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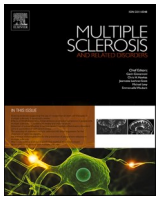

Correspondence

Immunotherapy responsive SARS-CoV-2 infection exacerbating opsoclonus myoclonus syndrome

A B S T R A C T

The global pandemic of SARS-CoV-2 has been known to have diverse neurologic complications among adult patients. The neurologic effects of SARS-CoV-2 in the pediatric population is poorly described, especially in those with rare underlying neurologic conditions. We describe the first known case of SARS-CoV-2 in a pediatric patient with refractory opsoclonus-myoclonus syndrome. A 25-month-old female with progressive opsoclonus-myoclonus syndrome secondary to metastatic neuroblastoma status-post resection and chemotherapy presented with worsening opsoclonus, tremor, and breakthrough seizures. She had no fever or respiratory symptoms at presentation. Urine catecholamines were unchanged, with low suspicion for tumor recurrence. She was found to have SARS-CoV-2 via nasopharnygeal PCR assay. She received intravenous immunoglobulin and dexamethasone therapy with improvement in opsoclonus-myoclonus syndrome symptoms and was discharged home at her neurologic baseline. Patients with opsoclonus-myoclonus syndrome may present with exacerbation of symptoms in the context of SARS-CoV-2. This case describes a sentinel report of a child with opsoclonus-myoclonus syndrome presenting with worsening symptoms with concomitant SARS-CoV-2. Improvement in symptoms was achieved with standard of care therapies.

1. Introduction

SARS-CoV-2 has primarily manifested as respiratory illness, however description of neurologic complications are now being reported. (Mao et al., 2020; Helms et al., 2020) Children are frequently asymptomatic or mildly symptomatic with fever and respiratory symptoms, (Lu et al., 2020) and rarely have neurologic manifestations. An Italian pediatric cohort reported that only 4% complained of headaches, with no other neurologic symptoms. (Parri et al., 2020) Little is known regarding the impact of SARS-CoV-2 in children with neurological disorders, especially those on the neuroimmunologic disease. Opsoclonus-myoclonus syndrome (OMS) is an autoimmune, presumably B-cell mediated, paraneoplastic disorder which primarily affects children. Infections have been associated with provocation of OMS symptoms. (De Grandis et al., 2009) Here the authors present a case of SARS-CoV-2 associated worsening of OMS in a young child.

2. Case

A 25-month-old female with a history of OMS secondary to metastatic neuroblastoma (diagnosed with opsoclonus and neuroblastoma at age 13 months, status-post resection and chemotherapy, with wean of immunotherapy five months prior to presentation), and epilepsy, presented with worsening of opsoclonus, ataxia, and concern for seizure. Four days prior to presentation, the patient was febrile (38°C) and had multiple family members with viral respiratory symptoms, all who had negative SARS-CoV-2 PCR testing. On presentation, the patient was postictal with a neurological exam notable for opsoclonus and ataxia, worsened from baseline (Table 1). Screening labs, chest radiograph, CT head and MRI brain were unremarkable. Due to concern for seizures, she received two doses of lorazepam and levetiracetam loading dose and remained seizure free. SARS-CoV-2 PCR assay was obtained upon admission and was positive. Her mental status improved but she continued to have marked opsoclonus and ataxia.

Once admitted, she underwent multidisciplinary evaluation. Urine catecholamines were unchanged and a metaiodobenzylguanidine (MIBG) I-123 scan demonstrated an absolute Curie score 0, making worsening symptoms secondary to relapse unlikely. Additional infectious studies were unrevealing including adenovirus, coxsackievirus, enterovirus, haemophillus influenza, influenza A/B, mycoplasma pneuomniae, parechovirus, parainfluenza, and rhinovirus. Lumbar puncture was not obtained.

On hospital day three (seven days after onset of fever, four days after onset of neurologic symptoms), the patient received intravenous immunoglobulin (2g/kg over 2 days) and a three day pulse dose of dexamethasone with return to her neurologic baseline over 48 hours. The patient has remained at her neurologic baseline at her six month follow up.

3. Discussion

We report a patient with known OMS found to be infected with the novel virus SARS-CoV-2. The primary complaint prompting emergent evaluation was not related to infectious symptoms, but rather worsening of her baseline OMS symptoms and a seizure-like event. Interestingly, while the patient did have fever at onset of her symptoms, they were otherwise asymptomatic from a respiratory standpoint and had a negative chest radiograph. Given our patient's infection with SARS-CoV-2, this virus should be considered a potential trigger of relapse in patients with paraneoplastic or neuroimmunologic phenomena even when systemic infectious symptoms are not present. Although CSF analysis would be ideal for this patient, data on CSF tested for SARS-CoV-2 has been reported to be negative in all cases to this point. (Helms et al., 2020)

Worsening of baseline OMS has been previously reported in children with a variety of viral infections, although members of the coronaviridae family have not been exclusively reported. (Pranzatelli and Tate, 2016) Virus induced relapses have been hypothesized to be related to

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Table 1
OMS symptoms and rating score (De Grandis et al., 2009) over disease course.

