Indications and Conditions for Neuroendocrine Dysfunction Screening Post Mild Traumatic Brain Injury

Introduction and Background

More than 233,345 traumatic brain injuries (TBI) have occurred in the military from 2000 through December 2011.[1] The majority of these (80-85 percent), have been classified as mild TBI (mTBI). Most patients with mTBI recover completely within three months or less of injury. However a small subset of these individuals experience persistent symptoms and difficulty in rehabilitation, particularly in the setting of co-occurring disorders.[2,3] Neuroendocrine dysfunction (NED) may be a contributing factor in the setting of prolonged symptoms or difficult rehabilitation following mTBI.[4,5]

NED following TBI is the result of direct trauma or biochemical response that interferes with the normal production and regulation of inter-related hormonal processes. The anterior pituitary is the most vulnerable and most often affected endocrine structure.[3,4,5] The neuroendocrine pathways most frequently affected in mTBI are growth hormone and gonadotropin.[3,4,6,7,8] Deficiency of these hormones in adults may lead to symptoms such as fatigue, weight gain, low blood pressure, low libido, loss of muscle mass and amenorrhea. The screening strategy described below is recommended to identify most individuals with NED related to mTBI.[4,5,6] The onset of NED can occur anytime between the event and up to 36 months post injury. NED may adversely affect prognosis and impede recovery from TBI.[6,8,9,10] The diagnosis of NED may be difficult and is sometimes not considered because the symptoms may significantly overlap with post-concussion syndrome as well as other co-occurring conditions such as sleep disorders, PTSD or depression.[6,11] Service members diagnosed with concussion who are experiencing persistent symptoms suggestive of NED for greater than three months (or new onset up to 36 months) following mTBI may benefit from post-injury NED screening.[6,8,11,12]

This Clinical Recommendation is intended to offer the health care provider an approach to identifying patients with mTBI who may benefit from further endocrine evaluation and care and is specifically intended to support the primary care provider. The recommendation is based on a review of current published literature as well as the proceedings of a December 2010 expert panel convened by DCoE that included clinical subject matter experts representing the military services, the Department of Veterans Affairs, DCoE and civilian sectors. It was reviewed and approved by the Defense Department's TBI Quad Services Cell, which includes TBI representation from the Air Force, Army, Marines and Navy.

Clinical Recommendation

- Consider NED in the differential diagnosis after confirmed mTBI when symptoms suggestive of NED persist for greater than three months (or new onset up to 36 months) following injury. These symptoms may include fatigue, insomnia, impaired cognition and memory loss, difficulty concentrating, emotional and mood disturbance.
- Symptoms of NED are similar to the symptoms of other post mTBI medical diagnoses such as sleep disorder, memory difficulties, depression, PTSD and/or post concussive syndrome.[12] Considering NED may avoid a delay in diagnosis and improve prognosis.[4,5,11]
- Anterior pituitary deficiencies account for the majority of chronic neuroendocrine disorders following mTBI. Growth hormone and gonadotropin deficiencies are most common, but TSH deficiency (secondary hypothyroidism) and ACTH deficiency (adrenal insufficiency) may occur as well (less than 10 percent of cases with TBI associated NED).[13] Therefore, the following screening strategy is recommended as a rational approach to the initial evaluation in the primary care environment.
- The following describes the typical symptoms suggestive of the previously stated neuroendocrine deficiencies.
  - **Growth Hormone Deficiencies:** Characterized by loss of lean muscle mass and strength, increased body fat around the waist, weight gain, reduced heart rate, low blood pressure, constipation, poor memory, lack of concentration, depression, anxiety, fatigue and decreased sex drive.
  - **Gonadotropin Deficiencies (LH/FSH/Testosterone/Estradiol):** Characterized by loss of libido, infertility, anemia, hair loss, decreased muscle mass and strength, amenorrhea and mood disorders.
  - **Adrenocorticotropic hormone deficiency:** Characterized by hypotension, weight loss, malaise and fatigue.
  - **TSH Deficiency:** Characterized by weight gain, cold intolerance, impaired short-term memory, dry skin and constipation.

