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SPECIAL ISSUE **COGNITION AND MENTAL HEALTH**
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Contents

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KELSEY ASPLIN, ND, is a naturopathic doctor and a certified Kinesio Taping Practitioner™ who graduated from Bastyr University and is seeing patients back home in Colorado. She also teaches in the Integrative Health Care program at Metropolitan State University of Denver. Asplin works with patients seeking general wellness guidance as well as those with more specific concerns, but she has a particular interest in rheumatology and immunology. To learn more about Asplin and her practice, visit her website at www.determinanthealth.com.


Kurt Beil, ND, LAc, MPH

KURT BEIL, ND, LAC, MPH, is a naturopathic physician and Chinese medicine practitioner, and holds a master's in public health with a focus on the health promotion potential of greenspaces. He completed his postdoctoral research at the National University of Natural Medicine's Helfgott Research Institute, where he examined biomarker and psychometric measures of the restorative and therapeutic effect of natural and built urban environments. Beil speaks frequently on the health benefits of contact with nature and maintains a Facebook group ("Naturopaths for Nature") about this topic. He has a private clinical practice in New York's Lower Hudson Valley region and can be reached at drkurt@earthlink.net or www.hudsonvalleynaturalhealth.com


Walter J Crinnion, ND

WALTER J CRINNION, ND, has specialized in environmental medicine for the last 35 years. He currently provides a monthly podcast, CrinnionOpinion, to keep practitioners current in environmental medicine and has a 12-month training program for those who wish to gain expertise in this field. He and Joe Pizzorno, ND, have coauthored the textbook *Clinical Environmental Medicine*, which Elsevier is set to release in June 2018.


Jill Crista, ND

JILL CRISTA, ND, is a nationally recognized educator on neuroinflammatory conditions. She graduated with honors from the National University of Natural Medicine in 2003, and in 2012 completed the Physician Training Program with International Lyme and Associated Diseases Society. She served as Wisconsin Naturopathic Doctors Association's president for 6 years and on the AANP committee for licensure. For more than a decade, she was director and practicing member of 2 integrative clinics, enjoying the synergy of a team approach to patient care. She's now focusing on research, teaching, and writing.

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MESSAGE FROM THE PUBLISHER

An Integrative Approach to Brain Health

Here's a fun fact: A piece of the human brain that is the size of a grain of sand contains about 100,000 neurons and one billion synapses. Every second, each of the billions of cells in the brain are transmitting thousands of nerve impulses, making the brain the most active and complex organ in the human body. This complexity means that supporting, enhancing, and treating the human brain correlates nicely with the whole-body, comprehensive approach that integrative practitioners employ.

In this special issue devoted to the brain, we feature a peer-reviewed paper by Jill Crista, ND, outlining what integrative practitioners need to know about the lasting effects of traumatic brain injury. Our interviews and abstracts & commentary represent a truly whole-person approach as we cover lifestyle factors like spending time outdoors and dietary issues like mixed berries for enhanced cognition. We also delve into the science behind the nutrient citicoline, as well as how the gut microbiota is linked to sleep and cognition. We wanted to give you a holistic view of tools and advice you can integrate into your practice immediately.

Yes the brain is complex. That's why a comprehensive approach that addresses diet, lifestyle and dietary supplements is needed to support brain function and treat brain illnesses. If you agree, please share this special issue with your colleagues.

I'd like to extend a special thank you to all of those who contributed to this issue. Their research and hard work help us all. If you'd like to contribute to a future issue of *Natural Medicine Journal*, email Deirdre Shevlin Bell, our VP of Content & Communications.

In good health,

Karolyn A. Gazella
Publisher, *Natural Medicine Journal*

Gut Bacteria, Sleep, and Brain Health

Could gut microbiota be driving sleep disturbance and cognitive decline?

Kelsey Asplin, ND

REFERENCE

Anderson JR, Carroll I, Azcarate-Peril MA, et al. A preliminary examination of gut microbiota, sleep, and cognitive flexibility in healthy older adults. *Sleep Medicine*. 2017;38:104-107.

STUDY OBJECTIVE

To assess relationships between gut microbiota, sleep quality, and cognitive flexibility in healthy older adults.

DESIGN

A preliminary observational study

PARTICIPANTS

Data was analyzed from 37 participants, ranging in age from 50 to 85 years (73% female, 92% Caucasian). People with significant neurological or gastrointestinal conditions were excluded, as were those who had used probiotics or antibiotics within a 30-day period prior to the study. Presence of hypertension, diabetes, and sleep apnea were tracked as covariates, as well as dietary macronutrient intake per participant report (EPIC-Norfolk Food Frequency Questionnaire).

OUTCOME MEASURES

Self-reported sleep quality was assessed with the Pittsburg Sleep Quality Index (PSQI), which tracked sleep latency and duration. Higher scores on the PSQI indicate poorer quality of sleep. Cognitive flexibility was assessed through Stroop Color-Word testing. During Stroop testing, participants read color words ("Stroop Word") aloud, identified the ink color of rows of Xs ("Stroop Color"), and identified the ink color of incongruent color words ("Stroop Color-Word") as quickly as possible. Higher scores indicate more properly identified items. Gut microbiome samples were analyzed by uBiome, using 16S ribosomal RNA amplicon sequencing and reported as percentage of phyla present.

KEY FINDINGS

Controlling for covariates, reduced sleep quality correlated with poorer Stroop test results (Stroop Word, P=0.018; Stroop Color-Word, P=0.010, and Stroop Color, P=0.053). Again, controlling for covariates, the study revealed participants with higher percentage of *Verrucomicrobia* had improved cognitive flexibility, as measured by Stroop Word (P=0.034) and Stroop Color (P=0.071) testing. The *Lentisphaerae* phylum did not display a similar correlation; however, it did show a stronger relationship with Stroop Color-Word performance (P=0.015), independent of sleep quality.

PRACTICE IMPLICATIONS

As the surge in research of the microbiota suggests, the potential impact of the gut microbiota on our understanding of human health, and our approach to treating various health conditions, is massive. This particular study, while slightly convoluted by the number of variables discussed, along with its admitted limitations (eg, results based more on observation than causal relationship, lack of detailed screening measures for sleep, and superficial exploration into mechanism of action), does provide some interesting food for thought: Could gut microbiota be a factor connecting sleep quality and cognitive health?

> "Observational studies, such as the one reviewed here, are the first steps in a direction that may ultimately help us harness manipulation of the microbiome for therapeutic use."

Given that more than 30% of Americans report deficient sleep on a nightly basis, and an estimated 50 million to 70 million adults report a sleep disorder,[1] continued exploration into modifiable factors is a necessity. The gut microbiome is a vastly uncharted territory, and our voyage into recognizing its implications on health demands is just beginning. The influence of the gut microbiome on human health must be more deeply understood. Observational studies, such as the one reviewed here, are the first steps in a direction that may ultimately help us harness manipulation of the microbiome for therapeutic use.

