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Traumatic Brain Injury-associated Hypopituitarism- A Case Report with Mini Review

Yuh-Min Song[1,2]

[1]Division of Endocrinology/Metabolism, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation; [2]School of Medicine, Tzu Chi University, Hualien, Taiwan

Abstract

The consequences caused by traumatic brain injury are not only limited to neurological, psychological, and cognitive dysfunctions but may also frequently involve injury to the pituitary gland, resulting in hypo-functioning of one or more of the pituitary- target endocrine organs, despite its deep location in the brain. All ranges of brain trauma (mild, moderate or severe) may have the potential of causing abnormal function of the pituitary gland and injured patients should all be carefully monitored for a timely diagnosis and treatment whenever indicated. All the hormones secreted from the pituitary gland may be affected after the traumatic insult, including adrenocorticotropin, thyroid-stimulating hormone, growth hormone, and gonadotropins from the adenohypophysis, as well as anti-diuretic hormone from the neurohypophysis. A major hope of this review article is to raise interest in clinicians about knowing the pathophysiology, proper diagnosis and treatment of any pituitary insufficiency caused by traumatic brain injury. Clinicians are encouraged to keep high vigilance of this disorder due to the increasingly high incidence of traumatic brain injury encountered in this modern world of high population density and crowded surroundings, with a notable high risk of injury to the pituitary gland and the endocrine functions thus incurred. (J Intern Med Taiwan 2020; 31: 359-371)

Key Words: Hypopituitarism, Traumatic brain injury

Introduction

Traumatic brain injury (TBI), the brain injury caused by traumatic external forces occurring mainly in traffic accidents, incidental falls, violence-related assaults, chronic repetitive head trauma in contact or combative sports (e.g. boxing), and blast injuries in battlefields, not only could cause immediate injury to brain parenchyma with neurological sequelae or even fatality depending on the severity of the trauma, but may also cause morphological and/or functional abnormalities of the pituitary gland, with consequent transient or permanent hypo-functioning of the multiple pituitary-target endocrine organs. Short or long-term, these endocrine morbidities may lead to declines in physical, cognitive, and behavioral performances, which in turn will increase the burden of the disease and the cost of care if not properly attended. On these concerns, the recognition of any functional abnormality of the pituitary-target endocrine organ axes after a TBI requires high clinical vigilance in order

Reprint requests and correspondence：Dr. Yuh-Min Song
Address：Division of Endocrinology/Metabolism, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation. No.88, Sec. 1, Fengxing Rd., Tanzi Dist., Taichung City 427, Taiwan

to make timely diagnosis and treatment to restore normal endocrine functions, maintain physiological homeostasis and generalized well-being of the suffering individuals. In this article, a real case is first presented to lead the readers to the clinical scenario, which is followed by a review synthesized from the collecting and reviewing of pertinent articles on TBI-associated hypopituitarism to form a prudent approach to the evaluation and management of any endocrine dysfunction in this specific group of patients.

Case presentation

A 68-year-old male who had suffered from traffic accident 2 years ago with consequent bilateral hemiplegia, aphasia, and dysphagia has been admitted into the chronic-care facility affiliated to this hospital over the past one more years. Initial CT scanning of the brain after the accident reported intra-ventricular hemorrhage, diffuse sub-arachnoid hemorrhage, and multiple fractures involving skull base, right temporal bone, bilateral frontal bones, right lamina papyracea, right sphenozygomatic fissure, sphenoid bone, right zygomatic arch, walls of bilateral maxillary sinuses, right mandibular condyle, bilateral nasal bones, nasal septum, and inferior wall of right orbit, as well as a suspected traumatic right internal carotid artery (ICA) dissection aneurysm rupture (categorized as Hunt and Hess grade V along with other neurological findings on presentation)[1,2]. Overall assessment by using the injury severity score on presenting to the emergency unit fell into the severe injury category (greater than 16 points according to the Injury Severity Score System)[3]. Because of recognized high incidence of pituitary dysfunction after a traumatic injury to the brain[4], especially when imaging study revealed skull base frature[5], endocrine function evaluation was performed during that hospitalization and the test results revealed central hypothyroidism and central adrenal insufficiency (AI), which was then followed by replacement therapy with thyroid hormone and cortisone acetate tablets, respectively. Serial follow-up laboratory tests during the chronic care period throughout the past one more years on serum free thyroxine (fT4) and cortisol and electrolytes levels were reported to be normal, but undetectable thyroid-stimulating hormone (TSH) and adrenocorticotropin (ACTH) levels, as expectable from the central origin of the hypo-function. Patient's conscious level gradually regained and daily activities improved after intensive rehabilitation programs, although still highly dependent on care-givers. Other pituitary-target endocrine functions were also evaluated during his chronic care period after consulting on endocrinologist and were reported as follows (all hormones of interest were checked at basal state): testosterone: 1.71 ng/dL (reference: 221-871 ng/dL), luteinizing hormone (LH): 0.33 mIU/mL (reference: 1.5-9.3 mIU/mL), follicular stimulating hormone (FSH): 4.64 mIU/mL (reference: 1.4-18.1 mIU/mL), growth hormone (GH): 0.07 ng/mL (reference: 0.003-0.971), insulin-like growth factor-1 (IGF-1): 74.5 ng/mL (lower than 82.5 ng/mL, which is 1 SD from the mean of 116.6 ng/mL for Chinese male and age)[6] , whereas higher prolactin level of 41.07 ng/mL (reference for male: 2.1-17.7 ng/mL) was measured on one occasion. Osmolality of blood was 327 mOsm/kg (reference:280-295 mOsm/kg) on one measurement, with concomitant urine osmolality 543 mOsm/kg (reference: 500-800 mOsm/kg), indicating possibility of impaired concentrating ability of the anti-diuretic hormone (ADH), at which time long term cortisone acetate supplement therapy has been kept in use. However, our patient has never been administered anti-diuretic hormone therapy throughout the period of chronic care due to normal findings of serum electrolytes (including sodium and potassium) on serial blood tests and absence of clinical symptoms or signs of dehydration, polydipsia, polyuria, or excessive urine output more than 3.5 L per day according to nurse chart

