COMMENT

Manifesto for the current understanding and management of traumatic brain injury-induced hypopituitarism

F. Tanriverdi1, A. Agha2, G. Aimaretti3, F.F. Casanueva4, F. Kelestimur1, M. Klose5, B.E. Masel6, A.M. Pereira7, V. Popovic8, and H.J. Schneider9

1Erciyes University Medical School, Department of Endocrinology, Kayseri, Turkey; 2Divisions of Endocrinology, Beaumont Hospital and the RCSI Medical School, Dublin, Ireland; 3Endocrinology, Department of Experimental and Clinical Medicine, University A. Avogadro del Piemonte Orientale, Novara, Italy; 4Department of Medicine, Santiago de Compostela University, Complejo Hospitalario Universitario de Santiago (CHUS); CIBER de Fisiopatologia Obesidad y Nutricion (CB06/03), Instituto Salud Carlos III; Santiago de Compostela, Spain; 5Department of Medical Endocrinology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; 6Department of Neurology, Transitional Learning Center at Galveston, The Moody Center for Traumatic Brain & Spinal Cord Injury Research/Mission Connect, The University of Texas Medical Branch, Galveston, Texas, USA; 7Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, The Netherlands;
8Neuroendocrine Unit, Endocrinology Clinical Center, School of Medicine, University Belgrade, Serbia; 9Medizinische Klinik-Innenstadt, Ludwig-Maximilians University, Munich, Germany

ABSTRACT. Traumatic brain injury (TBI)-induced hypopituitarism remains a relevant medical problem, because it may affect a significant proportion of the population. In the last decade important studies have been published investigating pituitary dysfunction after TBI. Recently, a group of experts gathered and revisited the topic of TBI-induced hypopitu-

INTRODUCTION

Traumatic brain injury (TBI) is an important public health problem all over the world (1-3). Although TBI has previously been considered as a rare cause of hypopituitarism, an increased prevalence of neuroendocrine dysfunction in patients with TBI has been reported in recent years in both retrospective and prospective studies (4-15). A meta-analysis that included 1015 TBI patients, showed that the pooled prevalences of hypopituitarism in mild, moderate and severe TBI were 16.8%, 10.9%, and 35.3%, respectively (3). Current data suggest that patients who need hospitalization after head trauma are at substantial risk for hypopituitarism (3, 13). In line with this finding, a lower prevalence of hypopituitarism was found in a study in patients who visited an emergency department for TBI without hospitalization in most cases (16). Therefore, the medical community is confronted with the following important and still unresolved issues: which TBI patients should be screened and what is the optimal screening strategy? In other words, which test or combination of endocrine tests at which time point should be used for optimal evaluation of pituitary function after TBI? Also, do we have to consider the natural histories of hormonal deficiencies to be different in mild, moderate, and severe TBI patients? Is GH replacement therapy useful in TBI patients with isolated severe GH deficiency? etc...

Therefore, a group of experts gathered in Istanbul in April 2011 and revisited the existing data on TBI-induced hypopituitarism. During the 2-day meeting, the main issues of this topic were presented and discussed with the conclusions. Given the persisting areas of uncertainty, these conclusions should be considered preliminary and not as guidelines. The authors agree that a consensus conference of interdisciplinary composition is necessary in order to produce a global guideline.

1. TBI-induced hypopituitarism remains a relevant medical problem, affecting a significant proportion of the populations tested. The great majority of these patients may not be diagnosed, and will thus be withheld from adequate hormone replacement therapy (3-15).
2. Although in the last 10 yr there has been accumulating evidence on the underlying pathophysiological basis, the natural history, the risks for the patients, and the benefits of treatment, we recognize that the medical community has not been adequately exposed to this knowledge. Even the endocrine community remains sparsely aware, or sceptical on this topic (2, 15).
3. For the above reasons, the general population and the healthcare practitioners, researchers, and healthcare administrators have not prioritized this medical problem (1, 2, 12).
4. TBI-induced hypopituitarism has common features

All the authors contributed equally. Other than the corresponding author names are listed according to alphabetic order.