The researchers propose that their findings, along with those from other related studies,[2-4] suggest sleep quality is directly proportional to presence of certain phyla of gut microbiota,

(continued on page 8)

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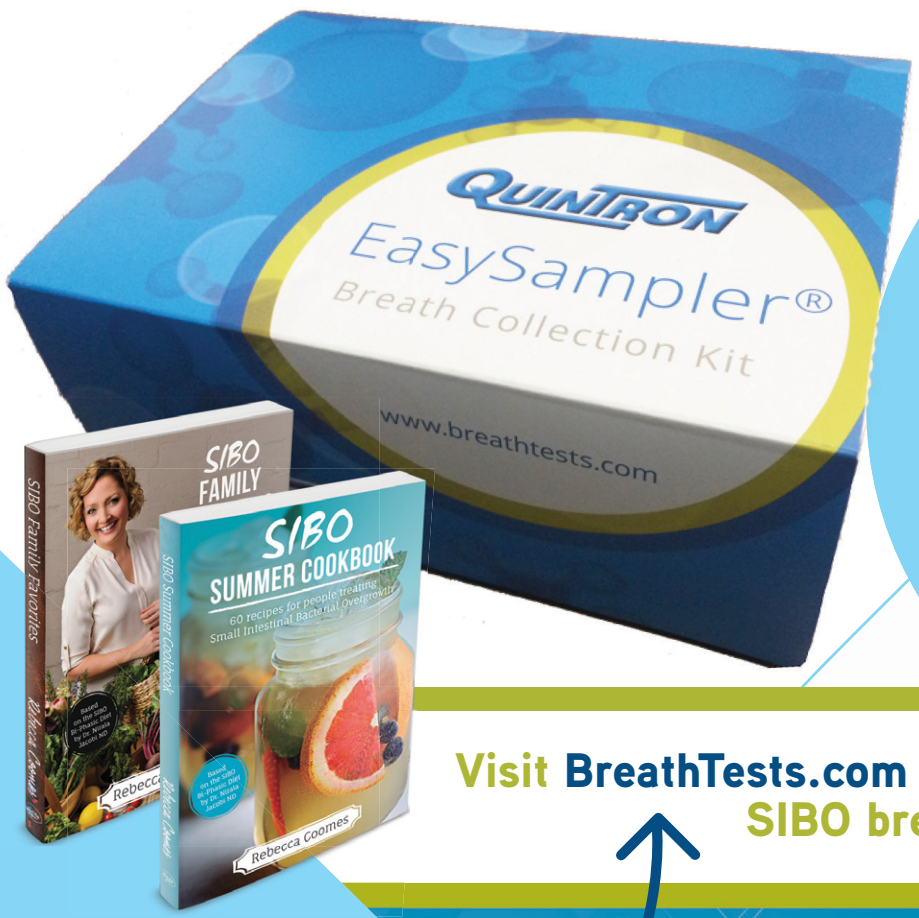

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which then correlate with cognitive function. Both phyla discussed in this paper were associated with disrupted sleep. The *Verrucomicrobia* was then directly correlated with cognition while *Lentisphaerae* was possibly indirectly correlated. The question not so clearly raised was if the cognitive impairment was a direct result of compromised gut flora, or if it was secondary to the chronic, noncommunicable health conditions also related to both, such as obesity, diabetes, and heart disease.

The researchers failed to discuss the potential reverse correlation, where poor microbiota proportions of the given phyla *Lentisphaerae* and *Verrocumicrobia* could be more directly causal to reduced sleep quality. We know that sleep quality is directly related to both chronic disease and cognitive decline; the Centers for Disease Control and Prevention show that adults who sleep less than 7 hours per night are more likely to report chronic health conditions compared to those who get enough sleep.[5] Given the observational design of this study, it is not possible to draw direct cause-and-effect conclusions. However, with increased community recognition of the gut-brain connection, the relationship between these 2 variables should perhaps be considered dynamic and bidirectional.

The pronounced correlation shown in this study between the *Verrucomicrobia* and *Lentisphaerae* phyla and sleep quality contrasts with a 2016 study by Benedict and colleagues, which showed correlation with phyla other than these 2.[2] Additionally, upon further investigation into the 2 aforementioned phyla, their associated genera and species are not part of the more commonly seen and prescribed probiotics today. All of this is to say that while this information is certainly fascinating, we are clearly in the very beginning of understanding how the microbiota of the gut may (or may not) affect sleep and cognition.

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Greenspace Exposure Improves Cognitive Performance in Children

Evidence for effects on brain volume

Kurt Beil, ND, LAc, MPH

REFERENCE

Dadvand P, Pujol J, Macià D, et al. The association between lifelong greenspace exposure and 3-dimensional brain magnetic resonance imaging in Barcelona schoolchildren. *Environ Health Perspect*. 2018;126(2):1-8.

OBJECTIVE

To assess the relationship between children's exposure to green space and morphological changes in cognitive areas of the brain.

DESIGN AND PARTICIPANTS

This study was conducted as a subset of the BREATHE (Brain Development and Air Pollution Ultrafine Particles in School Children) project in Barcelona, Spain.[1] School children (N=253, aged 7-9 y) were followed for a year and evaluated for the volume of their brain and individual brain regions, performance on cognitive tasks, and amount of green space surrounding their residence.

OUTCOME MEASURES

Each participant had MRI scans taken of their brain using high-resolution 3D MRI to measure voxel (ie, 3D pixel) imagery of the gray and white matter of both right and left cerebral and cerebellar areas of interest:[2]

- Prefrontal cortex, responsible for executive functioning and cognition
  - Superior area, associated with working memory and decision-making
  - Inferior area (specifically the opercula of insula), associated with conscious thought, motivation, and planning
- Premotor cortex, responsible for planning, learning, and imitation of movement
- Cerebellum, responsible for muscular coordination and balance, as well as attention, learning, and motor skills

In addition, the following tests were conducted every 3 months over a 12-month period, to assess cognitive function and performance in 2 areas:

- Working memory, assessed via a screen-based test ("*n*-back") in which participants are asked to identify whether an image in a rolling series is the same or different as an image presented previously.
- Attention, assessed via the screen-based Attentional Network Task (ANT) in which 3 aspects of attention (alerting, orienting, and executive control) are measured via stimulus reaction time with warning cues, spatial cues, and decisional cues, respectively.

Green space around each participant's residence was determined using normalized difference vegetation index (NDVI) satellite data, a common method for assessing land-use quantity and type. The NDVI for a 100-m radius of all residential addresses from time of birth to the date of MRI data collection was used, and results were averaged and weighted according to duration of residence at each location to create a lifelong greenspace exposure (LGE) value for each participant.

