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Hypopituitarism After Multiple Concussions: A Retrospective Case Study in an Adolescent Male

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Objective: To describe the development of hypopituitarism in an adolescent athlete after multiple concussions and to raise awareness among sports medicine clinicians concerning the growing concern of hypopituitarism in concussion injury surveillance and management.

Background: A 14-year-old, previously healthy male athlete suffered 4 head traumas over a 4-month period. The first 3 traumas were considered by the athlete to be minor and were not reported to medical personnel. The fourth trauma was a medically diagnosed concussion suffered during soccer play. Over the next year, the patient noted a decline in strength and conditioning and a failure to grow.

Differential Diagnosis: After physical examination and a full battery of endocrine tests, the patient, then 16.5 years old, was diagnosed with hypopituitarism. Follow-up interviews provided evidence that at least 2 of the 3 head injuries suffered before the last concussion could also be considered concussions, which may have contributed to the severity of the last head injury.

Treatment: The patient is currently being treated with physiologic replacement hormones (growth hormone, cortisol, and thyroxine), with resumption of linear growth and strength. He is progressing well.

Uniqueness: In the past few years in the medical literature, increased attention has been drawn to the occult occurrence of hypopituitarism after traumatic brain injury in adults. Initial reports indicate that children are also at risk. To our knowledge, this is the first reported case of hypopituitarism after mild traumatic brain injury in the sports medicine literature.

Conclusions: Symptoms of hypopituitarism are often masked by trauma and postconcussion symptoms and may not appear until months or years after the trauma incident, which can lead to significant delay in proper diagnosis and treatment. We urge greater vigilance by, and training of, sports medicine clinicians toward the goal of recognizing the possibility of pituitary disorders after sports concussion.

Key Words: neuroendocrinology, mild traumatic brain injury, sports

Mild traumatic brain injuries, which include injuries classified as concussions, are prevalent among young athletes. These injuries often have more serious consequences than previously thought, including cognitive, behavioral, and biological deficits that can linger long after the return-to-play criteria stipulated by conventional concussion management guidelines have been met.[1–4] A new area of concern in traumatic brain injury (TBI) management is pituitary gland dysfunction.[5] Although not reported in the sports medicine literature, the growing incidence of hypopituitarism among TBI patients has prompted some in the neurology and endocrinology fields to suggest screening of pituitary function in all TBI patients.[5] The prevalence of hormonal complications after sport-related concussions is unknown, in part because hormonal assessment is not a component of the normal diagnostic test battery, because hormonal problems might not show up for months or years after the typical healing time period, and because typical brain imaging for concussion (computed tomography, magnetic resonance imaging) is not sensitive enough to detect the diffuse neuronal damage or pituitary abnormalities that occur at the microscopic structural level. We believe, however, that enough circumstantial and theoretic evidence exists to prompt surveillance for pituitary insufficiency after concussion, particularly in children.

In support of this suggestion, we present the case study of an adolescent male soccer player who suffered a concussion after 3 other minor head injuries within a 4-month period and who, 1 year later, was on hormone replacement therapy after developing hypopituitarism. We cannot definitively prove that the concussion injury caused the pituitary dysfunction, but the epidemiologic sequence of events from head injuries to hormone therapy presents a strong case that multiple mild head injuries—commonly reported in adolescent athletes—initiated the development of hypopituitarism and life-threatening hormonal disturbances. Informed consent, as approved by the Ithaca College Human Subjects Review Board and the Institutional Review Board of the SUNY Upstate Medical University, was gathered from the patient and his parents for this report.

PERSONAL DATA AND CHIEF COMPLAINT

The patient was a high-level junior soccer player playing on travel teams comprising athletes above his age group. Each school year he had required larger clothing and shoe sizes, which is a hallmark of normal physiologic growth and development. Increase in size and maturity of genitalia had begun at the age of 12 years. From age 15 years, 8 months, through 16 years, 5 months, a nearly complete failure of physical growth, a stagnation of soccer abilities and physical skills, lower energy levels, and occasional orthostatic changes were noted.

