Diabetic ketoacidosis, cerebral venous sinus thrombosis and fulminant cerebral oedema in COVID-19 infection complicated by Klebsiella pneumoniae infection

Lindsey A Wallace,1 Sara E Hocker,2 Hilary Dubrock,3 Philippe Bauer4

SUMMARY
We present an unusual case of a woman in her 30s who was admitted for diabetic ketoacidosis (DKA) in the setting of newly diagnosed but late COVID-19 infection with associated Klebsiella pneumoniae infection. Her altered mental status, out of proportion with her metabolic decompensation, revealed a superimposed cerebral venous sinus thrombosis (CVST) with fulminant cerebral oedema and ultimately brain death. This unusual and fulminant case of cerebral oedema in the setting of COVID-19 infection with bacterial infection, DKA and CVST was the perfect storm with multiple interwoven factors. It offered diagnostic and treatment challenges with an unfortunate outcome. This unique case is a reminder that it is important to consider a broad neurological differential in patients with COVID-19 with unexplained neurological manifestations, which may require specific neurointensive care management.

BACKGROUND
Both thromboembolic events and neurological manifestations are frequent in COVID-19 infection and portend a poor prognosis. However, the incidence of cerebral venous sinus thrombosis (CVST) in the setting of COVID-19 is rare.

CASE PRESENTATION
We present the case of a woman in her 30s who was admitted to our intensive care unit (ICU) for diabetic ketoacidosis (DKA) in the setting of newly diagnosed diabetes mellitus type II, altered mental status and COVID-19. The patient was unable to provide written consent due to her presentation and critical illness.

Her spouse found her confused and agitated for an unknown period before he brought her to an outside emergency department. Her spouse said the patient reportedly had a headache the day prior but denied any history of injury or trauma. On examination in the emergency room, heart rate was 118 bpm, respiratory rate was 43 bpm and Glasgow Coma Scale was 10 without any focal neurological deficit. On laboratory testing, serum glucose was 628 mg/dL (70–140 mg/dL), beta-hydroxybutyrate was 2.3 mmol/L (0–0.5 mmol/L), white cell count was 12 300×10^9/L (5000–10000×10^9/L), platelet count 65×10^9/L (150–450×10^9/L), prothrombin time ratio 1.3 (0.8–1.2), activated partial thromboplastin time 37.9 seconds (12–35 seconds), fibrinogen >1000 mg/dL (200–393 mg/dL). Lactate was 1.1 (0.5–2.2 mmol/L), troponin was 6 ng/L (<10 ng/L), then <6 ng/L after 2 hours. Pregnancy test with quantitative human chorionic gonadotropin was negative at 0.7 IU/L (<5 IU/L). Plasma ethanol, acetaminophen and salicylate levels were negative. Serum ethanol, acetone, isopropanol and methanol levels were negative. Urine drug screen and volatile screen were negative. Chest radiograph showed patchy bilateral multifocal pulmonary opacity consistent with viral or bacterial pneumonia. SARS-CoV2 PCR swab came back positive. Head CT without intravenous contrast showed no intracranial abnormality (figure 1). She was given 1 mg of intravenous lorazepam for agitation, intubated for airway protection and sedated with ketamine. A nurse-driven titratable insulin infusion with hourly glucose checks, sodium bicarbonate was initiated, and she received 4 L of normal saline for DKA. She was transferred to our institution directly to the ICU.

On arrival in the ICU, she remained intubated, ventilated and haemodynamically stable. On arterial blood gas, pH was 7.15, PaCO₂ 30 mm Hg (32–45 mm Hg), PaO₂ 91 mm Hg (83–108 mm Hg) and bicarbonate 10 mmol/L. Calculated PaO₂/FiO₂ ratio was 227.5 mm Hg. She remained agitated and was kept sedated with fentanyl and propofol instead of ketamine for ventilator synchrony. Insulin infusion was continued. An arterial line and central line were placed. Chest radiograph showed again bilateral patchy airspace opacities consistent with acute respiratory distress syndrome. She received remdesivir, dexamethasone and tocilizumab for presumed severe COVID-19 pneumonia after emergent consultation with infectious diseases service. She was given deep vein thrombosis prophylaxis with enoxaparin 30 mg subcutaneously (patient’s weight was 43.5 kg, body mass index was 17.65 kg/m²).