Data was analyzed via separate linear regression analyses for each brain voxel compared to LGE, and aggregated into proximity clusters. Data was also analyzed using the working memory and attention task results as predictors, to identify if higher test scores correlated with increased brain volume in key areas. Participants' socioeconomic status (SES) was controlled for at both the individual (ie, maternal education) and neighborhood (ie, census-tract Urban Vulnerability Index) level, as was gender and age.

KEY FINDINGS

Overall, statistically significant associations were found between all measures, including the following:

- MRI voxel cluster size (indicating enlarged neuroanatomy) was positively associated with improved performance on *n*-back and ANT scores, demonstrating the relationship between brain structure and function, findings that are consistent with decades of neuroscience research.[3]
- Improved performance on both *n*-back and ANT scores was positively associated with increasing amount of LGE, showing that working memory and attention can be affected by quantity of residential green space, which is consistent with previous study results.[1]
- Amount of LGE was associated with size of MRI voxel clusters in all key brain areas mentioned. Areas of gray matter (right prefrontal cortex, inferior cluster, and left premotor cortex) and white matter (right prefrontal region, inferior cluster, and right and left cerebellum) still demonstrated statistically significant associations with LGE even after controlling for SES. This suggests that for the children participating in this study, there may be a link between quantity of residential green space and volume of anatomical brain structures.

There was also substantial overlap of MRI voxel clusters related to ***n***-back and ANT performance with those areas influenced by LGE, in some cases showing up to a 64% overlap.

Most importantly, the linear regression analyses predicted voxel cluster size effect on ***n***-back and ANT scores in specific MRI voxel clusters influenced by LGE, even after controlling for SES, gender and age, as indicated by regression coefficients:*

- *n*-back (working memory)
  - Right prefrontal cortex, superior cluster, gray matter (regression coefficient: 3.0; 95% confidence interval [CI]: 0.4-5.6; *P*=0.02)
  - Right prefrontal cortex, inferior cluster, gray matter (regression coefficient: 1.6; 95% CI: 0.2-3.1; *P*=0.02)
  - Left premotor cortex, gray matter (regression coefficient: 4.3; 95% CI: 1.2-7.4; *P*=0.01)
  - Left premotor region, white matter (regression coefficient: 3.1; 95% CI: 0.2-6.0; *P*=0.04)
- ANT (attention)
  - Left prefrontal cortex, gray matter (regression coefficient: –127; 95% CI: –2260-7; *P*=0.06)

**As a reminder, regression coefficients show the linear relationship between two variables—essentially the "slope" of the graph. For example, for every one voxel increase in rPFC-IA, there was a corresponding 3.0 increase in n-back score (in those voxels that were affected by LGE).*

PRACTICE IMPLICATIONS

This study found that children's vegetation exposure in their proximal residential environment increased brain volume and improved cognitive function. It is the first study of its kind to show that growing up in a greener home environment has measureable benefit on children's memory and attention *with* corresponding evidence of positive changes to related cerebral structures. This data goes a long way toward showing that being in nature is more than just a "feel-good" experience.

> "This data goes a long way toward showing that being in nature is more than just a 'feel-good' experience."

Of course, the beneficial qualities of the natural world have been recognized for millennia in cultures all around the world.[4] Writers like the 8th century Chinese poet Li Bai have beautifully described the value of "staying on the mountain smiling" for mental and physical health.[5] The 19th century naturalist and founder of landscape architecture, Frederick Law Olmsted, famously discussed how "the enjoyment of [natural] scenery employs the mind without fatigue and yet exercises it…and thus, through the influence of the mind over the body gives the effect of refreshing rests and reinvigoration to the whole system."[6]

This appreciation of the "healing power of nature" began to be investigated as an academic pursuit in the 1970s by researchers such as Rachel and Stephan Kaplan, who developed the Attention Restoration Theory (ART).[7] Their theory, which asserts that spending time in nature improves mental fatigue and concentration, has been supported by many studies.[8] These cognitive improvements are just one benefit of greenspace exposure, with other validated effects including reduced levels of depression and anxiety (both individually and epidemiologically), improved immune system and cardiovascular function, and reduced mortality.[9,10]

This current study is not the first to use brain imaging to measure green space's positive effects. An article in the February 2018 issue of *Natural Medicine Journal* discussed a study that used fMRI to detect changes in cerebral anatomy (particularly the amygdala) of adults in Germany relative to their residential green space.[11,12] Other studies have shown how being raised as children in urban vs rural settings can influence brain structures related to conflict monitoring, arousal, and hypervigilance[13,14] and how such environments may make individuals predisposed or more vulnerable to conditions such as post-traumatic stress disorder (PTSD) and schizophrenia.[15,16] These types of

studies suggest that the pursuit of optimal health may want to include consideration of environmental context and its impact on mental well-being and development.[17,18]

LIMITATIONS

Though regression models provide evidence of prediction rather than simply correlation, the design of the study does not permit exploration of the causal mechanisms linking LGE with cognitive changes. While theory and decades of research support ART as a viable explanation for these attention and working memory task results, it is possible other greenspace-related factors like increased physical activity[19] and social contacts[20] were also involved. This is difficult to determine since the children in this study did not have their physical or social activities recorded for analysis. Future studies may want to include these variables to better understand the causal effects green space has on cognitive development, as has been done with mental health conditions such as depression, anxiety, and psychologic stress.[21,22]

CONCLUSIONS

The amount of greenery surrounding children's homes has been shown to affect their cognition on an anatomical and functional level, with statistically significant effects on neuroanatomy and related working memory and attentional task performance. This should be noted by clinicians, parents, and teachers as well as anyone who works with pediatric populations with cognitive deficits, academic, or behavioral underperformance, and anyone who wants to maximize cognitive potential. This information may also benefit public health officials, urban planners, and policy makers interested in providing healthier, more optimal public spaces for people to live, work, and play.

