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Choreo-ballistic movements heralding COVID-19 induced diabetic ketoacidosis

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1. Introduction

Unmasking of diabetes mellitus by coronavirus infectious disease of 2019 (COVID-19) is well established [1,2]. This dangerous duo has an established bidirectional relationship [3]. Diabetic ketoacidosis (DKA) is a severe acute metabolic complication typically characterized by acidosis, ketosis and usually hyperglycaemia [4]. There are several reported cases of previously euglycemic, undiagnosed, pre-diabetic or controlled diabetic patients who presented with DKA after harboring COVID-19 [1,2]. Several pathogenic mechanisms have been proposed for the development of insulinopenia, decreased insulin sensitivity, and increased insulin resistance in the backdrop of severe acute respiratory syndrome-coronavirus (SARS-CoV-2) infection [1–3].

Chorea and ballism are well-recognized, acute onset and potentially reversible movement disorders in acute hyperglycemic surges, especially in hyperosmolar hyperglycemic states [5], but rarely in DKA [6]. On the other hand, *de novo* movement disorders are scantly reported in COVID-19 [7]. We hereby describe the first case of a previously non-diabetic healthy patient who acutely presented with choreo-ballistic movements as the initial manifestation of COVID-19 induced DKA. Albeit, evidently COVID-19 induced diabetic striatopathy seems to be the most acceptable etiopathogenic milieu [6], possibility of *de novo* appearance of a movement disorder solely due to the viral infection itself remains alive.

2. Case report

A 60-year-old previously non-diabetic healthy man from rural India was admitted as he experienced sudden onset involuntary, uncontrollable, abnormal movements affecting his right arm and

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right leg for the last 36 hours. He also complained of dull aching pain in his abdomen for last 3 days associated with fever, cough, throat ache, malaise, increased thirst, excessive frequency of urination and generalized weakness. His past medical history and drug history were unrevealing, and all vital signs were normal except fever. Neurological examination revealed right-sided involuntary violent flinging movements in both upper and lower limb (especially on right lower limb), intermingled with involuntary semi-purposeful dancing movement involving both right upper and lower limbs (more on the right upper limb) (Video), suggestive of hemichorea-hemiballismus, which were markedly reduced during sleep, except the ballistic component. His cognitive functions were intact. The patient's oropharyngeal swab test for SARS-CoV-2, by qualitative real-time reverse-transcriptase–polymerase-chain-reaction assay, was positive, meanwhile capillary blood glucose was 540 mg/dL (tested at bedside). Dipstick urinalysis was suggestive of ketonuria (aceto-acetate). Complete blood cell count, liver and thyroid function tests, serum electrolytes, cardiac troponins, lipase, electrocardiography, chest X-ray and abdominal ultrasound were normal except mild neutrophilic leukocytosis (13000/μl) and lymphopenia (15%) as well as increased erythrocyte sedimentation rate (50 mm/hour) and C-reactive protein (58 mg/L). Blood and urine cultures failed to demonstrate any hint of bacterial infections. HbA1c was 5.1% (by HPLC, NGSP certified method). Type-1 diabetes autoimmune panel (serum GAD-65, anti-IA-2, insulin antibodies and islet cell antibodies) was negative. Fasting serum C-peptide level was 0.6 ng/ml (normal 0.81–3.85). D-dimer, lactate dehydrogenase, ferritin, creatine kinase and interleukin-6 (IL-6) levels were normal. High resolution computed tomography scan of the thorax revealed no relevant significant abnormalities. Renal function tests revealed mild pre-renal azotemia and the arterial blood gas analysis revealed high anion gap metabolic acidosis (pH 7.20, normal: 7.35–7.45; bicarbonate 13 mmol/L, normal: 22–28; pCO_2 26 mmHg, normal 35–45; and anion gap 18, normal 8–16) with normal lactate. Serum beta-hydroxybutyrate levels were high (3.8 mmol/L, normal < 1.5 mmol/L). Magnetic resonance imaging (MRI) of the brain showed left striatal hyperintensity on T1-weighted imaging (Fig. 1). Acute symptomatic hyperglycemia associated with right hemichorea-hemiballismus and MRI showing striatal abnormalities pointed towards a diagnosis of diabetic striatopathy [6,8]. Other etiologies considered, but ruled out due to lack of evidential substantiation, were euglycemic acute metabolic chorea (dysthyroidism, dysparathyroidism, dyselectrolytemia, hepatic dysfunction, or osmotic demyelination), toxin-induced chorea (Mn, carbon monoxide), vascular chorea (lenticulo-striate infarct or hypertensive striatal bleed), senile chorea and *de novo* COVID-19 associated hemichorea-hemiballismus.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.dsx.2021.04.010