PHYSICAL EXAMINATION AND MEDICAL HISTORY

At 16 years, 5 months, the patient was seen by his longtime pediatrician. Radiographs of the hand and wrist showed a skeletal maturity (bone age) of 14 years. The pediatrician's records documented 0.75-in (1.90-cm) growth increment over

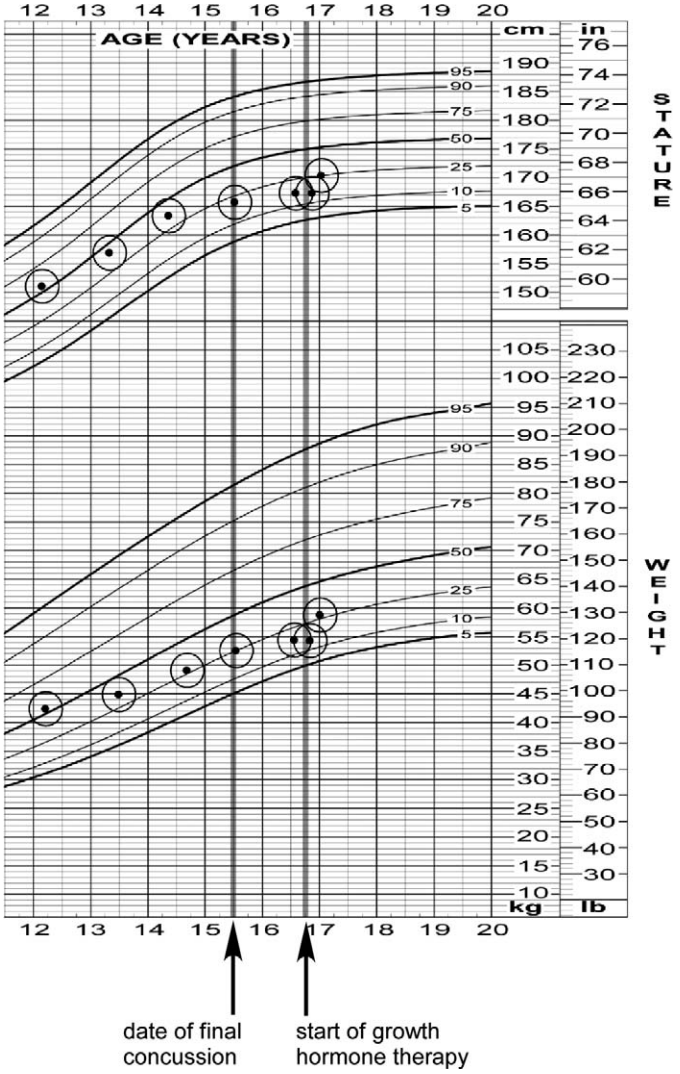

Figure 1. Height and weight from age 12 plotted against normative data. The slight slowing in growth since age 14 was not alarming; in contrast, the near zero growth velocity since the concussion was highly indicative of growth hormone disturbances. Note the rapid rise in growth after growth hormone replacement therapy.

the previous year, an increment that is significantly lower than the usual growth velocity for a young man with that bone age (3.75 in [9.53 cm]; Figure 1). Males do not complete their height growth until skeletal maturity exceeds 16 to 17 years, so this patient's growth velocity was clearly abnormal. The pediatrician's records showed some slowing of growth from about age 14, but this was accompanied by the development of appropriate secondary sexual characteristics at the ages of 14 and 15 years. Blood was drawn for thyroid-stimulating hormone (TSH) and insulin-like growth factor-1 (IGF-1) levels. Both hormone levels were very low for the patient's age, prompting referral to an endocrinologist.

An endocrinologic evaluation revealed a height of 5 feet, 6 inches (167.64 cm); this height is average for an adolescent male aged 14 years, 6 months. Mass was average for an adolescent aged 14 years, 0 months. Secondary sexual characteristics were late pubertal (early mustache, pubic hair at Tanner stage IV-V, penis at Tanner stage V, left testicle 18 mL and right testicle 15 mL in volume) and customary for a young man aged 15.5 to 16 years. The patient reported that he did experience erections. The patient had no galactorrhea, gynecomastia, polyuria, or polydipsia. The patient's blood pressure was 99/60 mm Hg, and his pulse was 45 beats/min. A delayed relaxation phase of deep tendon reflexes was observed, but skin, gait, speech, and mental status were normal. No obvious signs indicated brain tumor or TBI; such signs would include papilledema, double vision, and postural unsteadiness.

Delayed growth and puberty is a common heritable disorder, but no history of this condition was found in the patient's family. No family members had an endocrinologic disorder. The patient's father was just under 6 feet (182.88 cm) tall, an 18-year-old brother was 5 feet, 10 inches (177.80 cm) tall, and both grandfathers were over 6 feet tall. The genetic midparental height target was 70.5 $\pm$ 2 inches (179.07 $\pm$ 5.08 cm). The patient had no history of tobacco, alcohol, or illicit drug use. He had never been hospitalized after the newborn period, nor had he undergone any surgical procedures. He took no prescription or over-the-counter medications. The patient did have a recent history of minor head trauma. He had suffered a sport-related concussion and 3 other ''minor'' head blows within the past 14 months.

