Continuous positive airway pressure as treatment for catathrenia (nocturnal groaning)

To the Editor: Iriarte et al. report a patient with catathrenia and mild obstructive sleep apnea whose polysomnographic recording showed a respiratory dysrhythmia during all sleep stages that caused secondary oxygen desaturations and irregular movements of the abdominal wall. A trial with continuous positive airway pressure (CPAP) improved this condition.[1] These features are somehow atypical for catathrenia.[2,3]

Over 90% of the reported bradypneic events in catathrenia occur only, or predominantly, during REM sleep.[2] There is an internal, brainstem-based, excitatory drive to the respiratory system during REM sleep possibly independent of chemical stimuli.[4] The hallmark of catathrenia is a deep inspiration followed by a short expiratory phase and a long expiratory period with sound production. The output signal of the respiratory thoracoabdominal bands is flat or very low during these expiratory periods, while sound monitoring reflects the typical groaning.[2]

This pattern strongly suggests that post-inspiratory neurons, which are active during the early expiratory phase and play a key role in breathing generation during sleep, are responsible for this dysfunction. These neurons are located between the dorsal and ventral respiratory groups and have inhibitory connections with both of them. An excessive tonic discharge of the post-inspiratory neurons might protract expiration by inhibiting the expiratory neurons in the ventral group, whose axons descend through the medulla to innervate the expiratory muscles.

Orem et al. demonstrated that the activation of the respiratory system during REM sleep occurs after an average 34 seconds delay and then waxes and wanes.[4] This feature may account for the bradypneic events not to appear as soon as REM sleep starts, and to be most expressive in mid-REM sleep. Bradypnea index is higher in the second half of the night, probably because of the higher density and stability of REM sleep then. The simultaneous and erratic activation of the neuron groups of the internal drive system causes the characteristic irregularities of breathing in REM sleep in normal subjects.[4]

Catathrenia may be an exaggerated expression of these breathing irregularities that occur in young and otherwise healthy individuals, with unnoticeable consequences in spite of its chronic and recurrent nature. Accordingly, we believe catathrenia should be included in the sleep-related breathing disorders category of the International Classification of Sleep Disorders rather than in the group of parasomnias.[5]

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Reply from the Authors: Ortega-Albás et al. raise some interesting points regarding catathrenia. As we also explained, catathrenia is a REM-related sleep disorder. In our report, we signaled the peculiarity of our patient given that the groaning started in stage one and it was very severe in all sleep stages, including stage two and slow sleep during the entire night.[1]

In our case report, the video and the polysomnography indicated the sleep stage was not as essential as quoted in previous reports.[2,3,6] The pathophysiologic explanation proposed by Ortega-Albás et al. to support the REM relationship is interesting and probably true, but we cannot provide any more experimental data to support this hypothesis.

Another possibility is an alteration in the inspiration-expiration pattern.[7] The last idea in their correspondence is also of interest. They suggest that catathrenia should be included among the sleep-related breathing disorders. Actually, our example with the dramatic improvement with CPAP would support this idea. Nevertheless, we are not fully convinced of this change. Snoring is included under the group "Isolated symptoms, apparently normal variants and unresolved issues." In catathrenia, it is unclear whether the link with dysrhythmia and REM periods is always needed for the diagnosis. The answer is probably yes, but currently in the ICSD-2 there are two options for the diagnosis of catathrenia: the first one is descriptive (it does not need polysomnography), and for the second one only the polysomnographic criteria are required.[5]

We agree on the misplacement of catathrenia as a parasomnia, but we also think that longer series are needed before a definitive relationship with REM and the respiratory dysrhythmia are definitely established.

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Disclosure: The authors report no conflicts of interest.

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Left insular stroke is associated with adverse cardiac outcome

To the Editor: We read with interest the article by Laowattana et al.[1] They found that left insular stroke—as opposed to right insular stroke—was associated with an increased risk of adverse cardiac outcomes or cardiac wall motion impairment. This conflicts with other clinical studies that demonstrated substantive cardiovascular dysfunction including sudden death mainly after right insular stroke.[2]

In our study, cardiovascular (heart rate and blood pressure) and autonomic function (plasma norepinephrine and epinephrine concentration) was assessed sequentially at six defined timepoints within the first 5 days after insular stroke.[3] We could demonstrate a sustained upregulation of cardio-autonomic function in right insular stroke patients. This might be of prognostic significance since PET studies have shown a reduced hemodynamic reserve in hypertensive patients which renders the penumbra vulnerable even to a small reduction in blood pressure.[4] Reports of possible adverse effects of sympathovagal shifts as a progenitor of cardiac arrhythmogenesis[2] may be offset by an increase in penumbra viability. However, involvement of the insular cortex, the occurrence of a pathologic nighttime blood pressure increase, and an initially increased serum norepinephrine concentration appear to be independent predictors of poor long-term outcome in thromboembolic stroke.[5]

Instead of considering only either cardiac or neurologic sequelae like Laowattana et al., future clinical trials should relate

both neurologic and cardiac outcome to cardio-autonomic dysfunction in the acute phase after stroke.

Sascha Meyer, *Homburg/Saar, Germany*; Matthias Strittmatter, *Merzig, Germany*

Disclosure: The authors report no conflicts of interest.

Reply from the Authors: We thank Drs. Meyer and Strittmatter for their interest in our article.[1] They cite two articles evaluating autonomic lateralization, insular stroke, and sudden death.[2,3] These differ from ours in the timing of recruitment and in follow-up. For example, their study is confined to 5 days of follow-up and ours extends over 1 year. This complicates direct comparison. Additionally, their study examines laboratory and not clinical outcome (as in our study).

