Journal of Paediatrics and Child Health

doi:10.1111/jpc.15902

CASE REPORT

# Orofacial dyskinesia with choreoathetoid movements caused by brainstem encephalitis: A rare complication of SARS-CoV-2-related multisystem inflammatory syndrome in children

Sandipan Sen, Moumita Samanta, Arnab Biswas and Tapan K Sinhamahapatra

Department of Pediatrics, Nilratan Sircar Medical College and Hospital, Kolkata, India

## Key Points

1 We report a child with multisystem inflammatory syndrome in children (MIS-C) who developed chorea and neuropsychiatric behaviour disturbance as a result of brainstem encephalitis.
2 If a child develops signs or symptoms suggestive of MIS-C, the presence of SARS-CoV-2 antibodies supports such a diagnosis.
3 Early diagnosis and prompt treatment with IVIG and aggressive steroid therapy can help manage severe complications related to MIS-C.

COVID-19 infection, caused by SARS-CoV-2 virus, is largely a non-severe disease in children. Since mid-2020, numerous post-COVID-19 paediatric cases are reported presenting with abnormally enhanced immune system response, interchangeably termed as multisystem inflammatory syndrome in children (MIS-C)[1] or paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). Here we report a case of MIS-C complicated by brainstem encephalitis in a 10-year-old child who presented with persistent fever, generalised tonic–clonic convulsions and later developed orofacial dyskinesia, tremor, ptosis, choreoathetoid movements and neuropsychiatric manifestations.

## Case Report

A 10-year-old Indian boy from West Bengal presented with fever with generalised erythematous rash for 4 days, altered sensorium for 2 days and repeated convulsions, starting 12 hours earlier. Fever was gradual-onset, intermittent and progressive, accompanied by intermittent non-specific headache without skin excoriation, red eyes or oral lesions. The convulsions were initially focal, involving the upper limbs only, later progressing to generalised seizures with upward rolling of the eyeballs, tongue-biting and post-ictal confusion between episodes. Eighteen days previously, he had 3 days of low-grade fever responsive to anti-pyretic medications, after which he was asymptomatic for 10 days.

Neurological examination showed paediatric Glasgow Coma Scale (pGCS) E2V3M4, increased tone in all four limbs, bilateral extensor plantar response, and exaggerated knee and ankle jerks with clonus. Ophthalmoscopic examination revealed bilateral optic disc oedema. After initial stabilisation, he was managed with intravenous antibiotics and supportive care. For repeated seizures intravenous phenytoin 5 mg/kg/day in two divided doses was started, along with intracerebral tension (ICT) lowering drugs. Leviteracetam (30 mg/kg/day in three divided doses) and sodium valproate (30 mg/kg/day in three divided doses) were added later and the doses were increased to 60 mg/kg/day. With rapidly detoriating pGCS, he was shifted to the paediatric intensive care unit, intubated, mechanically ventilated and started on an intravenous midazolam infusion 1 μg/kg/min for refractory seizures. Bloods taken on admission to PICU showed anaemia, lymphopenia and thrombocytopenia, along with evidence of marked inflammation (Table 1). Cerebrospinal fluid (CSF) examination performed on day 2 showed a raised protein (92 mg/dL), normal sugar, and 20 cells/mm$^3$, predominantly mononuclear cells. D-Dimer level was 5.5 μg/mL for which prophylactic subcutaneous enoxaparin injection was started. Suspecting haemophagocytic lymphohistiocytosis (HLH)[2] secondary to an infective aetiology, he was given intravenous immunoglobulin (IVIG) 2 g/kg over 48 h. RT-PCR of a nasopharyngeal swab was negative for SARS-CoV-2. Other common tropical infections including malaria, dengue, scrub typhus and leptospirosis were excluded by blood films and serologically. On day 2 of admission, he developed features of heart failure with tachycardia, tachypnoea, and an S3 gallop rhythm. His N-terminal pro-brain natriuretic peptide (NT-pro-BNP) level was elevated He commenced on a dobutamine infusion at 0.1 μg/kg/min for 48 h. His SARS-CoV-2 IgG antibody titre, sent on day 2 of admission, was 3094.6 AU/mL by chemiluminescent microparticle immunoassay (reference range: positive ≥50 AU/mL).