records, the presence of which that are used for tentative diagnosis of diabetes insipidus (DI). In the presence of central AI, the release of arginine vasopressin from the posterior pituitary gland has been found to be exaggerated and cortisone replacement therapy would unmask the clinical features of DI[7]. If partial DI dose exist for this patient, this pathophysiology might partially explain the relative hypotonic urine and hypertonic plasma while cortisone acetate supplement has been kept in use. Patient has been taken care of attentively in the facility throughout these past one more years, with generalized condition stable.

Epidemiology of TBI-associated hypopituitarism

Intense attention should be given to the recognition and management of TBI due to its high incidence and significant impact on the general health status of the victims in this modern world of high population density and crowded surroundings. In the United States, the annual incidence has been reported to be approximately 2.8 million cases, with approximately 50,000 deaths thus incurred annually. Between 80,000 and 90,000 victims will experience long-term disability among the survivors. The leading causes of TBI in the US are falls (54-79%), being struck by an object (15%), and motor vehicle accidents (15%). Approximately 20-40% of those injured are classified as moderate or severe in severity assessment[8]. Aside from those several well-known chronic consequences after the central nervous system is traumatized (increased risk of stroke, schizophrenia, prolonged motor and cognitive deficits, decline in quality of life, and age-dependent neurodegenerative diseases)[9-12], another important but less well- recognized disorder is hypopituitarism after episode of TBI, which was first reported in literature more than a century ago by Cyran in 1918[13]. Larger series of reports have gradually entered into the literature due to heightened attention from both clinical and public health points of view, especially when the functional interactions between the brain and multiple endocrine functions became gradually elucidated[14-20]. A 5-year follow-up evaluation of endocrine disorders using data from the nationwide Health Insurance Database in Taiwan reported that in an assessment from 156,945 insured subjects included in the final analysis, the incidence rates of post-traumatic endocrinopathy were 0.4% (1-year) and 2% (5-year), respectively, indicating the presence of a long-run risk of endocrine dysfunctions in patients suffering from TBI. A history of skull bone fracture carried a higher risk of developing pituitary dysfunction at the 1-year follow-up ($p < 0.001$), whereas the 5-year follow-up analysis found a significant association between intracranial hemorrhage and future development of pituitary dysfunction ($p = 0.002$). Long-term monitoring of pituitary function is highly recommended after an incident TBI[21].

The incidence of post-traumatic diabetes insipidus (PTDI) in published studies ranged widely between 2.9% and 51%[22-26]. The following factors may have affected the inconsistencies reported: heterogeneity of the diagnostic criteria used, the characteristics of the studied population (e.g. different TBI severity degrees), and the timing of endocrine function evaluation.