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Correspondence: F. Tanriverdi, Erciyes University Medical School, Department of Endocrinology, Kayseri, Turkey.
E-mail: fatihtan@erciyes.edu.tr
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with hypopituitarism secondary to other causes (3). Of interest, isolated GHD is the most common deficiency observed after TBI. It remains to be clarified whether diagnostic specificity is affected when common diagnostic criteria are applied in this new group of patients with an a priori low pre-test probability of disease.

5. TBI-induced hypopituitarism often affects patients already suffering from a disabling head trauma. When present, this is likely to aggravate the morbidity in these patients (14).

6. There are observational data to suggest that hormonal replacement in these patients, and especially GH replacement, is beneficial to the patients regarding cardiovascular risk factors and some biochemical parameters (7, 10, 17, 18). However, clinical trials on the efficacy of hormone replacement in TBI-induced hypopituitarism are still lacking.

7. Additionally, there is still inadequate literature demonstrating that the appropriate pituitary replacement therapy can improve neuro-cognitive symptoms, psychosocial problems, and work-related activities in these patients (18-21). Randomized controlled clinical trials with GH replacement therapy are mandatory.

8. Considering the very high number of subjects with TBI, it is crucial to strictly define on a cost/benefit basis which patients should be investigated for hypopituitarism (15).

9. Such investigations must be done with an “intention to treat”. Patients who will not benefit from hormone replacement therapy should not be studied (3, 14, 15, 19).

10. There are new data about when patients should be diagnosed after TBI. Probably the most effective system would be to check morning cortisol level in the acute phase, interpret it in the clinical context, and perform a complete basal and dynamic study, unless otherwise clinically indicated, no earlier than 1 yr after trauma. Based on current data a screening strategy for TBI-induced hypopituitarism has been proposed (Fig. 1) (3, 6-9, 15).

11. The preferred dynamic test for GH secretion is still a matter of debate and should be at the discretion of the endocrinologist. Unless the IGF-I concentration is below 2 SD score, corrected for age, a confirmatory test is needed in case of isolated GH deficiency. One relevant problem is the absence of reliable normative data, and internationally validated assays for GH and IGF-I (22).

12. Disorders of salt and water balance, like diabetes insipidus and the syndrome of inappropriate anti-diuretic hormone (SIADH) are common in the acute phase of TBI, and should be promptly diagnosed and appropriately managed (12).

13. Besides endocrine parameters, neurocognitive, neurobehavioral and quality-of-life studies are urgently needed in studies on TBI induced hypopituitarism (19-21).

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**Patients with mild, moderate and severe TBI with risk factors**

- Assess ACTH deficiency by measuring morning basal cortisol levels in the acute-phase of TBI in case of clinical suspicion
- Reassess at 6 months if clinical findings suggest hypopituitarism
- At 12 months (baseline hormonal work-up, dynamic test for ACTH deficiency and GHD)

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**One or more hormone deficiencies**

- In mild and moderate TBI reassess yearly intervals until 3rd year post TBI (rarely new onset hormonal deficiencies may develop)
- In severe TBI no more investigation is required after 1st year (no new onset hormone deficiency was defined after 1st year)

**No hormone deficiencies**

- In mild and moderate TBI reassess yearly intervals until 3rd year post TBI (pituitary functions may recover in substantial number of patients)
- In severe TBI all the hormonal deficiencies should be replaced after 1st year if clinically indicated (no recovery was defined after 1st year)

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1 Those TBI patients who need hospitalization at least 24 h, and those with an abnormality on initial computed tomography after head trauma or with clinical signs of hypocortisolism should be screened regardless of the severity.

2 Decision of the hormone replacement therapy (GH replacement therapy in particular) should be done according to clinical context.

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Fig. 1 - Suggested screening strategy for the prospective follow-up of the patients with traumatic brain injury (TBI). GHD: GH deficiency.