Rehydration with intravenous fluids and continuous intravenous insulin infusion was initiated. Since respiratory symptoms were mild and high resolution computed tomography scan of the thorax was normal, he was not put on any specific therapy for the infection per se. After two days, ketonuria, ketonemia and acidemia disappeared and blood glucose level stabilized (capillary blood glucose was kept in the range 140–180 mg/dL) for which the insulin regime was shifted to the subcutaneous route after initial bridging with infusion regime. The abnormal movements abated with sustained normalization of blood glucose levels. He was discharged after seven days with a basal-bolus regime of insulin (insulin glargine (300 U/ml) 20 U/day subcutaneously as single basal therapy and 12 IU of soluble insulin (40 IU/ml) before breakfast, lunch and dinner) and diabetic medical nutrition therapy. Fig. 2 summarizes the timeline of events. He is continuously being followed up at regular intervals with achievement of good glycemic control and no evidence of recurrence of neurological ailments. It is worth mentioning that with each follow-up, total insulin requirement was showing a gradual yet definite downtrend; fasting serum C-peptide level at sixth month of follow-up was 0.86 ng/ml (normal 0.81–3.85). Since seventh month of follow-up, he is maintaining euglycemic state with insulin glargine (300 U/ml, single 14 U/day dose, subcutaneously) and soluble insulin (40 IU/ml, 6 IU subcutaneously 30 min before each major meal i.e. breakfast, lunch and dinner).

3. Discussion

SARS-CoV-2 infection can make a previously euglycemic person vulnerable to develop either transient or permanent hyperglycemia [1,2,9–11]. There are several possible explanations for development of DKA in SARS-CoV-2 infection (Fig. 3) [1–3,9–12]. First, ACE-2 receptor-mediated viral entry can directly damage the pancreatic beta cells. Furthermore, downregulation of the ACE-2 receptor hinders angiotensin II metabolism leading to its excess, which impedes insulin secretion. Second, counter-regulatory responses due to infection, inflammation and stress. Third, virus-triggered "autoimmune insulitis". Fourth, it might be an inflammation-induced insulin resistance. Fifth, renin-angiotensin-aldosterone system activation and reactive oxygen species over-production. Sixth, IL-6, elevated in COVID-19, may be a driver for ketosis. Seventh, exogenous glucocorticoids for combating cytokine storm in COVID-19 worsens glycemic control. Eighth, SARS-CoV-2 itself might have the potential for the development of type-1 diabetes like other viruses such as cytomegalovirus, Epstein-Barr virus, rotavirus, mumps, rubella, coxsackieviruses, enterovirus, and hepatitis C virus, among others [12]. First, second and fourth mechanisms separately or together might have played a role in this case. The striatum is a vulnerable region to acute metabolic perturbations due to both vascular and direct neuronal (dopaminergic and glutamatergic excitotoxicity) insults [13]. Diabetic striatopathy is one of the remarkably rare and reversible disorders in which an episode of acute hyperglycemia precipitates a transient, usually self-limiting movement disorder, with specific findings on neuroimaging involving striatum, having a particular predilection for elderly Asians [6,8]. Although this entity is increasingly being reported in hyperosmolar hyperglycemic states, it is rare in DKA, possibly due to the underlying pathological differences between the two [14]. Anaerobic cerebral metabolism in hyperglycemia leads to the depletion of gamma-amino-butyric acid (GABA) resulting in globus pallidus interna (GPi) mediated thalamic disinhibition, further culminating into hyperkinetic movement disorders [6,8,14]. Medical literature on "diabetic striatopathy" divulges that altered GABA metabolism in brain cells, hyperviscosity, cytotoxicity, obliterative vasculopathy, and hyperglycemia itself might lead to neuronal loss due to gemistocyte accumulation in the striatum, which can be considered as the genesis behind movement disorders [6,15]. However, this might not explain hyperkinetic movements in DKA as there exists an adequate supply of GABA (ketosis helps in resynthesizing this neurotransmitter in the liver from acetoacetate) [14].