BIOCHEMICAL AND RADIOLOGIC INVESTIGATION

Hormonal and metabolic levels from tests conducted in August and September of 2005 are displayed in Table 1. A comprehensive metabolic profile was unremarkable (eg, normal kidney and liver function). Thyroid function (thyroxine, TSH) and IGF-1 values were all low, and the prolactin level was mildly elevated. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone were all normal for his Tanner stage. Cortisol and adrenocorticotropin hormone (ACTH) levels were low to normal, and the glucose level was acceptable. Magnetic resonance imaging with fine cuts showed normal pituitary anatomy, a normal infundibulum, and no mass lesions or evidence of scarring.

DIFFERENTIAL DIAGNOSIS

The patient's medical and family history gave no reason to suspect congenital or chronic disease or adverse effects of pharmaceuticals with regard to his lack of growth and hormonal abnormalities. As noted above, a constitutional delay in growth (delayed puberty) seemed highly unlikely, as his progression through puberty had been timely, albeit modest with respect to height growth. His body mass index had stayed in a narrow range, between 18.5 and 19, between the ages of 12 years and 16.5 years, during which time the patient had participated in extensive and year-round involvement in soccer, indicating that at least some component of caloric limitation might have contributed to his slower height growth. Despite regular conditioning, however, after the injury the patient began experiencing lower energy levels and an inability to respond to training despite progressing through puberty (ie, increasing testosterone levels). This observation is significant and entirely consistent with the diagnoses of hypothyroidism and growth hormone deficiency.[6] Indeed, the elevated levels of prolactin provided strong evidence of damage to the hypothalamic-pituitary axis. Subtle central adrenal insufficiency might have been responsible for his orthostatic changes.

At the time of his first endocrinologic examination, prolactin elevation and TSH deficiency were confirmed. Growth hormone deficiency could neither be confirmed nor denied until

Table 1. Chronologic History of Injury, Growth, and Important Endocrine and Metabolic Markers Since the Head Traumas

Date	Age	Height, cm	Mass, kg	Head Trauma	Clinical Chemistry*	Comments
May 2004	15 y, 3 mo			1		
July 2004	15 y, 5 mo			2		
August 2004	15 y, 6 mo	165.7	52.2	3, 4 (concussion)		
July 2005	16 y, 5 mo	167.6	51.3		IGF-1 = 86 ng/mL (low) TSH = 0.89 μU/mL (low)	
August through September 2005	16 y, 6 mo	167.5	54.0		Comprehensive metabolic panel unremarkable IGF-1 = 81 ng/mL (low) TSH = 1.11 μU/mL (low) Total T4 = 4 μg/dL (low) Free T4 = 0.5 ng/dL (low) Prolactin = 37.5 mg/mL (mildly elevated) LH = 2.6 mU/mL (normal) FSH = 4.2 mU/mL (normal) Testosterone = 507 ng/dL (normal) Cortisol = 11.7 μg/dL (low normal) ACTH = 25 pg/mL (normal) Glucose = 81 mg/dL (normal)	Began thyroxine replacement therapy
October 2005	16 y, 8 mo	167.1	54.0		Total T4 = 9.2 μg/dL (normal) IGF-1 = 96 ng/mL (low)	Metabolic panel for signs of diabetes insipidus mostly unremarkable but with slight hemoconcentration; began growth hormone replacement therapy
December 2005	16 y, 10 mo	168.5	56.9		Cortisol = 5.6 μg/dL (low) ACTH = 13 pg/mL (low for cortisol level)	Began cortisol replacement therapy
May 2006	17 y, 3 mo	171.5	61.6			Height in 30th percentile, weight in 35th percentile

*IGF-1 indicates insulin-like growth factor; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; and ACTH, adrenocorticotropin hormone.

thyroid status had been normal for at least 1 month. Craniopharyngioma, a locally aggressive but generally nonmalignant mass arising from the pituitary or infundibulum, would be the most common cause of hypopituitarism in an adolescent of this age. Magnetic resonance imaging ruled out any such mass and ruled out infiltrative disease, infarction, or a congenital absence of the hypothalamic-pituitary structures as well.

Given these findings, strong weight had to be given to the probability of trauma as the cause of the pituitary failure. The only feature of the patient's medical history that stood out was the mild TBI (concussion) suffered the previous summer. For this reason, a provisional diagnosis of hypopituitarism resulting from mild TBI (posttraumatic hypopituitarism, or PTHP) was made.

