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Letter to the Editor: New Observation

Persistent Central Hypoventilation Following Probable Remission from Anti-N-methyl-D-aspartate Receptor Encephalitis

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Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis classically presents with prominent psychiatric disturbances, seizures, and cognitive dysfunction. Central hypoventilation is seen in 40–60% of adult patients within the first 2 months of illness.[1–2] Rarely occurring in patients with preserved consciousness,[3] central hypoventilation is usually associated with significant neuropsychiatric dysfunction, as the disease progresses to a catatonic-like state with depressed consciousness.[2] We report the case of a patient with anti-NMDAR encephalitis who, following an initial self-limited neuropsychiatric presentation, predominantly had persistent, and ultimately immunotherapy-responsive, central hypoventilation.

A 48-year-old woman was admitted in September 2020 to the McGill University Health Center (Montreal, QC, Canada) for hypercapnic respiratory failure, following 7 months of worsening idiopathic central sleep apnea. Her past medical history included a left oophorectomy in 1996 for a large painful ovarian mass, which was defined as a mature teratoma and serous cystadenoma on pathology.

Her initial presentation to Neurology goes back to July 2019, when she presented to the emergency department (ED) with an abdominal rash, fever (38.0°C), transaminitis (alanine aminotransferase 320 U/L) and lymphopenia (absolute lymphocyte count 0.72 * 10^9/L) following days of disorientation, word-finding difficulties, and psychomotor slowing. A lumbar puncture revealed lymphocytic pleocytosis (99 leukocytes/μL), normal protein and glucose, negative bacterial culture, Herpes Simplex Virus 1-2, and Enterovirus polymerase chain reaction (PCR). Extensive infectious and neoplastic work-up, including whole body PET scan, was otherwise unrevealing. Brain MRI showed nonspecific supratentorial white matter abnormalities. Intracellular antineuronal antibodies were tested and not detected in her serum, but cell-surface autoimmune encephalitis antibodies, including anti-NMDAR, were not tested given her multisystemic presentation and spontaneous improvement. While hospitalized, she had one episode of nocturnal oxygen desaturation (76%), which was not further investigated. After 2 weeks, she was discharged with a diagnosis of "viral encephalitis", after normalization of systemic disturbances and cognition.

Following discharge, she remained ostensibly asymptomatic, with her and her family denying any behavioral, cognitive, psychiatric, seizure-like, dyskinesia-like, or dysautonomia symptoms. In February 2020, she was referred to the Respirology outpatient clinic for excessive daytime sleepiness. Polysomnogram showed severe mixed obstructive and central sleep apnea (central origin in 57% of apneic–hypopneic events). In April 2020, she started using home nocturnal continuous positive airway pressure (CPAP), which was augmented to bi-level positive airway pressure (BiPAP) 2 months later given persistent central apneas and hypercapnia. She was able to remain awake more easily with this therapy, but she remained hypercapnic.

By September 2020, she was admitted from the ED following 3 days of drowsiness, disorientation, psychomotor slowing, and impaired concentration and recall in the context of reduced BiPAP compliance. She was hypoxic and severely hypercapnic ($PaCO_2$ 86 mmHg), requiring positive pressure ventilatory support. On examination, she was obtunded with occasional diffuse myoclonus without focal neurological deficits. Electroencephalogram showed diffuse slowing, without epileptic activity. Brain MRI showed stable nonspecific faint white matter abnormalities and routine CSF analysis 5 leukocytes/μL, normal protein and negative cultures. A comprehensive serum and CSF autoimmune encephalitis panel were requested. Three days after admission, she was intubated for refractory hypercapnia. Her mental status improved rapidly, concurrently with CO_2 normalization: she was alert and appropriately responsive within 2 days of initiation of mechanical ventilation. In contrast to the improvement of her mental status, she generated insufficient respiratory efforts and remained ventilator-dependent, eventually requiring tracheostomy. Peripheral and phrenic nerve conduction studies were normal. Encephalopathy at presentation was deemed secondary to hypercapnia: she was transferred to the Montreal Chest Institute for diaphragmatic pacemaker evaluation.

