INSIGHTS AND OUTLOOK

MEMORY
& Cognitive Function

AHC Media

Insights and Outlook:
Memory and Cognitive Function

AHC Media

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Exercise and Brain Health: Food for Thought?

By Nancy J. Selfridge, MD

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The number of people in the United States age 65 and older has grown from 35 million in 2000 to 40 million in 2010, a 15% increase. This number is expected to be about 55 million by 2020, a 36% increase for the coming decade.[1] Decline in cognitive health, just like many other aspects of health, is associated with aging and exists on a continuum from normal functioning to mild measurable impairment to dementias such as Alzheimer's disease (AD). The health burden of mild cognitive impairment on individuals and society is hard to estimate, but AD currently afflicts one in eight people age 65 and older and has become the fifth leading cause of death in this age group. If present trends continue, it is estimated that as many as 16 million people will have AD by 2050 and health care costs related to this disease will increase from a current $183 billion to more than $1.1 trillion. The Centers for Disease Control and Prevention (CDC) reported in its most recent 2010 HealthStyles survey of 4183 U.S. adults that 70% of respondents expressed concern about memory loss and 20% feared becoming cognitively impaired.[2] Thus, identification of modifiable risk factors in the development of cognitive decline and dementia is important to stem the tide of this evolving problem.

Background

Exercise and physical activity are known to positively affect many of the common consequences of aging, including loss of muscle mass and strength, diminished bone density, impaired balance, reduced cardiorespiratory endurance, and increased incidence of chronic debilitating illnesses such as cardiovascular disease and diabetes mellitus.[3] A substantial body of both animal and human research suggests that exercise also appears to have a salutary effect on aspects of cognitive health, the components of which include: language, thought, memory, executive function, judgment, attention, perception, remembered skills, and the ability to live a purposeful life.[2,5,6] However, variability in research design and rigor has prevented the CDC and other agencies from developing clinical guidelines or recommendations for preserving cognitive functioning with exercise.[2]

Mechanism of Action

Several mutually compatible hypotheses exist for the beneficial mechanisms of physical activity and exercise on cognitive function in health and in dementia. One of the hallmarks of AD is amyloid ß plaque deposition in the brain. Laboratory studies have shown reduced amyloid ß plaque formation in mice provided exercise interventions compared to sedentary mice. In humans, amyloid ß brain load, plasma concentration, and serum levels have been shown to be lower in individuals with higher exercise and activity levels. These effects may be mediated by the ability of exercise to raise neurotransmitter levels (see below), increase testosterone levels, and increase growth factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1). Increase in cerebral blood flow associated with exercise also may play a role.[4]

Apart from an effect on amyloid ß deposition, the increase in BDNF and IGF-1 may reduce brain atrophy (normal hippocampal volume loss is 1-2% per year in older adults) and may even increase brain mass and volume. BNDF is known to be associated with neurogenesis and increased survival of neurons, and IGF-1 mediates both exercise induced angiogenesis and neurogenesis. In fact, higher levels of fitness in older adults have been associated with increased mass in the frontal and hippocampal areas of the brain. Exercise causes significant increases in several neurotransmitters including serotonin, norepinephrine, acetylcholine, dopamine, and epinephrine, all of which are known to decline with aging.[4,5]

Telomeres are nucleotide sequences on the ends of chromosomes that protect their integrity. Telomeres shorten with each successive cell division

and eventually lose their protective effect. Thus, progressive telomere shortening leading to cell and tissue growth arrest, damage, and senescence is one of the main theoretical mechanisms of physical and mental decline due to aging.[6] Telomerase is a ribonucleoprotein complex that preserves telomere length in proliferating cells. Telomerase activity appears to be upregulated in exercising mice and humans.[7]

Sex hormones may have a neuroprotective effect, and the increases in testosterone levels seen with exercise may play a role in preserving and improving cognitive function. Exercise may help reduce serum cortisol levels, one of the few hormones that increases with age and which may have a role in declining hypothalamic function with aging.[7]

Insulin resistance and type 2 diabetes have been implicated as having roles in AD because of the way that they alter amyloid ß processing. Exercise has a profound effect in improving insulin sensitivity and some of its beneficial effects on cognition may be mediated by this mechanism.[4]

The APOE ε4 allele has been associated with the strongest risk of late onset AD. Carriers of this allele are more susceptible to amyloid deposition if they are sedentary, but in exercising individuals the allele does not appear to increase brain amyloid load.[4]

Clinical Research

Summary of Epidemiological Studies. Several epidemiological studies have shown that exercise improves or helps maintain cognitive function. Most of these studies have assessed physical activity levels using self-reporting questionnaires but some have measured physical fitness or have made objective measures of physical activity with the use of an accelerometer device to measure body movement. Brown et al provide a systematic review of these.[4] In one cross-sectional study of 1927 healthy adults ages 45-70 years who self-reported their physical activity, Angevaren et al found higher intensity physical activity was associated with better processing speed ($P < 0.01$), memory ($P < 0.05$), mental flexibility ($P < 0.05$), and overall cognitive functioning ($P < 0.01$). In another cross-sectional study, Barnes et al noted higher global cognitive function in 349 healthy subjects 55 years of age and older who had higher levels of measured cardiorespiratory fitness measured by peak oxygen consumption, exercise duration, and oxygen uptake efficiency using a standard treadmill exercise test. Six longitudinal studies in older adults (n = 36,472) reported a statistically significant positive impact on cognitive measures or a reduction in cognitive decline with higher levels of physical activity or an increased risk of cognitive decline in subjects with lower levels of physical activity. *P* values, when reported for these studies, ranged from 0.02 to 0.001. Two prospective cohort studies by Wilson et al reported no association between self-reported physical activity and incident AD, but there are possible explanations for these negative findings. Both of these studies used smaller sample sizes than other epidemiological studies demonstrating an effect, both had follow-up periods of < 5 years and one of the studies used subjects from a limited and non-representative demographic.[4]

Sofi et al conducted a meta-analysis of 15 prospective cohort studies that included 33,816 initially healthy older individuals of which 3210 developed cognitive decline. Exercise conferred a significant protective effect on cognitive function. Follow-up periods ranged from 1 to 12 years. The highest levels of exercise, measured in various ways in all of these studies (see conclusions, below) provided the greatest protective effects (hazard ratio 0.62; 95% confidence interval [CI] 0.54-0.70; $P < 0.00001$); however, even low-to-moderate levels of exercise were beneficial compared to a sedentary lifestyle (hazard ratio 0.65; CI 0.57-0.75; $P < 0.00001$).[8]

