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GLOBAL CEREBRAL EDEMA FROM HYPERCAPNIC RESPIRATORY ACIDOSIS AND RESPONSE TO HYPEROSMOLAR THERAPY

Hypercapnic respiratory acidosis (HRA) causes cerebral vasodilation via perivascular extracellular pH changes.[1] Its ability to precipitate global cerebral edema (GCE) in the absence of acute brain injury is rare. Treatment in these reports involves mechanical ventilation.[2] We describe a rare case of HRA-induced GCE in a patient without brain injury and the efficacy of hyperosmolar treatment after mechanical ventilation failed.

This case provides Class IV evidence. This is a single observational study without controls.

Case report. A 32-year-old quadriparetic man with cervico-thoracic syringomyelia and ventriculoperitoneal shunt (VPS) presented with recurrent dyspnea. Prior episodes were treated with noninvasive positive pressure ventilation (NIPPV). However, he presented 6 hours after symptom onset, much later than prior episodes. He denied new sensorimotor or constitutional symptoms. He was afebrile, tachycardic, tachypneic, and without evidence of hypoxia or dysautonomia. General examination revealed rapid, shallow breathing. Mental status and cranial nerves were intact with baseline spastic quadriparesis and hyperreflexia.

Arterial blood gas (ABG) on room air revealed HRA (pH: 7.18, $PaCO_2$: >96 mm Hg, PaO_2: 128 mm Hg, HCO_3: 42 mEq/L). Routine laboratory studies, cardiopulmonary, and infectious workup were unrevealing. NIPPV failed to improve HRA. A previous do not intubate order was reversed after discussion with the patient. After 65 hours of HRA, the patient progressed to coma and was intubated. CT brain (figure, A) revealed GCE and he was transferred to the neurointensive care unit.

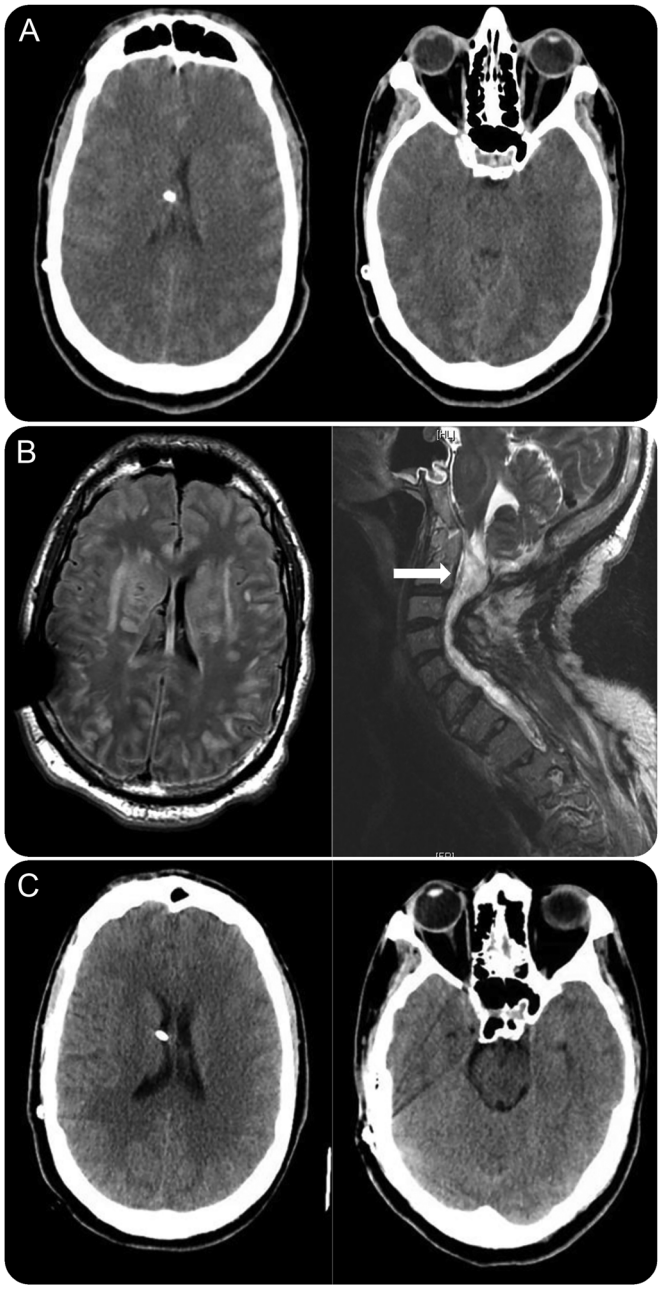
Despite HRA resolution after intubation (ABG: pH: 7.58, $PaCO_2$: 42 mm Hg), the patient had a Glasgow Coma Scale (GCS) score of 3T. A total of 30 mL of 23% NaCl on arrival provided transient improvement of GCS to 7T (motor localization) before returning to GCS 3T. Metabolic workup and EEG were unrevealing. MRI brain at 96 hours revealed diffuse subcortical hyperintensities despite HRA resolution for over 30 hours (figure, B). There was no evidence of hypoxic injury, thrombosis/infarct, infection, or hydrocephalus. VPS was functional via shunt series examination. MRI spine revealed stable syringomyelia. Persistent coma and prior response to hyperosmolar therapy prompted scheduled hyperosmolar therapy. Thirty milliliters of 23% NaCl at 103 hours improved the GCS from 3T to 10T within an hour (following commands). The GCS worsened from 10T to 7T at 105 hours and mannitol 80 g (1g/kg) was given, improving the GCS back to 10T within 3 hours.

