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CASE REPORT

Atypical complication of western equine encephalitis: central hypoventilation syndrome.

Síndrome de hipoventilación central, una complicación atípica de la encefalitis equina.

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Palabras clave:

Hipoventilación central alveolar; encefalitis equina del oeste; virus WEE; acetazolamida; togaviridae; zoonosis virales.

Abstract

Case Description:

A 49-year-old male patient, a rural worker, presented with a two-day history of fever. Initial treatment for suspected community-acquired pneumonia was followed by the development of confusion and signs of meningeal irritation. Western Equine Encephalitis Virus infection was confirmed. The patient required prolonged intensive care due to central hypoventilation syndrome, a complication not previously described for this condition.

Clinical Findings:

The patient exhibited hypercapnia-related encephalopathy, with MRI revealing pontine lesions. Respiratory drive testing confirmed central hypoventilation. Peripheral muscular strength was preserved, ruling out muscular or peripheral neurological involvement. Persistent metabolic alkalosis secondary to failed ventilator weaning attempts was noted.

Treatment and Outcome:

Treatment included mechanical ventilation, nocturnal invasive ventilation, and acetazolamide to address post-hypercapnic metabolic alkalosis. Gradual improvement led to successful decannulation after 46 days. At the 30-day follow-up, the patient reported full independence and returned to work, maintaining stable respiratory function and acid-base balance.

Clinical Relevance:

This case highlights central hypoventilation syndrome as a rare but significant complication of Western Equine Encephalitis Virus infection. The administration of acetazolamide proved effective in managing metabolic alkalosis, supporting its potential role in similar cases. Further investigation is needed to better understand this complication and to establish evidence-based management strategies.

Conflict of interest:

The authors declare no conflicts of interest.

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Resumen

Descripción del caso:

Paciente masculino de 49 años, trabajador rural, con un cuadro de dos días de evolución de fiebre. El tratamiento inicial para neumonía adquirida en la comunidad fue seguido por el desarrollo de confusión y signos meníngeos. Se confirmó infección por el virus de la encefalitis equina occidental, El paciente requirió cuidados intensivos prolongados debido a síndrome de hipoventilación central, una complicación no descrita previamente para esta enfermedad.

Hallazgos clínicos:

El paciente presentó encefalopatía por hipercapnia, con lesiones en la protuberancia visualizadas por resonancia magnética. Las pruebas de impulso respiratorio confirmaron hipoventilación central. La fuerza muscular periférica estaba conservada, descartándose compromiso muscular o neurológico periférico. Se observó alcalosis metabólica persistente secundaria a intentos fallidos de desvinculación de la ventilación mecánica.

Tratamiento y resultados:

El tratamiento incluyó ventilación mecánica, ventilación invasiva nocturna y acetazolamida para abordar la alcalosis metabólica post-hipercapnia. La mejoría gradual permitió una decanulación exitosa a los 46 días. A los 30 días del alta, el paciente reportó independencia total y reincorporación laboral, con función respiratoria y equilibrio ácido-base estables.

Relevancia clínica:

Este caso destaca el síndrome de hipoventilación central como una complicación rara pero significativa de la encefalitis equina occidental. El uso de acetazolamida fue efectivo para manejar la alcalosis metabólica, respaldando su potencial utilidad en casos similares. Se requiere más investigación para explorar esta complicación y establecer estrategias de manejo basadas en evidencia.

Introduction

The western equine encephalitis virus is an alphavirus belonging to the Togaviridae family [1]. In Argentina, its primary vector is the mosquito *Aedes albifasciatus*[2], and birds serve as its main reservoir [1]. Horses, humans, and domestic animals are accidental hosts, as they can develop the disease but do not transmit it. Western equine encephalitis virus can cause a spectrum of illness ranging from asymptomatic infection and nonspecific febrile illness to encephalitis [1].