	OMS Rating Score	
Age 11 months: Diagnosis	13	**Stance -** 3: unable to sit without using hands to prop or other support; **Gait -** 3: unable to walk even with support from person or equipment; **Arm/hand function -** 3: Major difficulties in all age-appropriate fine motor and manipulative tasks; **Opsoclonus -** 3: Persistent, interfering continuously with function and tracking; **Mood/ Behavior -** 1: mild increase in irritability but consolable; and/or mild sleep disturbances; **Speech -** 0: normal for age, no loss
Age 12 months: After treatment with intravenous immunoglobulin, corticosteroids, and tumor resection	4	**Stance -** 0: standing and sitting balance normal for age; **Gait -** 1: mildly wide-based gait for age, but able to walk indoors and outdoors independently; **Arm/hand function -** 1: mild, infrequent tremor or jerkiness without functional impairment; **Opsoclonus -** 1: rare or only when elicited by change in fixation or "squeeze test"; **Mood/ Behavior -** 0: normal; **Speech -** 1: mildly unclear, plateaued in development
Age 25 months: At presentation with COVID-19 infection	10	**Stance -** 1: mildly unstable standing for age, slightly wide based; **Gait -** 2: walks only or predominantly with support from person or equipment; **Arm/hand function -** 2: fine motor function persistently impaired for age, but less precise manipulative tasks normal or almost normal; **Opsoclonus -** 2: Frequent, interferes intermittently with fixation or tracking; **Mood/Behavior -** 1: mild increase in irritability but consolable; and/or mild sleep disturbances; **Speech -** 2: loss of some words or some grammatical constructs (i.e. from sentences to phrases) but still communicates verbally

worsened B-cell dysregulation and indiscriminate induction of the humoral immune response, although the exact etiology remains obscure. Of note, our patient was not immunosuppressed at the time of SARS-CoV-2 infection (last rituximab infusion was one year prior, with interval repopulation of B-cell lines). The patient's symptoms improved dramatically with administration of standard therapies for OMS, namely, intravenous immunoglobulin and corticosteroids. Though the exact mechanism for improvement is unknown, viral induction of immune dysregulation is presumed, especially in the setting of response to the therapeutic interventions made and the speed of recovery with prompt administration.

Of note, post-infectious opsoclonus has been reported, often in older individuals without a history of paraneoplastic OMS. (Saini et al., 2020) In this case, there would be no mechanism to distinguish if SARS-CoV-2 caused a post-infectious opsoclonus although the short time course between fever and opsoclonus and her past medical history make this less likely. Similarly, other immune mediated phenomenon such as Guillain Barre syndrome have been reported in following infection with SARS-CoV-2 although these have predominantly been in adults without a history of neuroimmunologic disorders such as OMS. (Guijarro-Castro et al., 2020) The spike protein of SARS-CoV-2 has been hypothesized to be a trigger for autoimmune responses although definitive correlation remains elusive. Although novel in the report of SARS-CoV-2 exacerbating OMS, this report must also be tempered in that other viruses have also been linked to this phenomenon in pediatric patients. (Pranzatelli and Tate, 2016)

Management of exacerbations of paraneoplastic and neuroimmune mediated neurological conditions during this pandemic should include standard of care immunomodulating therapies, preferably administered quickly following identification of SARS-CoV-2 status, although further large-scale study is needed.

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5. Contributors' statement

Dr. Sarah Wiegand conceptualized the manuscript, drafted the initial manuscript, and reviewed and revised the manuscript.

Drs. Wendy Mitchell, and Jonathan Santoro conceptualized the manuscript, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

6. Data sharing

No data was collected for this study.

Declaration of Competing Interest

The authors have indicated they have no conflicts of interest relevant to this article to disclose.

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References

De Grandis, E., Parodi, S., Conte, M., et al., 2009. Long-term follow-up of neuroblastoma-associated opsoclonus-myoclonus-ataxia syndrome. Neuropediatrics 40 (3), 103–111. https://doi.org/10.1055/s-0029-1237723.

Guijarro-Castro, C., Roson-Gonzalez, M., Abreu, A., Garcia-Arratibel, A., Ochoa-Mulas, M., 2020. Guillain-Barré syndrome associated with SARS-CoV-2 infection. Comments after 16 published cases. Neurologia 35 (6), 412–415. https://doi.org/10.1016/j.nrl.2020.06.002.

Helms, J., Kremer, S., Merdji, H., et al., 2020. Neurologic features in severe SARS-CoV-2 infection. N Engl. J. Med. https://doi.org/10.1056/NEJMc2008597.

Lu, X., Zhang, L., Du, H., et al., 2020. SARS-CoV-2 infection in children. N Engl. J. Med. 382 (17), 1663–1665. https://doi.org/10.1056/NEJMc2005073.

Mao, L., Jin, H., Wang, M., et al., 2020. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, china. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2020.1127.

Parri, N., Lenge, M., Buonsenso, D., 2020. Coronavirus infection in pediatric emergency departments (CONFIDENCE) research group. children with covid-19 in pediatric emergency departments in italy. N Engl. J. Med. https://doi.org/10.1056/NEJMc2007617.

Pranzatelli, M.R., Tate, ED., 2016. Trends and tenets in relapsing and progressive opsoclonus-myoclonus syndrome. Brain Dev. 38 (5), 439–448. https://doi.org/10.1016/j.braindev.2015.11.007.

Saini, L., Dhawan, S.R., Madaan, P., et al., 2020. Infection-associated opsoclonus: a retrospective case record analysis and review of literature. J. Child Neurol. 35 (7), 480–484. https://doi.org/10.1177/0883073820911327.

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