level was positive in serum at a titre of 39 U/ml (0-10) but was negative in CSF. ANA and ANCA were negative. ENA was transiently positive with a low-positive Ro post IVIG and was subsequently negative. Oligoclonal band testing in CSF was negative. Antibody screening was repeated in serum and CSF and was negative (Table 1).

EEGs, performed on days 7, 32 and 72 post-admission, featured delta slowing, more prominent in the right hemisphere posteriorly; there were no epileptiform discharges, triphasic complexes or periodic phenomena; no sleep periods were recorded (Figure 1).

Management

One course of IVIG (0.4mg/kg/day) was completed over five days from day 3 of admission for initially suspected autoimmune encephalitis, followed by IV methylprednisolone 1g per day over three days. A second course of IVIG was commenced on day 14 but was discontinued after the patient developed a widespread rash. We did not proceed with second line immunosuppression due to normal neuroimaging and autoantibody profile, and subtle clinical improvement. She was treated with low dose benzodiazepines and low dose antipsychotic medication early in her clinical course due to hallucinations and injury during perseveration.

Four weeks after initial presentation she began to improve, with increased voluntary movement, attempts at speech with immediate family members only and a reduction in limb rigidity and abnormal movements. Interestingly spontaneous singing was

noted prior to spontaneous speech. Gait remained hesitant, with a festinant quality. She was discharged home on day 98 requiring significant support in her continence, washing and feeding, awaiting admission to an appropriate facility for ongoing rehabilitation. Whilst this patient had significant ongoing cognitive and physical difficulties four months post onset of symptoms, at six months she has exhibited significant improvement. Neurological examination, including gait, has normalized. Speech is fluent with an engaged affect. She has regained her activities of daily living and has resumed local dance classes. She has ongoing difficulties with memory and fatigue and is awaiting detailed psychological assessment. Psychiatric symptoms have fully abated. She is due to return to school on a part-time basis. She recalls little of her prolonged hospital stay

Discussion

This case demonstrates severe COVID-19 associated encephalopathy in a teenage patient with mild COVID-19 respiratory symptoms. There were several clinical features characteristic of akinetic mutism including: lack of voluntary spontaneous movements; absence of speech and preserved visual tracking. Furthermore, the patient did not eat or drink of her own volition but could do so when she was fed. Motor perseveration in the context of akinetic mutism has been well described. These symptoms drove the suspicion of autoimmune encephalitis. [5] As with multiple other clinical cases described, [6 7] imaging and CSF remained normal, although advanced imaging including MR angiography was not performed in the acute phase due to resource restrictions at the height of the pandemic. Transiently positive anti-Ro and GAD antibody were felt to be most likely due to IVIG, which was commenced urgently due to the severity of symptoms.

This was a devastating, presumed parainfectious encephalopathy, with slow and incomplete recovery to date. The patient will require close neurological and psychiatric long-term follow-up.

Appendix. Authors

Name	Location	Contribution
Maria Gaughan, MB BAO BCH	University College Dublin, St. Vincent's University Hospital	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Sean Connolly MD FRCPI	St. Vincent's University Hospital	Data collection and analysis, drafting and revision of manuscript
Sean O'Riordan MD	St. Vincent's University Hospital	Revision of manuscript
Niall Tubridy MD FRCPI	St. Vincent's University Hospital	Drafting and revision for intellectual content.
Christopher McGuigan MD FRCPI	St. Vincent's University Hospital	Drafting and revision for intellectual content
Justin A. Kinsella MB PhD MRCPI	St. Vincent's University Hospital	Study design, drafting and revision of manuscript.

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Figure 1. Electroencephalogram (EEG) of a 16-year-old female six weeks after COVID-19 infection, awake and uncooperative

10-20 International system of scalp electrode placement; ECG = electrocardiogram; EOG = electrooculogram; μV = microVolts; Hz = Hertz; bipolar montage; the tracing depicts an excess of theta and delta activity especially in the right temporal channels.

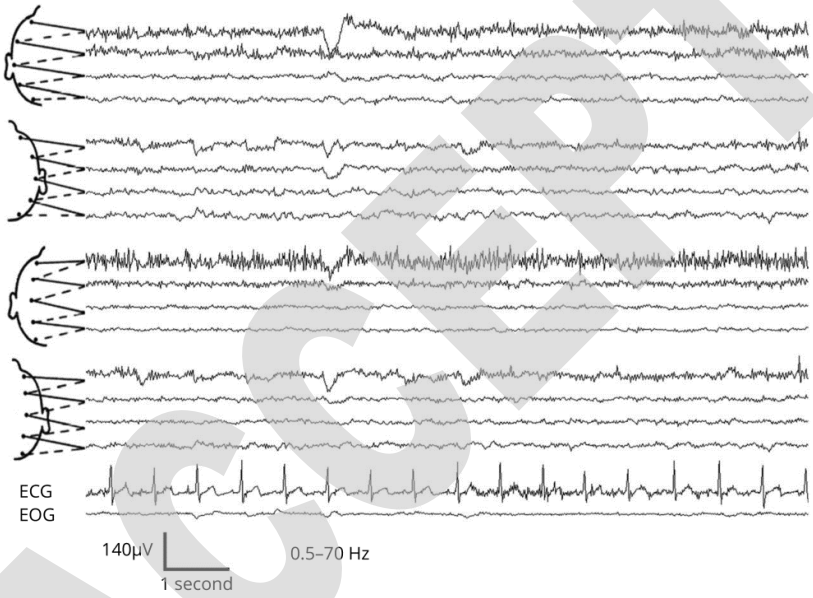

Table 1. Laboratory investigations at three time points during admission.

	Time 1 D 3 post admission	Time 2 D 20 - 30 post admission	Time 3 D > 40 post admission
CSF WCC	2 per cmm	2 per cmm	
CSF Protein	0.43 g/L	0.59 g/L	
CSF Glucose	2.9 mmol/L	2.7 mmol/L	
CSF Oligoclonal bands	No OCBs present	No OCBs present	
CSF HSV PCR	Negative		
CSF Anti-VGKC	Negative	Negative	
CSF Anti-GABA – b	Negative	Negative	
CSF Anti-AMPA1 CSF Anti-AMPA2	Negative	Negative	
CSF Anti-Glycine Receptor	Negative	Negative	
CSF Anti-GAD	Negative	Negative	
CSF Anti-NMDA	Negative	Negative	
CSF 14-3-3		Negative	
CSF S-100b		Negative	
Serum Anti-AMPA1 / AMPA2		Negative	Negative
Serum Anti-NMDA	Negative	Negative	Negative
Serum GABAb		Negative	Negative
Serum Anti-DPPX		Negative	Negative
Anti-CASPR2		Negative	Negative
Anti-LGI1		Negative	Negative
Anti-GAD antibody		Positive: 39 U/L (0-10)	Positive 10 U/L (0-10)

Anti-HIV		Negative	
Hepatitis Serology		Negative	
Anti-Yo		Negative	Negative
Anti-Hu		Negative	Negative
Anti-Ri		Negative	Negative
Anti-Ma2		Negative	Negative
Anti-CV2		Negative	Negative
Anti-SOX-1		Negative	Negative
Anti-Zic-4		Negative	Negative
Anti-TR		Negative	Negative
ANA		Negative	Negative
ANCA		Negative	Negative
ENA		Positive	Negative
Anti-Ro Ab		7.7 U/ml (0.0 – 6.9)	
C Reactive Protein	3.8 mg/L (0 – 5)	2.6 mg/L	2.6 mg/L