Pathophysiology of hypopituitarism after TBI

Although the pathophysiology of hypopituitarism following TBI is still not fully comprehended, multiple contributing factors have been implicated as to the development of the neuroendocrine dysfunction after the brain trauma. A vascular damage to the pituitary gland causing infarction or ischemia is an important mechanism and can be caused by (1) Traumatic injury to the long hypophyseal portal veins which causes venous infarction. (2) Direct injury to the pituitary gland (as demonstrated in postmortem examinations showing high preva-

lence of necrosis or hemorrhage into the pituitary gland). (3) Secondary insults from hypotension, hypoxia, anemia, and brain swelling that may also lead to ischemia in the pituitary gland. (4) Infarction of the pituitary gland due to transection of the pituitary stalk. Factors including direct shearing forces, raised intracranial pressure, brain hemorrhage, local parasellar brain swelling, and vasospasm may all cause mechanical injury and compression to the susceptible hypophyseal portal vessels which pass through the diaphragma sella to supply the anterior pituitary[27].

Although less in incidence compared to that of the anterior lobe, injury to the posterior lobe of pituitary gland may also cause its endocrine dysfunction manifesting as DI after episode of TBI. Infarction and hemorrhage lesions not only in the anterior but also in the posterior lobe of pituitary gland have been observed in autopsy examinations in victims of head-injury[28].

Risk factors for TBI-associated hypopituitarism

In a prospective study carried out in 78 consecutive patients with mild to severe TBI whose hormonal assessments were done at 3 and 12 month interval after the episode, Schneider et al.[29] had found, in addition to well-known clinical presentations and radiological findings after head injury, a higher frequency of post-traumatic hypopituitarism has been noted in those with evidence of diffuse axonal injury (DAI), which is defined as the presence of typical micro-bleedings on CT images, along with a clinical course of prolonged unconsciousness and recovery. The high-speed and long-duration of acceleration/deceleration forces that are frequently encountered in motor vehicle crash (MVC) may cause DAI. The histological findings are notable to be cascade of biochemical insults induced by shear stress.

In a retrospective study in 166 adults with TBI (median age: 41.6 years; range: 18-76) who had been followed-up for a median interval of 40.4 months (0.2-430.4), Silva et al.[30] found that post-traumatic seizures, intracranial hemorrhage, petechial brain hemorrhage, and focal cortical contusion on image findings may predict the development of central AI. MVC, as a frequent cause of TBI, was a risk factor for both TSH and ACTH deficiencies. The need for hospitalization and the presence of intracranial hemorrhage showed trends toward higher risk for GH deficiency. Other features in association with hypopituitarism include advanced age, increased intracranial pressure, prolonged intubation for more than 10 days, fracture of basal skull, hypoxia, hypotension, and the duration of coma.

Acute PTDI is generally associated with more severe TBI[22,23,25,26]. Low Glasgow Coma Scale (GCS) score, cerebral edema and severe injury were noted to be risk factors for development of PTDI[26]. The mean onset time of DI in non-survivors (1.5 +/- 0.7 days) occurred faster than that of the survivors (8.9 +/- 10.2 days) [23].

Who should be screened for pituitary function after TBI

Since most cases of the pituitary hypo-functioning after TBI are seen in those with moderate to severe severity, a routine screening is not indicated in all patients on the concern of cost-effectiveness, unless there are significant clinical evidences of hypo-functioning[4,30,31]. In one well-executed study carried out in 107 patients (77 with mild and 30 with moderate/severe TBI), those with abnormal acute stage screening results were evaluated extensively further with additional confirmative hormone provocation tests. It was then found that anterior pituitary dysfunction is very rare at < 1% when strict diagnostic criteria were applied[32]. However, it has also been suggested that for those with mild TBI but labeled as “complicated” cases should be also included in the initial screening process. Patients

with features of a complicated mild TBI include those who were admitted into hospital for longer than 24 hours, admitted to the intensive care unit, requiring neurosurgical intervention, suffering pituitary dysfunction within 2 weeks of their TBI, or having new anatomical changes on their follow-up brain imaging[33].

The time for screening tests for pituitary function after TBI

The optimal time for screening is still debatable as pituitary dysfunction during the acute phase of TBI up to three weeks does not necessarily lead to long-term hypopituitarism[34,35]. Instead, after 3-6 months post TBI, all patients with all ranges of severities should have an assessment of their adrenal, thyroid, and gonadal axes in this post-acute stage. In a prospective longitudinal, diagnostic study applying both basal fasting measurements and stimulating tests (including combined growth hormone-releasing hormone (GHRH) + arginine stimulation test and short-acting synthetic ACTH test) to assess hormonal status in 78 patients (M/F:52/26, mean age 36.0 years) with TBI grades I – III (stratified by initial GCS score in this investigation as follows: a GCS of 3-8 indicating severe (grade III), 9-12 moderate (grade II) and 13-15 mild TBI (grade I)), Schneider et al.[29] had found 56% of the patients had impairments of at least one pituitary axis within 3 months after TBI, with the following frequencies: gonadotropic 32%, corticotropic 19%, somatotropic 9%, and thyrotropic 8%. When again assessed at 12 months, there were still a total of 36% who had impairments as follows: gonadotropic 21%, somatotropic 10%, corticotropic 9% and thyrotropic 3%. The authors concluded that a significant rate of hypopituitarism occurs often in the post-acute phase after TBI which may normalize later, but a significant portion of hypopituitarism may still persist or newly develop during longer term follow-up after the post-acute phase and a re-assessment of the hormonal status at this stage is still warranted. The initial GCS score may not be discriminative enough to reliably assess the severity of injury. In many patients with a high initial GCS score, secondary worsening through bleeding or brain edema might render TBI more severe than indicated by initial GCS score and pituitary function after TBI should be assessed in all patients, regardless of the severity of the trauma. An algorithm of pituitary function evaluation after TBI is provided in figure 1 and figure 2[27].