Hamer et al reviewed data from 16 studies assessing the impact of physical activity on neurodegenerative disease risk (n = 163,797). In their analysis, the relative risk of dementia in the highest physical activity groups compared to the lowest activity or control groups was determined to be 0.72 (CI 0.60-0.86; $P < 0.001$) and the relative risk of AD was determined to be 0.55 (CI 0.36-0.84; $P = 0.006$). Again, exercise levels in these studies were measured and reported in highly variable ways.[9]

In a recent observational study of 104 early-stage AD patients, Winchester et al noted that sedentary patients experienced a significant decline in mini-mental status exam (MMSE) scores, while active patients had an attenuation in global cognitive decline. Those patients who walked for more than 2 hours per week demonstrated a significant improve-

ment in MMSE scores over 1 year.[10]

In another observational study, Kattenstroth et al reported that subjects who maintained a regular schedule of dancing into old age had better cognitive, motor, and perceptual abilities compared to education-, gender-, and age-matched controls having no history of dancing or sports participation activities.[11]

Summary of Intervention Studies. Brown et al summarized seven intervention trials assessing the impact of physical activity or exercise on cognitive function in healthy older adults. The interventions in these studies varied widely in type (strength, balance, stretching, aerobic, or combination), intensity, and duration of exercise. All provided supervised exercise, sometimes in group training and sometimes in a home-based program. All studies included men and women subjects; follow-up periods ranged from 6 months to 18 months, and several different measures of cognitive function were used as outcome measures. All but one of these studies demonstrated statistically significant or clinically significant improvement in cognitive performance in subjects after the exercise intervention.[4]

In a summary of eight studies of exercise intervention in subjects with cognitive decline, van Uffelen et al noted a statistically significant ($P < 0.05$) beneficial effect of exercise on cognitive decline in two-thirds of these studies. Again, the exercise interventions varied widely in type and volume as did the outcome measures. Attendance/adherence and drop-out rates in intervention and control groups were not reported or not included in intention-to-treat analysis of data in a number of these studies.[12]

In results from the Austrian Stroke Prevention Study, Sen et al assessed MRIs in 725 elderly community-dwelling subjects for brain parenchymal fraction (a measure of brain atrophy) and volume of white matter lesions (a measure of ischemic cerebral damage), and compared these measures to individuals' fitness represented by VO_{2max}. VO_{2max} was inversely associated with white matter lesion volume in men ($P = 0.02$). There was no relationship between fitness level and brain parenchymal fraction in this study.[13]

In a randomized controlled trial assessing the impact of chronic endurance exercise training (supervised exercise, 3 hours per week for 23 months) in community-dwelling older adults (n = 120) in Italy, Muscari et al reported that MMSE scores decreased significantly in the non-exercising control group (mean difference -1.21, CI -1.83 to -0.60, $P = 0.0002$) though not significantly in the intervention group (-0.21, CI -0.79 to 0.37, $P = 0.47$). Odds ratio for the exercising adults to have stable cognitive status at the end of 1 year compared to the control group was 2.74 (CI 1.16-6.48) after adjustment for possible confounders.[14]

Conclusion

Though epidemiological evidence appears to support regular exercise and maintenance of physical fitness for reducing risk of cognitive decline due to aging, interventional studies are not yet numerous nor robust enough to support the development of clinical guidelines for exercise as a lifestyle strategy to preserve cognition by the CDC. Studies to date have had significant methodological flaws.

Most of the longitudinal or cross-sectional epidemiological studies have used self-report questionnaires to measure exercise and activity levels, a notoriously unreliable way to gauge physical activity or fitness levels. Further, the questionnaires have not employed consistent definitions of low, moderate, and high levels of physical activity and exercise. These two shortcomings create a significant problem when trying to determine what levels and types of exercise are most effective for preventing cognitive decline. Some of the studies have used an accelerometer device or measures of physical fitness that sidestep this dilemma to a degree. But even measures of physical fitness, such as the VO_{2max} or oxygen consumption, require maximal treadmill or cycle ergometer exercise tests wherein subjects are required to run or cycle until they reach their maximal power; the test is terminated when the subject reports exhaustion or the supervising physician orders it for medical reasons. Thus, even these measures may be strongly influenced by subjective sensations and motivation. Many diverse tools have been used in these studies to measure cognitive functioning and different outcomes chosen, as well. Some have looked at level of cognitive function, some at cognitive decline, and others have used a diagnosis of AD as an outcome. The clinical significance of outcomes is important and needs to be considered and addressed in all studies, but often is not. An increase in

a point or two on the MMSE score, for example, may take a person out of the range associated with early dementia (less than 21) or mild cognitive decline (21 to 24). Further, since not all cognitive decline results in functional impairment and not all cognitive decline in aging results in dementia, results and conclusions are difficult to compare and interpret clinically.

The interventional studies to date have looked at the effect of exercise both on healthy elderly and in persons already afflicted with dementia. These studies have employed very diverse exercise interventions ranging from "individualized programs," to purely aerobic programs in prescriptive weekly doses, to combinations of aerobic, strength, balance, and flexibility training. Volumes of exercise interventions have varied as have durations of the interventions. As previously mentioned, some of the interventional studies have failed to report adherence and dropout rates and some have failed to perform intention-to-treat analysis on data. In some instances, the control group was sedentary, and in others the control group also exercised or took part in some other non-exercise group activity, helping to control for group effect on outcomes. Again, cognitive function measures were very diverse and comparisons and clinically relevant conclusions are difficult to discern.

Recommendations

Exercise for middle aged and elderly people has proven benefit for prevention and attenuation of many chronic diseases strongly supported by research evidence. Larger and better designed interventional studies addressing the precise types and volumes of exercise needed to prevent cognitive decline or dementia are necessary before clinical guidelines can be made for exercise as a lifestyle intervention for these problems, though. Nonetheless, because of the low cost and low risk of increasing physical activity, physicians may counsel their aging patients that among other health benefits accumulating 150 minutes per week of moderate exercise according to present clinical guidelines may help promote brain health and prevent decline in cognitive function while we await the research supporting definitive guidelines for this specific benefit. ■

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Omega-3s and Brain Aging: A Connection?

Abstract and Commentary

By David Kiefer, MD

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Synopsis: The researchers behind this study attempted to correlate quantitative measurements of omega-3 levels in red blood cells (RBC) with a variety of cognitive measures and tests for dementia. They found that people with lower RBC omega-3 levels had significantly worse results in brain testing.

Source: Tan ZS, et al. Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. *Neurology* 2012;78:658-664.