Over the next 4 hours, she became progressively hypertensive reaching a blood pressure of 176/101 mm Hg for which she received 10 mg of labetalol intravenously. She stabilised for a few hours before she suddenly developed decerebrate posturing, with fixed and dilated pupils, no corneal or gag reflex and no spontaneous ventilation. Then she became hypotensive and was started on norepinephrine. She also developed polyuria and hypernatremia, with a sodium level of 163 mmol/L (135–145 mmol/L) consistent with diabetes.
insipidus for which she received desmopressin (four doses of 2 μg over 12 hours), and dextrose 5% water infusion which was initiated at 50 mL/hour, then increased to 125 mL/hour based on sodium levels and increased urine output. An emergent repeat head CT revealed diffuse cerebral oedema without herniation or haemorrhage. Neurology was consulted emergently. Sedation was stopped and mannitol was given. Meanwhile, her blood cultures came back positive for *Klebsiella pneumoniae* for which she was started on piperacillin–tazobactam.

Brain magnetic resonance venography (figure 2) was performed a few hours later and demonstrated diffuse cerebral oedema with marked attenuation of arterial flow voids at the skull base and non-opacification of the internal cerebral veins, vein of Galen and the dural venous sinuses. She was started on high-intensity heparin. Antiphospholipid serologies were normal (phospholipid Ab IgM 11.1, IgG <9.4 GPL). COVID-19 IgG antibodies came back positive and consistent with late COVID-19 infection. Remdesivir was discontinued, dexamethasone was maintained, and antibiotics were broadened to vancomycin and cefepime.

Head CT angiography (figure 3) the next day revealed worsening diffuse cerebral oedema with signs concerning for increased intracranial pressure, new dart haemorrhages of the midbrain and upper pons, non-opacification of the bilateral supraclinoid internal carotid and vertebral arteries and similar marked attenuation and thrombosis of the deep venous system and dural venous sinuses. She was declared brain dead soon thereafter.

**DISCUSSION**

This patient with previously undiagnosed diabetes mellitus type II presented initially with symptoms of DKA in the setting of newly diagnosed but already established COVID-19 infection based on positive serology. She was also diagnosed with a bloodstream infection soon after, likely a secondary infection linked to the known immune suppressive effect of both COVID-19 and diabetes mellitus, whereas bacterial co-infections are less frequent at the early phase of COVID-19. Despite supportive measures aiming at correcting the DKA and intravenous antibiotics, the patient’s neurological status deteriorated further, which was highly unusual. Diabetes mellitus is a known risk factor for severe COVID-19, and diabetic ketoacidosis has been observed frequently leading to increased mortality. Patients with COVID-19 are also at a higher risk for thromboembolic events with a higher risk of mortality, especially among patients who are hospitalised. Neurological manifestations are frequent with COVID-19 and associated with a higher mortality in hospitalised patients. Potential mechanisms include direct neuroinvasion (eg, meningitis, encephalitis), neuroinflammation (eg, acute necrotising encephalopathy), autoimmune disorders and other complications (eg, ischaemic stroke, endotheliopathy and hypercoagulability). The incidence of CVST has rarely been reported in patients with COVID-19, and a high suspicion is necessary because of its potentially life-threatening condition and challenging diagnosis. CVST has now been reported after adenovirus-based vaccine as well. Prior to the pandemic, CVST was relatively rare, accounting for 0.5%–1.0% of cerebrovascular accidents in adults. Usually patients present with headache, 90% of the time, and have underlying risk factors such as oral contraceptives, pregnancy, systemic infections, meningitis, cancer, antiphospholipid syndrome and many others. It is important to note that this patient had been reporting of headache prior to presentation to support that her neurological changes may have been insidiously manifesting prior to her admission.

The patient was also encephalopathic, which ultimately lead to rapid intubation with ongoing sedation to control agitation and maintain ventilator synchrony in the context of hypoxemic respiratory failure. Additionally, her initial head CT was not alarming, which further supported a toxic/metabolic process
rather than a neurological process for her altered mentation on presentation, and the bloodstream infection would only be confirmed later. Meningitis was unlikely given the lack of pachymeningeal findings on brain imaging. Encephalitis could have explained the cerebral oedema from an acute infection; however, this patient’s COVID-19 infection was established prior to her hospitalisation making the diagnosis of encephalitis less likely.

In general, acute cerebrovascular accidents may not be so infrequent in patients with COVID-19, especially in those who are severely infected and have pre-existing vascular risk factors such as diabetes mellitus. Independent of COVID-19, the finding of cerebral oedema has been associated with deep cerebral venous thrombosis and poor clinical outcomes. While cerebral oedema associated with DKA management in paediatric patients has been well documented in the literature, the role of specific aspects of DKA management in the development of cerebral oedema is extremely rare in adults and remains controversial. Case reports regarding diabetic patients with COVID-19 and resulting cerebral oedema from CVST have not been published.