The clinical picture of persistent fever for 4 days, rash, heart failure, neurological involvement, evidence of hypercytokinaemia with raised inflammatory markers and serological evidence of recent COVID-19 infection supported the diagnosis of SARS-CoV-2-related MIS-C.[1] Our patient had encephalitis causing altered consciousness and repeated convulsions. On day 5, methylprednisolone pulse therapy was initiated for 5 days, followed by gradual tapering. The frequency of convulsions and febrile episodes decreased with improving pGCS from day 8 and the child became afebrile on day 10 of admission. Blood and urine cultures were sterile. CSF for bacterial culture and pan-neurotropic virus sent on day 2 (AmPATH Laboratory, BIOFIRE automated FilmArray system for detection of Pan-flavivirus RNA, Pan-

**Correspondence:** Dr Sandipan Sen, Department of Pediatrics, Nilratan Sircar Medical College and Hospital, 138, AJC Bose Road, Kolkata-14, India. email: drsandipansen79@gmail.com

Conflict of interest: None declared.

Accepted for publication 4 January 2022.

**Table 1** Laboratory investigations

| Day of hospital stay | Normal range | Day 1 | Day 4 (post-IVIG) | Day 12 (post-MPD pulse) | Day 18 (pre-discharge) |
|---|---|---|---|---|---|
| Haemoglobin (g/dL) | 11–15 | 9.3 | 11.7 | 10.8 | 12.2 |
| Total leukocyte count ($\times 10^9$/L) | 5–12 | 13.8 | 9.0 | 17.0 | 10.4 |
| Neutrophil count ($\times 10^9$/L) | 2–7.5 | 12.8 (91) | 7.8 (86) | 14.9 (88) | 7.5 (72) |
| Lymphocyte count ($\times 10^9$/L) | 1.5–4 | 0.9 (7) | 1.0 (12) | 1.8 (11) | 2.4 (25) |
| Platelet count ($\times 10^9$/L) | 150–400 | 71 | 55 | 170 | 350 |
| ESR (mm/1st hour) | 14–20 | 68 | 35 | 24 | 20 |
| CRP (mg/L) | <5 | 57.3 | 37.8 | 1.6 | 1.5 |
| Triglycerides (mg/dL) | <150 | 269 | 350 | 105 | 184 |
| Ferritin (ng/mL) | 28–397 | 1500 | 1160.3 | 460.3 | 226 |
| Fibrinogen (mg/dL) | 200–450 | 112 | 160 | 354 | 260 |
| PT (s) | 11–15 | 17.7 | 20.2 | 15.1 | 13.3 |
| APTT (s) | 29–35 | 38.7 | 42 | 33.2 | 34.1 |
| D-Dimer (mcg/mL) | <0.5 | 5.5 | 4.6 | 0.88 | 0.4 |
| Interleukin-6 (pg/mL) | <5 | | 52 | | 20 |
| NT-pro BNP (pg/mL) | <125 | 647 | | | 115 |

IVIG, intravenous immunoglobulin; MPD, methyl prednisolone.

herpesvirus DNA, Pan-enterovirus RNA, Pan-paramyxovirus RNA, human parvovirus B19, human adenoviruses, human parechoviruses) and Japanese encephalitis virus (both serum and CSF by ELISA method) were negative. The child was weaned off mechanical ventilation and was extubated on day 11 of admission. His inflammatory markers improved (Table 1) and an echocardiogram on day 16 was normal.