Hypo-functioning of anterior pituitary gland

Among various hypothalamic-pituitary-target endocrine axes that might be involved, central AI during the acute phase has a major impact on general health for the patients, which therefore deserves special clinical attention. Cohan et al.[36] reported that 50% of patients with moderate-to-severe TBI had at least transient AI in the acute phase (defined by a total cortisol concentration below the 25th percentile or one measurement of cortisol of < 5 μg/dL) which was associated with lower blood pressure and higher use of vasopressor. Risk factors for developing AI were younger age, higher injury severity, and a higher frequency of early ischemic insults presenting with hypotension, hypoxia, and severe anemia. The authors had also advised that monitoring of cortisol levels should be considered in intubated patients. In another study, Hannon et al.[37] reported a frequent occurrence of acute hypocortisolemia and central DI in patients with acute TBI, the presence of which could predict mortality. Another prospective study in which hormonal functions evaluated at first within 24-hour of admission and then 12-month after TBI in 52 patients could not identify the relationship between early and late pituitary dysfunction from initial individual laboratory data. The most common deficiency at initial assessment was gonadotropic (41.6%). However, on the 12-month follow-up assessment, rate of GH defi-

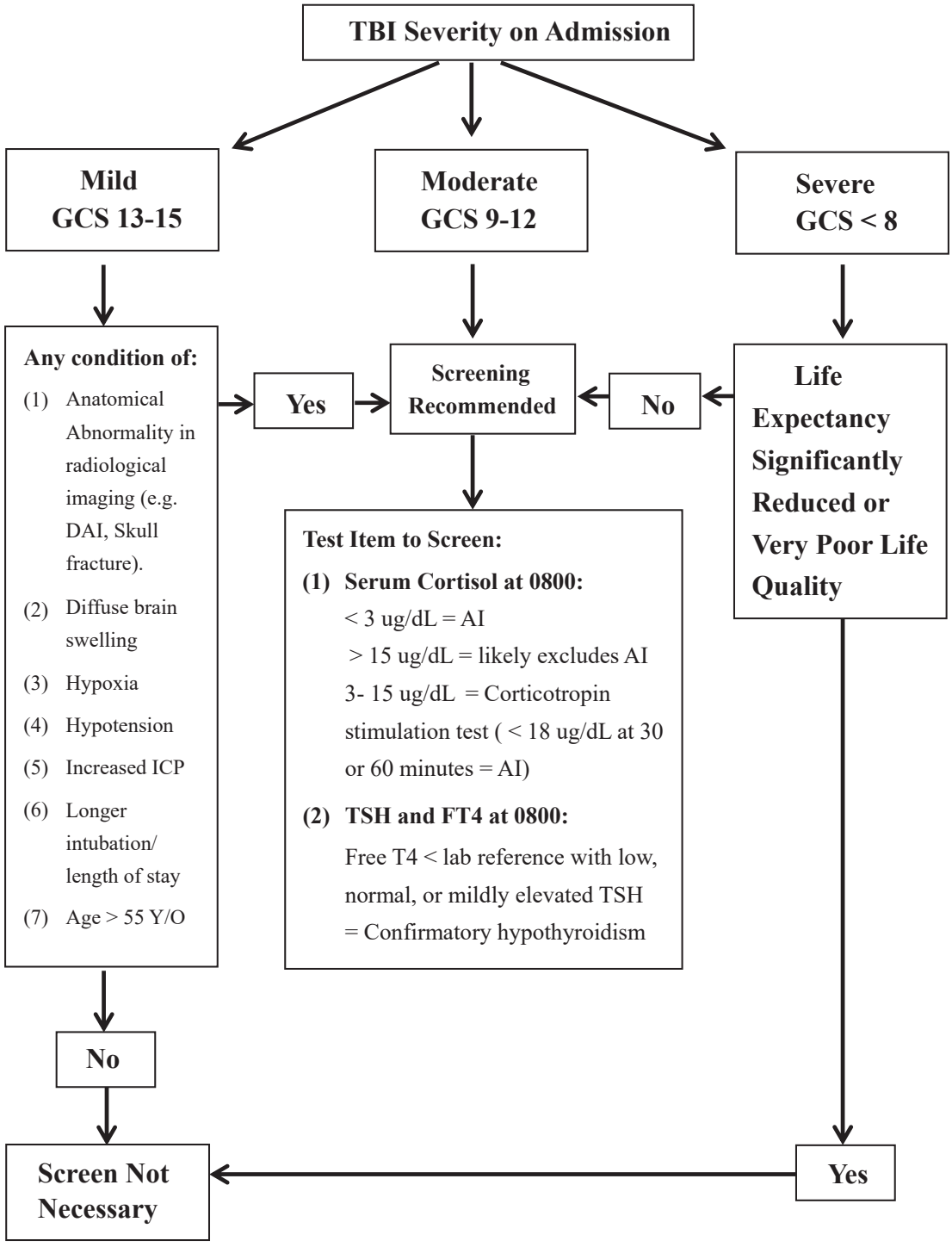

Figure 1. Acute Phase Screening for Hypopituitarism after Traumatic Brain Injury.

Abbreviation: AI- Adrenal insufficiency; DAI: Diffuse axonal injury; GCS: Glasgow Coma Scale; ICP: Intracranial pressure; TBI: Traumatic brain injury; TSH: Thyroid stimulating hormone. (Adapted from reference 27.)

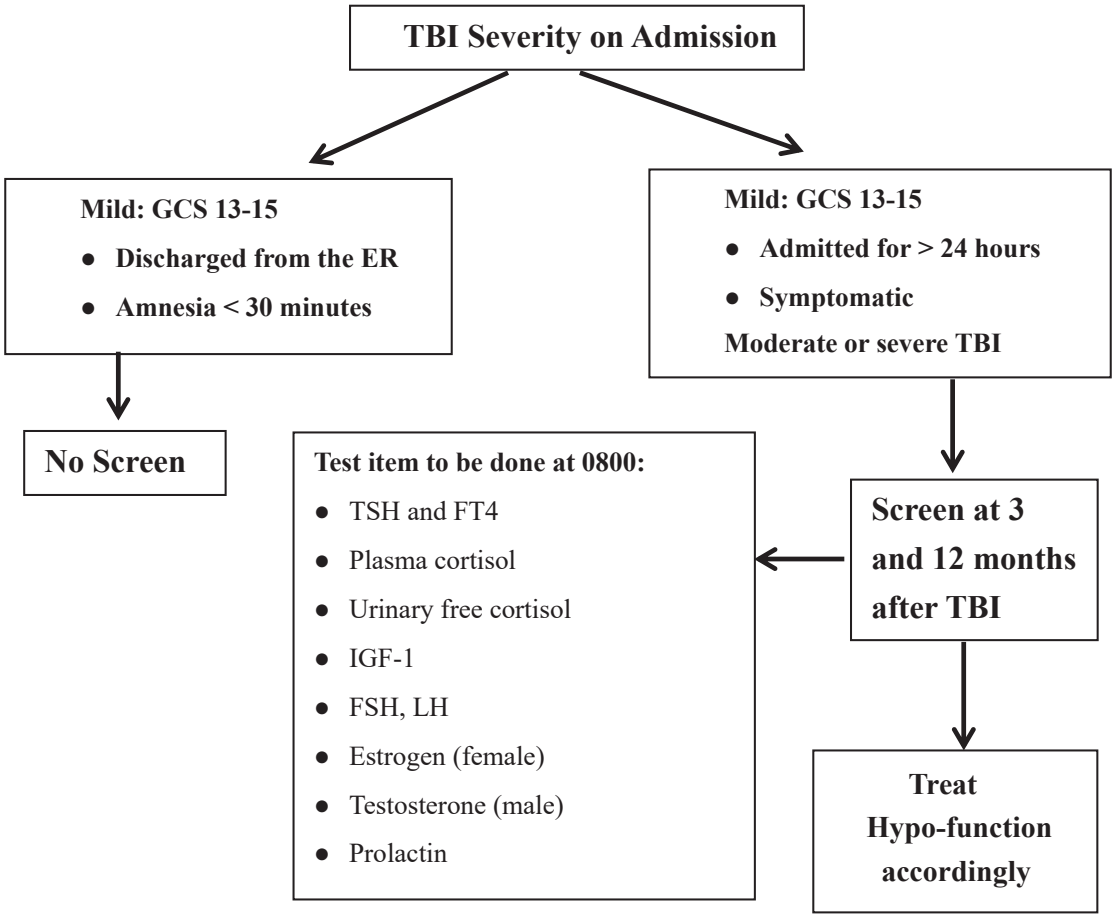

Figure 2. Follow-up Screening for Hypopituitarism after Traumatic Brain Injury.

