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Neurol Neuroimmunol Neuroinflamm
2017;4:e303; doi: 10.1212/NXI.0000000000000303

PAROXYSMAL SNEEZING IN NMOSD: FURTHER EVIDENCE OF THE LOCALIZATION OF THE HUMAN SNEEZE CENTER

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Intractable nausea, vomiting, and hiccups are characteristic symptoms associated with neuromyelitis optica spectrum disorder (NMOSD) as the result of immune-mediated lesions affecting the area postrema and medullary floor of the fourth ventricle. Reports of paroxysmal sneezing as part of the NMOSD phenotype are rare. We present a case of a patient who developed symptoms of NMOSD associated with prominent paroxysmal sneezing as a heralding symptom. The precise location of the human sneeze center has not been identified; this case provides further evidence for its location in the dorsolateral medulla as previously proposed.[1]

Case report. A 55-year-old woman with a medical history of hypothyroidism developed hypersomnolence (sleeping up to 22 hours daily). Soon after, she began to experience severe nausea and vomiting, intractable hiccups, and then violent paroxysmal sneezing lasting several minutes that would awaken her from sleep. The sneezing spells lasted several days. During each paroxysm, she sneezed several times, sometimes in a stereotypic cyclic fashion alternating with bouts of hiccups. She then developed urinary retention, vertigo, and diplopia, followed by new-onset atrial fibrillation and ataxia.

The patient had no history of allergies, pulmonary disease, or sinusitis and was a lifelong nonsmoker. Otolaryngologic and pulmonary examinations were unremarkable. Neurologic examination showed oscillopsia on primary gaze, multidirectional nystagmus, and gait ataxia. Laboratory analysis showed normal blood count and liver, kidney, and thyroid function; vitamin levels, autoimmune screens, and paraneoplastic antibodies were negative. CSF analysis revealed a white blood cell count of 19 cells/μL (93% lymphocytes) with normal flow cytometry, glucose, and protein and no oligoclonal bands. MRI (figure) showed fluid-attenuated inversion recovery hyperintensities in the hypothalamus, fourth ventricle, periependymal, periventricular, and periaqueductal regions. Prominent involvement of the dorsolateral aspect of the medulla was noted bilaterally.

Methylprednisolone 1 g was administered for 5 days; significant improvement of the nausea, vomiting, hiccups, and paroxysmal sneezing was noted. Given that the ataxia, oscillopsia, and diplopia were still prominent, she underwent plasmapheresis with good clinical response.

Aquaporin-4 immunoglobulin G (AQP4-IgG) was identified via cell-based assay in the serum obtained on admission; it was negative in the CSF.

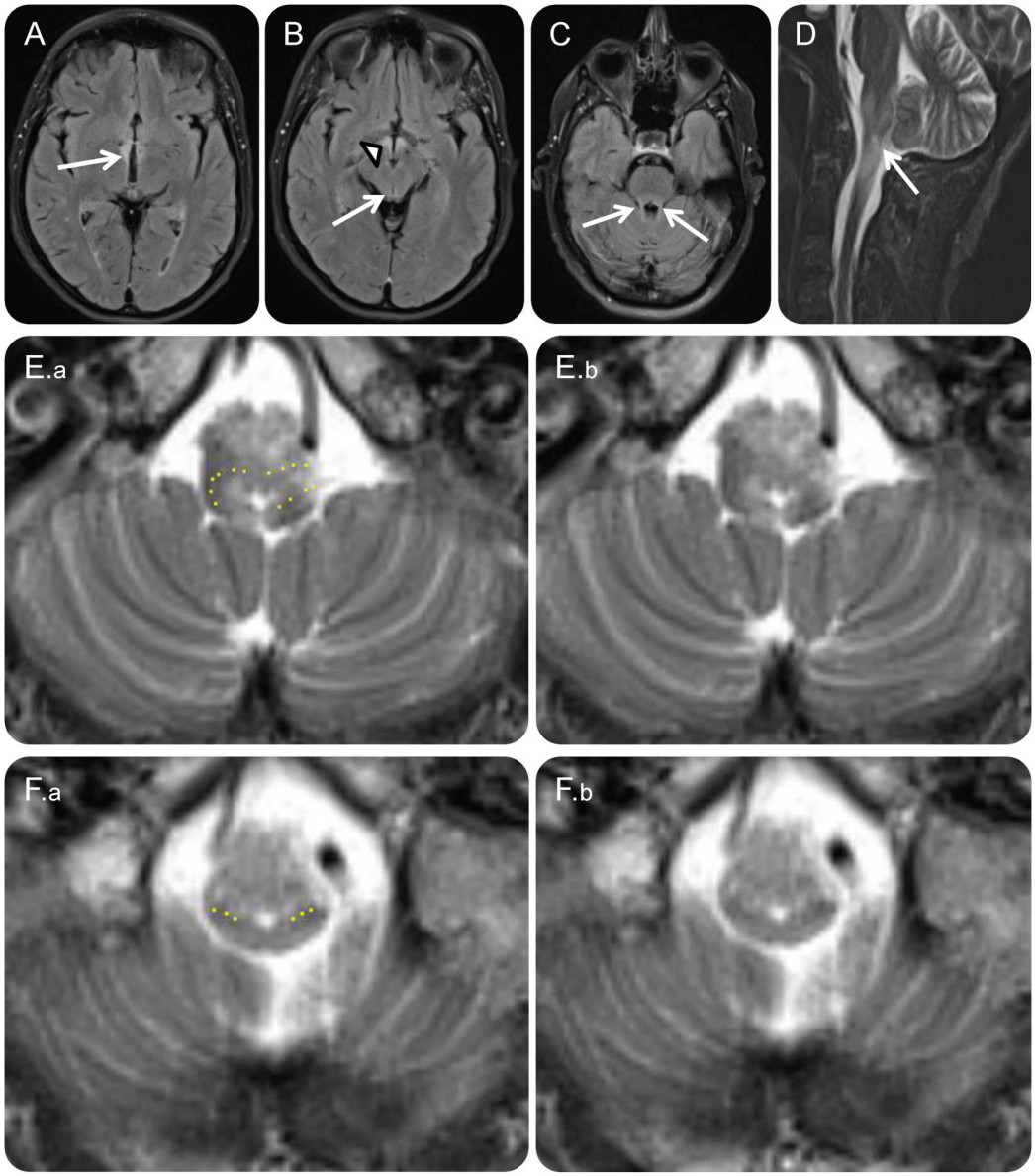
She had no further spells of paroxysmal sneezing and has remained clinically stable on rituximab monotherapy for 16 months.