With improvement in consciousness, on day 12, the child developed axial and appendicular hypertonia, a coarse intension tremor in the upper limbs that improved at rest, and low amplitude, high frequency choreoathetoid movements involving his distal upper limbs. He developed behavioural changes, in terms of irritability and self-mutilating behaviour (biting of his fingers and self-inflicted genital injuries). He also had orofacial hyperkinesia (Video S1, Supporting Information), and bilateral ptosis (right > left) with absent pupillary reflexes, in the absence of dysdiadochokinesia, past pointing or nystagmus. His upper and lower limb reflexes were normal. An electroencephalogram on day 18 was normal. Other causes of encephalopathy were excluded: systemic lupus erythematosus (negative ANA, Hep-20-10, IIFT), autoimmune encephalitis (negative Anti NMDA, GABA-B1/B2, AMPA1/2, LGI-1, CASPR2 in both CSF and blood, IIFT-EUROIMMUN with 1:10 dilution), Wilson's disease (normal 24 h urinary copper excretion), subacute sclerosing panencephalitis (low anti-measles antibody titre in CSF) and paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (low anti-streptolysin O and anti DN-ase B titres). Brain MRI showed mild diffusion restricted altered signal intensity with hyperintensity in the T2 flair image in the substantia nigra (Fig. 1) on both sides of the midbrain, suggestive of brainstem encephalitis.

A trial of oral haloperidol worsened the involuntary movements and aggression. Oral risperidone improved the psychiatric symptoms with resolution of the self-biting and physical aggression. Later, oral trihexaphenidyl resulted in little improvement in his abnormal movements, but oral L-Dopa with carbidopa was associated with some improvement over time. By day 25, he had minimal, bilateral, residual tremors with normalisation of tone and return of his pupillary reflexes. The patient was discharged on day 28 of admission, taking oral L-Dopa, sodium valproate, risperidone

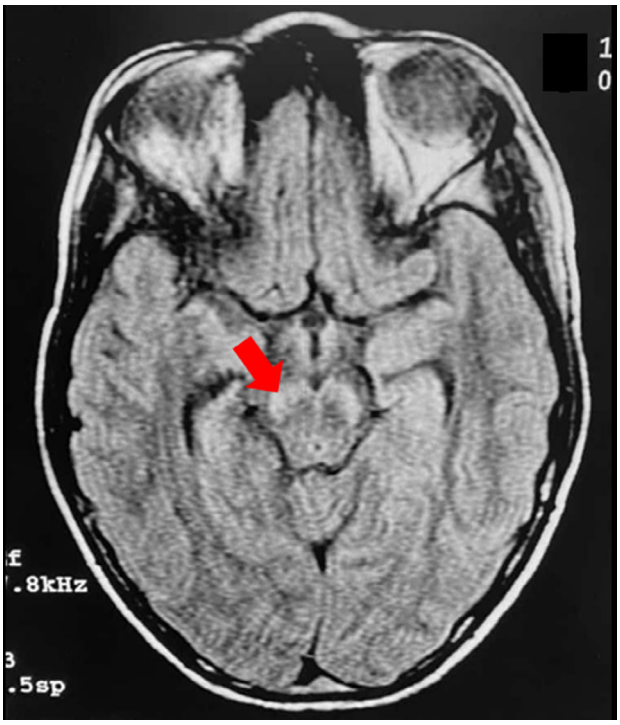


**Fig. 1** Transverse section of brain (at the level of midbrain) in T2-FLAIR MRI brain showing increased signal intensity in substantia nigra of midbrain bilaterally (arrow).