COURSE OF TREATMENT

Thyroxine supplementation was prescribed (Levoxyl; King Pharmaceuticals Inc, Bristol, TN), and the dose was adjusted based on subsequent serum levels of thyroxine. Despite this appropriate treatment, IGF-1 remained in the normal range for a 2-year-old, and no resumption of height growth was noted. No signs of adrenal insufficiency or diabetes insipidus were seen. Growth hormone therapy (Nutropin AQ; Genentech Inc, South San Francisco, CA) was initiated at a dose appropriately matched to weight, bone age, and existing hormone levels.

Five weeks after starting growth hormone therapy, the patient was seen urgently with a number of new symptoms, including sore muscles, ''head rushes,'' dramatic fatigue, occasional early morning vomiting, loose stools, and an increase in the shedding of hair. Emergency evaluation of cortisol and ACTH indicated that levels of these hormones had dropped dramatically from 5 months previously, prompting a diagnosis of evolving failure of the hypothalamic-pituitary-adrenal system. An ACTH deficiency may be demonstrated in patients with hypopituitarism soon after growth hormone therapy is begun. This finding has been attributed to changes in the ratios of endogenous cortisol to cortisone metabolites by altered expressions of 11-beta-hydroxysteroid dehydrogenase activity in the liver, kidney, and adipose tissue in response to the sudden appearance of previously deficient growth hormone.[7] That this circumstance arose in our patient is one more piece of evidence for evolving hypopituitarism. Cortisol replacement (Cortef; Pharmacia and Upjohn Co, Kalamazoo, MI) at full replacement dose for size was started immediately to combat this life-threatening condition. The progression of signs and symptoms supported the original reasoning and prompted a formal diagnosis of hypopituitarism secondary to TBI (concussion). We cannot dismiss the possibility that the prior minor head traumas themselves contributed directly to pituitary dysfunction, nor can we entirely exclude the possibility that a preexisting condition, which could not be appreciated on magnetic resonance imaging, contributed in some fashion.

As of this writing, the patient was progressing well on physiologic replacement doses of levothyroxine, growth hormone,

and cortisol, which are being adjusted in dose as he grows. Height velocity rose markedly to 4 in (10.16 cm) per year. The patient's current predicted final adult height is 70 in (177.80 cm). His body mass index is up to 20, and the patient reports improved stamina and conditioning. He wears a medical identification bracelet, must be alert to the need for stress doses of hydrocortisone for any illness or injury, and will require lifelong monitoring for diabetes insipidus, hypogonadism, and other complications.

HISTORY OF TRAUMATIC BRAIN INJURY

The sequence of abrupt growth and hormonal disturbances after head injury in this patient indicated a diagnosis of hypopituitarism secondary to TBI. To evaluate this association more closely, investigators interviewed the patient and his parents in March 2006 to gather head injury and general medical history data. The postconcussion symptom scale and concussion history of the Sport Concussion Assessment Tool[8] were administered to the patient for each head injury incident, with help from his parents and brother. The patient's brother, a teammate on the field during the final injury, provided additional details of that incident. Recall of symptoms over such a long time period can be unreliable, so we reported only those symptoms on which all parties agreed and for which they could provide definitive examples. Other data were compared with medical records. Results from the Sport Concussion Assessment Tool and the circumstances surrounding each head injury are reported in Tables 2 and 3.

The patient disclosed that he had suffered 4 head traumas within a 3-month period. Except for the final injury, none of these were reported to medical personnel. The first incident was a result of the patient running his head into the shoulder of another player during a soccer match. He was removed from the game and refused to play later in the game because he ''didn't feel right.'' Our inquiry into this injury strongly indicates a mild concussion. Injury number 2 occurred when the patient's face whiplashed into the back of the head of another person while the patient was tandem tubing behind a speedboat at 15 to 20 mph (24.14 to 32.19 km/h). The patient remembers little of the incident, only ''waking up in the water.'' It is unclear if this trauma caused a concussive injury, but the ecchymoses from the periorbital contusion remained for at least 7 weeks. Injury number 3 occurred minutes before the final injury, when the patient was hit in the head by a forcefully kicked soccer ball. The patient claims he was dazed by the blow but continued to play. These circumstances are consistent with reports of soccer ball impacts causing concussive injuries.[9,10] The medically diagnosed concussion occurred 10 minutes later and was the result of the patient falling and hitting the back of his head on the ground. Within an hour of the injury, he was evaluated at a level II trauma center and was discharged 3 to 4 hours later after computed tomography scans proved normal. The emergency room medical report diagnosed the injury as a concussion with loss of consciousness, but in retrospect, witnesses to the incident could not concur on loss of consciousness. No concussion grade or Glasgow Coma Scale ratings were provided by the hospital. Neuropsychological testing was not conducted after any of the injuries.