On december 20, 2023, the World Health Organization was notified of a case of western equine encephalitis in a person from Argentina. This represents the first confirmed human case reported in over two decades in the country [1]. By the end of february 2024, 91 cases had been confirmed in humans and 1,496 in horses. Among these confirmed cases, seven deaths were reported across various provinces [3].

We describe a patient with western equine encephalitis who developed a complication not previously reported for this disease: central hypoventilation syndrome, which required the patient to remain in the intensive care unit for 48 days. The therapeutic approach applied is also described.

This study was approved by the institutional review board, and informed consent was obtained from the patient.

Case presentation

We present the case of a 49-year-old male rural worker with a body mass index of 25, and a history of tobacco use and alcohol consumption, which he ceased one year prior. Figure 1 provides a timeline of the key events.

The patient consulted for a clinicals symptom of 48 hours of evolution characterized by fever. The initial diagnosis was community-acquired pneumonia, and he was started on outpatient treatment with amoxicillin and clavulanic acid. Forty-eight hours later, he returned due to persistent fever, headache, and confusion. Photophobia and neck stiffness were observed. cerebrospinal fluid analysis was normal (clear, 1 leukocyte, 3 red blood cells, protein 47 mg/dL, glucose 119 mg/dL), and cultures for common pathogens were negative. Samples were sent for testing to rule out viral meningoencephalitis. Empirical treatment was initiated with ceftriaxone, acyclovir, and dexamethasone. Days later, western equine encephalitis virus was confirmed.

At 24 hours, the patient's Glasgow Coma Scale score deteriorated to 8/15, requiring orotracheal intubation and admission to the intensive care unit, where mechanical ventilation was initiated (day 0).

At 48 hours, the patient was off sedation and underwent a spontaneous breathing trial. However, he could follow only two out of four simple commands and was reconnected to mechanical ventilation. On the third day, he self-extubated and developed impaired level of consciousness due to hypercapnia ($PaCO_2$ 122 mm Hg), leading to the decision to reintubate.

On the fifth day, the patient had a Richmond Agitation-Sedation Scale (RASS) score of 0 and a negative Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). He passed a spontaneous breathing trial and was extubated. However, two hours later, intermittent non-invasive ventilation was initiated due to hypercapnia (pH 7.19, PaCO2 77 mm Hg, HCO_3^- 29 mmol/L, PaO2 88 mm Hg, oxygen saturation 94%). Neurological evaluation revealed reactive, isochoric pupils and preserved visual fields. Paralysis of conjugate gaze in horizontal and, to a lesser extent, upward directions was observed, with intact downward movement and convergence impairment. No motor weakness or sensory deficits were noted. Mild ataxia was observed in all four limbs during finger-to-nose and heel-to-shin tests. Brain magnetic resonance imaging showed a focal hyperintense signal on T2 and FLAIR in the central pons region and the right lenticular nucleus, along with incipient periventricular leukoaraiosis. The imaging equipment's low resolution precluded diffusion-weighted imaging and apparent diffusion coefficient mapping. Based on these findings and the history of alcohol use, vitamin B12 supplementation was added to the treatment.

On the 9th day, the patient's Glasgow Coma Scale score deteriorated to 3/15, requiring orotracheal intubation. One hour later, the patient had a RASS score of 0. Respiratory drive was assessed using the Neumovent Graph by measuring P0.1 (0.2 cmH_2O), which indicated a diminished central respiratory impulse (normal range 0.5 to 1.5 cmH_2O). Additionally, inspiratory muscle strength was evaluated by measuring maximal inspiratory pressure, which was 44.5 cmH_2O, showing adequate inspiratory capacity.

Peripheral muscular strength was evaluated using the Medical Research Council scale, with a score of 60. Quadriceps strength measured with dynamometry was within normal ranges.

Since the patient did not exhibit muscular strength impairment but experienced recurrent episodes of carbon dioxide (CO_2) retention and desaturation during spontaneous breathing, a diagnosis of central hypoventilation syndrome was suggested.

In the following days, daily spontaneous breathing trials were performed, all of which failed due to hypercapnia.