This new analysis of the well-known Framingham cohort (1575 community dwellers, aged 67 ± 9 years, free of stroke and dementia) attempted to improve on prior studies showing mixed results for a connection between omega-3 intake (usually fatty fish) and dementia risk. By incorporating RBC fatty acid composition (with a lifespan of 120 days), rather than just dietary recall (known to be an inaccurate reflection of blood fatty acids) or plasma omega-3 levels (which only reflect a few days' intake), the researchers were hoping to more definitively assess this connection.

The participants in this study had blood drawn and analyzed for RBC fatty acid composition, and had a brain MRI (many measurements recorded) and neuropsychiatric (NP) testing approximately three months later. The three NP testing subsets that were a part of this study focused on cognitive domains that correlate with increased risk of Alzheimer's disease: the verbal memory component of the Logical Memory test, the visuospatial memory component of the Visual Reproductions test, and the Similarities test for abstract reasoning skills.

The RBC fatty acid testing yielded multiple fatty acid results, but the researchers focused on just the two that have been shown to correlate with the risk of dementia, RBC docosahexaenoic acid (DHA) and the omega-3 index (RBC DHA and eicosapentaenoic acid [EPA] expressed as a weight percentage of the total fatty acids).

When RBC DHA levels and omega-3 index were compared to the brain MRI findings, no linear correlation was seen. However, the lowest quartile of DHA levels and omega-3 index correlated with a lower total cerebral brain volume when compared to the upper three quartiles; the authors claim that this loss of brain volume correlates with an additional two years of brain aging. Other brain MRI findings were insignificant between the quartiles for both RBC DHA and omega-3 index.

With respect to NP testing, a positive association was seen between omega-3 index and RBC DHA levels on all tests except verbal memory. Some attenuation of the relationship between the omega-3 parameters and visual memory and executive function was seen when factoring in other know risk factors for dementia and cognitive decline.

Of note, given that this was a cross-sectional study, the authors point out that it was not possible to examine this cohort for the *development* of dementia, rather just look for connections between the omega-3 parameters and *risk* for dementia.

Commentary

This paper is an interesting addition to the literature exploring a connection between omega-3 status and brain health. The neurological effects of omega-3 fatty acids fit with the known high concentrations of phospholipids in the central nervous system; in particular, DHA is abundant in the brain. Recent research has demonstrated, in some but not all clinical trials, a relationship between maternal supplementation and childhood neurological development.[1] One

Table 1. Approximate eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) content in fish and amount of fish required to provide 1 g EPA + DHA

Type of fish	EPA + DHA content, g per 3 oz serving of fish (edible portion)	Amount of fish (oz) required to provide approximately 1 g of EPA + DHA per day*
Catfish		
Farmed	0.15	20.0
Wild	0.20	15.0
Crab, Alaskan King	0.35	8.5
Flounder/Sole	0.42	7.0
Haddock	0.20	15.0
Halibut	0.40-1.00	3.0-7.5
Herring		
Atlantic	1.71	2.0
Pacific	1.81	1.5
Mackerel	0.34-1.57	2.0-8.5
Salmon		
Atlantic, farmed	1.09-1.83	1.5-2.5
Atlantic, wild	0.90-1.56	2.0-3.5
Chinook	1.48	2.0
Sockeye	0.68	4.5
Sardines	0.98-1.7	2.0-3.0
Shrimp, mixed species	0.27	11.0
Tuna		
Fresh	0.24-1.28	2.5-12.0
White, canned in water, drained	0.73	4.0

* The intakes of fish given are rough estimates because oil content can vary markedly (> 300%) with species, season, diet, and packaging and cooking methods.

Adapted from Kris-Ehterton PM, et al. American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002;106:2753.

compelling and media-friendly result showed that increasing maternal DHA intake by 100 mg daily could lead to an improvement in a child's IQ of 0.13.[2] In addition, low serum DHA levels may be associated with any number of neuropsychiatric disorders.[3]

On the other end of the human lifespan, some studies have shown that omega-3 supplementation may improve cognitive function, and that lower dietary intake of omega-3 fatty acids can lead to increased cognitive decline in the elderly. However, as hinted at above, there have been pitfalls in the dietary intake research. The study being reviewed here is an interesting approach to quantifying and improving on the omega-3 intake research and cognitive changes in a late-middle age cohort by measuring RBC omega-3 levels. RBCs don't cheat on dietary recall so this research approach should lead to more accurate results.

Table 2. Sources of omega-3 fatty acids

- Cold water, fatty fish
- Cold-expeller-pressed canoloa oil
- Ground flaxseed
- Walnuts
- Unprocessed soy products
- Fortified eggs

As much as the results of the study lend some

hope to what might help prevent the development of dementia or, more generally, cognitive decline in this demographic, they remain preliminary and leave unanswered a few important questions. For example, why did some of the NP results correlate with RBC omega-3s, while other tests did not? How do the different RBC omega-3 levels relate to particular omega-3 intake (either dietary or supplementation), so as to make these results more clinically applicable? And, would these same results apply to non-Caucasian populations? Hopefully, follow-up research will address these questions and more in the process of refining our knowledge about omega-3s and the brain. ■

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Does HRT Improve Cognitive Function?

Abstract & Commentary

By Jeffrey T. Jensen, MD, MPH

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Synopsis: In a cross-sectional sample of postmenopausal women not using hormonal therapy, higher serum levels of estrogen were associated with improved semantic memory and verbal episodic memory abilities.

Source: Ryan J, et al. Hormone levels and cognitive function in postmenopausal midlife women. *Neurobiol Aging* 2012; 33:617.e611-e622.

To investigate whether gonadal hormones influence cognitive function in postmenopausal women, the authors administered a comprehensive battery of neuropsychological tests on two occasions (2 years apart) to participants enrolled in the population-based, longitudinal Melbourne Women's Midlife Health Project. A total of 148 women (mean age 60 years) who had undergone natural menopause and were not using hormone therapy underwent the neuropsychological testing at year 11 of the study, with 108 completing retesting at year 13. Total and free estradiol, estrone, and testosterone levels were measured at the time of the first testing. The tests included an adaption of the California Verbal Learning Test II, using semantically related words and a 10-item list learning task using unrelated words. Both of these tests assessed immediate and delayed recall. A variety of other tasks related to immediate and delayed recognition, letter-number sequencing, category fluency, and naming also were administered. To reduce the number of cognitive outcomes examined and thus the risk of a Type 1 error, the investigators incorporated a principal-component analysis to identify four groupings of correlated cognitive tests: verbal episodic memory, visual episodic memory, semantic memory (the ability to recall words or names), and executive function-visuospatial skills.

