CONSENSUS OF OPINION

Hypopituitarism following traumatic brain injury (TBI): A guideline decalogue

F.F. Casanueva, E. Ghigo, V. Popovic, and the Athens TBI and Hypopituitarism Study Group*

ABSTRACT. In order to gain further insight into hypopituitarism, that ensues moderate to severe traumatic brain injury (TBI), a group of experts actively working in the field gathered to exchange recent data and concepts. The objective arising from the meeting was to enhance the awareness of both medical specialists and health care administrators on the problem, whose prevalence is higher than previously thought. Guidelines for the diagnosis and management of TBI-mediated hypopituitarism were produced.
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INTRODUCTION

Traumatic brain injury (TBI) has been associated with hypopituitarism in general and GH deficiency in particular, but the precise prevalence and characteristics of the problem remain unclear. Although TBI-mediated hypopituitarism as a cause of neuroendocrine dysfunction was reported more than 50 yr ago (1-4), and was listed in textbooks, it was often mentioned as case report or on confirmatory basis (5-23). However, data emerging since the year 2000 suggested new aspects of the topic. Between them, that after severe or moderate TBI ensuing hypopituitarism could be more frequent than previously thought, and that the hormonal deficits may significantly contribute to the chronic disability of TBI and its cognitive, physical and social sequelae (24-27).

The interest spurred by those reports led to the gathering of numerous experts on the field, in the yr 2002 and 2003 (28). The main conclusions of these meetings were: 1) TBI-mediated hypopituitarism was frequent, underdiagnosed and undertreated; 2) hyperprolactinemia and diabetes insipidus were not necessarily adequate markers of this dysfunction; 3) diagnosis and adequate hormone replacement therapy could be severely delayed or lacking, and 4) a relevant proportion of the affected subjects were walking the streets trying to undertake a normal life without an adequate evaluation and hormone replacement therapy (28). The basis of this situation was attributed to a general lack of awareness of the problem by the medical community. Several published works have subsequently helped to gain insight in the characteristics and relevance of the TBI-mediated hypopituitarism as a relevant medical problem (29-31).

In the year 2004, a group of experts actively devoted to this topic gathered in Athens. They reviewed the current results of their work and briefly defined guidelines to help physicians and allied health authorities address this problem. The main conclusion of this meeting was that rigorous and systematic research into the problem of TBI-mediated hypopituitarism, as well as a dissemination of results, are needed to raise awareness of the problem within

***The Athens TBI and Hypopituitarism Study Group:**

Casanueva F.F, University of Santiago de Compostela, Santiago de Compostela, Spain; Ghigo E., University of Turin, Turin, Italy; Popovic V., University Clinical Center, Belgrade, Serbia; Agelopoulos N., Hippocration Hospital, Athens, Greece; Aimaretti G., University of Turin, Turin, Italy; Baldelli R., University of Piemonte Orientale "Amedeo Avogadro," Italy; Baptista F., Hospital Santa Maria, Lisbon, Portugal; Carvalho D., Hospital de S. João, Porto, Portugal; Colao A., University "Federico II", Naples, Italy; Di Somma C., University "Federico II", Naples, Italy; Djurovic B., Clinical Center of Serbia, Belgrade, Serbia; Cordero J.F.C., Hospital Universitario Virgen del Rocio, Seville, Spain; Gurlek A., Haceteppe University School of Medicine, Ankara, Turkey; Kelestimur F., Erciyes University Medical School, Kayseri, Turkey; Kelly D.F., Department of Neurosurgery, UCLA, Los Angeles, USA; Leal Cerro A., Hospital Universitario Virgen del Rocio, Sevilla, Spain; Leon-Carrion J., University of Seville, Seville, Spain; Maric N.P., Clinical Centre of Serbia, Belgrade, Serbia; Greece; Masel B.E., Transitional Learning Center, Galveston, USA; Movalilar S., Istanbul Faculty of Medicine, Istanbul, Turkey; Murillo-Cabezas F., Hospital Universitario Virgen Del Rocio, Seville, Spain; Perino C., Presidio Ospedaliero Ausiliatrice, Turin, Italy; Pavlovic D., Institute of Neurology, Clinical Center of Serbia, Belgrade, Serbia; Selcuklu A., Department of Neurosurgery, Erciyes University, Kayseri, Turkey; Tolis G. Hippocratio Hospital, Athens, Greece; Touraine P., Necker Hospital, Paris, France; Tsagarakis S., Athens Polyclinic, Athens, Greece; Urban R., University of Texas, Medical Branch, Galveston, USA; Vilarinho A., Hospital de S. João, Porto, Portugal.

Correspondence: Prof. F.F. Casanueva, Department of Medicine, School of Medicine, University of Santago de Campostela, Colle San Francisco SN PO BOX 563, E-15780 Santiago de Campostela, Spain.