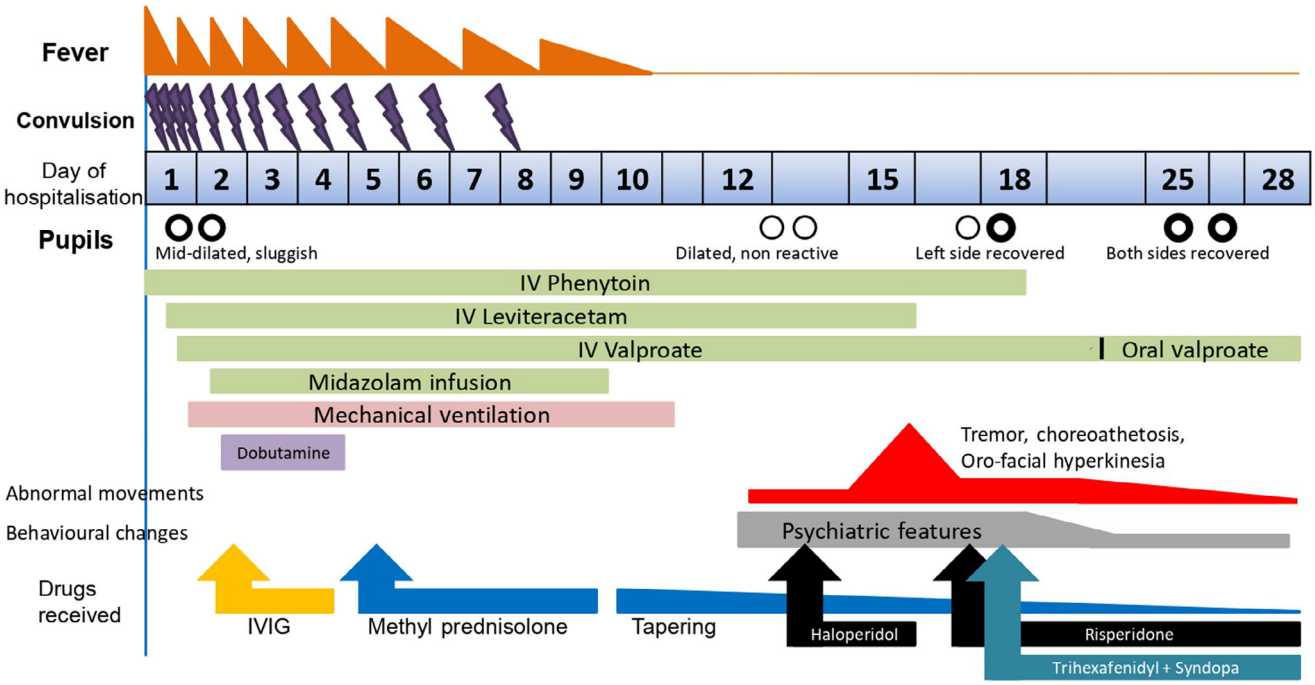


**Fig. 2** Diagrammatic representation of detailed clinical presentations of the case along with major drugs and treatment modalities received and their duration with respect to day of hospitalisation. Graphs are not as per scales.

and aspirin. Currently he is receiving outpatient physical rehabilitation (Fig. 2).

## Discussion

MIS-C is a rare but potentially devastating inflammatory complication of SARS-CoV-2 infection in children. The majority of cases are reported 2–6 weeks after SARS-CoV-2 infection.[3] To describe this hyperinflammatory[4–6] phenotype, different terminologies and case definitions are used in different regions,[3] resulting in a lack of universally accepted case definition of MIS-C. Both the US CDC and the WHO have published similar preliminary case definitions based on fever, involvement of two or more systems, evidence of hyperinflammation and hypercytokinaemia, a positive test for current or recent SARS-CoV-2 infection and exclusion of alternative diagnoses. Similar criteria were used in the case definition of PIMS-TS by the RCPCH in the UK.[4] Our patient presented with neurological and muco-cutaneous manifestations and later developed cardiovascular features along with biochemical evidence of hypercytokinaemia and immune-mediated injury, although haemodynamic instability, for example shock or hypotension was absent.

Early prompt diagnosis of MIS-C is a challenge and warrants a high index of suspicion, especially in resource poor settings. Various studies on different populations reported strikingly low rates of RT-PCR positivity and high serological titres of SARS-CoV-2 antibodies in affected children, suggesting MIS-C is a post-viral inflammatory phenomenon.[7–11] Our patient had no detectable SARS-CoV-2 but was seropositive. The history of a febrile illness 18 days earlier could have been due to active SARS-CoV-2 infection, but RT-PCR was not performed at the time.

MIS-C sometimes mimics Kawasaki disease,[6,8,12,13] a childhood vasculitis, but children have also been reported presenting with prominent gastrointestinal symptoms[11,14] and heart failure due to myocarditis.[15,16] Rarely, children with neurological manifestations such as seizures, encephalopathy and headache have also been reported.[9,17] A recent meta-analysis described neurological manifestations in 27% of MIS-C cases, headache (27%) followed by meningism (17%) and encephalopathy (8%) being the most frequent neurological manifestations.[18] Our patient had repeated seizures with altered sensorium and intracranial hypertension, suggesting encephalopathy.