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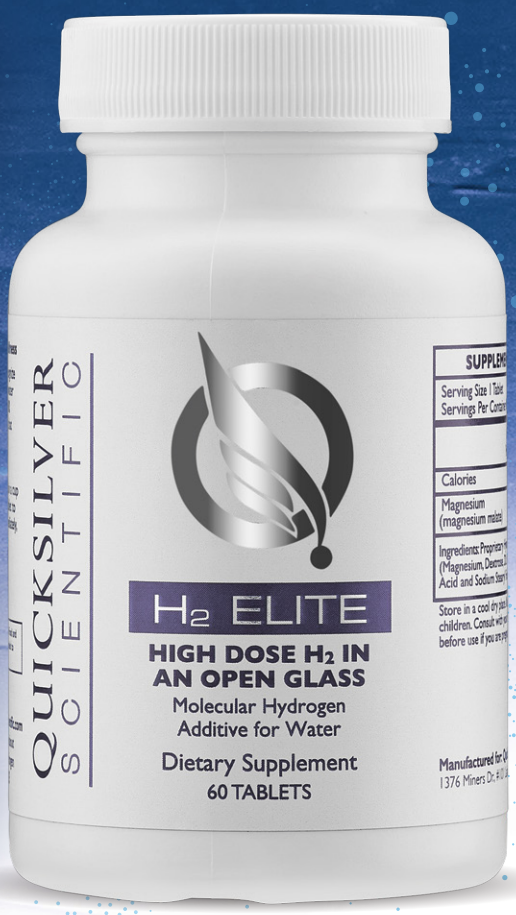

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Berry Pigments Help Cognition, Insulin Response, and Cardiovascular Risk in Adults

Five weeks of berry juice yields benefits

Walter J Crinnion, ND

REFERENCE

Nilsson A, Salo I, Plaza M, Björck I. Effects of a mixed berry beverage on cognitive functions and cardiometabolic risk markers; a randomized cross-over study in healthy older adults. *PLoS One.* 2017;12(11):e0188173.

OBJECTIVE

To evaluate the effects on cognitive function and cardiometabolic risk markers from 5 weeks of consuming a drink made primarily from dark berries.

DESIGN

Randomized crossover trial; 5-week intervention, 5-week washout, 5-week intervention

PARTICIPANTS

Forty healthy Swedish adults aged 50 to 70 (average age 63), 30 women and 10 men, normal to slightly overweight (average BMI≤28), all nonsmokers with no evidence of disease. All participants avoided alcohol, antibiotics, probiotics, and dietary intake of berries or high-fiber foods during the study period.

INTERVENTION

Participants were randomized into either the BC group (n=20) or the CB group (n=20); the first 5 weeks the BC group consumed the berry drink while the CB group consumed the control drink. During the second 5-week intervention period (following a 5-week washout period), the BC group consumed the control drink and the CB group consumed the berry drink.

During each 5-week intervention period participants consumed 600 mL of the berry drink or control drink per day (200 mL with each meal). The berry drink was made from 150 grams of frozen blueberries and 50 grams each of frozen black currants, elderberries, lingon berries, and strawberries, all combined with 6 grams of tomato powder (from 100 g of tomatoes). The control drink (water-based) was similar in carbohydrate content, volume, and pH.

STUDY PARAMETERS ASSESSED

Participants were assessed 4 times during the study, first at baseline then again after each of the 5-week intervention segments. Working memory and selective attention were assessed with standard neurocognitive testing methods. Vital signs were recorded and blood was drawn and assessed for the following cardiometabolic risk markers: glucose, insulin, homeostatic model assessment of insulin resistance (HOMA-IR), free fatty acids (FFAs), cholesterol, interleukin (IL)-6, IL-18, malondialdehyde (MDA), and oxidized low-density lipoprotein (LDL).

Both study and control drinks were assessed for total phenolic content, antioxidant activity, carbohydrates, fiber, protein, fat, and pH.

PRIMARY OUTCOME MEASURES

Changes in the above parameters (cardiometabolic risk markers and cognitive performance) following a 5-week consumption of the berry drink compared to 5-week consumption of the control drink.

KEY FINDINGS

Participants

Based on cardiometabolic risk markers, all except 7 of the 40 participants who completed the study had one or more of the common diagnostic components of metabolic syndrome, as defined by the International Diabetes Federation, at baseline.

Berry drink analysis

The berry drinks averaged 1,300 mg of polyphenols per liter and exhibited good antioxidant ability. The control drink had no polyphenols and no antioxidant activity. Both the control and berry beverages contained 2.2% glucose and 3.4% fructose. The berry beverage also had 0.6% protein, 0.3% fat, 1.35% insoluble fiber, and 0.45% soluble fiber compared to 0% of all of those for the control beverage.

Berry vs control group comparison

Five weeks of 600 mL berry beverage per day reduced total and LDL cholesterol, insulin, and insulin resistance, while 5 weeks on the control beverage increased each of those markers. The differences for all of those 4 findings were statistically significant.

Working memory, 30 minutes postprandial, was better after 5 weeks of the berry drink than it was after 5 weeks of the control drink.

PRACTICE IMPLICATIONS

This group of researchers included some very nice references about the association between both type 2 diabetes mellitus and metabolic syndrome and cognitive decline.[1,2] Reduced cognitive function was actually found in some to precede changes in glucose tolerance.[2,3] Previous studies also found that berries improved insulin sensitivity in obese adults and slowed the rate of cognitive decline in the elderly.[4,5] While I must admit that I was amazed to learn about the ability of berry pigments (anthocyanins) to improve insulin response, I was not at all surprised to read about their neurological impact. Berry pigments are able to cross the blood-brain barrier and are highly effective at reducing neuroinflammation.[6] These compounds are able to reduce nuclear factor-kappaB (NF-kB) levels in the brain.[7]

The researchers used frozen rather than fresh berries for the study drink. Bill Mitchell, ND, an early promoter of berry pigments, frequently said that freezing broke the cell walls and allowed more of the phenolic compounds to be available. While elderberries, black currants, and lingonberries are not readily available, frozen blueberries are. One can purchase a large bag of them at any Costco and every grocery store. While some individuals have been concerned that the Environmental Working Group (EWG) has listed blueberries on the "dirty dozen" list, according to the Pesticide Data Program website (where EWG gets their list), frozen blueberries failed to show the small amounts of residue found on fresh blueberries.[8] I often recommend that individuals consume a cup of blueberries each day, yet this study may indicate that 3 cups may be better if it can be tolerated.

The researchers only used 2 of the many available neurocognitive testing methods and only found modest improvement in working memory after 5 weeks of the berry drink. Neurocognitive testing is readily available to clinicians for use in their office. It is a low-cost, quick, and easy-to-use test that provides a quantitative assessment of executive functioning. With this test clinicians could easily track patients' cognitive improvement with naturopathic care.

"While I must admit that I was amazed to learn about the ability of berry pigments (anthocyanins) to improve insulin response, I was not at all surprised to read about their neurological impact."

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Beyond Brain Damage

Endocrine effects of traumatic brain injury

Jill Crista, ND

ABSTRACT

Traumatic brain injury (TBI) incidence and survivorship is on the rise, leading to an increase in people suffering from post-TBI complications and post-concussion syndrome. Regardless of severity, the injury event can also damage endocrine tissue in the brain, causing downstream endocrine dysregulation in nearly half of all TBI cases. Recognition and management of the endocrine sequelae provides a possible pathway to alleviate post-TBI symptoms.