Abbreviation: AI- Adrenal insufficiency; FSH: Follicular stimulating hormone; GCS: Glasgow Coma Scale; ICP: Intracranial pressure; IGF-1:Insulin-like growth factor-1;LH: Luteinizing hormone; TBI: Traumatic brain injury; TSH: Thyroid stimulating hormone. (Adapted from reference 27.)

ciency (GHD) increased from the initial 20.4% to 37.7%, ranking first among the other pituitary hormones deficiency evaluated, namely ACTH (19.2%), gonadotropin (7.7%), and TSH (5.8%), respectively. Overall, a high prevalence of 50% in pituitary hormone deficiencies was identified initially, and re-assessment one year later revealed recovery in 57.7% (30/52) of the patients and, on the other hand, new pituitary hormone deficiencies had developed in 51.9% (27/52) during this one-year period[38]. From the above prospective studies, it can be concluded that hormonal deficiencies are common findings in the acute phase after TBI but might be regarded as acute physiological response as observed in other non-traumatic acute illnesses. With the high spontaneous recovery rate noted in long-term follow-ups, there is no evidence to support a clinical benefit from hormonal replacement therapy with GH, thyroid hormone, or reproductive hormones at this stage. Nevertheless, an immediate therapeutic trial with glucocorticoids replacement is still warranted when AI is highly suspected as judged from the presence of other pertinent clinical symptoms and signs indicating a life-threatening clinical scenario[36,37].

The prevalence of chronic deficiency in ante-

rior pituitary hormone varied widely from negligible to well above 50% from different studies, and fell to an average overall prevalence of 26%, both in adults and children/adolescent populations[39]. The factors affecting the variable findings may reflect differences in methodology applied, including patient selection, study designs, and diagnostic protocols and criteria used.

Early stage assessment

There is currently no clinical evidence to support the treatment of acute GH, thyroid hormones or gonadotropins deficiencies, or hyperprolactinemia in the acute phase following TBI. Besides, interpretation of the results in the acute phase is difficult and confusing. Therefore, early assessment of the above-mentioned axes is unnecessary. However, exceptions do exist which are pertaining to the assessment of ACTH deficiency and central DI. In a prospective study carried out in 100 sequential TBI patients, Hannon et al.[37] had found that the development of these two disorders in acute stage were associated with higher mortality and the future development of other pituitary dysfunctions.

Adrenal insufficiency

According to guidelines endorsed and released by several academic societies (the Endocrine Society, the American Association for Clinical Chemistry, the Pituitary Society, and the European Society of Endocrinology), the initial assessment of adrenocortical function should include basal cortisol measurement between 8-9 AM, instead of random time sampling. A basal cortisol level of < 3 μg/dL (83 nmol/L) is indicative of AI, and a level of > 15 μg/dL (415 nmol/L) is likely to exclude the diagnosis. When the basal assessment value falls between these two limits, a corticotropin stimulation test is suggested. A peak cortisol level of < 18.1 μg/dL (500 nmol/L) at 30 or 60 minutes indicates AI[40].

Hypothyroidism

To assess central hypothyroidism, the measuring of serum fT4 and TSH is recommended. A fT4 level below the laboratory references in conjunction with a low, normal or mildly elevated TSH level usually confirms the diagnosis and the dynamic TSH-secretion test is not required[40]. A transient state of hormonal aberration is frequently encountered in severe illness other than the thyroid gland disorder per se (sick euthyroid syndrome). The early phase change in hormonal profile (mainly low triiodothyronine (T3) and normal fT4 and TSH levels) seems to reflect adaptive changes occurring primarily in the peripheral thyroid hormone metabolism to pathological stresses[41,42]. However, in extremely severe illness, the hypothalamic-pituitary axis may also be so severely inflicted that a suppression of TSH synthesis and secretion may result. With a consequent reduced production of T3 and T4, a true status of central hypothyroidism could thus ensue[43]. Nevertheless, since the normalization of thyroid hormone levels by providing either T3 or T4 preparation has not been proved to have clear benefits in improving outcomes in these critically ill patients in clinical trials, the thyroid function status could and should be re-assessed in later stage after TBI[42].

Growth hormone insufficiency

Early GHD post TBI can be transient and the assessment for its possible deficiency was recommend to be deferred in chronic stage assessment (i.e. 6-12 months post TBI episode)[44].