In the week after this final injury, the patient refrained from physical activity, slept more than usual, and voluntarily minimized his social activity. Exertion, such as walking up stairs, gave him a headache. One week after the incident, he tried boating but being on the boat left him nauseous and ''not feeling right.'' On the ninth day postconcussion, he was back to limited soccer practice with no heading and no contact. The patient's normal yearly physical examination in September 2004 also served as a postconcussion follow-up. No specific postconcussion tests were administered, but the family's interpretation of that visit was that the physician indicated that all was normal.

DISCUSSION

We believe that the head trauma(s) reported by our patient resulted in hypopituitarism. As with most cases of PTHP, diagnosis relies largely on symptoms, circumstantial evidence, and ruling out alternative explanations. We present here information on PTHP and pediatric concussions and discuss the use of this information in the clinical decision-making process.

MILD TRAUMATIC BRAIN INJURY AND HYPOPITUITARISM

In preparing this case report, we noted brief mentions in the endocrine literature, but not in the sports medicine literature, of sport-related concussion in children leading to hypopituitarism.[11,12] Traumatic brain injury is receiving considerable attention as a cause of hypopituitarism in adults because of the growing body of evidence that some symptoms of TBI, including mild TBI, may have a neuroendocrine basis. Mild TBI is characterized by cognitive impairment and memory loss. Secondary symptoms that persist after trauma (ie, postconcussion syndrome[13]) include additional cognitive problems, headaches, anxiety, fatigue, and psychosocial problems. Ten years ago, symptoms persisting past 3 months were thought to be primarily psychological in origin, but we now recognize that demonstrable neurologic conditions may contribute to these symptoms.[1,13] Sophisticated techniques able to pinpoint subtle changes in the brain strongly indicate that neuroendocrine disorders may be causing some symptoms persisting for many months after injury.

Prevalence studies indicate that hypopituitarism and the associated decline of growth hormone, adrenal hormones, and gonadal hormones accompany 15% to nearly 60% of all TBIs.[14–18] The severity of hormonal disturbances generally corresponds with TBI severity, but even minor head trauma can contribute to pituitary dysfunction.[19,20] For instance, Bondanelli et al[15] reported signs of pituitary dysfunction in 37.5% of their subjects with mild TBI versus 59.3% of subjects with severe TBI. Pituitary disturbances can be overlooked because many of the symptoms are masked by identical postconcussion symptoms or overshadowed by more noticeable symptoms.[19,21,22] Hypopituitarism symptoms may not show up for several years after TBI, which is long after most patients with mild injuries are monitored for complications. This fact has prompted some authors[17–19] to suggest that hypopituitarism may be undiagnosed in many patients with mild TBI.

Several direct and indirect factors have been strongly implicated when traumatic insult leads to pituitary insufficiency. Penetrating force can, in severe cases, damage the pituitary directly. Alternately, and more commonly, transection of the infundibulum, intracranial shear forces at the dural reflection that provides a partial covering for the sella, impaired perfusion, and inflammation are suspected.[17,18] The pituitary's location deep within the skull offers some protection from me-

Table 2. Circumstances of Each Head Injury*

Factor	Head Injury 1	Head Injury 2	Head Injuries 3, 4
Date of injury	May 2004	July 10, 2004	August 21, 2004
Patient's age	15 y, 3 mo	15 y, 5 mo	15 y, 6 mo
Circumstances	Soccer (head to shoulder?)	Tubing behind speedboat; crashed face (orbit) into back of another person's head; boat speed = 15 to 20 mph (24.14 to 32.19 km/h)	3) Blindsided and dazed by soccer corner kick; continued play 4) Slammed back of head into ground; was dazed and could not continue practice
Medical treatment	None; injury self-reported	None; injury self-reported; severe periorbital contusion and ecchymoses	At hospital within 60 min of incident; no Glasgow Coma Scale rating obtained but concussion with loss of consciousness diagnosed
Mouth guard?	No	No	No
Unresponsiveness or loss of consciousness?	Maybe	Maybe	Conflicting reports but likely
Seizure or convulsive activity?	No	No	No
Balance problem or unsteadiness?	Yes	Maybe	Yes
Imaging	None	None	Computed tomography scan normal
Other comments	Patient refused to return to game because he "did not feel right"	Continued tubing within 15 min of incident; did not remember falling off tube	Memory loss for approximately 2 h