Alternating scheduled 23% NaCl and mannitol were continued every 6 hours with titration to clinical response. The patient returned to his neurologic baseline in 24 hours but required a tracheostomy and phrenic nerve pacer placement for ventilator support. A 2-month follow-up CT scan revealed resolution of GCE (figure, C).

Discussion. Etiologies for edema such as hydrocephalus, cervical dysautonomia, infection, stroke, toxins, and hepatic failure[3] were excluded in our patient. Without other provoking factors, his delayed presentation and subtle extension of the syringomyelia (not appreciated on imaging) resulted in severe HRA. Central respiratory drive was intact, but was limited by neuromuscular weakness resulting in GCE.

$PaCO_2$ >80 mm Hg increases cerebral blood flow up to 6 times its baseline[4] via pH-induced chemoregulatory cerebrovasodilation. Hyperemia in conjunction with increased vascular permeability from severe vasodilation allowed for resultant edema formation and subsequent elevated intracranial pressure. The length of time required to precipitate GCE from HRA is unknown. Our patient had

Figure Hypercapnic cerebral edema and resolution after hyperosmolar therapy



(A) CT (65 hours): global cerebral edema (GCE) (functioning ventriculoperitoneal shunt). (B) MRI (96 hours): diffuse subcortical hyperintensities despite 30 hours of acidosis/CO_2 correction; severe/stable cervico-thoracic syringomyelia. (C) CT (2-month follow-up): resolved GCE.

severe HRA for more than 60 hours prior to deterioration. Furthermore, he remained comatose for approximately 30 hours following HRA correction until hyperosmolar therapy was initiated. Although documented as >96 mm Hg, our patient's $PaCO_2$ level was most likely much higher than what was reported (due to laboratory limitations) and continued to rise until mechanical ventilation was implemented. This prolonged HRA led to sustained cerebral acidosis unamenable to compensatory measures inducing a vasoplegia in which correction of arterial pH no longer mitigated a vasoconstrictive response.