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), traumatic brain injury (TBI) is a major cause of death and disability, contributing to about 30% of all injury deaths in the United States. Due to improved acute management and emergency care, survivorship of TBI events has increased, resulting in more people suffering post-TBI complications. Those who survive a TBI can have effects that last anywhere from a few days to the rest of their lifetimes. The realm of natural medicine has many tools to offer, but even natural medicine may be approaching TBI too narrowly. For instance, could previous TBI be contributing to seemingly unrelated health issues?

The missing link may be the endocrine system of the brain, the body's central hormone control center. Among TBI survivors, 30% to 50% have one or more endocrinopathies.[1,2] Studies suggest 35% to 40% of TBI survivors have some degree of hypopituitarism, which is associated with serious morbidity and an estimated 20% reduction in life expectancy.[3,4] Injury to the endocrine systems of the brain can occur both during, and as a result of, the TBI. A TBI of any severity compromises the integrity of the blood-brain barrier and induces localized neuroinflammation. Endocrine areas potentially involved include the thalamus, hypothalamus, pituitary gland, and pineal gland.

Endocrine system injury comprises at least 2 known mechanisms: direct mechanical injury and chemical injury from chronic neuroinflammation. In mechanical injury, the forces affecting the brain tissue may also affect the endocrine glands as follows. Nestled in the bony structures at the base of the skull in the sella turcica, or saddle, the hypothalamus and pituitary may sustain a blunt trauma by being pulled by the neighboring brain tissue and thrust into the bony prominences which normally hold the gland safely in place. A similar blunt trauma may occur to the other endocrine areas of the brain causing a cascade of inflammation that affects neighboring tissue. That neuroinflammation can cause downstream neurotransmitter and hormone dysregulation, as well as persistent ketosis of the brain tissues.[5] The resulting post-TBI endocrinopathies not only create a confusing clinical picture, but significantly delay treatment progress and negatively impact overall outcomes.

There is little correlation between the severity of the TBI and the degree of endocrine impairment. A mild TBI may induce significant endocrinopathies, while a patient with moderate-to-severe TBI requiring hospitalization may walk away from the event with little or no endocrine complications. Chronic traumatic encephalopathy (CTE) is not even linked to concussion or TBI, but to repetitive subconcussive contacts to the head. Even so, endocrinopathies could be contributing to the progressive degeneration of the brain in this condition.[6] It is important for the clinician to remember that no 2 brain injuries are alike. As aptly stated on the Brain Injury Association of North Carolina website, "if you've seen one brain injury, you've seen one brain injury."[7]

The determinants of post-TBI endocrinopathies are still being identified, but similar to metrics for general TBI outcomes, the total number of TBIs and "recency" are sure to be important for the endocrine glands of the brain as well. For instance, repetitive head injury syndrome (RHIS) describes the phenomenon of significant delays in treatment progress with each subsequent TBI. In addition, a well-known phenomenon called second impact syndrome (SIS) occurs when a person sustains a repeat TBI before adequate healing of the first. It's hard to fathom, but once a person sustains a brain injury, their risk of future TBIs increases exponentially. There's a 3 times greater risk of getting a

(continued on page 18)

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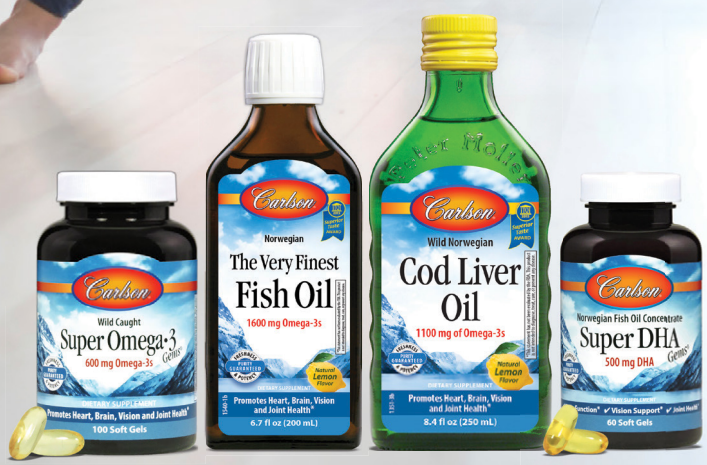

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second TBI after the initial TBI, and 7 to 9 times greater risk of a third TBI after a second.[8] The cause for this is yet to be uncovered.

One potential determinant that plays a role in overall outcome is thyroid function. Low thyroid function at the time of injury is shown to contribute to poorer outcomes following a TBI.[9] Therefore, immediate thyroid assessment and treatment is warranted. In addition, neuroinflammatory specialists theorize that brain tissue docosahexaenoic acid (DHA)[10] and glutathione levels may be related due to their use in TBI treatment, though their roles as determinants of outcome have yet to be studied.

To date, the generally accepted later stage symptoms of TBI, such as fatigue, headache, chronic muscle pain, and sleep issues are symptomatically managed conventionally with medications. Treatments such as cognitive behavioral therapy are offered for other common later stage symptoms, such as balance issues, difficulty activating and allocating working memory, and personality changes. Furthermore, we find additional statistics such as greater incidence of chronic infections,[11] greater incidence of all-cause morbidity, and earlier onset of dementia.[12] To what extent could this suffering be due to unrecognized endocrinopathies?

Post-TBI endocrinopathies are well-understood in the literature, but have yet to be translated into clinical trials, leaving clinicians without guidelines for testing and treatment. In clinical practice, the difficulty recognizing them can be due to many factors. Lack of awareness is chief among them, but so are their delayed onset and difficulty with laboratory assessment. Many post-TBI endocrinopathies have a delayed onset of up to 6 to 12 months following the TBI, so they often aren't intuitively tied back to the brain injury. Therefore, evaluations for post-TBI endocrinopathies are recommended for symptomatic patients with TBI of any severity,[13] done at regular intervals for up to 2 years. Regarding laboratory values, practitioners must understand that dysregulation may not present as frank deficiency or excess. The hormone may not be able to respond when demanded or sufficiently communicate with its targets, making it dysfunctional. Laboratory clarification of the picture can be aided with more expanded panels and the use of 24-hour urine assessments.

"One notable finding is that the more delayed the onset of the endocrinopathy, the poorer the prognosis for spontaneous recovery of the source gland."

The term dysregulation regarding post-TBI endocrinopathies is used purposefully. Befitting the complicated interconnectedness of the endocrine system, each hormone follows its own reactionary path after TBI, and can be dictated by reactions to injury from related endocrine systems. With no association to location or severity of the TBI, a particular hormone may increase, decrease, increase then decrease, or display any number of wave patterns and with no concrete timeline. One notable finding is that the more delayed the onset of the endocrinopathy, the poorer the prognosis for spontaneous recovery of the source gland. Without supportive treatment there is little hope of full restoration of the affected endocrine gland. As it relates to clinical practice, a review of downstream endocrinopathies will be examined, beginning with the hypothalamus.