Chronic stage assessment

After 3-6 months post episode of TBI, all patients with all ranges of severities should again receive an assessment of their adrenal, thyroid, gonadal, and GH axes in this post-acute phase, since there could be normalization of previous endocrine dysfunction or newly developed deficiencies during

the course of follow-up[34].

Measurement of fT4 and TSH levels at the same time is enough for diagnosis of central hypothyroidism at this chronic stage.

Measurement of sex steroids (estrogen or testosterone) levels along with gonadotrophins (LH and FSH) and menstrual history in pre-menopausal women are used to assess the hypothalamic-pituitary-gonadal axis functions without need of provocative tests. Plasma prolactin levels should be measured at the same time to rule out hyperprolactinemia as one infrequent cause of hypogonadism.

Early GHD is a frequent finding after episode of TBI. Although this could be a transient phenomenon, its deficiency has been found to rank high on the list of the commonly encountered pituitary deficiencies when again tested 6 months or longer after TBI[38]. To help diagnosis, clinical pictures including generalized lethargy, central obesity, pale face, and fine wrinkles on face may raise diagnostic alertness. Laboratory test of a normal IGF-1 level alone may not be accurate enough to exclude GHD. In a retrospective chart review study in patients evaluated for GHD after different severities of TBI (48 patients with mild, 6 moderate, and 8 severe), the authors found that in those 27 patients confirmed to have GHD by insulin tolerance test (ITT) or glucagon stimulation test (peak hGH < 5 μg/L), the IGF-1 levels represented by Z-scores all fell within the age- and gender- specific reference ranges. The authors concluded that baseline serum IGF-1 level had no value in predicting GHD, emphasizing the need for dynamic testing in this population of TBI[45]. However, when the IGF-1 level is lower than the age- and gender-matched normal ranges and especially when there is co-existent evidence of deficiencies of 3 or more other pituitary-end-organ axes, a diagnosis of GHD is established without a need for further affirmative tests.

When GHD is highly suspected, a baseline measurement of GH only is usually not precise for definite diagnosis because of its variability in secretion and a dynamic test is usually required[39]. Among several dynamic tests, the GHRH-arginine stimulation test has been found to have sufficient sensitivity and specificity, allowing good separation between healthy subjects and those with GHD to establish a reliable diagnosis, and could be a reliable alternative to ITT which carries risk in vulnerable patients[46]. A notable pitfall in interpreting GH secretion in any of the dynamic tests that should be kept in mind is in cases of obesity. Corneli et al.[47] studied GH secretion after the GHRH-arginine stimulation test in patients with various pituitary hormone deficiencies caused by hypothalamic-pituitary organic disorders and found that the cutoff value for the stimulated peak GH level differed significantly according to the body mass index (BMI) as follows: 4.2 ug/L in obese subjects (BMI ≧ 30 kg/m2), 8.0 ug/L in overweight subjects (BMI ≧ 25 and < 30 kg/m2), and 11.5 ug/L in lean subjects (BMI < 25 kg/m2).

One agent that has been recently approved by the US FDA for the diagnosis of GHD in adults is a ghrelin mimetic (macimorelin). Use of this drug is convenient because of its oral route administration. In a validation study carried out in adults with GHD versus controls, this oral test was found to have accuracy comparable to the GHRH-arginine stimulation test. The peak stimulated GH was also noted to have an inverse association with BMI in control subjects with obesity (BMI > 30 kg/m2), a finding not different from previous findings. This test can be completed within 90 minutes[48]. The efficacy and safety of single-dose oral macimorelin for adult GHD has been further confirmed recently in an open-label, randomized, two-way crossover trial compared with ITT[49].

Hypo-functioning of posterior pituitary gland diabetes insipidus

The clinical presentation of hypotonic polyuria in the first few days after TBI usually raises the

possible diagnosis of DI. Dehydration and hypernatremia may also emerge when the poor general condition of the patients prevents adequate approach to fluid intake to compensate for the water lost.

The clinical signs and symptoms indicating suspicious ADH deficiency include polyuria (e.g. more than 50 mL/kg of body weight/24 hours, or 3.5 liters/day in a 70-kg person). The serum and urine osmolarity should be measured simultaneously and urine dipstick test performed to rule out other causes of high urine osmolarity, such as hyperglycosuria (a differential diagnosis that can also be aided by simultaneous test of plasma glucose level). In the presence of high serum osmolarity (> 295 mOsmol/L), urine osmolarity should normally reach approximately 600 mOsmol/L (urine osmolality/plasma osmolality ratio should be ≥ 2)[50].

In recent years, the measurement of hypertonic saline-stimulated plasma copeptin, the C-terminal fragment of the arginine vasopressin (AVP) prohormone which has release and clearance characteristics similar to those of AVP, has been investigated and proposed to carry a greater diagnostic accuracy than the water-deprivation test for diagnosis of DI[51].