*Adapted from the Sport Concussion Assessment Tool.[7]

Table 3. Postconcussion Symptom Scale for the 3 Primary Head Traumas*

	Head Injury 1	Head Injury 2	Head Injury 4
Date of injury	May 2004	July 10, 2004	August 21, 2004
Patient's age	15 y, 3 mo	15 y, 5 mo	15 y, 6 mo
Postconcussion Symptom Scale			
Headache	Yes	Yes	Yes
"Pressure in head"	No	No	No
Neck pain	No	No	No
Balance problems or dizziness	Yes	No	Yes
Nausea or vomiting	No	No	No
Vision problems	No	No	No
Hearing problems/ringing	No	No	No
"Don't feel right"	Yes	No	Yes
Feeling "dinged" or "dazed"	Yes	Yes	Yes
Confusion	No	No	Yes
Feeling slowed down	No	No	Yes
Feeling like "in a fog"	No	No	Yes
Drowsiness	No	No	No
Fatigue or low energy	No	No	No
More emotional than usual	No	No	Yes
Irritability	No	No	No
Difficulty concentrating	No	No	Yes
Difficulty remembering	No	No	Severe
Follow-up symptoms only			
Sadness	No	No	No
Nervousness or anxiety	No	No	No
Trouble falling asleep	No	No	No
Sleeping more than usual	Maybe	No	Yes
Sensitivity to light	No	No	No
Sensitivity to noise	No	No	No
Other	Practiced on a normal schedule afterward; self-medicated with ibuprofen but did not complain to parents	Continued tubing after incident; periorbital ecchymoses for 7 wk, headache for 2 d; self-medicated with ibuprofen	Headache for 1 wk

*Adapted from the Sport Concussion Assessment Tool.[7]

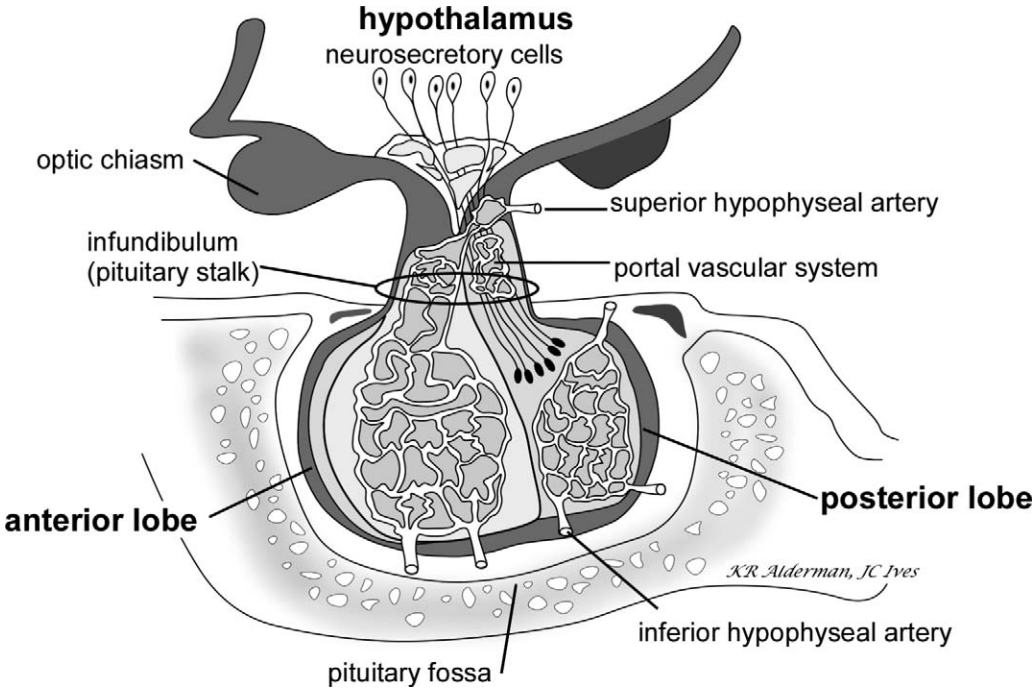

Figure 2. Pituitary gland anatomy. The hypophyseal portal vascular system in the stalk is particularly vulnerable to injury. Encasement of the lobes by the bones of the pituitary fossa may result in high pressures following edema.

chanical trauma, but magnetic resonance imaging and computed tomography scans have revealed that this location actually makes it vulnerable to portal vascular injury and edema, which can further lead to ischemia or necrosis (Figure 2). Even trauma that does not cause fracture may result in subdural hemorrhage and high intracranial pressure, which can predispose an individual to pituitary damage. Unfortunately, current brain imaging techniques can neither confirm nor entirely rule out abnormal function of a structurally intact pituitary gland.[15,18] It is not surprising then that the imaging of our patient showed no evidence of pituitary damage. The diagnosis of hypopituitarism is thus made by weighing the body of test results, reinforced by consistency with the mechanism of injury: in our case, head trauma.