Initial analyses compared the characteristics of women at the time of baseline testing, according to cognitive factor scores, using correlations and t-tests. The change in cognitive function over the 2-year period was calculated by subtracting each baseline test score from the corresponding score 2 years later. Low change scores indicated a decline in cognitive function. Linear regression analysis was used to model the association between individual hormone measures and cognitive function at baseline, and analyses were adjusted a priori for potential confounders (age, education level, depressive symptoms, and age at menopause).

In the multiple linear regression analyses, better semantic memory performance was associated with higher total ($P = 0.02$) and free ($P = 0.03$) estradiol levels and a lower ratio of testosterone to estradiol ($P = 0.007$). There were no statistically significant associations between hormone levels and verbal episodic memory (although this was at the $P = 0.08$ level), verbal episodic memory, visual episodic memory, or executive function-visuospatial skills. The authors concluded that in postmenopausal women, endogenous estradiol and testosterone levels and the testosterone/estradiol ratio are associated with semantic memory and verbal episodic memory abilities.

Commentary

Although most of the basic research in nonprimate species and functional studies in nonhuman primates and women support that estrogen has a profound effect on memory and executive function,[1] we lack strong clinical data to support whether postmenopausal women should consider estrogen replacement therapy for cognitive protection. This is unfortunate, as memory complaints are common in midlife, and many women would choose to use a product that would improve or prevent these symptoms if one existed. Although cognitive protection is not a labeling indication for any hormonal product, a number of other interventions designed for healthy brain aging have been accepted by the public, unencumbered by the regulatory burden of evidence of efficacy and with no comprehensive evaluation of risk. *Ginkgo biloba* anyone?

Since the publication of the main results from the Women's Health Initiative (WHI) almost 10 years ago, the public debate on hormone replacement therapy (HRT) has focused primarily on risk. When I talk to young clinicians, I find they have limited experience counseling women regarding postmenopausal hormone therapy. I think it is important to discuss the very real possibility of benefit with my patients, and put risk in perspective. But how should a clinician counsel a newly menopausal women presenting for HRT for cognitive protection? Is the evidence compelling? What if she has no other menopausal symptoms?

The WHI Memory Study, a planned substudy of the WHI that evaluated the incidence of dementia and mild cognitive impairment in postmenopausal women, concluded that HRT not only failed to protect against cognitive decline, but actually increased the risk of dementia.[2] But we know that the WHI enrolled a group of women with cardiovascular risk factors at an average age of 10 years after menopause. Do these results apply to otherwise young, healthy recently menopausal women? They do not seem to when cardiovascular outcomes are evaluated, and I suspect the brain is the same. For the cardiovascular system, clinical trials and surrogate studies support that timing is critical: protection occurs with early (shortly after onset of menopause) and continued exposure while prolonged estrogen deprivation results in irreversible changes that limit the benefit of estrogens in older initiators.[3]

Similar data exist for the brain, suggesting that early and often applies to HRT initiation if the goal is cognitive protection.[4] The Ryan study puts a slightly different perspective on this, showing that semantic memory (the ability to recall words or names) is correlated with serum estrogen levels in postmenopausal women not using HRT. A couple of observations: First, the mean estrogen levels were quite low in this study, certainly in the range we expect with menopause. Does this mean that we are measuring an effect that takes many years to develop? Second, testosterone/estrogen levels were inversely related to semantic memory. In other words, as women move to a more androgen-dominant endocrine environment (due to ovarian production of androstenedione and testosterone following the loss of follicular activity and rising luteinizing hormone), their memory declines. This is a red flag for women with intact ovaries in natural menopause; they may be more at risk for memory problems. I would want to hedge my bet with a little exogenous estradiol to move to a more favorable balance.

Brain function is another extremely important potential benefit of hormonal therapy. Although there is some inconsistency in the results of current clinical information, animal studies and functional imaging studies in women suggest benefit. High-quality longitudinal studies will be needed to determine whether the Timing Hypothesis is true with respect to brain function. Women taking estrogen now may be in a position to remember the question when the story is complete! ■

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Can We Predict Long-Term Cognitive Impairment in Survivors of Critical Illness?

Abstract & Commentary

By Linda L. Chlan, RN, PhD
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Synopsis: In survivors of critical illness with documented cognitive impairment at discharge, commonly used cognitive screening tests do not predict which of these patients will experience long-term cognitive impairment.

Source: Woon FL, et al. Predicting cognitive sequelae in survivors of critical illness with cognitive screening tests. *Am J Respir Crit Care Med* 2012; 186:333-340.

As more patients are surviving critical illness, there is documentation of serious cognitive, physical, and psychiatric consequences arising from lengthy ICU stays in these patients. Numerous studies have demonstrated new cognitive impairments in ICU survivors, yet there is no evidence available as to which patients are likely to experience long-term cognitive impairments after hospital discharge. The study by Woon and colleagues was conducted to address this knowledge gap. The researchers wanted to determine if commonly used cognitive screening tests administered at hospital discharge could be used to predict cognitive impairments, termed cognitive sequelae, 6 months later.

The baseline cognitive screening tests were the Mini-Mental State Examination (MMSE), which is the "gold standard" for cognitive status screening, and the Mini-Cog used to detect cognitive impairments; both were administered at hospital discharge. A battery of cognitive tests was administered 6 months after discharge from the hospital, including the Wide Range Achievement Test-3 Reading subtest (WRAT-3) and the Wechsler Abbreviated Scale of Intelligence (WASI). A number of neuropsychological tests were also administered 6 months after discharge to look for the presence of cognitive sequelae, including attention, upper extremity motor speed, language, memory-delayed recall, long-delay recall, mental processing speed, and executive function. Detailed information on this extensive battery of cognitive and neuropsychological tests can be found in the article by Woon et al.

Patients receiving mechanical ventilation for > 48 hours who were 18-85 years of age were recruited from the Shock Trauma ICU and Respiratory ICU at LDS Hospital and Intermountain Medical Center in Salt Lake City, Utah, from August 2007, through December 2008. Of the 319 patients who initially met the study inclusion criteria, only 70 (50% male) participated in the cognitive assessments at hospital discharge. Of these 70 participants evaluated at hospital discharge, 10 died between discharge and the 6-month follow-up period, three declined to participate, and four were lost to follow-up contact. A final sample of 53 participants completed the 6-month follow-up, with an average age of 54 years, mean hospital length of stay of 25 days, mean ICU length of stay of 13.3 days, and mean duration of mechanical ventilation of 8.8 days.