Evidence suggests that SARS-CoV-2 infects the astrocytes and triggers neuropathological changes [16]. Specifically, a LC/MS-based metabolomic analysis has revealed extensive glycolytic changes and anaplerotic reactions, including a decrease in pyruvate, lactate, glutamine, glutamate and GABA in the brain of COVID-19 patients [16]. Therefore, increased metabolic activity of the SARS-CoV-2 infected cells, as well as a decrease in essential metabolites, especially glutamine and glutamine metabolism intermediates, may be responsible for affecting neuronal functions and the genesis of movement disorders (Fig. 3) [16]. Further, the

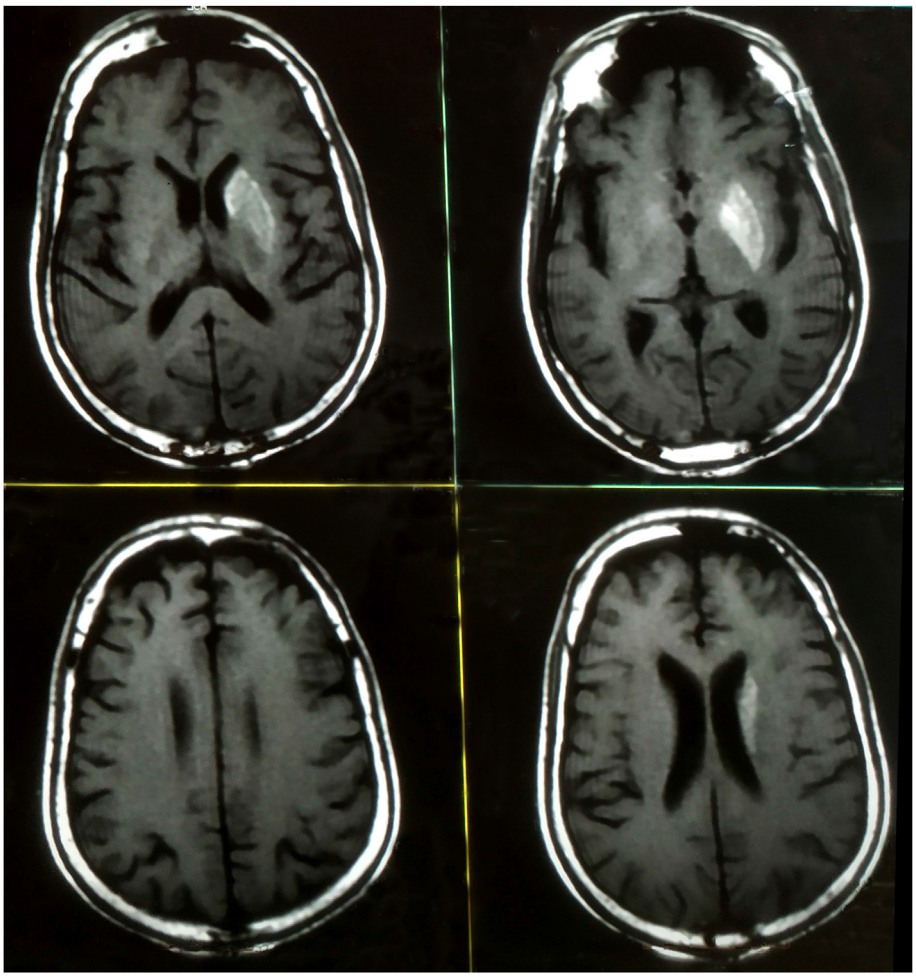

Fig. 1. MRI of the brain revealing increased signal intensity on T1-weighted imaging in the left caudate, putamen and globus pallidus, suggestive of striatopathy.

