Brain Injury, Hormone Issues, and the Endocrine System: Q&A with Dr. Tamara Wexler

By Dianna Fahel, Director of Marketing & Communications, Brain Injury Association of America and Tamara L. Wexler, M.D., Ph.D., Clinical Associate Professor, NYU School of Medicine/Rusk Rehabilitation

Tamara L. Wexler, M.D., Ph.D., is an endocrinologist specializing in neuroendocrinology and reproductive endocrinology. We spoke with her about the pituitary system, the endocrine system, and common hormonal issues that might occur after brain injury. Here's what she had to say:

What is the pituitary system and how does it work?

The pituitary is a gland that sits in your brain, right behind the top of your nose – if you place one finger at the top of your nose and the other just behind your temple, the pituitary can be found approximately where your fingers would intersect.

The hormones most relevant in the chronic period after traumatic brain injury (TBI), defined as three months or more after the injury, come from the anterior pituitary. The anterior pituitary secretes a number of hormones that stimulate production of other hormones from other organs, known as "end organs," as follows:

- Adrenocorticotropin hormone (ACTH) leads to the production of **cortisol**, or "stress hormone," from the adrenal glands.
- Thyroid stimulating hormone (TSH) leads to the production of **thyroid hormone** from the thyroid gland.
- Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) lead to the production of **estrogen or testosterone** and are also involved in ovulation and spermatogenesis.
- Growth Hormone (GH) leads to the production of **IGF-1** from the liver.
- The pituitary also makes **prolactin**, which is involved with lactation.

Working together with the hypothalamus and end organs, the pituitary keeps these hormonal systems in balance, via elegant feedback loops. The pituitary senses if levels of end-organ hormones are too low or too high, and alters secretion of its hormones accordingly. For example, if thyroid hormone is too low, the pituitary senses that and sends out more of the signal (the thyroid stimulating hormone, or TSH) to the thyroid gland to let it know to make more thyroid hormone; if the thyroid hormone is too high, the pituitary senses that and secretes less TSH. The pituitary, this master regulator, functions in this way a bit like the thermostat in your house.

How can brain injury affect the endocrine system?

We know that there is a higher rate of pituitary deficiencies after certain types of brain injuries, such as TBIs. The reason that a TBI can lead to a pituitary hormone deficiency is not entirely clear; it may be related to damage caused to the pituitary itself or to the blood vessels or nerves that feed the pituitary, or it could be the result of inflammatory

changes that may occur after an injury. It is important to consider whether pituitary dysfunction has occurred. If left untreated, pituitary deficiencies can have negative effects on physical, cognitive, and emotional health.

How common are endocrine issues after brain injury? Do they occur immediately after injury or can they appear later?

We know that there is a higher rate of pituitary deficiencies after concussion. As for the exact rate, that depends on what population was investigated in any given study. Chronic anterior pituitary deficiencies have been reported in 15-60% of adults after a TBI, and up to 42% of children and adolescents. The rates are even higher when measured in the first months after an injury. It's important to note that these rates come from studies, and reflect the specific population being studied. If a clinical trial reports that 35% of adults receiving inpatient rehabilitation 6 months after a severe TBI, for example, that may only apply to adults who are also undergoing inpatient rehabilitation after a severe TBI.

The question of timing is such an interesting one! Pituitary deficiencies can arise over time. Patients can recover, or they may develop new deficiencies in the months and year(s) after an injury. I focus here on the "chronic" period, at least three months after injury. While there may be a high rate of hormone deficiencies in the first weeks and months after an injury, it's not clear what they reflect, other than cortisol (often referred to as the "stress hormone"). It's recommended, therefore, that only testing and replacement of the cortisol axis be considered in the acute period.

How are brain injury-related hormone issues diagnosed?

When I'm deciding whether I should conduct an evaluation, I base my decision on history and symptoms. The diagnosis itself is straightforward – there are clear guidelines as to what constitutes a deficiency in any of the pituitary hormones. Many of the hormonal systems can be evaluated with a simple blood draw, frequently in the morning.

Evaluation of some of the systems may require a stimulation test, in which something is given to stimulate hormone release and the body's response is measured. For example, the diagnosis of growth hormone deficiency often requires stimulating growth hormone and measuring the levels of growth hormone over time. The replacement of deficient hormones must proceed in a specific order: first, cortisol ("stress hormone") if someone has adrenal insufficiency; then, thyroid hormone; then estrogen or testosterone if needed; then, growth hormone. If someone has adrenal insufficiency, for example, it must be corrected before continuing with testing of the other hormones.

What symptoms or warning signs should caregivers look for in their loved ones? How would endocrine issues present?

Given how many people have suffered a concussion, there have been studies investigating whether biomarkers, imaging results, or aspects of the injury itself might predict which people should undergo testing for pituitary dysfunction, but, thus far, none

have consistently yielded a clinically useful predictor. The best indicator appears to be symptoms.

This can be tricky, since symptoms from pituitary dysfunction can be broad and nonspecific, and overlap with symptoms from other aspects of a brain injury. Symptoms might include persistent menstrual cycle irregularity or sexual dysfunction, difficulties with confusion or cognitive slowing, mood changes such as anxiety or depression, or changes in weight or energy. In children and adolescents, symptoms may be different, with school performance and behavior affected.

If someone continues to suffer from persistent symptoms more than three months after a brain injury, it is worth considering whether a pituitary dysfunction might be contributing. Not every individual with fatigue, brain fog, or other symptoms will have pituitary dysfunction; however, if a hormone deficiency does exist, replacing the hormone should help improve or reverse symptoms that stem from that deficiency.

What questions should you ask your doctor if you think you're experiencing endocrine issues?

Despite increased understanding of many health effects of brain injury, there is a lack of widespread awareness of the increased risk of pituitary deficiencies. If you started having some of the symptoms noted above after sustaining a brain injury, and if they have persisted beyond at least three months after the injury, you may want to approach your doctor to discuss this by saying something like the following: "I've read that there is an increased rate of pituitary deficiency after brain injury. Some of my symptoms sound like symptoms of pituitary hormone dysfunction, and I'm interested in an evaluation to see if a hormone deficiency is contributing to my symptoms. Is that something that you might do, or could you refer me to a neuroendocrinologist who could do so?" Your doctor may also have other explanations for some of your symptoms, but it's always appropriate to raise the question.

In terms of the evaluation itself, it is important to see a doctor who is able to interpret the results and manage any identified deficiencies. This person may be an endocrinologist, though the area of post-TBI pituitary dysfunction encompasses many specialties including neurology, physiatry internal medicine, psychiatry and psychology, physical therapy, and others. Any doctor you are seeing will likely be able to discuss this with you.

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