

**Clinical Case Seminar**

**A7(1-3)**

# Permanent hypogonadism after traumatic brain injury: a case report

Roberto Vita <sup>1</sup>, Salvatore Benvenga <sup>1,2,3</sup>

<sup>1</sup> Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

<sup>2</sup> Master Program on Childhood, Adolescent and Women's Endocrine Health, University of Messina, Messina, Italy

<sup>3</sup> Interdepartmental Program of Molecular & Clinical Endocrinology and Women's Endocrine Health, University hospital, A.O.U. Policlinico G. Martino, Messina, Italy.

## Abstract

We report here a case of male post-traumatic hypogonadism, whose clinical manifestations occurred three years after a traumatic brain injury (TBI). The selective pituitary deficit was proven to be irreversible by discontinuing for six months testosterone replacement. The present case confirms that gonadotrophs failure is not uncommon after a TBI. Therefore, regular pituitary function monitoring after a TBI, especially if associated with loss of consciousness, is important for the early detection of hypopituitarism.

**KeyWords:** hypogonadism; traumatic brain injury; pituitary

**Introducing Member:** Roberto Vita

**Corresponding Author:** Roberto Vita - rvita@unime.it

## Introduction

Hypogonadism is the failure of the testis to produce adequate levels of testosterone (androgen deficiency). Clinical symptoms of hypogonadism include erectile dysfunction, hypoactive sexual desire, decreased muscular strength and depression. Androgen deficiency may stem from primary testicular failure or hypothalamus-pituitary impairment. Apart from men seeking fertility, treatment of hypogonadism consists in testosterone replacement (1).

## Case Report

A 37-year-old man was referred to our clinic because of severe erectile dysfunction. Family history was negative for relevant diseases. Past history taking revealed a car accident with brain injury and a 2-min loss of consciousness three years before. At that time he was not hospitalized. He also had a three-year story of severe ulcerative pancolitis that had been managed first with 5-aminosalicylic acid and azathioprine. Because of resistance to these drugs, infliximab was added from 12 months before our first observation. At visit the patient complained moderate fatigue, reduced muscular strength, lethargy and apathy. Vaginal penetration was greatly impaired, morning erections were absent, and libido was very reduced. Clinical examination revealed slight overweight (BMI 26 kg/m<sup>2</sup>), minimal gynecomastia and reduced testis size (right testis, 10 ml; left testis, 12 ml). His

International Index of Erectile Function, which scored 5, confirmed the severity of erectile dysfunction. Thyroid and adrenal function were normal, as well as IGF-1 levels. Gonadotropin and testosterone levels were low (FSH 0.12 mU/ml, normal values 1.27-19.26, LH 0.12 mU/ml, normal values 1.24-8-62, testosterone normal 79.90 ng/dl values 175-781), whereas prolactin levels were slightly high (338.70 mU/ml, normal values 56-278). Macroprolactin was excluded by treating the sample with poly-ethylene-glycol prior to the assay (131 mU/ml, normal values < 252). Nuclear Magnetic Resonance was normal. Semen examination revealed severe oligo-astheno-teratospermia. He started testosterone replacement therapy (250 mg testosterone enanthate i.m. every 21 days) with normalization of testosterone levels after two months (751.8 ng/dl) and improvement of symptoms. Upon discontinuing replacement therapy, testosterone dropped after 6 months to 146.70 ng/dl and asthenia and muscular strength worsened. Therefore, he started again replacement therapy with testosterone, but he elected the transdermal formulation in lieu of the intramuscular one.

### **Discussion.**

Traumatic brain injury (TBI) is one of the leading causes of disability and death worldwide. In Western countries, the incidence of TBI is 200 cases per 100,000 inhabitants per year (2). An impairment of the pituitary has been reported in 15-50% of TBI cases, especially in those classified as severe by the Glasgow Coma Scale (< 8). Post-traumatic hypopituitarism is caused in most cases by an indirect damage of the pituitary, which results from the concussion, namely the external forces directed to the skull (3,4). Recently, autoimmunity against pituitary has been proposed. Particularly, post-traumatic disruption of the blood-brain-barrier with subsequent leakage of pituitary antigens may trigger the production of antibodies directed to these antigens. This mechanism may explain the delayed onset of hypopituitarism even years after a TBI (2). The most frequent pituitary deficit regards the gonadotrophs, which are located in areas supplied by the long hypophyseal portal vessels (2,3). The ensuing hypogonadism may be either reversible (2) or irreversible (5).

In the case herewith reported, isolated central hypogonadism occurred three years after a car accident, which was complicated with a brief loss of consciousness. The man had also a severe-grade ulcerative colitis, which is an autoimmune, relapsing-remitting, inflammatory disease of the large intestine (6). Hypogonadism is an uncommon endocrine manifestation of ulcerative colitis, and may result from i) disruption of the hypothalamus-pituitary-gonad axis by inflammation and inflammatory cytokines, ii) undernutrition and reduced leptin levels, iii) and the effect of glucocorticoid treatment on gonadotrophin secretion (7). Returning to our case: i) the inflammatory disease was well-controlled with infliximab, even though inflammation and inflammatory cytokines had been not measured, ii) the patient was neither underfed, iii) nor on glucocorticoids. However,

we cannot exclude a role of ulcerative colitis and related inflammatory cytokines in the pathogenesis of central hypogonadism in the case presented. Concerning the first point, infliximab, an anti-TNF- $\alpha$  monoclonal antibody, has been reported to protect the gonad (8) and the spermatozoon against TNF- $\alpha$ -mediated detrimental effects (9). Furthermore, in adolescents with Crohn's disease, infliximab has been recently reported to increase significantly sex hormones and gonadotropin levels (10).

In conclusion, we confirm that TBI can cause a disruption of hypothalamus-pituitary-testis axis even after years. A regular monitoring of pituitary function of subjects who had had TBI is important for early detecting and treating this endocrine abnormality.

**Conflicts of Interest:** There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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