Nervous system involvement in the form of headache, encephalopathy[19] cerebral edema, demyelination,[20] limbic encephalitis, ischaemic stroke, even psychosis[17] is well documented and studied among children with active SARS-CoV-2 infection. Initial case series from UK reported a disproportionately higher incidence of COVID-19-induced neurological and psychiatric manifestations among African and Asian populations.[17,19]

The exact mechanism of neurological involvement in MIS-C is still unclear.[21] Immune-mediated neuronal damage due to cytokine storm is one possible cause.[21] Another possible explanation is SARS-CoV-2-induced blood–brain barrier damage causing immune system exposure to new CNS antigens, resulting in endotheliopathy and immune-mediated CNS injury.[22]

When our patient's post-COVID hyper-inflammatory state was suppressed with IVIG and pulsed methylprednisolone, it unmasked behavioural changes and choreiform movement abnormalities. In a

UK-based study,[17] chorea was found in six children with active COVID-19, but none of them had or developed MIS-C. In the same study, nine (36%) out of 25 MIS-C patients presented with behavioural changes.[17] Although an acute encephalopathy-like presentation in MIS-C is as high as 88% in some case series,[17] movement disorders and neuropsychiatric manifestations are extremely rare in MIS-C, unlike in active disease. A single case report from New York described neuropsychiatric manifestations of MIS-C, including delirium, physical and verbal aggression and fluctuation of attention that worsened with haloperidol.[23]

We report brainstem encephalitis in a 10-year-old boy with MIS-C. His extra-pyramidal symptoms pointed towards a basal ganglia lesion, which can also cause psychiatric manifestations by disrupting the balance between dopamine and other brain neurotransmitters. His MRI brain revealed a focal lesion in the substantia nigra of midbrain consistent with this clinical diagnosis.

A 15-year-old Afro-Caribbean girl with MIS-C who presented with behavioural changes and audio-visual hallucinations was found on MRI to have lesions of the splenium of the corpus callosum (SCC) and bilateral hippocampal[24] lesions. SCC involvement[17,25,26] seems to be the most consistent MRI finding associated with MIS-C patients who have neurological manifestations. MIS-C-related brainstem or substantia nigra involvement as seen in our patient has not yet been reported to our knowledge. In the adult population, there is a single case report of a 65-year-old who presented with involuntary movements, generalised myoclonus and cognitive dysfunction, and who was diagnosed with post SARS-CoV-2 immune-mediated brainstem encephalitis on clinical grounds, as neuroimaging and serological studies were negative.[27]

Hence, our patient may be the first ever child with MIS-C to present with extra-pyramidal symptoms, chorea and neuropsychiatric behavioural disturbance due to brainstem encephalitis. Consent has been taken from patient's father regarding disclosure of patient's medical history and disease for publication purpose without revealing his identity.

## Acknowledgements

The authors thank all members of the paediatric intensive care unit team caring for the complex needs of the patient described in this article.