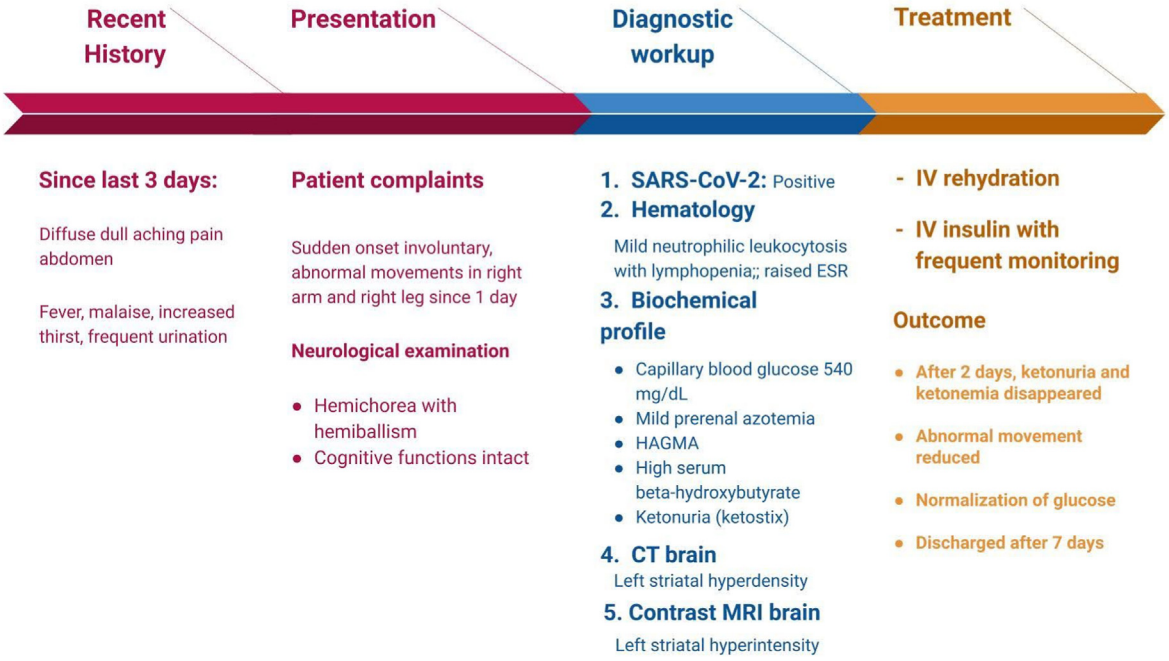

Fig. 2. A schematic flow of the timeline of events in this case.