- Recommended NED serum screening labs include*:
  - 0800 Cortisol levels (<12 mcg/dl, recommend follow up)
  - TSH — Thyroid Stimulating Hormone
  - LH — Luteinizing Hormone
  - FSH — Follicle Stimulating Hormone
  - IGF — 1 Insulin–like Growth Factor
  - FT4 — Free Thyroxine
  - Testosterone (males only)
  - Estradiol (females only)

** Local and lab specific reference ranges should be utilized to determine deficiencies*

- Post-injury screening for NED should only be used as one component of a thorough clinical evaluation by a qualified provider. It should not be used in isolation for clinical decision making.
- Referral to Endocrinology is advised if lab results suggest NED or if strong clinical suspicion of NED remains despite negative screening tests and other potential causes for symptoms have been excluded.

Conclusion

NED should be a considered following a confirmed diagnosis of TBI when a service member remains symptomatic beyond 3 months and/or becomes symptomatic up to 36 months after injury. NED screening studies should not be routinely ordered as a screening or diagnostic tool during the early post injury period. Screening for NED can provide valuable clinical insight leading to prompt treatment and improved overall prognosis for this subset of patients.

As with all clinical decisions, field and operational circumstances may at times require deviation from these recommendations.

References

1. Defense Medical Surveillance System and the Theater Medical Data Store. (2012). Prepared by the Armed Forces Surveillance Center. www.dvbic.org/TBI-Numbers.aspx
2. Ghigo,E., Masel, B., Aimaretti, G., et al. (2005). Consensus guidelines on screening for hypopituitarism following traumatic brain injury. Brain Injury 19; 711-724.
3. Krahulik, D., Zapletalova, J., Frysak, Z., & Vaverka, M. (2009). Dysfunction of hypothalamic-hyperphysical axis after traumatic brain injury in adults. Journal of Neurosurgery, EPub ahead of print. www.ncbi.nlm.nih.gov/pubmed/19929195. Accessed January 15, 2010.
4. Tanriverdi,F., Unluhizarci, K. & Kelestimur, F. (2010) Pituitary function in subjects with mild traumatic brain injury: A Review of literature and proposal of a screening strategy. *Pituitary* 13; 146-153.
5. Bondanelli, M., Ambrosio, M., Zatelli, M., Marinis, L., & Uberti, E. (2005). Hypopituitarism after traumatic brain injury. *European Journal of Endocrinology* 152; 679-691.
6. Guerrero, A., & Alfonso, A. (2010). Traumatic Brain Injury Related Hypopituitarism: A Review and recommendations for screening combat veterans. *Military Medicine* 175(8); 574-580.
7. Van der Eerden, A., Twickler, M., Sweep, F., Beems, T., Hendricks, H., Hermus, A., & Vos, P. (2010). Should anterior pituitary function be tested of all patients presenting at the emergency department because of traumatic brain injury? *European Journal of Endocrinology* 162;19-28
8. Masel, B. & DeWitt, D. (2010). Traumatic brain injury: A Disease process, not an event. *Journal of Neurotrauma* 27; 1529-1540.
9. IOM (Institute of Medicine). 2009. Gulf war and Health, Volume 7: Long-term consequences of traumatic brain injury. Washington, DC: The National Academies Press.
10. Gasco, V., Prodam, F., Pagano, L., Grottoli, S., Belcastro, S., Marzullo, P., Beccuti, G., Ghigo, E. & Aimaretti, G. (2010). Hypopituitarism following brain injury: When does it occur and how best to test? *Pituitary*. DOI 10.1007/s11102-010-023506.
11. Rothman, M., Arciniegas, D., Filley, C., Wierman, M. (2007). The Neuroendocrine effects of traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences* 19: 363-373.
12. Wilkinson, C., Pagulayan, K., Petrie, E., Mayer, C., Colasurdo, E., Shofer, J., Hart, K., Hoff, D., Tarabochia, M., & Peskind, E. (2012). High prevalence of chronic pituitary and target-hormone abnormalities after blast related mild traumatic brain injury. *Frontiers in Neurotrauma* 3(11). DOI:10.3389/fneur.2012.00011.
13. Schneider, H., Kreitschman-Andermahr, I, Ghigo, E., Stalla, G. & Agha, A. (2007). Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage; A Systematic review. *JAMA* 298(12): 1429-1438.

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