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EDITORIAL

It's time to stop saying "the mind is unaffected" in ALS

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Page 686

When Professor Stephen Hawking died in March 2018 after living with amyotrophic lateral sclerosis (ALS) for 55 years, the obituaries rightly celebrated a brilliant mind trapped in a failing body. Unfortunately, this shorthand description of ALS (found throughout the medical and lay literature alike) is firmly contradicted by a research base that finds frontotemporal dementia in 10% to 15% of cases and subtle cognitive deficits in 33% to 50%.[1] In this issue of *Neurology*®, Crockford et al.[2] report a large and carefully controlled study of 161 patients with ALS across 3 centers with 80 matched healthy controls to address a question that has puzzled the field for 40 years: are the cognitive and behavioral symptoms in ALS more prevalent at more advanced stages of disease?

The authors combined 2 elegant tools: the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)[3] and the King's ALS staging system.[4] They report higher rates of ALS-specific cognitive dysfunction (executive function, language, letter fluency) and behavioral issues across disease stages. In contrast, rates of ALS-nonspecific memory disturbance and visuospatial dysfunction were low and did not differ by stage. Most patients (55%) exhibited at least 1 caregiver-reported behavioral issue such as apathy, loss of sympathy/empathy, changes in eating behaviors, disinhibition, perseveration, or even psychosis. By King's stage 4, most patients (80%) had some kind of cognitive or behavioral deficit (table).

This study supports the routine deployment of these tools in clinical practice. The ECAS offers a brief 15- to 20-minute assessment of the specific cognitive and behavioral issues consistently affected in ALS.[3] It can be administered by any health care professional after a brief online training course. It is substantially less burdensome than traditional neuropsychological assessment, provides more actionable results, and controls for the motor disability that can make timed elements of other cognitive tests unreliable in ALS. The King's staging system is a simple way of classifying patients that has utility in trials and clinical practice,[5] cutting through the multitudinous ways of classifying ALS.[1]

If cognitive and behavioral issues are so common, why does the myth persist? Is it wishful thinking, paternalism, or a failure to translate research findings into clinical practice? While reports of ALS co-occurring with dementia go back more than a century, the field has only recently acknowledged that cognitive and behavioral issues occur in ALS.[6] A decades-long body of research leveraging neuropsychology, neuroimaging, and neuropathology has described extramotor involvement in ALS, including the 2011 discovery of C9ORF72 as the cause of ALS with frontotemporal dementia.[7] The field journal was even renamed *ALS and Frontotemporal Dementia* in acknowledgement.[8] And yet, even today, news stories and patient literature about ALS found in a simple online search continue to claim that the mind remains unaffected. While some literature has been updated to include the word "usually," the current study casts doubt on that assertion, too.

While the authors stress behavioral and cognitive effects, ALS progression may have broader mental health effects as well. Major depression and depressed mood increase across stages, and the authors highlight a strong correlation between Hospital Anxiety and Depression Scale

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Table Summary of cognitive, behavioral, and psychological issues across ALS King's stages

King's stage	Stage 1 (first region involved)	Stage 2 (second region involved)	Stage 3 (third region involved)	Stage 4 (nutritional or respiratory failure)
Cognitive impairment, %	18	18	33	39
Behavioral impairment, %	18	27	36	65
Anxiety, %	5	5	10	18
Depression, %	0	5	10	14
Psychosis, %	3	2	0	15

Abbreviation: ALS = amyotrophic lateral sclerosis.
Regions are upper limbs, lower limbs, or bulbar region (adapted from Crockford et al.[2]). Percentages rounded to nearest whole number.

depression score and behavioral impairment. A full appreciation of ALS should likely include a broader array of psychiatric effects, consistent with research on other neurologic diseases.

What are the clinical implications of this research? In a survey of 247 patients and 87 caregivers, 90% of patients and their caregivers reported that they had not been told by their health care professional that cognitive or psychological symptoms can arise in ALS.[9] A generous interpretation would be that cognitive and behavioral issues are subtle and masked by disability and that such issues are less pressing than other symptoms. However, in our experience, colleagues report keeping the information from patients in order to spare them further distress. Although this approach is perhaps well intentioned, when such symptoms do eventually arise, patients and their family members are stuck in a quandary: "Didn't the neurologist tell us the mind wasn't affected?" In the face of this dissonance, we have seen caregivers feel that they are imagining things, that they have done something wrong, or that doctors simply do not know what they are talking about. If caregivers do not even know what to look for or what to call these manifestations, then flagging them in the brief biannual clinic appointments that focus primarily on the patient's motor symptoms can be challenging.

In the same survey, most respondents (62% of patients, 71% of caregivers) said that they would have liked to have been told that these issues may arise.[9] Educating patients and caregivers that cognitive change is a part of ALS should be no different from similar discussions to be had in multiple sclerosis, Parkinson disease, and a range of other conditions.[10] Keeping the truth from patients and caregivers is not protective; it is paternalistic, and it is time to stop. Only by facing up to the hard truth that one of the most dreaded conditions in medicine is even worse than we previously acknowledged can we take stock, marshal our resources, and make renewed plans to defeat our common enemy.

Author contributions

P. Wicks and S.M. Albert: Drafting/revising the manuscript.

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Disclosures

P. Wicks is an employee of PatientsLikeMe and holds stock options in the company; is an associate editor of the *Journal of Medical Internet Research*; is on the editorial boards of the *BMJ*, *BMC Medicine*, and *Digital Biomarkers*; has received speaker honoraria from Bayer, the *BMJ*, and PWC; has received honoraria from Roche, Fondazione Italiana di Ricerca per la Sclerosi Laterale Amiotrofica, AMIA, Innovative Medicines Initiative, Statisticians in the Pharmaceutical Industry, and the *BMJ*; holds patents for personalized management and monitoring of medical conditions, systems and methods for encouragement of data submission in online communities, and systems, methods, and computer-readable media for context-linked importation of user information; has received research support from the Robert Wood Johnson Foundation; and is a caregiver to a person living with ALS. In addition, the PatientsLikeMe Research Team has received research funding (including conference support and consulting fees) from Abbvie, Accorda, Actelion, Alexion, Amgen, AstraZeneca, Avanir, Biogen, Boehringer Ingelheim, Celgene, EMD, Genentech, Genzyme, Janssen, Johnson & Johnson, Merck, Neuraltus, Novartis, Otsuka, Permobil, Pfizer, Sanofi, Shire, Takeda, Teva, and UCB; and the PatientsLikeMe R&D team has received research grant funding from Kaiser Permanente, the Robert Wood Johnson Foundation, Sage Bionetworks, The AKU Society, and the University of Maryland. S.M. Albert has received travel funding from the University of Wisconsin and the Gerontological Society of America; has served on the editorial boards of *Preventive Medicine*, *The Gerontologist*, the *Journal of the American Directors Association*, and *Innovation in Aging*; receives publishing royalties from Springer Publishing Co; has been a consultant for the Gerontological Society of America and the University of Wisconsin, School of Pharmacy; and has received research support from the NIH, the Richard King Mellon Foundation, and the Roy Hunt Foundation. Go to Neurology.org/N for full disclosures.

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