E-mail: endocrine@usc.es

the medical community at large. The creativity of the meeting is reflected in the surprising fact that the ensuing guideline Decalogue actually has fifteen points.

TBI-INDUCED HYPOPITUITARISM DECALOGUE

1. Traumatic brain injury (TBI)-induced hypopituitarism in general, and GH deficiency in particular, are more common than previously thought.
2. Although data emerging since 2000 demonstrate the relevance of the problem, in general there is a lack of awareness in the medical community about the incidence and clinical repercussions of this pathology.
3. The physiopathological basis of hypopituitarism following head trauma is not well defined, and a clinico-pathological correlation is lacking. Nevertheless, necrotic, hypoxic, ischemic and shearing lesions at the hypothalamus and/or the pituitary are likely important factors. Pituitary stalk trans-section appears to be an uncommon cause of this pituitary pathology in both fatal and non-fatal head injuries.
4. The majority of post-TBI hypopituitarism appears to result from motor vehicle accidents, but all types of head injury, including falls, assaults, child abuse and cranial gunshot wounds can lead to this problem. Despite the decline in these accidents in selected countries due to strong regulatory measures, the astounding number of car accidents worldwide would probably continue to be the leading cause of TBI-mediated hypopituitarism. In any case, specific epidemiological studies, with clear biological endpoints, are needed by both scientists and health care providers.
5. The subjects at highest risk appear to be those who have suffered a moderate to severe head trauma. Although even mild TBI victims (Glasgow Coma Scale score 14 and 15) may precede hypopituitarism, for operational purposes the subjects who should be tested and followed closely are those with an initial Glasgow Coma Scale score of 13 or less, those with intracranial hemorrhagic lesions, and those with signs or symptoms of hypopituitarism. Patients in a chronic vegetative state are not targeted at this stage. Particular attention should be paid to this problem in children and adolescents, as the burden of the disease on their development may be extensive.
6. Typically, moderate and severe TBI patients are treated by a succession of physicians including neurosurgeons, intensive care unit specialists, neurologists, rehabilitation doctors and primary care physicians. However, the majority of patients with TBI-induced hypopituitarism are likely to be undiagnosed and untreated while attempting to recover from their brain injury.
7. Two initiatives are needed to identify potentially affected TBI patients. The first is to retrospectively identify and evaluate TBI patients (as defined above in #5) who may have been injured years earlier but are still functioning poorly. This can be done through medical record review. The second is to prospectively study TBI patients at risk during the acute injury phase and during the first 12 months of recovery.
8. The clinical, neuropsychological, and endocrine evaluation of these patients should be performed in a period between 6 and 12 months after TBI. Early evaluation in the peritrauma period or at 3 months post-injury is currently under investigation.
9. Neuropsychological and quality-of-life (QoL) tests are needed in order to evaluate the status of these patients. Such testing will hopefully allow determination of the relative impact of the brain injury and associated hypopituitarism on neuropsychological recovery and QoL.
10. A clear definition of the relevant signs and symptoms of hypopituitarism is needed. Endocrinologist-directed testing of pituitary hormones and their target glands should be performed. For the somatotropic axis, determination of IGF-I levels, plus dynamic testing with GHRH-arginine, GHRH-GHRP-6, glucagon etc. is indicated. Insulin induced hypoglycemia (ITT) testing can be used when not contraindicated. The specific cut-offs of these tests (as defined by international guidelines), need to be used and should be adjusted for the GH peak-reducing effects of obesity (BMI>30).
11. Antidiuretic hormone (ADH), thyroid hormone, glucocorticoids, and GH should be replaced when a deficit is detected, in accordance with international guidelines. Gonadal hormone replacement should follow standard procedures and be individualized. The effectiveness of such replacement therapy on patient outcome should be evaluated.
12. Close liaison between endocrinologists, paediatric endocrinologists, rehabilitation doctors, ICU specialists, neurologists, neurosurgeons, psychiatrists, neuropsychologists and primary care physicians is needed to better diagnose and manage TBI-induced hypopituitarism. The foundation for such collaborative work is to raise awareness of this relatively common but under-appreciated problem.
13. In order to further increase awareness of this problem, presentation of scientific data at national and international symposia, and its publication in high-profile, peer-reviewed journals is encouraged. The journals to be targeted should not only be those that are directed at endocrinolo-

gists, but also journals targeting other specialists involved in managing these patients.

14. Given the paucity of data on experimentally-induced hypopituitarism, animal models should be developed to help better understand the pathophysiology of the problem and to identify effective measures to mitigate or prevent this problem in human TBI patients.
15. Clinical, basic, and epidemiological investigation into the problem should be increased and encouraged as only solid data can permeate the scientific community and health authorities.

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