

Sars-Cov-2 in a Patient with Acute Chorea: Innocent Bystander or Unexpected Actor?

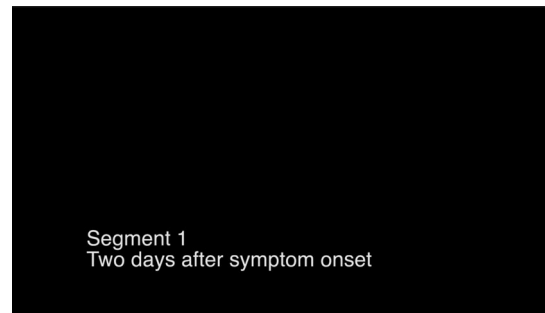
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Chorea mostly presents as a slow-course neurodegenerative disorder with a genetic cause (Huntington's disease). However, subacute-onset forms often have an organic (eg, vascular, infectious, paraneoplastic) or metabolic etiology.^{1,2} Here we provide a brief report, with videotape documentation, of a case of acute choreiform syndrome in a patient with Sars-Cov-2 infection, along with a review of the literature on this topic.

Case Report

A 62-year-old man suffering from type 2 diabetes mellitus and arterial hypertension developed choreiform movements involving all four limbs, head and trunk, together with mild signs of encephalopathy (intrusive thoughts, impulsivity, hyperactivity and attention impairment) the day before hospital admission. On admission, the shaking precluded execution of neuroimaging and lumbar puncture and necessitated pharmacological treatment with haloperidol (4.5 mg/day) and tetrabenazine (50 mg/day) (Video 1, segment 1). Fasting blood glucose was 98 mg/dL. Two days later, the patient presented mental confusion and fever (up to 39°C) and had a molecular swab test, which was positive for Sars-CoV-2. The infection evolved into mild bilateral interstitial pneumonia, which gradually resolved with dexamethasone. Over the following days, the involuntary movements gradually decreased, and after a further 10 days, a new swab for Sars-Cov-2 was negative. Haloperidol was discontinued (Video 1, segment 2). Brain contrast-enhanced magnetic resonance imaging (MRI) was performed, with susceptibility-weighted imaging (SWI) showing a hypointense signal in the dorsolateral portion of both putamina (Fig. 1). Cerebrospinal fluid (CSF) examination revealed mildly decreased glucose (48 mg/dL, n.v. 50–80; CSF/serum ratio 32%, n.v. >45), mildly increased albumin (45 mg/dL, n.v. 10–30; CSF/serum ratio of 1.5% corresponding to mild barrier damage), a lymphocyte count of 30/mm³ with

normal immunophenotype, and absence of oligoclonal bands. All microbiological analyses of CSF (polymerase chain reaction for Herpes simplex 1–2, Epstein–Barr virus, cytomegalovirus, Sars-Cov-2, and cultures for aerobic and anaerobic bacteria) were negative, as was screening for antibodies directed against the central nervous system (CNS), specifically onconeural antibodies (ie, anti-Hu, Yo, CV2, Ri, Ma1/2, Tr, amphiphysin, glutamic acid decarboxylase (GAD)) and cell-surface antibodies (anti-N-methyl D-aspartate receptor (NMDAR), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA1/2), leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), glycine receptor (GlyR), γ -aminobutyric acid receptors (GABA_AR and GABA_B1R), IgLON5, and dipeptidyl-peptidase-like protein 6 (DPPX)), which were tested both in serum



Video 1. Segment 1: The reported patient 2 days after symptom onset: he shows choreiform movements involving upper and lower limbs, head and trunk. Segment 2: The reported patient 1 week after a negative swab for Sars-Cov-2. The choreiform movements were greatly reduced with minimal pharmacological treatment (ie, tetrabenazine 25 mg a day) Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13274>

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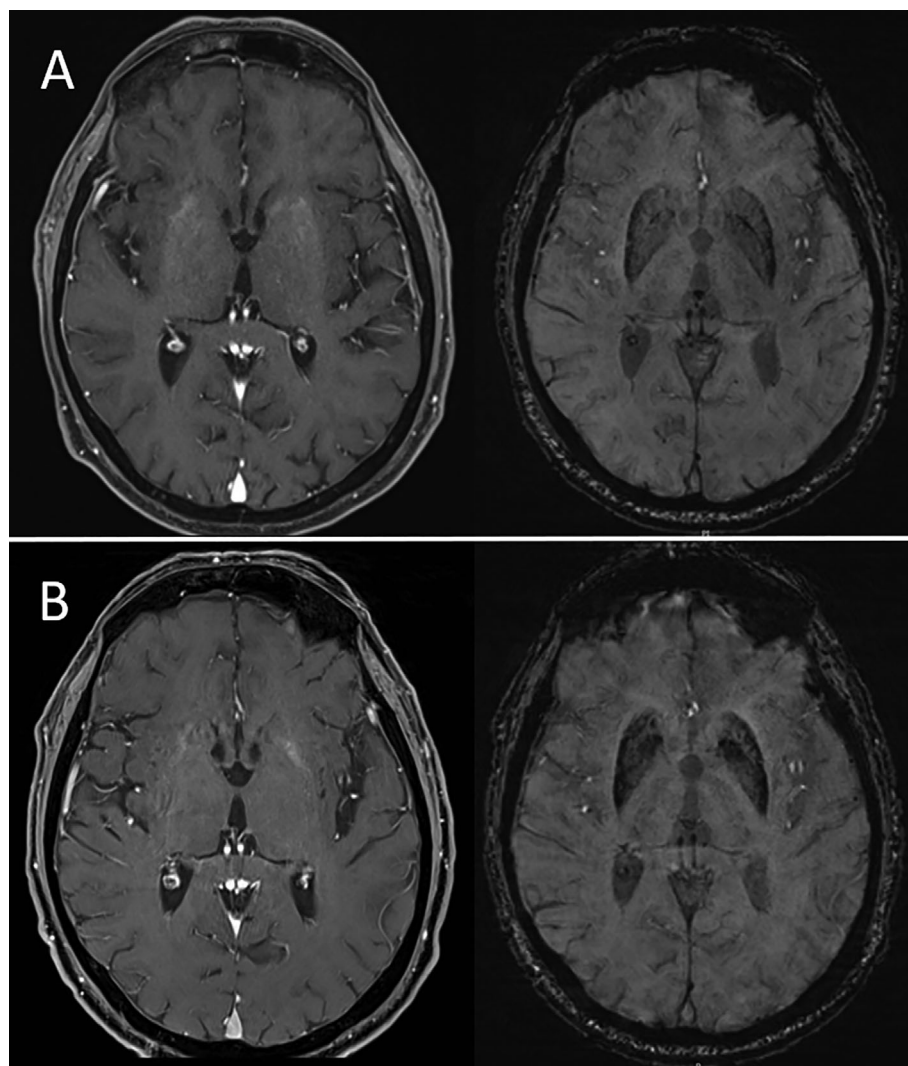