Meyer and Strittmatter mention a report to show an association between location and sudden death; 5/23 patients with right insular stroke and 2/25 with left insular stroke had this outcome. Statistical analysis was not performed but we compute $p = 0.42$ (Fisher exact test).[2] This would actually indicate no difference in sudden death between left vs right insular stroke. To our knowledge, there has been only one previous evaluation of stroke lateralization and sudden death including sufficient numbers for statistical analysis. This indicates an association with left and not right hemispheric stroke.[6]

Finally, the association of long-term clinical outcome with acute laboratory measures is complicated. Any such assessments can be potentially confounded by intervening medication changes and medical events. which should therefore be accommodated in such predictive assessments.

Stephen Oppenheimer, Somchai Laowattana, *Baltimore, MD*

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IM interferon β-1a delays definite multiple sclerosis 5 years after a first demyelinating event

To the Editor: The recently published CHAMPIONS trial[1] reported that the early use of weekly IFN beta-1a (compared to delayed treatment) reduced the likelihood of developing clinically definite (CD) multiple sclerosis (MS) after a 5-year follow-up period in patients who had initially presented with clinically isolated syndromes (CIS) suggestive of MS. There are concerns both about the trial design and this conclusion.

For example, this trial was planned only after the completion of the CHAMPS trial[2] and with full knowledge of the CHAMPS results. Additionally, the primary endpoint of the CHAMPIONS trial was the development of CDMS at any time after CIS onset. Consequently, at the outset of CHAMPIONS, there was already a highly significant difference (bias) between groups with respect to the primary outcome measure. Significantly more patients in the delayed treatment group had already reached (and were known to have reached) their final endpoint before the trial even began compared to the early treatment group. Conversely, there were significantly more "survivors" (i.e., those without a second clinical attack) in the early treatment group.

Therefore, as a consequence of this experimental design, the final result of the CHAMPIONS study was already assured before the trial even began, unless for some reason the rate of development of CDMS happened to be significantly greater in the "surviving" patients of the early treatment group compared to the delayed treatment group.

During the CHAMPIONS trial, there was no suggestion of a difference between groups in the rate of development of CDMS (Figure 2 of the article). Indeed, the principal study result can be completely attributed to the experimental bias and is not due not to any observations made during the CHAMPIONS trial itself. This result should have been anticipated.

First, it is unclear how such an increased rate of CDMS in the early treatment group could have been explained, let alone anticipated. Second, if the known experimental bias is removed from the CHAMPIONS study by excluding those patients who had already reached their endpoint at study entry, the CHAMPIONS trial effectively boils down to an investigation of the likelihood of developing CDMS in two groups of patients, currently receiving active therapy, who have not had a second clinical attack 2 to 3 years after their initial clinical episode suggestive of MS. It seems hardly surprising that, at this point, early vs delayed treatment makes little or no difference.

Douglas S. Goodin, *San Francisco, CA*

Disclosure: The author reports no conflicts of interest.

Reply from the Authors: We thank Dr. Goodin for his comments on our article and the opportunity to further discuss this important issue. He is correct that the CHAMPIONS study was planned with full knowledge of the CHAMPS outcome, but the primary outcome in the CHAMPIONS study was determined by the same group of blinded, independent outcome committee members that determined this outcome in the original CHAMPS study.

We disagree with Dr. Goodin's assertion that the differences between treatment groups at CHAMPIONS onset (i.e., at the end of CHAMPS) assured the study outcome. Although the CHAMPS study reported that AVONEX reduces the incidence of CDMS 2 years following CIS onset, this does not guarantee that the benefit of immediate treatment will last indefinitely, particularly when compared to an active treatment group. It is possible that the effect of AVONEX is only to delay the conversion to CDMS. If so, the incidence of CDMS in the immediate treatment group (originally randomized to AVONEX) will eventually catch up to that in the delayed treatment group (originally randomized to placebo). The primary question in the CHAMPIONS study was whether the benefit of immediate treatment would persist beyond 2 years.

Dr Goodin suggests that there is no reason to expect the surviving immediate treatment patients at the end of CHAMPS to develop CDMS during CHAMPIONS at a rate greater than the surviving delayed treatment patients. In fact this is exactly what one would expect if the higher risk immediate treatment patients survived at a greater rate until the end of CHAMPS because the treatment was effective. For the same reason, we disagree with his interpretation of Figure 2. Kaplan-Meier curves that eventually run parallel to one another do not imply a loss of treatment effect.

Dr. Goodin suggests that a more appropriate analysis would be to exclude patients who already developed CDMS during CHAMPS, essentially looking at the conditional probability of CDMS at 5 years given that it had not yet occurred at 2 years. This analysis would be flawed on both clinical and statistical grounds. Comparison of conditional rates would be of little value clinically since the decision whether to treat immediately with AVONEX must be made at CIS onset, not 2 years later.

Furthermore, excluding patients who converted to CDMS during CHAMPS would selectively remove more of the higher risk cases from the denominator of the original placebo group leaving

inherently different cohorts of patients. This would confound any comparison of subsequent failure rates.

Revere P. Kinkel, Craig Kollman, *Boston, MA*

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Correction

CSF BACE1 activity is increased in CJD and Alzheimer disease versus other dementias

In the article "CSF BACE1 activity is increased in CJD and Alzheimer disease other dementias" by R.M.D. Holsinger et al. (*Neurology* 2006;67:710–712), the word *versus* was omitted from the title. The title should read as follows: "CSF BACE1 activity is increased in CJD and Alzheimer disease versus other dementias."

This error was corrected on www.neurology.org on August 22, 2006. The publisher regrets the error.