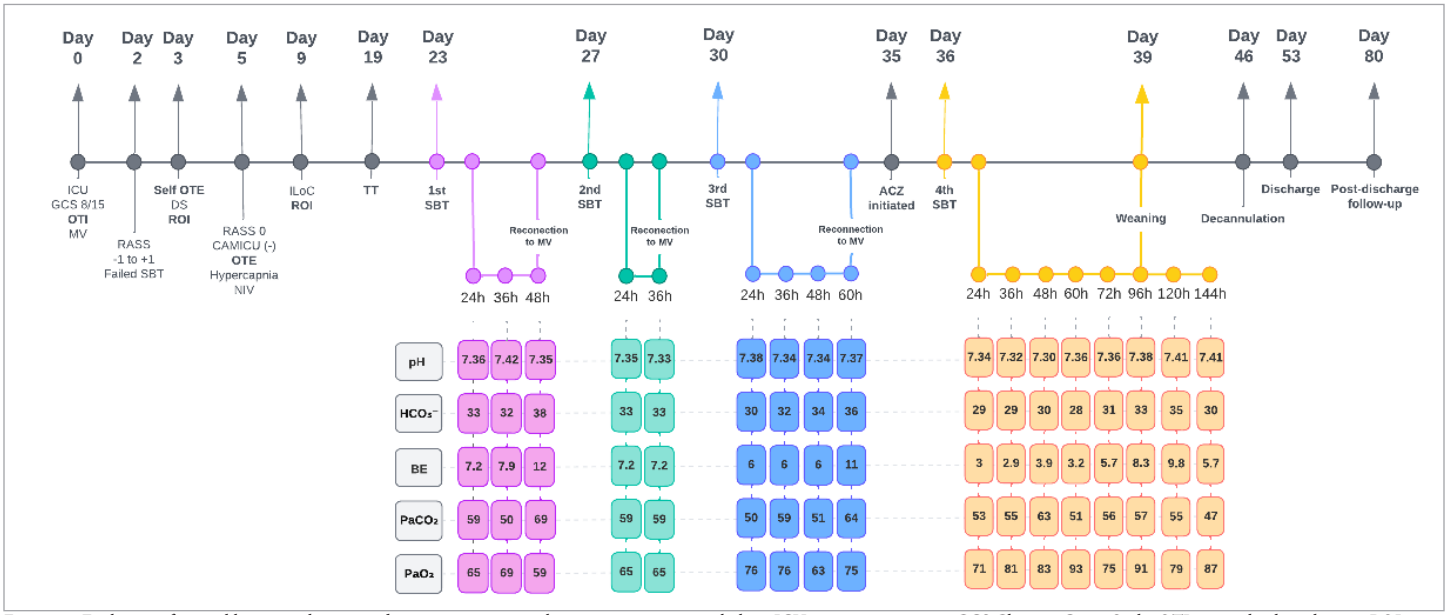

Figure 1. Evolution of central hypoventilation syndrome in a patient with western equine encephalitis. ICU intensive care unit. GCS Glasgow Coma Scale. OTI orotracheal intubation. ROI re-orotracheal intubation. MV mechanical ventilation. SBT spontaneous breathing trial. OTE orotracheal extubation. CAMICU Confusion Assessment Method for the Intensive Care Unit. RASS Richmond Agitation-Sedation Scale. ILoC impaired level of consciousness. NIV non-invasive ventilation. TT tracheostomy tube. ACZ acetazolamide.

On the 19th day of hospitalization, a tracheostomy was performed. Within 24 hours, the patient achieved 12 hours of spontaneous ventilation followed by 12 hours of invasive nocturnal ventilation for three consecutive days. Rehabilitation continued, enabling the patient to walk unassisted, use a deflated tracheostomy cuff with a speaking valve, and tolerate oral feeding.