HYPOTHALAMUS

The hypothalamus essentially has 3 key roles. It secretes releasing hormones targeting the pituitary gland, produces the wakefulness hormone orexin (also named hypocretin), and plays a role in central pain/analgesia. In TBI, both the physical trauma and neuroinflammation damage the hypothalamus, and in some cases may spark an autoimmune reaction against the gland, called hypophysitis.[14] TBI can disrupt both the formation of, and the responsiveness to, hypothalamic releasing hormones, creating symptoms categorized

Table 1. Endocrine Systems of the Brain and Their Functions

Hormone/ Peptide	Primary Target Tissues	Action
THALAMUS		
Neurotrans-mitters	Cerebral cortex Cranial nerve sensory feedback (except olfactory) Hippocampus Cerebellum	Information hub Process and relay sensory information Consciousness Regulation of sleep/ alertness Relay sensory and motor signals Pain perception
HYPOTHALAMUS		
Releasing hormones: GHRH, TRH, CRH, GnRH, HCRT, MC4	Hypothalamus (self) Anterior pituitary Pineal	Central endocrine regulation Autoimmune hypophysitis antibody production
Orexin (hypocretin)	ANS/CNS Midbrain/ descending pain tract Feedback to pituitary Adrenals Adipocytes	Wakefulness Chronic inflammatory pain modulation Appetite feeding behavior Thermogenic brown fat activation Energy homeostasis Addiction/reward processes
ANTERIOR PITUITARY		
GH	Most tissues	Growth and thermoregulation Tissue repair Bone density Muscle mass and strength Central adiposity and insulin sensitivity Appropriate cardiovascular repair Central and peripheral neuronal repair
TSH	Thyroid	Metabolic regulation
ACTH	Adrenals	Liver: glucose regulation Cardiovascular Immune regulation
α-MSH	Melanocytes Immune cells (T-cells)	Skin pigmentation Immunomodulation Anti-inflammatory Anti-autoinflammatory
FSH/LH	Testes Ovaries	Secondary sex characteristics Fertility Bone and soft tissue maintenance Cardiovascular protection
Prolactin	Mammary glands Gonads Immune system Oligodendrocyte precursors Kidneys and adrenals Vasculature	Lactation Fertility Immunomodulation Homeostasis CNS myelination Hematopoiesis and angiogenesis role
Beta-endorphin	Opioid receptors	Regulate central pain sensitivity
POSTERIOR PITUITARY		
ADH	Kidneys	Water resorption Vasoconstriction
Oxytocin	Uterus Mammary glands	Labor induction Breastfeeding Bonding Vaginal tissue integrity
PINEAL		
Melatonin	Hypothalamus Anterior pituitary Retina Pigment cells Sex organs	Circadian rhythm Sleep cycle Skin pigmentation Seasonal reproductive behaviors
Neurotrans-mitters	Primary respiratory mechanism Body proprioceptors	Basal respiratory rhythm Basal CSF pulse ECM ebb and flow

Abbreviations: GHRH, growth hormone–releasing hormone; TRH, thyrotropin-releasing hormone; CRH, corticotropin-releasing hormone; GnRH, gonadotropin-releasing hormone; HCRT, hypocretin; MC4, melanocortin 4; GH, growth hormone; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; α-MSH, alpha-melanocyte–stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ADH, antidiuretic hormone; ANS, autonomic nervous system; CNS, central nervous system; CSF, cerebrospinal fluid; ECM, extracellular matrix.

as hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Persistent inflammation, or astrocytosis, of the cortico-hypothalamic-pituitary axis causes persistence of TBI symptoms and delayed healing progress.

OREXIN

Regarding the direct hypothalamic hormone orexin, TBI reduces production of this wakefulness hormone and is correlated with up to 30% of new onset narcoleptic symptoms.[15] Narcolepsy, commonly thought of as a sleep disorder, is actually a wakefulness disorder. Lack of discernment between day and night presents clinically similar to insomnia. Therefore, a daytime sleep study is warranted in any case of insomnia, hypersomnia, or nonrestful sleep following a TBI.

Orexin also preserves thermogenic brown fat stores and regulates feeding and reward-seeking. Weight gain, body mass composition changes, and sarcopenic fat can be seen in the post-TBI patient who has sustained hypothalamic injury. In the case of comorbid pituitary endocrinopathies, low growth hormone may compound the reduction of the thermogenic brown fat by increasing leptin, which inhibits orexin formation at the cellular level.

The hypothalamus's role in central pain management cannot be overstated, especially in the era of an opioid crisis. Utilizing orexin, the hypothalamus modulates chronic inflammatory pain globally from the lateral hypothalamus.[16] Pondering those suffering with post-TBI chronic pain, might they be managed better with natural medicine interventions than by sedating and addicting medications? Intermittent fasting, preventing glucose surges, and essential amino acid supplementation appear to be possible interventions to stimulate orexin neurons, though human trials are needed.[17]