Hypopituitarism, pituitary insufficiency, and multiple pituitary hormone deficiency all describe underperformance of the anterior pituitary gland, with or without concomitant posterior pituitary insufficiency (eg, diabetes insipidus). Because the hypothalamus releases hormones into the hypophyseal portal vasculature, regulating secretion of downstream hormones by the pituitary gland, injury to the hypothalamus may result in hypopituitarism. Pituitary problems often follow a predictable path from the most vulnerable to the least vulnerable functions: growth hormone, gonadotropins, TSH, and then ACTH. Deficiencies in these hormones create further irregularities in hormone secretion in downstream glands. Because some of the injury mechanisms may be transient, may develop slowly, or may resolve without complications, hormonal imbalances seen just after injury may not correlate with hormonal levels 1 year later.[23]

Growth hormone deficiency leads to a lack of growth in children, but less commonly recognized is that growth hormone remains necessary in adults, albeit at lower concentrations, to maintain proper body composition. Additional symptoms of growth hormone deficiency include lowered initiative, energy level, and exercise performance and, sometimes, poorer mental functions. Growth hormone replacement therapy by injection is currently the only successful treatment option.

Gonadotropin deficiency (LH, FSH) in males leads to failure of testicular growth (teens) or shrinkage of testicular size (adults). Testosterone production declines and, thus, reduced libido, poor erectile and ejaculatory function, loss of mustache and body hair, weakness, and anemia may eventually be noted. In premenopausal women, secondary amenorrhea is usually noticed promptly when gonadotropin secretion plummets. Disinhibition of prolactin may lead to galactorrhea and, in severe cases, interferes with any residual gonadotropin function.

Deficient TSH leads to underproduction of thyroid hormone, resulting in decreased energy, increased need to sleep, intolerance to cold, constipation, dry skin, aching muscles, mental slowing, and secondary growth hormone deficiency.

Adrenocorticotropin hormone deficiency directly results in decreased secretion of cortisol by the adrenal glands, which is generally regarded as the most life-threatening of the hormone deficiencies. Symptoms of gradual decline in cortisol production (fatigue, weakness, nausea, and apathy) can be subtle and nonspecific and, therefore, are often overlooked. These symptoms can easily be mistaken for postconcussion depression. As the deficiency progresses, or in cases of rapid onset, symptoms can include psychosis, abnormal electrolytes, and vascular collapse, which can be fatal. Damage to the posterior pituitary may cause antidiuretic hormone deficiency and lead to symptoms consistent with diabetes insipidus.[17,18]

MULTIPLE CONCUSSIONS, PEDIATRIC CONCUSSIONS, AND THE RISK OF POSTTRAUMATIC HYPOPITUITARISM

To date, we can find but one obscure report linking multiple mild head traumas, rather than a single incident, to pituitary dysfunction.[12] Kelestimur et al[12] reported that time spent boxing (length of career or number of bouts) was inversely related

to peak growth hormone levels. Kelestimur[24] later concluded that acute or chronic head trauma in sports is a possible cause of hypopituitarism. This conclusion is consistent with the observation that the appearance and severity of PTHP can be linked to the severity of the head trauma[15] and a compelling body of evidence associating increased severity and incidence of head injuries with prior multiple mild head traumas.[2,25–29] The precise mechanism for this increased vulnerability is unknown, but most of these authors speculate a biological basis. Gaetz et al,[30] for instance, showed that 3 or more concussions had a lasting effect on brain cortical potentials in athletes ages 16 to 20 years. It is reasonable to suspect that the biological vulnerability experienced after repeated trauma may also include vulnerability of those systems maintaining pituitary function.