Discussion. We present the case of a woman with NMOSD with a positive serum AQP4-IgG, presenting with paroxysmal sneezing accompanying an area postrema syndrome. Brain MRI revealed abnormalities in multiple areas with high AQP4 expression and significant medulla oblongata (MO) involvement. The symptoms correlated with the findings on MRI: the hypersomnia with the hypothalamic involvement, the hiccups, intractable nausea, and vomiting with the periventricular and area postrema lesions, and the paroxysmal sneezing with the posterolateral MO lesions.[2] Reports of paroxysmal sneezing in patients with NMOSD are rare, perhaps because it has not been recognized as part of the syndrome. We speculate that, since the patient developed atrial fibrillation concomitantly with the neurologic symptoms, the origin of the cardiac arrhythmia was neurogenic secondary to dysregulation of autonomic control due to loss of parasympathetic innervation, which originates predominantly in the nucleus ambiguus of the MO.

Brainstem manifestations in NMOSD are common with studies suggesting that MO MRI lesions can be found in up to 26% of patients,[3] and pathologic lesions at the medullary floor of the fourth ventricle and area postrema are found in 40% of NMOSD autopsied cases.[4] Pathologic yawning, orthostatic hypotension, postural orthostatic tachycardia syndrome, and intractable cough[5] are symptoms rarely described in patients with NMOSD with brainstem involvement.

The precise location of the sneeze center in the human brain has not been confirmed; a case with

Figure **Brain MRI**



Axial MRI demonstrates T2 flair hyperintensity areas in the third ventricle (A, arrow), hypothalamus (B, arrowhead), periaqueductal region (B, arrow), fourth ventricle (C, arrows), and cervicomedullary junction and dorsal medulla (D, arrow). T2-weighted axial images show bilateral dorsolateral medullary involvement (E.a, F.a, yellow dots). (E.a, E.b) Medulla. (F.a, F.b) Cervicomedullary junction.

strikingly similar MRI abnormalities (dorsolateral medulla involvement) in a patient with a demyelinating syndrome developing inability to sneeze and 5 minutes of hiccups following meals was reported in 2001 and attributed to systemic lupus erythematosus.[1] It is possible this patient had NMOSD as it was published before the discovery of AQP4-IgG and the recognition of the strong association of NMOSD with lupus and systemic autoimmune disorders.[6] Pathologic sneezing has also been reported in patients with lateral medullary infarcts and compression of the dorsal medulla from Arnold-Chiari malformation.[7]

This case provides further evidence for the localization of the human sneeze center in the dorsolateral aspect of the medulla, and adds another symptom (paroxysmal sneezing) to the NMOSD phenotype. Recognition of area postrema involvement in patients with NMOSD is extremely important as early immunotherapy is essential to prevent persistent brainstem inflammation, which can lead to significant disability, serious complications, or death.

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Author contributions: A. Sebastian López-Chiriboga: study concept and design, acquisition of data, drafting manuscript. Josephine F. Huang, Eoin P. Flanagan, William P. Cheshire: analysis and interpretation of data, revising the manuscript.

Study funding: No targeted funding reported.

Disclosure: A.S. López-Chiriboga, J.F. Huang, and E.P. Flanagan report no disclosures. W.P. Cheshire received honoraria for serving on the scientific advisory board for Biogen-inVentiv Health, served on editorial board of Autonomic Neuroscience: Basic and Clinical, Parkinsonism and Related Disorders*, consulted for the American Academy of Neurology, received research support from NIH, Mayo Clinic. Go to Neurology.org/nn for full disclosure forms. The Article Processing Charge was paid by the authors.*

Received August 15, 2016. Accepted in final form September 21, 2016.

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