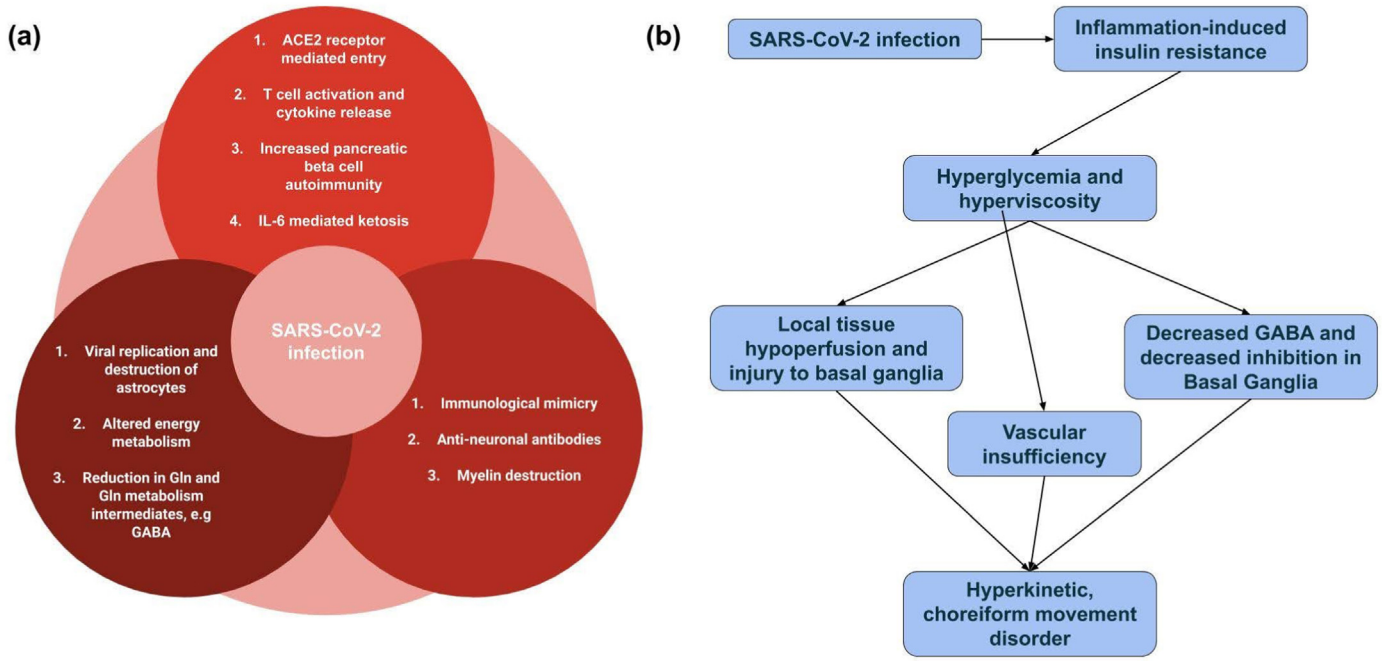

Fig. 3. A comparative enumeration of the possible pathogenic mechanisms leading to diabetic ketoacidosis and movement disorders in COVID-19.

presence of the virus has also been associated with astrogliosis and immune cell accumulation, pointing towards immune-mediated neurodegeneration (Fig. 3) [16].

We feel that both DKA and SARS-CoV-2 could have jointly contributed to the genesis of movement disorders. Also, the viral infection could have precipitated DKA and striatopathy that favored the movement disorders [14]. SARS-CoV-2 infection could also lead to depletion of GABA, which caused GPi-mediated thalamic disinhibition and resultant choreo-ballistic movements. These interconnections might well be one of the appropriate explanations for the apparent clinical and radiological discordance in this case, i.e. clinical presence of a ballistic movement disorder in absence of any demonstrable lesion over sub-thalamic nucleus or thalamus on MRI rather lesion was seen predominantly over caudate, putamen and globus pallidus.

Gradual downtrend in requirement of insulin for maintenance of euglycemia and relative normalization of C-peptide level might be suggestive of gradual recovery from “glucotoxicity”, decreasing insulin resistance that was associated with infection and inflammation, increasing insulin sensitivity, or rejuvenation of islet cells from infection/inflammation related transient dormancy.

To conclude, our case shows the potential of SARS-CoV-2 to cause movement disorders in the setting of COVID-19 induced DKA.

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2021.04.010.

Author contributions

Ritwik Ghosh, Souvik Dubey, Dipayan Roy, Adrija Ray, Alak Pandit, Biman Kanti Ray and Julián Benito-León: drafting/revising the manuscript, study concept or design; accept responsibility for the conduct of research and final approval, acquisition of data.

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