At hospital discharge, 39% of the participants were impaired on both the MMSE and the Mini-Cog; 64% were impaired on the MMSE only with 45% impaired only on the Mini-Cog. Perhaps not surprisingly, only 28% of the patients had normal scores on both cognitive screening tests. At 6 months post-hospital discharge, controlling for pre-ICU cognitive function, education, depression, and days of mechanical ventilation, the MMSE and Mini-Cog scores were not found to predict cognitive sequelae in this sample. However, a number of the measured cognitive sequelae were found in these ICU survivors at the 6-month follow-up including, most prominently, impaired memory (38%), executive dysfunction (36%), and slow upper extremity motor speed (26%). Of note, the researchers did not assess for the presence of delirium at any time in this study.

Commentary

The primary aim of the study by Woon and colleagues was to determine if the MMSE and the Mini-

Cog could predict cognitive sequelae in survivors of prolonged critical illness. While the findings addressing the primary aim were not found to be statistically significant, the most clinically significant finding from this article is the marked cognitive sequelae in this sample of ICU survivors. Of note, this sample of study participants was relatively young (54 years of age) with impairments in memory and executive function 6 months after hospital discharge. These findings have important implications for quality-of-life outcomes in survivors of prolonged critical illness and their ability to return to work.

The small sample of only 53 participants out of an initial group of more than 300 patients limits the generalizability of these findings to ICU survivors in general. However, the marked cognitive impairments in these patients should give pause to all ICU clinicians when discussing post-ICU outcomes with patients and their family members. Surviving a prolonged critical illness may come with significant cognitive, physical, and psychiatric consequences that can directly impact quality of life. ■

Cognitive Function in Breast Cancer Survivors

Abstract & Commentary

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Synopsis: There has long been an appreciation of the risk of cognitive decline associated with chemotherapy but questions remain about the magnitude and duration of the observed deficits. In this meta-analysis of studies that included neuropsychological assessments at a minimum of 6 months after completion of breast cancer chemotherapy, definite but small deficits were found for both verbal and visuospatial capabilities. In this analysis, age and educational status were not found to be moderators of acquired deficits.

Source: Jim HSL, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol* 2012;30:3578-3587.

Whereas there has been substantial research on the cognitive effects of chemotherapy, including prior meta-analyses,[1-4] the issue remains unclear whether such treatment produces long-term deficits, and if so, how much. It remains well-established that moderate-to-severe cognitive impairment occurs in a substantial percent of chemotherapy-treated breast cancer patients (between 15% and 75%[5,6]). Yet, evidence is mixed regarding long-term cognitive deficits in patients treated with chemotherapy. Furthermore, some data now suggest that cognitive deficits may develop after the completion of treatment.[7]

Previous meta-analyses, the latest of which was published in 2006, were not focused specifically on the post-chemotherapy period, and since these publications there have been several reports providing additional information. Thus, Jim and colleagues performed the current meta-analysis, the goal of which was to assess cognitive functioning in breast cancer survivors who were treated with chemotherapy a minimum of 6 months prior to analysis.

The investigators, by searching PubMed and other major databases, found 2751 abstracts, and from these they found 17 studies that met stringent criteria for inclusion in this analysis. The 17 studies included 807 patients previously treated with standard-dose chemotherapy for breast cancer and on whom cognitive studies were performed 6 months or more after completion of chemotherapy. Neuropsychological tests were categorized according to eight cognitive domains: attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability.

Deficits in cognitive functioning were observed in patients treated with chemotherapy relative to controls or prechemotherapy baseline in the domains of verbal ability ($g = -0.19$; $P < 0.01$) and visuospatial ability ($g = -0.27$; $P < 0.01$). Patients treated with chemotherapy performed worse than non-cancer controls in verbal ability and worse than patients treated without chemotherapy in visuospatial ability (both $P < 0.01$). Age, education, time since treatment, and endocrine therapy did not moderate observed cognitive deficits in verbal ability or visuospatial ability (all $P \geq 0.51$).

Commentary

Results indicate that, on average, observed cognitive deficits in patients with breast cancer previously treated with chemotherapy are small in magnitude and limited to the domains of verbal ability and visuospatial ability. That the magnitude of observed deficits is small is reassuring, particularly when considering some of the fairly dramatic changes that have been reported for breast cancer patients actively receiving therapy. However, persistence of deficits 6 months and beyond raises concerns that such deficits might be long lasting, if not permanent.

One unexpected finding was that age and education status were not shown to moderate the effects of chemotherapy-induced cognitive change. However, the strength of this and other conclusions based on

meta-analysis is only as robust as the studies examined in the analysis, and the authors acknowledged that there might not have been sufficient numbers of older or less-educated patients to demonstrate significant associations. In contrast, in one recent report,[8] age and "cognitive reserve" (an attribute comprised of such factors as education, employment, and cognitive stimulation) were shown to be important factors predicting chemotherapy-associated decline. Thus, older patients with low levels of pretreatment cognitive reserve were found to be most vulnerable to post-treatment cognitive decline.

Another concern is that this, as with many of the reports of chemotherapy-associated brain deficits, focused on breast cancer patients only. Such patients often receive additional and somewhat complex treatment regimens that include surgery, radiation, and hormonal treatments, all of which may confound interpretation of observed findings. Thus, it would be premature to generalize these findings to chemotherapy treatment in general. Further, most of the primary studies on this topic exclude patients who might be at highest risk for cognitive decline, such as those with significant comorbidities, depression, or neurologic disorders. Thus, as highlighted by the accompanying editorial,[9] the findings from this meta-analysis might significantly under represent the magnitude of the cognitive impact of cancer treatments. ■

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Energy Drinks to Improve Performance

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Energy drinks have rapidly become very popular, especially among adolescents and young adults. Recent trends can be traced to the introduction of Red Bull in Austria in 1987 and the United States in 1997.[1] Hundreds of brands are now available, with sales increasing exponentially. Six billion energy drinks were sold in the United States in 2010, up from 2.3 billion in 2005.[2] They are most commonly consumed to counteract tiredness, increase energy, and maintain alertness for driving or studying.[3] Highly concentrated products are now available as "energy shots" and "energy sheets" which dissolve on the tongue.[2] Energy drinks also are consumed with alcohol to enhance its intoxicant effects, and then afterward to relieve hangovers.[2]

The primary ingredients in energy drinks are caffeine, taurine, and simple sugars (like sucrose, fructose, or beet sugar).[3] Guarana (*Paulinia cupana*) from South America often is added as it provides about 250 mg caffeine per 3-5 g herb *(see Table for comparison with other caffeine sources)*.[4] Guarana contains other compounds related to caffeine with similar effects, so its addition is not equivalent to adding more caffeine. A variety of herbs and other compounds are contained in specific brands, including *Gingko biloba*, *Panax ginseng*, L-carnitine, and B vitamins.[2] The actual ingredients, and their amounts, vary widely *(see Table)*.

