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# Pathologic yawning in neuromyelitis optica spectrum disorders

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Brainstem lesions;
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Hiccups

**Abstract**
*Introduction:* Brainstem, hypothalamic and cerebral symptoms may occur in neuromyelitis optica spectrum disorders (NMOSD). However, pathologic yawning has not been previously described in NMOSD patients.
*Patients and methods:* Nine AQP4-IgG seropositive NMOSD patients experienced excessive yawning not related to sleep deprivation or fatigue.
*Results:* Patients were female, aged 19–57 years (median, 39 years) at disease onset. Excessive yawning spells were the presenting symptom of the disease in five patients, lasted 2–16 weeks, and usually occurred in association with nausea, vomiting and hiccups. Brain MRI was abnormal in all patients and most frequently showed brainstem and hypothalamic lesions.
*Conclusion:* Pathologic yawning may be a neglected although not a rare symptom in NMOSD.


## 1. Introduction

Neuromyelitis optica (NMO) is an immune-mediated inflammatory disease of the central nervous system (CNS), which predominantly affects the optic nerve and spinal cord. Since the discovery of NMO-IgG as a highly specific marker of the disease (Lennon et al., 2004), a wide variety of brainstem, hypothalamic, cortical and subcortical symptoms have been added to the classical association of optic neuritis (ON) and

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transverse myelitis (TM) (Jarius et al., 2012; Poppe et al., 2005; Magana et al., 2009). In over 60% of NMO patients, brain MRI may detect lesions, which are often localized at sites of high AQP4 expression (Pittock et al., 2006a, 2006b). The term neuromyelitis optica spectrum disorders (NMOSD) (Wingerchuk et al., 2007) includes definite NMO (Wingerchuk et al., 2006) and limited forms of the disease such as recurrent ON, bilateral and simultaneous ON, and longitudinally extensive transverse myelitis (LETM) in AQP4-IgG-seropositive patients.

Patients with NMOSD who complained of excessive yawning spells initially drew our attention to this symptom. The spells were distressing and embarrassing, and even drew attention from the patients' family and caregivers. Most frequently, the yawns occurred in association with nausea and vomiting, hiccups and other brainstem or hypothalamic symptoms. Some patients also reported recurring spells of excessive yawning preceding TM or ON for months or years. Because yawning is a primitive complex involuntary paroxysmal phenomenon involved in brainstem and hypothalamic mechanisms of brain thermoregulation and homeostasis (Walusinski, 2006; Gallup and Gallup, 2008), we postulated that excessive yawning in NMOSD may reflect sleep and thermoregulatory dysfunction due to brainstem or hypothalamic involvement. Pathologic yawning has also been reported in multiple sclerosis (Postert et al., 1996) and a variety of conditions as well as an adverse effect of drugs (Walusinski., 2009). However, it had not been previously described in NMOSD patients.

## 2. Patients and methods

Written formal consent was obtained from all patients. The institutional Ethical Committee approved the study. Patients were selected from a group of 145 AQP4 seropositive NMOSD patients examined at CIEM MS Research Center, University of Minas Gerais Medical School, or the Department of Neurology of Sao Paulo State University by at least one of the authors of this study. We reviewed data from patients who spontaneously complained of excessive yawning. The diagnosis of NMO was performed on the basis of the revised criteria of Wingerchuk et al. (2006), and the term NMOSD was used as defined by Wingerchuk et al. (2007). Serum AQP4-IgG was determined using cell-based assay (Takahashi et al., 2006). Pathologic yawning was defined as a frequency higher than three yawns per 15 min or 28 yawns per day (Singer et al., 2007).

## 3. Results

### 3.1. Clinical findings

Nine AQP4-IgG-seropositive patients experienced excessive yawning that were not related to periods of fatigue or sleep debt (Table 1). All patients were women aged 19–57 years (median: 39 years) at disease onset. Seven patients had ON and TM, whereas two patients demonstrated LETM as a limited form of NMO. Excessive yawning occurred at disease presentation in five patients, preceded ON or TM in three patients, and followed the presentation in four patients. In one patent (Case 6) abnormal yawning occurred 15 years after the first attack of optic neuritis and transverse myelitis which followed a severe and unexplained episode of vertigo and nystagmus for four years. Eight patients exhibited incoercible nausea and vomiting, and seven patients had hiccups in association with abnormal yawning. Although pathological yawning appeared during the acute phase of disease in six patients it persisted during remission in three patients. Yawning occurred in clusters of three to 10 yawns, which tended to repeat at a frequency of five to over 20 times a day, continuously lasting for two to 16 weeks. Two patients were still experiencing intermittent abnormal yawning at their last visit, which was four and 12 years after their onset, respectively. Brainstem symptoms other than nausea, vomiting and hiccups, were observed in six patients whereas hypothalamic symptoms were observed in five. Five out of six patients who received high-dosage IV methylprednisolone for ON/TM attacks observed a relief of the accompanied pathologic yawning.

### 3.2. MRI findings

Eight patients had brain MRI within 1 month whereas one patient had it at 32 months following the onset of excessive yawning. In all patients, the brain MRI was abnormal and atypical for MS. An abnormal hyperintense signal was found in the optic nerve in eight patients, in the brainstem in eight patients and in the hypothalamus in five patients. Figure 1 shows representative MRI lesions in two NMO patients with excessive yawning. Three patients had lesions in the periventricular region; two patients demonstrated lesions in the corpus callosum, and one patient had a large anterior hemispheric lesion. Unspecific small patches or dots in the deep white matter or subcortical regions were found in four patients. In all patients spinal MRI showed hyperintense signal in the central part of the cord contiguously involving three or more vertebral segments (Table 2).

## 4. Discussion

The present observation suggests that pathological yawning should be added to the wide variety of clinical manifestations of NMOSD. Yawning is a phylogenetically old reflexive phenomenon involving the activity of motor nuclei of the cranial nerves V, VII, IX, X, XI and XII, brainstem reticular formation, hypothalamic paraventricular nucleus (PVN) and connections to the frontal lobe and cervical spinal cord (Walusinski, 2009). The PVN also plays a role in the control of osmolarity, blood pressure, heart rate and sexuality (Walusinski, 2009).

Although the ultimate function of yawning is still a matter of dispute, a number of results suggest that it may serve multiple purposes. Yawning may have a social and communicative function and may be related to complex psychological mechanisms involved in imitation and boredom (Guggisberg et al., 2011). In addition, it may also be involved in interoceptiveness via its capacity to increase arousal and self-awareness. The hypothalamus, thalamus, locus coeruleus, brainstem reticular formation, and insula are CNS structures that are predominantly involved in yawning, which are also related to the representation and regulation of homeostasis (Walusinski, 2007). Moreover, a better understanding of the physiological sympathetic hypothalamic activity that accompanies yawning, such as sharp increases in lung volume, blood pressure and heart rate as well as an increase in facial temperature and decrease in respiratory rate, suggests that yawning may play a role in brain cooling mechanisms. An