In the following days, several weaning attempts were made, which led to increased levels of carbon dioxide ($PaCO_2$) and a subsequent rise in bicarbonate (HCO_3^-) levels. When the patient was reconnected to mechanical ventilation, post-hypercapnic metabolic alkalosis (pH 7.59) developed. Consequently, nocturnal ventilation was maintained to reduce bicarbonate levels (32 mmol/L).

Treatment with acetazolamide (250 mg/day) was initiated for three consecutive days to reduce metabolic alkalosis. On day 39, the patient was successfully weaned off mechanical ventilatory support. As bicarbonate (HCO_3^-) levels increased again, acetazolamide was reintroduced at a dose of 125 mg/day on alternate days. The patient was decannulated without complications 46 days after admission.

After 48 days in the intensive care unit, the patient was transferred to the general ward, presenting only mild left-sided brachiocrural dysmetria. Finally, on day 53, he was discharged.

At 30 days post-discharge, the patient reported living independently with optimal performance in daily activities (Barthel Index score 100) and had returned to work. Evaluation using the SF-36 questionnaire revealed the following scores: physical functioning 95%, role limitations due to physical health 0%, bodily pain 80%, general health 65%, vitality 70%, social functioning 62.5%, role limitations due to emotional health 100%, and mental health 60%. The patient's health remained stable, with acid-base balance parameters as follows: pH 7.43, bicarbonate (HCO_3^-) 27 mmol/L, partial pressure of carbon dioxide ($PaCO_2$) 40 mmHg, and partial pressure of oxygen (PaO_2) 102 mmHg, while continuing acetazolamide therapy. Spirometry results indicated a FEV_1 of 88% and an FEV_1/ FVC of 95%.

Discussion

In this case, we present a patient with central hypoventilation syndrome secondary to western equine encephalitis. This diagnosis was suggested after confirming the integrity of peripheral muscle strength and the absence of a respiratory center response to hypercapnia observed during spontaneous ventilation.

Central hypoventilation syndrome is characterized by an inadequate response of the respiratory center to hypercapnia and hypoxemia, caused by a decrease in respiratory rate and tidal volume. The diagnosis is primarily clinical and can be confirmed through polysomnography or cardiorespiratory polygraphy [4], procedures that were not available at our hospital.

Central hypoventilation syndrome is associated with brainstem tumors, ischemia, Arnold-Chiari malformation [5], as well as autoimmune and paraneoplastic encephalitis [5-8]. However, we found only one reported case linked to viral encephalitis. It involved a 46-year-old male patient who developed meningoencephalitis caused by the West Nile virus. This patient presented with hypercapnic respiratory failure without muscular involvement and, after multiple failed extubation attempts, required a tracheostomy and remained dependent on mechanical ventilatory support [7].

There are published reports of central hypoventilation syndrome associated with non-viral encephalitis [5,6,8], where the proposed mechanism is believed to involve the destruction of respiratory nuclei in the brainstem [4].

To date, there is no established medical treatment for central hypoventilation syndrome, and management focuses on ensuring adequate ventilation [9]. In our case, the patient's clinical improvement encouraged multiple weaning attempts, which led to an increase in plasma bicarbonate (HCO_3^-) levels and the development of post-hypercapnic metabolic alkalosis when reconnected to mechanical ventilatory support. For this reason, acetazolamide was added to the treatment to stabilize HCO_3^- levels, based on its proven benefits in chronic obstructive pulmonary disease [10].

A 2017 review suggests that acetazolamide should be considered for patients with hypercapnic respiratory failure, as it is well-tolerated and has a beneficial effect on $PaCO_2$ and PaO_2 levels [10]. Adverse effects are rare but potentially severe [10,11]; however, in our case, no complications related to its use were observed.

Although the use of acetazolamide has not been studied in patients with encephalitis, metabolic alkalosis must be treated due to its association with high morbidity and mortality. It can depress cardiac output, worsen hypokalemia and hypophosphatemia, and disrupt oxyhemoglobin dissociation and respiratory drive. These mechanisms further exacerbate hypoventilation and may lead to respiratory failure [11].