Energy drinks will be distinguished here from sports drinks that contain primarily glucose and electrolytes and are consumed to counteract dehydration, improve muscle function, and decrease exercise-related exhaustion. Both drinks are used by athletes, but energy drinks are distinguished by their high caffeine levels. Health care professionals should be aware of the effects of energy drinks because of their widespread consumption, especially among young males, and growing concerns about the adverse effects of their overconsumption.

Background

Caffeine is the most widely used stimulant in the world, and is generally recognized as safe. About 90% of adults drink caffeinated beverages, with an average daily intake of 227 mg caffeine.[6] What is new with energy drinks is the amount of caffeine being consumed by adolescents, and how it is being consumed with other substances.[7] Energy drink marketing specifically targets adolescents and young adults through its catchy slogans and sponsorship of extreme sports and high-risk activities.[6]

Regulation of energy drinks varies widely. Some countries ban all energy drinks (like Uruguay), restrict their sale to pharmacies (like Norway), or limit their caffeine content.[8] Some European countries initially banned Red Bull, but these bans were overturned and applicable energy drinks must now carry a "high caffeine content" label.[1] In Canada, labels must include warnings, a maximum daily consumption, and caution against mixing energy drinks with alcohol.[8]

Regulation of energy drinks in the United States has been complicated. Historically, caffeinated beverages were regulated by FDA as foods.[1] In 1980, FDA proposed eliminating caffeine from such drinks because of concerns about its health effects. Soft drink manufacturers responded that caffeine was a flavor enhancer and FDA introduced a maximum caffeine content of 0.02% or 71 mg per 12 oz container for soft drinks.

Many energy drinks exceed the FDA limit, but sanctions are avoided by using the 1994 Dietary Supplement Health and Education Act. The drinks can be classified as dietary supplements because they contain herbs and other natural products.[1] Thus, an over-the-counter medication like NoDoz (containing 100 mg caffeine per tablet) must include several warnings on its label, while an energy drink containing more than 500 mg caffeine carries no information or warnings. However, premixed alcoholic drinks containing caffeine were effectively banned in 2010 when the FDA declared caffeine an "unsafe food additive" in alcoholic beverages.[2]

Mechanism of Action

Caffeine is a central and peripheral nervous system stimulant, which antagonizes adenosine receptors and potentiates dopamine neurotransmission.[6] Interactions with different receptors lead to numerous effects. In adults, moderate acute doses (200-350 mg) decrease heart rate and increase blood pressure, while also enhancing feelings of well-being, improving concentration, and increasing arousal.[7] At higher doses (> 400 mg), feelings of anxiety, nervousness, and jitteriness predominate. Little research has focused on children and adolescents, but similar effects have been observed, except that negative effects have been observed in children (13-17 years) after 100 mg.

Taurine is an organic acid that is found throughout the body, especially within the central nervous system. Because of its role in healthy development, it has been added to infant formula since the 1980s.[8] Taurine has many roles, and is essential for cardiovascular functioning and in skeletal muscle. Although many popular energy drinks contain 1-2 g/serving, its role is unclear.[3] Claims are made that it promotes energy utilization and exercise performance, but these are based on studies involving taurine combined with other ingredients. A study of 11 male endurance cyclists found no performance improvement with 1.66 g taurine, while total fat oxidation increased 16% compared to placebo ($P < 0.05$).[9]

Simple sugars are a rapidly absorbed source of energy and are added to energy drinks for this reason and to improve cognitive performance. Drinks typically contain about 27 g sugar per 8 oz.[3] Larger volume energy drinks exceed the maximum recommended daily intake of 32 g sugar.[4]

Clinical Studies

Individual energy drinks constituents will be discussed first. The best-researched of these is caffeine, with several studies showing it counteracts poor performance due to reduced alertness, increases long-term exercise endurance, and improves speed and power output.[7] Age-related differences in caffeine's effects have been identified. One study involved 26 boys and 26 men given a 5 mg/kg caffeinated drink.[10] No differences were found in either group for blood pressure or exercise performance. However, heart rate was significantly lower for the boys at rest and during exercise, while no changes occurred in the men. Other studies have found age-related differences in caffeine's cognitive effects, such as boys showing greater reduction in reaction time than men and greater increases in speech rates.[8]

Almost all the research on taurine has been conducted with animals. Studies found that when animals are given neurotoxins, taurine prevents or reverses resulting deficits in learning and memory, but does not enhance cognitive performance in healthy animals.[3] A 2012 review found no human studies of taurine's influence on caffeine-induced changes in cognitive performance.

Table. Caffeine Content of a Representative Sample of Caffeinated Beverages[1,5]

Name	Bottle/can volume (oz)	Caffeine concentration (mg/oz)	Total caffeine (mg) per serving size listed in second column
Full Throttle	16	9	144
Monster	16	10	160
Powershot	1	100	100
Red Bull	8.3	9.6	80
RedLine Power Rush	2.5	140	350
Wired X505	24	21	505
Coca-Cola Classic	12	3	34.5
Mountain Dew	12	4.5	54
Coffee, Starbucks brewed	12 (Tall)	20	240
Coffee, generic brewed	12	16	195 (range 150-300)
Tea, brewed	12	6	76 (range 60-180)

The effect of simple sugars on cognition has produced inconsistent results. A systematic review identified about 30 clinical trials, most examining memory.[11] Among these, about half found some beneficial effects but the other half did not. Positive findings were more consistently found with elderly subjects, with little impact on younger subjects. Four studies examined mood, with increased vigilance and decreased fatigue identified in one study each, while two other studies found no significant impact on mood. Glucose's cognitive effects in combination with caffeine have been studied in three trials. Two showed reduced reaction time and improved attention and memory, while one showed no impact on attention.[3]

Relatively few randomized controlled trials (RCTs) have been published on energy drinks. In one, 20 undergraduate students (mean age 21 years) participated in a 5-way crossover study.[12] They consumed 250 mL containing either 37.5 g glucose, 75 mg caffeine, ginseng, and gingko as flavorants (not intended to have physiological effects), the energy drink (glucose, caffeine, ginseng, and gingko), or a placebo consisting of the vehicle used for the other drinks. Compared to placebo, the energy drink significantly improved "secondary memory" ($P = 0.007$) and "speed of attention" ($P = 0.044$), but no other cognitive measures, mood, or heart rate. No significant changes in cognitive factors were found with any of the individual components.