## References

1 Headquarters WHO. Multisystem inflammatory syndrome in children and adolescents with COVID-19. World Health Organization; 2020. Available from: https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
2 Verbsky JW, Grossman WJ. Hemophagocytic lymphohistiocytosis: Diagnosis, pathophysiology, treatment, and future perspectives. *Ann. Med.* 2006; **38**: 20–31.
3 Henderson LA, Canna SW, Friedman KG *et al*. American College of Rheumatology Clinical Guidance for pediatric patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 2. *Arthritis Rheumatol.* 2021; **73**:e13–29.
4 Singh-Grewal D, Lucas R, Macartney K *et al*. Update on the COVID-19-associated inflammatory syndrome in children and adolescents; paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2. *J. Paediatr. Child Health* 2020; **56**:1173–7.
5 Feldstein LR, Rose EB, Horwitz SM *et al*. Multisystem inflammatory syndrome in U.S. children and adolescents. *N. Engl. J. Med.* 2020; **383**: 334–46.
6 Dufort EM, Koumans EH, Chow EJ *et al*. New York State and Centers for Disease Control and Prevention multisystem inflammatory syndrome in children investigation team. Multisystem inflammatory syndrome in children in New York state. *N. Engl. J. Med.* 2020; **383**: 347–58.
7 Belot A, Antona D, Renolleau S *et al*. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. *Euro Surveill.* 2020; **25**: 2001010.
8 Davies P, Evans C, Kanthimathinathan HK *et al*. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: A multicentre observational study. *Lancet Child Adolesc. Health* 2020; **4**: 669–77.
9 Dhanalakshmi K, Venkataraman A, Balasubramanian S *et al*. Epidemiological and clinical profile of pediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-2 (PIMS-TS) in Indian children. *Indian Pediatr.* 2020; **57**: 1010–4.
10 Shobhavat L, Solomon R, Rao S *et al*. Multisystem inflammatory syndrome in children: Clinical features and management-intensive care experience from a pediatric public Hospital in Western India. *Ind. J. Crit. Care Med.* 2020; **24**: 1089–94.
11 Angurana SK, Awasthi P, Thakur A *et al*. Intensive care needs and short-term outcome of multisystem inflammatory syndrome in children (MIS-C): Experience from North India. *J. Trop. Pediatr.* 2021; **67**: fmab055.
12 Crayne C, Cron RQ. Pediatric macrophage activation syndrome, recognizing the tip of the iceberg. *Eur. J. Rheumatol.* 2019; **7**:(Suppl 1): 1–8.
13 Wang W, Gong F, Zhu W, Fu S, Zhang Q. Macrophage activation syndrome in Kawasaki disease: More common than we thought? *Semin. Arthritis Rheum.* 2015; **44**: 405–10.
14 Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children (MIS-C) that is related to COVID-19: A single center experience of 44 cases. *Gastroenterology* 2020; **159**:1571–4.e2.
15 Belhadjer Z, Méot M, Bajolle F *et al*. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation* 2020; **142**: 429–36.
16 Capone CA, Subramony A, Sweberg T *et al*. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 infection. *J. Pediatr.* 2020; **224**: 141–5.
17 Ray STJ, Abdel-Mannan O, Sa M *et al*. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: A prospective national cohort study. *Lancet Child Adolesc. Health.* 2021; **5**: 631–41.
18 Nepal G, Shrestha GS, Rehrig JH *et al*. Neurological manifestations of COVID-19 associated multi-system inflammatory syndrome in children: A systematic review and meta-analysis. *J. Nepal Health Res. Counc.* 2021; **19**: 10–8.
19 Panda PK, Sharawat IK, Panda P, Natarajan V, Bhakat R, Dawman L. Neurological complications of SARS-CoV-2 infection in children: A systematic review and meta-analysis. *J. Trop. Pediatr.* 2021; **67**: fmaa070.
20 LaRovere KL, Riggs BJ, Poussaint TY *et al*. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. *JAMA Neurol.* 2021; **78**: 536–47.
21 Aghagoli G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological involvement in COVID-19 and potential mechanisms: A review. *Neurocrit. Care* 2020; **34**:1062–71.

22 Chen T-H. Neurological involvement associated with COVID-19 infection in children. *J. Neurol. Sci.* 2020; **418**: 117096.
23 Hutchison L, Plichta AM, Lerea Y, Madora M, Ushay HM. Neuropsychiatric symptoms in an adolescent boy with multisystem inflammatory syndrome in children. *Psychosomatics* 2020; **61**: 739–44.
24 Sa M, Mirza L, Carter M *et al*. Systemic inflammation is associated with neurologic involvement in pediatric inflammatory multisystem syndrome associated with SARS-CoV-2. *Neurol Neuroimmunol Neuroinflamm.* 2021; **8**: e999.
25 Abdel-Mannan O, Eyre M, Löbel U *et al*. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol.* 2020; **77**: 1440–5.
26 Lad SS, Kait SP, Suryawanshi PB *et al*. Neurological manifestations in pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). *Indian J. Pediatr.* 2021; **88**: 294–5.
27 Khoo A, McLoughlin B, Cheema S *et al*. Postinfectious brainstem encephalitis associated with SARS-CoV-2. *J. Neurol. Neurosurg. Psychiatry* 2020; **91**: 1013–4.

## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Video S1** Supporting information shows orofacial hyperkinesia with persisting choreoathetoid movement with continuous finger biting. Bilateral ptosis can be noted with right > left eye affected.