Four weeks into her hospitalization, testing for anti-NMDAR returned positive in serum and CSF by fixed cell-based assay and tissue indirect immunofluorescence. Oligoclonal bands were positive in CSF; other autoimmune and paraneoplastic antibodies,

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including anti-Hu, were negative. Testing for anti-IgLON5 was not performed. By then, she scored 26/30 on the Montreal Cognitive Assessment (MoCA), which is the lower bound of normal range suggested by its authors.[4] She was appropriate and coherent, showing no evidence of psychiatric disturbances.

She was treated for possible anti-NMDAR encephalitis resulting in refractory central hypoventilation. She received IV methyprednisolone 1g/day and intravenous immunoglobulin (IVIg) 0.4 g/kg/day for 5 days, followed by rituximab induction of 1g IV × 2 doses given 2 weeks apart. The patient, who was menopaused, consented to undergo a right oophorectomy for resection of possible microscopic teratoma not seen on transvaginal ultrasound. No teratoma was found on pathology.

Over the following month, her respiratory status improved dramatically: daytime ventilation was weaned, tracheostomy was decannulated, and nocturnal support was transitioned to BiPAP. Repeat diagnostic polysomnogram showed mild obstructive sleep apnea, with a single central apnea event. By December 2020, she was discharged home and received a maintenance dose of rituximab 1g IV in August 2021. To date, she remains with mild hypercapnia and nocturnal hypoventilation, stable on BiPAP, and has shown near-complete recovery to her premorbid functioning.

Formes frustes of anti-NMDAR encephalitis have been described, but they usually consist of predominant psychiatric symptoms, seizures, or abnormal movements.[3] Cases of severe dysautonomia preceding or prevailing over neuropsychiatric disturbances in anti-NMDAR encephalitis were described,[5] but syndromes with prominent central hypoventilation were only reported in anti-Hu brainstem encephalitis.[6] In hindsight, our patient's presumed viral meningoencephalitis in 2019 was most likely a paucisymptomatic initial presentation of anti-NMDAR encephalitis. The antibodies' pathogenicity was also presumably contributing to her encephalopathic state at admission in September 2020. Nonetheless, following spontaneous improvement of these more "classical" neurocognitive symptoms, central hypoventilation persisted as the main expression of her disease for the following 18 months of disease progression. To our knowledge, this is therefore the first reported case of anti-NMDAR encephalitis characterized by persistent predominant central hypoventilation, following probable recovery from an initial neuropsychiatric presentation, which showed remarkable improvement of respiratory status with typical immunotherapy recommended for this disorder, despite a significant delay in recognition and therapy initiation.

Central hypoventilation in anti-NMDAR encephalitis can be explained by the abundance of NMDA-NR1 receptors in the Kollinger-Fuse nuclei, a group of brainstem nuclei essential to the central control of breathing.[7] However, as in other *formes frustes* of the disease, the predilection of the anti-NMDAR antibodies for the brainstem respiratory centers in our patient is unclear. Of note, our patient's prior history of ovarian teratoma removal, a well-known etiological cause of anti-NMDAR encephalitis, is also of particular interest. However, even though a few anti-NMDAR encephalitis cases following ovarian teratoma removal have been described in the literature,[8–9] an interval as remote as 20 years between tumor removal and symptomatology has never been reported, therefore the significance of the teratoma in this case is difficult to establish.

In conclusion, this case highlights the importance of considering anti-NMDAR encephalitis when confronted with persistent idiopathic central sleep apnea following an initial meningoencephalitis, given its potential reversibility and significant impact on functional outcome and autonomy, as seen in our patient.

Statement of Authorship. **Samantha Rivet**: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Liam Durcan: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

François Dubeau: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data.

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