This unusual and fulminant case of cerebral oedema in the setting of COVID-19 infection with bacterial infection, DKA and CVST was the perfect storm with multiple interwoven factors. It offered diagnostic and treatment challenges with an unfortunate outcome. While this case may be unique, it is important to consider a broad neurological differential in patients with COVID-19 with unexplained neurological manifestations, which may require specific neurointensive care management. It is now well established that COVID-19 can be complicated by coinfections, secondary infections and venous and arterial thromboembolic events as well as metabolic decompensation such as diabetes mellitus. A high index of suspicion and frequent neuro checks should prevail during and after the initial onset of COVID-19 infection.

Contributors LAW: planning, conduct, reporting, conception and design, analysis and interpretation of all data in the case, manuscript writing, revising and editing. PRB: planning, conduct, reporting, conception and design, analysis and interpretation of all data in the case, manuscript revision and editing, SEH: planning, analysis and interpretation of neurological data in the case, manuscript editing. HD: analysis and interpretation of data related to critical care aspects of the case, manuscript editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID ID
Lindsey A Wallace http://orcid.org/0000-0001-7264-9704

REFERENCES
1 Karimi Z, Knoop BT, Dofferhoff ASM, et al. Few bacterial co-infections but frequent empiric antibiotic use in the early phase of hospitalized patients with COVID-19: results from a multicentre retrospective cohort study in the Netherlands. *Infect Dis 2021;53:102–10.*
2 Targher G, Mantovani A, Wang X-B, et al. Patients with diabetes are at higher risk for severe illness from COVID-19. *Diabetes Metab 2020;46:335–7.*
3 Papadopoulos VP, Koutroulou M-V, Zikoudi D-G, et al. Diabetes-related acute metabolic emergencies in COVID-19 patients: a systematic review and meta-analysis. *Diabetol Int 2021;12:445–59.*
4 Malais MB, Naazie IN, Elsayed N, et al. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: a systematic review and meta-analysis. *EClinicalMedicine 2020;29:30:100639.*
5 Fontana P, Casini A, Robert- Ebadi H, et al. Venous thromboembolism in COVID-19: systematic review of reported risks and current guidelines. *Swiss Med Wkly 2020;150:w20301.*
6 Chou SH-Y, Beghi E, Helbok R, et al. Global incidence of neurological manifestations among patients hospitalised with COVID-19: a report for the GCS-NeuroCOVID Consortium and the energy Consortium. *JAMA Netw Open 2021;4:e2112131.*
7 Newcombe VFJ, Danayach NS, Sonnville R. Neurological complications of COVID-19. *Intensive Care Med 2021;47:1021–3.*
8 Baldini T, Asloli GM, Romolli M, et al. Cerebral venous thrombosis and severe acute respiratory syndrome coronavirus-2 infection: a systematic review and meta-analysis. *Eur J Neurol 2021;28:3478–90.*
9 See I, Su IR, Lale A, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. *JAMA 2021;325:e217517:2448.*
10 Saponigk N, Barinagarrementeria F, Brown RD, et al. Diagnosis and management of cerebral venous thrombosis. *Stroke 2011;42:1158–92.*
11 Coutinho JM. Cerebral venous thrombosis. *J Thromb Haemost 2015;13:5238–44.*
12 Nannoni S, de Groot R, Bell S, et al. Stroke in COVID-19: a systematic review and meta-analysis. *Int J Stroke 2021;16:137–49.*
13 Nasr DM, Brinjikji W, Cofli H, et al. Mortality in cerebral venous thrombosis: results from the National inpatient sample database. *Cerebrovasc Dis 2013;35:40–4.*
14 Zuurbier SM, van den Berg R, Troost D, et al. Hydrocephalus in cerebral venous thrombosis. *J Neurol 2015;262:931–7.*
15 Natarajan S, Kulakami R, Tangri A. Fatal cerebral edema in a young adult with diabetic ketoacidosis: blame the bicarbonate? *Case Rep Crit Care 2020;2020:1–4.*
16 Azoua S, Rappaport R, Wolfsdorf J. Brain injury in children with diabetic ketoacidosis: review of the literature and a proposed pathophysiologic pathway for the development of cerebral edema. *Pediatr Diabetes 2021;22:148–60.*