PITUITARY

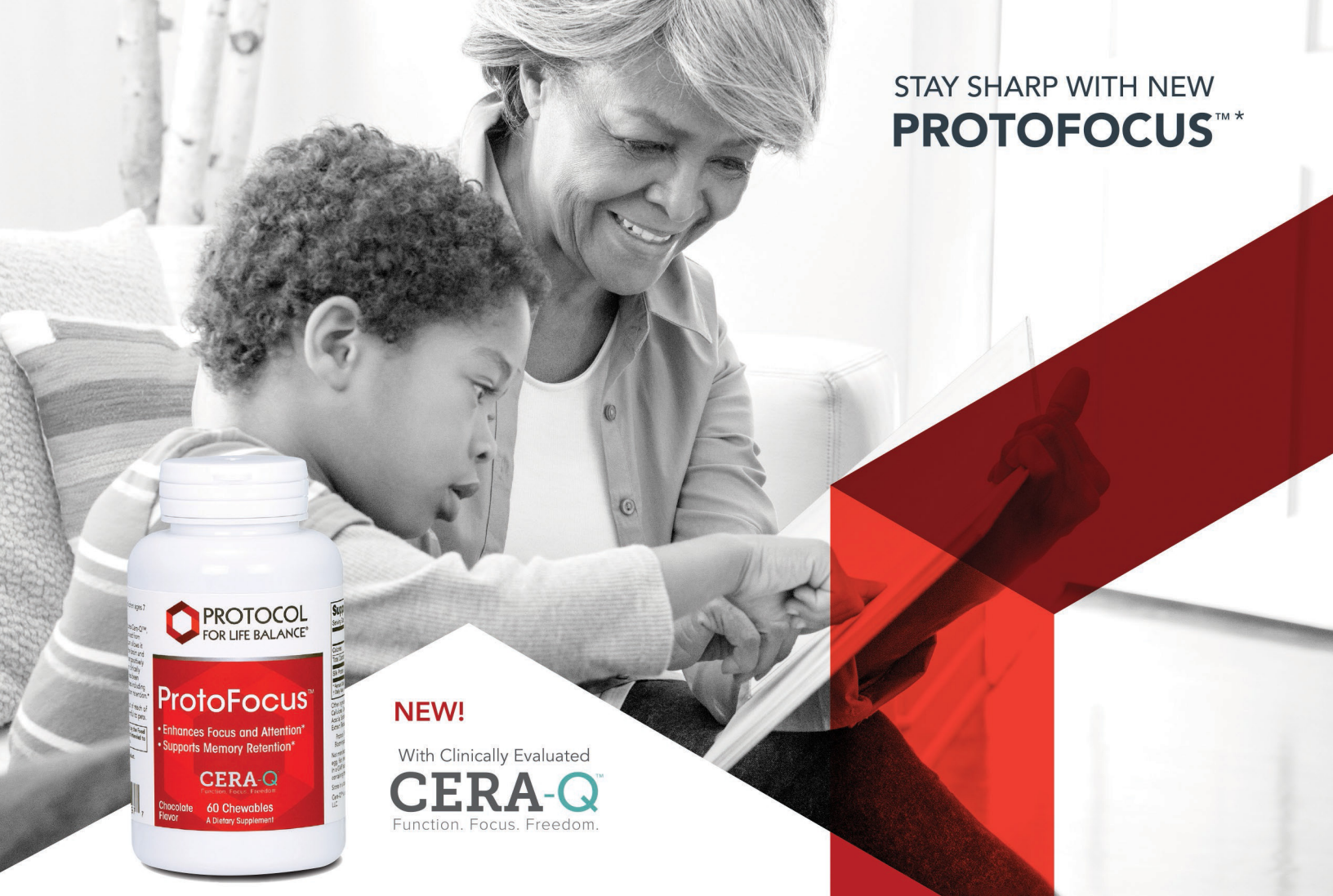
Injury to the pituitary, resulting in hypopituitarism, is the most prevalent endocrinopathy following a TBI, with both the anterior and posterior gland affected.[18] Studies show that all pituitary hormones are affected, but are commonly missed clinically. The individual reactions of all downstream pituitary hormones must be understood to better manage the TBI patient.

> "Many post-TBI endocrinopathies have a delayed onset of up to 6 to 12 months following the TBI, so they often aren't intuitively tied back to the brain injury."

GROWTH HORMONE

Growth hormone (GH) deficiency is the most common pituitary endocrinopathy after TBI, and in some cases it may be the only endocrinopathy that develops.[19] Despite the statistics, adult TBI patients may not be assessed for GH deficiency due to the common misperception that GH is no longer important past puberty. Growth hormone deficiency in the pediatric TBI patient does indeed stunt growth and development, but also causes the same risks as adult GH deficiency. The symptoms of adult GH deficiency are vast but can be summarized as lack of tissue integrity, growth, and repair; persistent inflammation in the brain; and insulin resistance.[20]

Tissue integrity symptoms from lack of GH include soft-tissue complaints, endothelial cardiovascular risks, prolapses, and decreased muscle mass and bone density. Growth hormone's action on insulin accounts for weight gain, cognitive changes, energy depletion, insulin resistance, and central adiposity.[21] Growth hormone deficiency also alters lipoprotein metabolism and elevates fibrinogen.[22] On laboratory evaluation, it is common for GH deficiency to present with increased fibrinogen and an increased low-density lipoprotein (LDL) that is resistant to treatment. Evaluation of insulin-like growth factor (IGF)-1 may be used as a reflection of GH deficiency unless the patient has concomitant liver disease, as this hormone is formed in the liver.[23] In a rat study, injected flavonoids from ginkgo were capable of stimulating growth



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hormone release from the anterior pituitary.[24] Translational study is needed to establish an effective oral dose.

THYROID-STIMULATING HORMONE

Secondary hypothyroidism can present after TBI with a reduction in pituitary production of thyroid-stimulating hormone (TSH). The resulting secondary hypothyroidism can complicate clinical management of the post-TBI hypothyroid patient, since the standard practice is to only monitor TSH on lab assessment. This practice is not sufficient for secondary hypothyroidism. Full thyroid panels, tracking both free and total T4 (thyroxine) and T3 (triiodothyronine), are necessary to intricately control hypothyroid symptoms in a post-TBI patient.

ADRENOCORTICOTROPIC HORMONE

The adrenals are true to form following a TBI. In reaction to the stress and injury, adrenocorticotropic hormone (ACTH) increases temporarily in an attempt to continue to manage the cognitive and endocrine load, as well as reduce inflammation.[25] This can present as an almost heroic or stoic reaction by the patient, masking other endocrinopathies for up to 1 year. A possible survival mechanism so as not to be culled from the herd, it is quite common to hear the overcompensation statement, "I'm fine!" from the TBI patient. As time passes, and this singular heroic effort on the part of the adrenals can no longer be sustained, post-TBI survivors exhibit adrenal insufficiency.

ALPHA-MELANOCYTE–STIMULATING HORMONE

A more recently understood pituitary hormone, alpha-melanocyte–stimulating hormone (α-MSH), is a neuropeptide with immunomodulatory properties, which may also offer neuroprotection. It acts as a suppressor of proinflammatory cytokine production and induces interleukin (IL)-10 expression, which is one of the most important mediators of the anti-inflammatory effect of α-MSH.[26] Alpha-melanocyte-stimulating hormone controls hypothalamic production of melatonin and endorphins. Deficiency creates chronic nonrestful sleep and chronic increased perception of pain. A single administration of α-MSH offers a promising neuroprotective property by modulating inflammation and preventing apoptosis after TBI. However, the potential therapeutic value of α-MSH is limited by its short half-life and melanotropic effects.[27]

GONADOTROPINS

Both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are reduced as the body prioritizes fight or flight over procreation.[28] The resultant andropause/menopause risks need to be mitigated. There are many schools of thought regarding evaluation and treatment of gonadotropin deficiencies, but because of lipid storage of these hormones, practitioners must be aware that these deficiencies may be the last to present clinically. All other protective benefits of balanced sex hormones aside, as they relate to TBI, management is recommended for the neuroprotective benefits.