While critical in other types of brain injury, the role of hyperosmolar therapy in GCE incited by HRA has not been described previously.[5] The use of hyperosmolar therapy may have had a 2-fold effect in returning the patient back to baseline: (1) water extraction through the creation of an intravascular osmotic gradient and (2) rheologic and cardiac output augmentation resulting in mechanoregulatory vasoconstriction and a subsequent decrease in intracranial pressure.[6] The role of hyperosmolar therapy in treating GCE in this case is further supported by the temporal synchronization of our patient's clinical fluctuations reflecting the pharmacokinetic profile of mannitol/hypertonic saline: onset 30 minutes and duration of action 2–12 hours.[7] Our patient's extreme hypercapnia in the absence of hypoxemia did not alter the cerebral energy state and subsequently did not result in irreversible cell damage. Consequently, our patient's case illustrates that hyperosmolar therapy in patients with GCE secondary to HRA should be considered should mechanical ventilation fail.

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Comment: Revisiting Lassen cerebral blood flow constancy with hysteresis and 3D

Roh et al.[1] present a unique case of severe, prolonged hypercapnic respiratory failure that triggered refractory global cerebral edema (GCE). This case report is interesting because edema was not abatable by hyperventilation, despite adequate reversal to a normocapnic state, and responded only to aggressive osmotherapy.

The relationship between cerebral blood flow (CBF) and arterial partial pressure of carbon dioxide ($PaCO_2$) may thus be represented visually by an S-curve with a delayed return in response to prolonged hypercapnia (figure 1). At a certain threshold of $PaCO_2$ that is sustained for a substantial duration, a state of "vasoplegia" might be triggered, whereby reversal of $PaCO_2$ levels is no longer effective in decreasing CBF. In reality, regulation of CBF is a complex process[2] that can be further comprehended by examining correlations between cerebral perfusion pressure (CPP) and CBF, and also between $PaCO_2$ and CBF, with a 3D interplay (figure 2). It is worth emphasizing that autoregulation, vasoreactivity, and blood–brain barrier impermeability are nuanced physiologic functions, not always directly related,[3] and each can lead to dysregulated CBF and to GCE. Serial measurements of CBF, CPP, and permeability, by neuroimaging and intracranial probes, would have been ideal to scrutinize the effects during hyperventilation and osmotic treatment in this patient.

Readers should not extrapolate these therapeutic suggestions for a noninjured brain with acute on chronic hypoventilation to common cases of brief exposure to severe hypercapnia. Finally, the fluid-attenuated inversion recovery image depicts GCE with an intriguing predilection for subcortical U fibers and periventricular CSF spaces, suggesting venular hypertension, rather than diffuse white and gray matter involvement, as expected in global cerebral capillary vasoplegia.

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Figure 1 **Effect of arterial partial pressure of carbon dioxide ($PaCO_2$) onto cerebral blood flow (CBF) in usual circumstances and in this acute on chronic prolonged hypercarbic case triggering hysteresis**

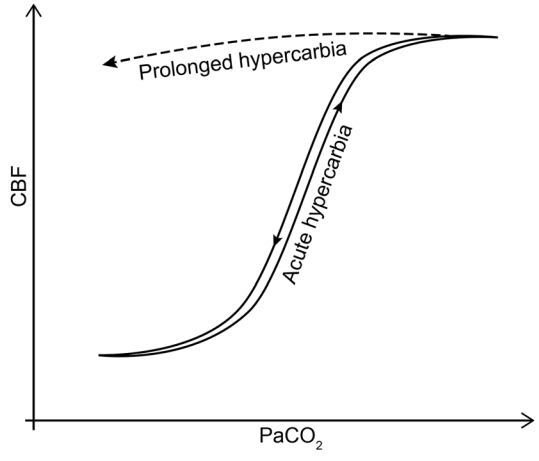

Figure 2 **Three-dimensional representation of the interplay among cerebral perfusion pressure (CPP), arterial partial pressure of carbon dioxide ($PaCO_2$), and cerebral blood flow (CBF)**