A high prevalence of single and multiple concussions exists in children between the ages of 5 and 18 years.[31,32] These injuries can have more severe biological and neuropsychological consequences in the immature brain than in adults.[33] Even within the relatively narrow age span of high school and college athletes, sizable differences exist in neuropsychological recovery from mild concussions.[34] Children with mild TBI may display postconcussion symptoms for 3 to 12 months after injury[35–37] and, in some cases, from 3 to 5 years after injury.[38,39] Gagnon et al[40–43] showed that children with very mild TBI have some visuomotor response time programming difficulties, decreased balance performance, and self-efficacy disturbances up to 4 months postinjury. These findings are consistent with reports using computed tomography scans that show that medial temporal hypoperfusion lasts at least 3 months in children with mild TBI exhibiting postconcussion symptoms.[44] Apparent delays in recovery from pediatric concussions may be the result of unreported prior head injuries. As with the patient in our case, it appears that adolescents, particularly athletes in some sports, minimize and underreport head injuries that only daze them, even if they are knocked momentarily unconscious.[34,45,46]

At this time, a limited number of investigations into the incidence of PTHP in young children and adolescents have been undertaken. Einaudi et al[11] reported that PTHP was present at 6 or 12 months after injury in 6 of 48 pediatric TBI patients they examined, including 1 with sport-related mild TBI and 2 with other sport-related moderate TBIs. Acerini et al[47] reviewed case reports of 20 children and noted that mild TBIs from falls, traffic accidents, and sports (ie, judo) had been implicated in the development of PTHP. These authors and others[48] have suggested that adolescents in the ''transition age'' to adulthood appear to be at high risk for developing PTHP and for developing more serious complications.

In sum, the body of epidemiologic and neurologic evidence in the literature is consistent with the injury and medical history of our patient and firmly supports our position that the cumulative effects of each minor head trauma could contribute to an increased severity of the final concussion and, ultimately, to pituitary damage.

CONCLUSIONS AND RECOMMENDATIONS

The pattern of head injury followed by a decline in pituitary function and quality of life in this young athlete occurred over a period of 15 months, which may have hindered diagnosis. As this case clearly illustrates, symptoms may emerge after a return to normal activities. Thus, it can be challenging for those as yet unfamiliar with hypopituitarism to associate nonspecific symptoms with an injury occurring months or even years previously. Although the reported incidence of hypopituitarism after sport-related concussion is currently modest, we predict that it may rise as identification improves, and its severity warrants attention.

We recommend a 3-tiered, yet modest, approach to PTHP surveillance and management based on guidelines from Casanueva et al[49] and Ghigo et al[21] and adapted for athletic trainers and other sports medicine clinicians dealing with concussion injury. This approach involves the following:

1. Enhanced awareness and education regarding hypopituitarism;
2. Adjustments to the preparticipation physical examination; and
3. Adjustments to concussion management and surveillance.

Education and awareness is the first and most important step in dealing with PTHP. We recommend the dissemination of background information, potential symptoms, and management strategies. Definitive symptoms and strategies have yet to be recognized, but basic screening procedures may help athletic trainers and physicians to identify patients who warrant prompt referral for further examination. One step in screening is the use of a symptoms-based concussion survey as a component of the health questionnaire given as part of preparticipation physical examinations. A symptoms-based concussion survey better determines concussion incidence[50] and may identify symptoms consistent with hypopituitarism, raise awareness in athletes about areas of concern, and establish baseline symptoms in nonconcussed athletes. Because growth failure is a key symptom, it is imperative that preparticipation physical examinations include accurate height and mass data obtained from trained operators using standardized methods on calibrated instruments. All athletes with a history of head injury should be measured every 6 months for height and mass. In the absence of reliable height and mass data or in older athletes who may be past periods of noticeable growth, we advocate that athletic trainers be prompt with physician referrals for symptomatic athletes.

All concussion incidents should be examined in depth to document their severity. Athletes are notoriously poor in self-reporting symptoms,[51] so athletic trainers must probe athletes and witnesses (teammates, coaches) with regard to the events surrounding each head injury episode. Damage to the hypothalamus-pituitary axis should be suspected in any athlete with a history of concussive trauma, and, thus, we urge that concussed athletes be monitored every 3 months for up to 1 year for signs of postconcussion and PTHP symptoms. Athletes with symptoms persisting past 6 months should be referred to a physician and, possibly, for neuropsychological and endocrine testing. Worsening symptoms should always prompt an immediate physician referral. For those with multiple episodes of trauma, we advocate that the ''surveillance clock'' be reset with each episode.

In summary, we propose this standard of care for sports concussion should include suspicion of possible hypopituitarism within the proper clinical context, and concussed athletes should be monitored for months, even long after an athlete has returned to play. Athletic trainers are on the ''front line'' of concussion management, and their role in identifying potential cases of PTHP cannot be overstated.

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During the preparation of this manuscript, Mark Alderman, MS, ATC, passed away suddenly. It was his passion to disseminate this important information, and we dedicate this article to his memory.

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