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Letter

REM sleep physiology and selective neuronal vulnerability in amyotrophic lateral sclerosis

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Sir,

The widespread and relentless progression of skeletal muscle weakness secondary to motor neuronal degeneration in amyotrophic lateral sclerosis (ALS) is all the more striking in the *relative* preservation of those motor neurons subserving oculomotor function and continence. The molecular and broader physiological basis for selective neuronal vulnerability in ALS remains a subject of intense study and speculation. We note significant similarities with the pattern of muscle involvement associated with rapid eye movement (REM) sleep, raising the possibility of shared motor networks and so novel avenues for study.

The stage of normal sleep associated with REM involves a temporary but profound state of motor paralysis during which there is, by definition, preservation of eye movements, and also continence. Respiration enters a more wakeful pattern of activity with the REM sleep state (1) and the observation that respiratory insufficiency is typically a late-stage feature is consistent with its relative sparing in ALS, so that the increased respiratory activity noted in healthy REM sleep is compatible with the hypothesis of shared motor networks. Eventual diaphragmatic weakness is associated with shorter duration of REM sleep in ALS (2), and there is additional pathological extension to involve potentially REM-controlling brainstem areas in ALS, with Bunina bodies and TDP-43 inclusions (both with high specificity for ALS) found respectively within the locus coeruleus (3) and in the reticular formation of severely paralysed individuals (4). MRI studies have revealed progressive brainstem medullary morphometric atrophy in ALS (5), and more widespread cortical influences on the pattern-generating circuits of the pre-Bötzinger complex have been postulated (6), which might independently increase respiratory network vulnerability in more advanced ALS.

Spontaneous middle ear muscle activity is also found in REM sleep (7), with hearing-associated musculature also being spared in ALS (although mildly abnormal stapedial reflexes were noted in a sub-group of patients with bulbar involvement, presumably reflecting a greater brainstem pathological burden (8, 9)). Onuf's nucleus is part of the somatic cell column, and partial denervation

in the external anal sphincter and Onuf motor cells is observed early in ALS (10). Despite such early involvement, incontinence is not a feature of ALS. Similar findings exist with regard to the cardiac oesophageal sphincter, and the abductor muscles of the larynx, though reflux and stridor are not a feature of the disease, in keeping with the observation that REM sleep-active neuronal groups are relatively spared.

The neuronal circuitry governing REM sleep involves glutamatergic neurons of the sublaterodorsal (SLD) nucleus in the region of the pontine tegmentum (11), and inhibitory hyperpolarization of ventromedial medullary and spinal cord lower motor neurons by glycinergic neurons (12). GABA-ergic projections from the tegmental area may exert an important control over the REM-atonia neurons of the SLD, inhibiting their activity in wakefulness (13). A consistent pathological hallmark of the peri- and early symptomatic phases of ALS is increased cortical excitability (14), which has been linked across a range of experimental platforms to a relative reduction of inhibitory versus excitatory interneuronal influences ((15, 16)), including brainstem interneuronal circuits (17), but also potential spinal inhibitory influences (18). The observation that REM sleep appears to reversibly disable the motor pathways preferentially targeted by ALS, while preserving functions that are relatively spared, may be further evidence for an imbalance of inhibitory versus excitatory interneuronal influences at the heart of ALS pathogenesis. Therapeutic strategies specifically targeting its restoration and biomarkers based on such phenomena are worthy of focused study (19).

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