FIG. 1. Brain MRI at baseline and after a 2-month follow-up. Signal abnormalities are visible as T1 hyperintensities (on the left) and SWI hypointensity (on the right) in the dorsolateral portion of both putamina, at baseline (A) and at 2-month follow-up (B).

and in CSF using in-house immunohistochemistry assays. Ceruloplasmin levels and antistreptolysin-O titer were normal, as was screening for rheumatological diseases; acanthocyte search was negative. Two months after the acute onset, the patient had almost fully recovered and it was possible to taper the tetrabenazine. Brain MRI showed a more marked SWI hyposignal of both putamina (Fig. 1), while CSF analysis showed persistence of the mildly increased albumin (39 mg/dL, with CSF/serum ratio of 1.1%) and lymphomonocytic pleocytosis (33 cells/mm³).

Discussion

The acute onset of generalized choreiform movements in a patient with diabetes would usually suggest a metabolic

etiology.³ However, the concurrent Sars-Cov-2 infection and the evidence of CSF pleocytosis together make a parainfectious mechanism involving the CNS the more likely cause of the chorea in this patient, whose picture may therefore be consistent with several neurological conditions that are clearly autoimmune in nature but show no detectable antibody reaction (eg, acute disseminated encephalomyelitis, ADEM).

We reviewed the relevant literature published up to April 2021 and extracted three reports of acute chorea with mild signs of encephalopathy and evidence of concurrent Covid-19 (see Table 1).⁴⁻⁶ All the patients had mild-to-moderate leukocytosis and absence of oligoclonal bands in the CSF. Our case, the only one with CSF follow-up, suggests that the immune response, in the absence of an effective immunomodulating therapy, can persist for a long time after resolution of the triggering event. When detectable, striatal involvement can present as a T1 enhancement

Table 1 Literature review of acute choreiform syndrome in patients with Sars-Cov-2

Patients	Clinical features	CSF	CSF Sars-Cov-2 PCR or antibody	CSF autoantibodies	Brain MRI	Treatment	Reference
14 years, F	Bilateral shoulder shrugging, choreiform movements in all four limbs	n.a.	n.a.	n.a.	Normal	Carbamazepine	Yüksel MF et al. ⁴
58 years, M	Choreiform movements in all four limbs, mild encephalopathy (irritability)	4 cells/mm ³ , no OCB	PCR positive	Absent	Mild periventricular ischemic changes (Fazekas=2)	Methylprednisolone, Risperidone, Amantadine, Haloperidol	Hassan M et al. ⁵
36 years, M	Choreiform movements in all four limbs, mild encephalopathy (agitation)	Mildly elevated lymphocytes	PCR negative	n.a.	Enhancement of bilateral medial putamen	Methylprednisolone, Ivlg	Byrnes S et al. ⁶
62 years, M	Bilateral shoulder shrugging, choreiform movements in all four limbs, mild encephalopathy (impulsivity, hyperactivity and attention impairment)	30 cells/mm ³ , no OCB	PCR negative	Absent	SWI abnormalities in bilateral dorsolateral putamen	Tetrabenazine, Haloperidol	This paper

Abbreviations: CSF, cerebrospinal fluid; n.a., not available; OCB, oligoclonal bands; PCR, polymerase chain reaction.

or a deposition of paramagnetic material visible on SWI. Although this finding does not have a single explanation, it is likely due to iron deposition caused by an inflammation-related oxidative status. This case series supports Sars-Cov-2 as a possible trigger of subacute movement disorders through a parainfectious mechanism, even when CSF is negative for Sars-Cov-2 (PCR or antibody test).^{7,8} As observed with other viruses, the release of cytokines/chemokines could be the main mechanism responsible for triggering a choreiform syndrome during Sars-Cov-2 infection.⁹

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

M.C.R.: 1A, 1B, 1C, 3A, 3B

G.P.: 1A, 1B, 1C, 3A

G.C.: 1B, 1C

L.F.: 1C

G.B.: 1A, 3B

M.C.: 1C, 3B

A.C.: 1C, 3B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. The patient provided a written informed consent for the publication of the video on this Journal. We confirm that we have read the Journal's position on issues involved in ethical

publication and affirm that this work is consistent with those guidelines.

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