A double-blind RCT was conducted with 81 subjects undergoing firefighter training.[13] Each received a 330 mL drink containing either 50 g glucose and 40 mg caffeine, 10.25 g fructose/glucose and 80 mg caffeine, or placebo (no details given on its composition or taste). Several cognitive, mood, and performance measures were used. Both energy drinks resulted in significant improvements in information-processing tasks ($P = 0.039$), while the 50 g glucose plus 40 mg caffeine drink showed improved grip strength ($P = 0.01$) and memory ($P < 0.05$), and decreased anxiety ($P = 0.038$) and self-reported stress levels ($P < 0.05$).

One article reported on three small studies involving Red Bull energy drink and sports performance.[14] Whether the study was sponsored by Red Bull was not mentioned. Each study involved 10-14 undergraduate students (mean ages 20-24 years). Participants drank either Red Bull or a placebo drink. The Red Bull groups improved aerobic endurance by 9% ($P < 0.05$) and anaerobic performance by up to 24% ($P < 0.05$). Significant improvements also occurred in mental performance, including choice reaction time, concentration, and memory.

Red Bull sponsored an RCT that examined the effect of Red Bull on driving performance in 24 adults (mean age 22.8 years).[15] Subjects drove for 2 hours on a simulator that monitored weaving and speed. During a 15-minute break, participants consumed 250 mL of either Red Bull or placebo Red Bull made by the manufacturer. They drove for another 2 hours. Driving quality, mental effort, and sleepiness also were measured subjectively. When authentic Red Bull was consumed, significant reductions in weaving and sleepiness were found during the third and fourth hours of driving. During the third hour only, improvements were found in speed consistency, subjective driving quality, and mental effort.

Adverse Effects

One energy drink taken by an adult appears to be safe. However, many reports raise concerns about the over-consumption of energy drinks, mixing them with alcohol, and their use by adolescents. Case reports are linked to concerns about caffeine toxicity. Case studies reporting adverse effects typically involve large volumes of energy drinks, such as atrial fibrillation after 575 mg caffeine daily, acute hepatitis after 10 cans per day, jaundice after several cans, five cases of epilepsy after at least 480 mg caffeine, and severe anxiety after 6-8 energy drinks per day.[2] Australian poison control centers reported 12 energy drink-related cases in 2004, which increased to 65 in 2010.[16] These patients had an average age of 17 years, with a median consumption of 5 units per session. The most common symptoms were palpitations, agitation, tremor, and gastrointestinal upset, but serious cardiac and neurological effects also were reported, with more than half requiring hospitalization.

The manufacturers of Monster Energy Drink were sued in October 2012 following the death of a 14-year-old girl. She consumed two 24 oz cans of Monster in the 24 hours before her death and the autopsy report attributed her death to "cardiac arrhythmia due to caffeine toxicity."[17] Following this, the FDA stated they were investigating reports that Monster was linked to five deaths, and reports of 13 deaths associated with 5-Hour Energy, a concentrated energy shot.

Concerns also exist about the use of energy drinks along with other substances. The Australian report found that in almost half the cases involving energy drinks, patients had consumed other substances, usually other caffeinated products or alcohol.[16] Numerous studies have identified higher rates of alcohol-related harm (such as being taken advantage of sexually, driving under the influence, or being injured) when people consume large quantities of alcohol mixed with energy drinks.[18] Compared to alcohol alone, alcohol plus energy drinks increased self-reported sense of stimulation, counteracted some alcohol-related impairments, but did not change inhibition nor ability to drive.[19] Numerous cases of intoxicated young adults requiring emergency room treatment have been published where energy drinks were involved. The average age of those involved in one case series was 16 years.[20]

Conclusion

Energy drinks increase alertness and may improve physical performance. They serve as stimulants like others drink tea or coffee. They are the subject of intensive marketing, especially to younger people. The resulting increased consumption of caffeine by adolescents has unknown consequences. Over-consumption of energy drinks puts people at risk of caffeine toxicity, although the level at which this occurs varies individually and with age. Combined with alcohol, they place people at higher risk of intoxication and many adverse effects. Other indirect concerns are raised about energy drinks because consumption of caffeine-containing beverages in children is associated with greater BMI, greater intake of unhealthy foods, and lower intake of fruits and vegetables.[7]

Recommendation

Many people are consuming more caffeine younger, and health care professionals should be alert to symptoms of caffeine toxicity, especially in adolescents and young adults. There should be an increase in education on the risks of overconsumption of energy drinks and the dangers of mixing them with alcohol. The long-term effects of regular consumption of energy drinks are not known. Chronic use of any stimulant is not an adequate replacement for adequate rest and sleep. As with most areas, moderation should be encouraged. For most healthy adults, 200-300 mg caffeine per day is not harmful, whether obtained from coffee or energy drinks. For adolescents, the tolerable amount is lower, but evidence for clear guidance is lacking. What is clear is that energy drinks and alcohol are an unsafe combination, especially for adolescents. ■

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Inhaled Anesthetics Have Differential Experimental Effect on Memory Mechanisms

Abstract & Commentary

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Synopsis: Isoflurane causes mitochondrial disruption and apoptosis in neuronal and hippocampal cells, and decreases memory consolidation in mice. Such effects are not seen with desflurane. This may impact selection of anesthetic agents for patients with Alzheimer's disease undergoing surgical procedures.

Source: Zhang Y, et al. Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. *Ann Neurol* 2012;71:687-698.

There are a large number of patients with Alzheimer's disease (AD) who need and undergo surgery and anesthesia every year. Cognitive dysfunction has been reported postoperatively, placing patients with AD at increased risk. Therefore, these investigators studied cellular mechanisms that may play a role.

The authors studied caspase 3 activation, mitochondrial destabilization via reactive oxygen species (ROS) generation, and decreased levels of ATP. Hippocampal neurons and neuroblastoma cell line B104 were used. Behavioral testing in mice treated with isoflurane or desflurane was done using fear conditioning test.

Results showed isoflurane but not desflurane increased ROS generation, lowered mitochondrial membrane potential, increased caspase 3 activation, and lowered ATP levels. Many of these were mediated via opening of the mitochondrial permeability transition pore (mPTP). These effects were attenuated by cyclosporine A, a potent mPTP blocking agent. Behavioral testing showed decreased fear conditioning by isoflurane, likely from decreased memory consolidation.

The inference from this study is that isoflurane activates pathways that have been shown to be involved in the pathogenesis of AD and mimics failure of memory consolidation. This would make desflurane an anesthetic of better choice over isoflurane in patients with AD. Therefore, it would be important to emphasize the selection of anesthetic agents in patients with AD who undergo surgery.