PROLACTIN

Even though hypopituitarism is associated with suppression of all downstream hormones, the issue with prolactin is excess, or hyperprolactinemia. Prolactin rises due to inhibition of transport of prolactin inhibitory factor down the pituitary stalk into the gland. Prolactin plays a role in homeostasis as a mediator of the immuno-neuroendocrine network, osmoregulation, and angiogenesis.[29] Increased prolactin also counteracts dopamine and reduces gonadotropin releasing hormone (GnRH). Excess prolactin symptoms include sexual and female cycle changes, headaches, and neurological symptoms, particularly visual field defects. There are recent promising rat studies on *Schisandra chinensis* and its ability to modulate prolactin.[30]

ANTIDIURETIC HORMONE

Both increases and decreases in antidiuretic hormone (ADH) are seen post-TBI. The immediate response is an increase, causing a temporary syndrome of inappropriate secretion of antidiuretic hormone (SIADH), including symptoms of headache and increased blood pressure. This soon shifts into deficiency of ADH as the pituitary reduces production and secretion, correlated with an increased incidence of later onset diabetes insipidus in TBI patients.[31,32] This results in increased thirst, increased urinary volume, and urinary frequency. Traumatic brain injury patients with unrecognized diabetes insipidus left untreated are at risk for severe dehydration, chronic electrolyte imbalances, and neuropathies.

> “Nearly half of all TBI patients may suffer from at least one endocrinopathy following the injury event, with hypopituitarism being chief among them.”

OXYTOCIN

Known best as the bonding hormone, oxytocin plays a role in determining a sense of safety, sexual function, and stress management. Much more than a female-only lactation hormone, oxytocin is a neuromodulator and modulates pain perception in both genders.[33] It alters the synapses toward empathy and prosocial behavior, and is intricately woven with the HPA axis and dopamine. It's involved in weight management by suppressing food intake. Oxytocin deficiency can lead to leptin resistance.

PINEAL

Pineal gland damage causes a reduction in melatonin, a potent brain antioxidant known best as the sleep hormone.[34] Imagine a post-TBI survivor who sustained damage to both the hypothalamus and pineal gland—making neither the wakefulness hormone nor the sleep hormone—with no distinction between day and night. In some cases, enforcing a circadian cycle with wakefulness measures improves sleep.

VITAMIN D

This vitamin could easily be renamed hormone D and is included herein as such. As it relates to TBI outcomes, vitamin D plays a key role assisting overall endocrine balance and endocrine intercommunication. In its immune modulation role, vitamin D reduces the risk of further morbidity, such as bone loss and cardiovascular disease. In an observational study of post-TBI patients, participants with optimum vitamin D levels reported an increase in overall quality of life.[35] Therefore maintaining adequate vitamin D levels post-TBI is recommended.

CONCLUSION

Nearly half of all TBI patients may suffer from at least one endocrinopathy following the injury event, with hypopituitarism being chief among them. All endocrine systems of the brain may be affected, including the thalamus, the hypothalamus, and the pituitary and pineal glands. Unrecognized post-TBI endocrinopathies significantly delay treatment progress, negatively impact overall outcomes, and are associated with serious morbidity and reduced life expectancy. Endocrinopathy symptoms may not be recognized as post-TBI sequelae due to their breadth and typical delay in onset.

Because no 2 brain injuries are alike, defining the severity of the TBI does not help the clinician determine the extent of endocrine dysregulation. It is time to explore broader standard-of-care options for TBI. Other than a practitioner's chief role of TBI risk reduction education, evaluation and management of the TBI patient should be guided by an understanding of the mechanisms of injury and the strong possibility of a resultant endocrinopathy. Even though research related to post-TBI endocrinopathies is robust, clinical trials are not. Clinicians therefore have to assess for endocrinopathies and manage this aspect of the TBI patient with little guidance. A path to clinical management has yet to be designed, and so at this point it must be forged in clinical practice, one TBI patient at a time.

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An interview with Deborah Yurgelun-Todd, PhD, and Perry Renshaw, MD, PhD

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Approximate listening time: 30 minutes

In this interview with *Natural Medicine Journal*'s publisher, Deborah Yurgelun-Todd, PhD, and Perry Renshaw, MD, PhD, discuss the research they are conducting at The University of Utah in the Neuroscience Department. They specifically describe research associated with the safety and efficacy of supplemental citicoline, as well as evaluate emerging research in this area.

ABOUT THE EXPERTS

DEBORAH YURGELUN-TODD, PHD, is director of the Neuroscience Initiative and a USTAR Professor of Psychiatry at the University of Utah School of Medicine. Her research focus is on identifying the neuropsychological and neurobiological bases of human behavior. Yurgelun-Todd is an expert in the application of structural and functional magnetic resonance imaging, the administration and analysis of neurocognitive tests, and the integration of the results obtained by these multiple modalities. She has examined the etiologic bases of neural models of dysfunction in psychiatric disorders including depression, bipolar illness, substance misuse, and schizophrenia. She is also recognized for applying imaging techniques to study cortical changes during development in healthy children and adolescents, and during treatment intervention in adult patients.

PERRY RENSHAW, MD, PHD, is a USTAR Professor of Psychiatry at the University of Utah School of Medicine and a Medical Director of the VISN 19 Mental Illness Research, Education and Clinical Center (MIRECC) at the Salt Lake City Veterans Affairs Medical Center. His training as a biophysicist and psychiatrist has led to a primary research interest in the use of multinuclear magnetic resonance spectroscopy (MRS) neuroimaging to identify changes in brain chemistry associated with psychiatric disorders and substance abuse. Current clinical trials are focused on the use of citicoline as a treatment for methamphetamine dependence, creatine as a treatment for depression, and uridine as a treatment for bipolar disorder. Renshaw's recent work focuses on brain chemistry changes that may increase depression and suicide for people living at high altitudes.

A Proactive Approach to Reducing Dementia Risk

Maintaining a Healthy Brain Today, Tomorrow, and Years to Come
A Conversation with Carrie Decker, ND

Sponsored by Allergy Research Group

By Natural Medicine Journal

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In this interview, naturopathic physician Carrie Decker, ND, describes some of the actions she takes with patients to help reduce the risk of developing dementia and cognitive decline. Her integrative approach includes nutritional and lifestyle assessment, assessment for common risk factors or other potential exposures, and nutritional supplementation to meet her patients' individual needs.

ABOUT THE EXPERT

Carrie Decker, ND, is a certified Naturopathic Doctor, graduating with honors from the National College of Natural Medicine (now the National University of Natural Medicine) in Portland, Oregon. Decker sees patients at her office in Portland as well as remotely, with a focus on gastrointestinal disease, mood imbalances, eating disorders, autoimmune disease, and chronic fatigue.

Prior to becoming a naturopathic physician, Decker was an engineer, and obtained graduate degrees in biomedical and mechanical engineering from the University of Wisconsin-Madison and University of Illinois at Urbana-Champaign respectively. Decker continues to enjoy academic research and writing and uses these skills to support integrative medicine education as a writer and contributor to various resources.

Decker supports Allergy Research Group as a member of their education and product development team.

ABOUT THE SPONSOR

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