It is important to highlight certain limitations of this case. Although the diagnosis of central hypoventilation syndrome was based on the patient's clinical presentation, we believe that performing polysomnography would have been valuable to complement the diagnosis. Additionally, we are unable to compare our findings with other cases, as our country reports the number of infections but not the clinical outcomes, leaving us uncertain whether similar cases have occurred.

Another limitation encountered during the patient's stay in the intensive care unit was that, although the patient was ready for decannulation, the lack of routine use of non-invasive ventilation in the general ward posed a potential risk to the patient.

Likewise, this type of study does not allow for establishing a cause-effect relationship, raising questions about the mechanism of improvement and highlighting the need for further research: Was there remyelination? Would the natural progression of the condition alone have produced the same results? When post-hypercapnic metabolic alkalosis was corrected, was the respiratory drive stimulated, or was it the combination of all variables that achieved the outcome?

Conclusions

In conclusion, our case highlights the importance of considering central hypoventilation syndrome as a potential neurological complication of western equine encephalitis and the need for further research in this field. Efforts should focus on disease prevention, as there is currently no specific treatment for this complication.

References

1. Ministerio de Salud Argentina. Vigilancia de Encefalitis Equina del Oeste. Boletin Epidemiologico 50. Ministerio de Salud de la provincia de Buenos Aires; 2023. https://www.ms.gba.gov.ar/sitios/media/files/2023/12/Bolet%C3%ADn-epidemiol%C3%B3gico_50.pdf

2. Avilés G, Sabattini MS, Mitchell CJ. Transmission of western equine encephalomyelitis virus by Argentine Aedes albifasciatus (Diptera: Culicidae). J Med Entomol. 1992;29(5):850-853.

3. Fernandez, G; Amelotti, L; Nicolau, V; Guereca Reyes, C; Vallone, A; Buyayisqui, MP, et al. Boletín epidemiológico nacional. Argentina: Ministerio de salud de la República Argentina, 2024: 693.

4. Trang, H; Samuels, M; Ceccherini, I; Frerick, M; García-Teresa, MA; Peters, J: et alGuidelines for diagnosis and managment of congenital central hypoventilation syndrome. Orphanet J Rare Dis. 2020; 15(1): 252.

5. Xu Q, Wang Q, Han J, Mao F, Zeng S, Chen S, et al. Central hypoventilation is a key risk factor for mechanical ventilation during the acute phase of Anti-N-Methyl-D-Aspartate Receptor encephalitis. Frontiers in Neurology. 2021; 12:728594

6. Voronova M, Shark A. Severe central hypoventilation syndrome in a patient with Anti-N-Methyl-D-Aspartate receptor encephalitis: case report and review of the literature. Cureus. 2022; 14(10):e30749.

7. Tso G, Kaldas K, Springer J, Barot N, Kamangar N. West Nile Meningoencephalitis presenting as isolated bulbar palsy with hypercapnic respiratory failure: case report and literature review. J Intensive Care Med. 2016; 31(4):285-287

8. Gómez-Choco MJ, Zarranz JJ, Saiz A, Forcadas MI, Graus F. Central hypoventilation as the presenting symptom in Hu associated paraneoplastic encephalomyelitis. J Neurol Neurosurg Psychiatry. 2007; 78(10):1143-5

9. AlOtair HA, Alzeer AH, Abdou MA, Qasrawi SO. Unusual case of central alveolar hypoventilation. Saudi Med J. 2018;39(3):305-310.

10. Jones P, Greenstone M. Carbonic anhydrase inhibitors for hypercapnic ventilatory failure in chronic obstructive pulmonary disease. Cochrane Database Systematic Reviews. 2001; 1: CD002881.

11. Fontana V, Santinelli S, Internullo M, Marinelli P, Sardo L, Alessandrini G, et al. Effect of acetazolamide on post-NIV metabolic alkalosis in acute exacerbated COPD patients. Eur Rev Med Pharmacol Sci. 2016;20(1):37-43