Commentary

Inhaled anesthetics, such as isoflurane and desflurane, affect cognitive function in humans. In a clinical trial involving 45 patients undergoing non-neurological surgery, isoflurane anesthesia was associated with higher impairment in cognitive tests compared to spinal anesthesia or desflurane.[1] The latter also has a lower incidence of cognitive impairment compared to propofol.[2]

The mechanisms behind such cognitive impairment may be numerous. Isoflurane causes increased generation of Ab.[3] It has been shown to cause loss of neural stem cells and decreased neurogenesis in young rodents. These effects were not seen in adult rodents, implying an age-dependent mechanism.[4] In the opposite spectrum, it induces NMDA receptor NR2B subunit composition. This is responsible for LTP in hippocampal CA1 neurons and memory formation.[5] In another study, isoflurane induced cognitive impairment in mice with the lowest administered dose, but this did not persist at 56 hours post anesthesia.[6]

This study examines the effects of isoflurane and desflurane on some of the pathways that are involved in pathogenesis of AD. The test of memory used in this experiment is that of associative memory. A more elaborate test of memory would be a Morris water maze or a radial T-maze.

Caspase 3 activation and mitochondrial ATP deple-

tion are important mechanisms. There are other pathological mechanisms that are also affected by isoflurane as above. The overall balance seems to indicate a detrimental effect on cognition. That the pathways of injury seem to be similar to those seen in AD should make the use of isoflurane a matter of caution in patients with AD. ■

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REM Behavior Disorder as a Predictor of Mild Cognitive Impairment

Abstract & Commentary

By Alan Z. Segal, MD

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Synopsis: REM behavior disorder can be reliably diagnosed using a simple bed-partner questionnaire and its presence is a risk factor for a future neurodegenerative disease.

Source: Boot BP, et al. Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: A population-based study. *Ann Neurol* 2012;71: 49-56.

Rapid eye movement (REM) behavior disorder (RBD) is a parasomnia in which patients physically enact events taking place during their dreams. Muscle atonia, usually present in REM sleep, is replaced by "normal" muscle activity allowing the patients to move their limbs. Patients may kick, punch, or perform other aggressive acts that can potentially be dangerous to themselves and their bed partner.

There is a well-known association between RBD and disorders of alpha-synuclein, including Parkinson's disease (PD), dementia with Lewy bodies, and multiple system atrophy. It has been previously thought that the link between RBD and PD related to alpha-synuclein deposition in brainstem structures is responsible for REM-atonia, and that these directly overlapped with striato-nigral pathways affected in PD. More recent data, however, have suggested that RBD may be a cortical process and that it may be associated with minimal cognitive impairment (MCI), with or without PD. Studies of cerebral perfusion in RBD have shown parietal hypometabolism, and cases of MCI in association with RBD have shown a specific predilection for visual-spatial deficits. Patients with PD who also have RBD have a somewhat unique phenotype, including a paucity of tremor, hallucinosis, and a poor response to dopamine therapy. This suggests that RBD may be associated with cortical Lewy bodies, although this has never been proven pathologically.

Longitudinal studies of RBD patients show that parkinsonism or dementia may develop in up to 65% of cases, but these data are derived from selected populations, either through sleep or movement disorder clinics. A referral bias likely exists, since it is known that the severity of RBD does correlate with a greater risk of developing a neurodegenerative syndrome. The current study is unique in that it examines a general population-based sample from the Mayo Clinic Study of Aging (MCSA).

Subjects were diagnosed as having probable RBD (pRBD) based on the Mayo Sleep Questionnaire (MSQ), which has 100% sensitivity and 95% specificity for RBD as confirmed by polysomnography (PSG). The bed partner was asked the question, "Have you ever seen the patient appear to 'act out his/her dreams' while sleeping?" pRBD was confirmed if this occurred a minimum of three times. The MSQ also screens for obstructive sleep apnea (OSA). This was considered present if there was a positive response to the questions, "Has the patient ever snorted or choked him/herself awake?" and "Does the patient ever seem to stop breathing during sleep?" Accurate diagnosis of OSA is important, since OSA has been shown to produce behaviors mimicking RBD. On formal sleep testing, these "pseudo-RBD" patients demonstrate normal REM atonia rather than the increased muscle activity seen in true RBD. There were 44 pRBD+ subjects enrolled in the study and 607 pRBD- subjects, followed prospectively for 3.8 years. MCI developed in 14/44 pRBD+ subjects. One subject developed PD, for a total of 15/44 (34%) showing MCI/PD. This was compared to 94/607 control subjects (15%), yielding a hazard ratio of 2.2 (95% confidence interval 1.3-3.9). The duration of pRBD symptoms did not predict MCI, with a range of 2 months to 60 years. None of the pRBD+ subjects developed dementia, while eight cases were identified in the pRBD- group (commensurate with the mark-

edly larger size of this study group). pRBD+ subjects were more likely to be taking an antidepressant, but exclusion of these 10 subjects did not change the results. Of the 10 pRBD+ subjects taking antidepressants, eight had RBD symptoms predating the drug. Two subjects developed RBD after taking medication and therefore were assumed to have "medication-associated RBD" since tricyclics and SSRIs are known the precipitate this disorder.

Commentary

In their discussion, the authors note that the true risk of pRBD may be underestimated in their study. Although the specificity of the MSQ for RBD is 95%, the authors estimate that since the prevalence of RBD is relatively low (they estimate it at 9%), the positive-predictive value of the MSQ is likely only 0.66. Because false-positive subjects would be at an MCI risk equivalent to the general population, the authors reason that the true risk of MCI in pRBD could be significantly higher than their study showed. Also, in the absence of formal sleep studies, a proportion of the RBD+ subjects may actually have had OSA (since as previously noted, these syndromes can often overlap clinically). Although OSA itself has recently been linked to cognitive impairment, inclusion of OSA subjects in the pRBD+ group would likely have further diluted any ability to connect true RBD to MCI.

This study suggests that RBD not only may be a harbinger of a movement disorder but also may portend other neurodegenerative processes, more specifically a cortical dementia related to Lewy bodies. Should disease-modifying therapies for Alzheimer's disease and other neurodegenerative syndromes be developed, permitting intervention at preclinical stages of disease, identification of MCI will become of the utmost importance. Because MCI appears to be closely linked to RBD, this sleep disorder may become a powerful tool in the identification of potentially treatable patients. RBD is not difficult to diagnose. Although a formal diagnosis of RBD requires a sleep study (which the authors plan to perform in a further investigation), this study demonstrates that important conclusions regarding "possible" RBD patients can be made using a simple bed partner questionnaire. ■