Treatment of hypopituitarism

It is always critical to initiate a prompt replacement therapy with glucocorticoid in patients with known or suspected central AI. Acutely ill patients should be started with stress doses of glucocorticoids (i.e., hydrocortisone 100 mg intravenously every 6 to 8 hours) without awaiting biochemical confirmation for diagnosis. Stable patients can be treated with hydrocortisone (15-25 mg/day in divided doses, with higher dose given in the morning) or prednisone (2.5-5.0 mg/day), titrated based on clinical criteria. Mineralocorticoid replacement is not needed, since aldosterone secretion from the adrenal gland is preserved[52]. There is a potential interaction with GH replacement when glucocorticoid therapy is being introduced. GHD results in reduced cortisol clearance because of enhanced cortisone to cortisol conversion mediated by 11β-hydroxysteroid dehydrogenase type 1. When starting GH replacement, cortisol clearance increases and patients may need a slight increase in hydrocortisone dose (on average 5 mg per day)[53,54].

Patients with central hypothyroidism are treated with levothyroxine, a mean full replacement dose of approximately 1.6 μg/kg/day is suggested. A lower starting dose should be considered in older patients and those with cardiovascular disease (CVD) or mild hypothyroidism. To avoid precipitating adrenal crisis, levothyroxine replacement should only commence after adrenal function has been assured to be intact or glucocorticoids already replaced. Serum fT4 levels (instead of TSH) should be monitored in follow-up assessment for adequacy of dosage[52,55].

If not contraindicated, patients with central hypogonadism, pursuing fertility or not, can receive sex steroid replacement. It is not known whether testosterone replacement may help improve the functional independence of male patients after TBI. As the cardiovascular safety of testosterone replacement in older men, particularly those with CVD, has been called into question in recent observational studies[56], caution is advised before considering testosterone replacement in these groups until more definitive data from clinical trials become available. Women of premenopausal age and with intact uterus who have central hypogonadism can receive estrogen and progestin replacement therapy, or estrogen replacement only with history of hysterectomy, based on careful gynecologic evaluation and follow-up[52].

Patients with central DI are treated with desmopressin. In hospitalized patients, desmopressin should be administered on demand (1-2 μg administered subcutaneously or intravenously every 8-12 hours), as central DI is often transient in acute stage after TBI. Careful monitoring of fluid balance and serum sodium is required in order to avoid hyper-

or hyponatremia. When stable, outpatients can be treated with oral (100-400 μg) or nasal desmopressin (10-20 μg) administered every 8-24 hours, titrated to maintain comfortable sleep and permit daytime activities without polyuria or excessive thirst, while maintaining plasma sodium within normal range[52].

Conclusion

Traumatic brain injury is one of the world's leading causes of morbidity and mortality, especially among young age population. TBI-associated hypopituitarism is now recognized as a common, but often underdiagnosed, complication which may contribute significantly to the morbidity and possibly mortality following moderate and severe TBI. Endocrine evaluation and management should be part of standard multidisciplinary care for these patients. Among patients with severe and moderate TBI, acute cortisol deficiency should be diagnosed and managed promptly while a more comprehensive assessment of the pituitary function should be undertaken in the post-acute phase. Randomized clinical trials examining the effect of GH replacement in patients with post-traumatic GHD are needed to assess the potential impact on recovery, rehabilitation, and quality of life.

The involvement of an endocrinologist is recommended to ensure that appropriate testing, treatment, and follow-up is provided[25,33].

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創傷性腦損傷後腦下垂體功能低下症—病例報告及小型文獻回顧

宋育民

[1]台中慈濟醫院　內科部內分泌新陳代謝科
[2]慈濟大學醫學系

摘　要

創傷性腦損傷可因多種外力因素導致，在現今人口擁擠與交通頻繁的環境中常見的原因有交通事故、跌倒、或高撞擊性運動，腦損傷不僅產生神經、精神、及認知等各種系統或功能異常之後遺症，同時也可能傷害位於腦部深處的腦下垂體，引起各種內分泌功能低下症，例如：若發生在腦創傷後急性期即需立即給予治療的腎上腺功能低下症或是中樞性尿崩症，在慢性時期仍持續存在或新發生的甲狀腺功能低下症、性腺功能低下症、生長激素缺乏症。在診治創傷性腦損傷患者的同時，臨床醫師需認知如何診斷各類腦下垂體功能低下症，並如何適時與適當給予補充治療，以保持各種內分泌系統功能之正常運作。此一日漸多見的內分泌疾病值得做一探討。