

Special Article

Surgical diseases related to disorders of the Hypothalamus- Hypophysis- Adrenals Axis

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Abstract

Hypothalamus-Hypophysis-Adrenals (HPA) Axis disorders are not a chapter of general surgery and especially of emergency surgery or surgery of minor and moderate degree. Specialization in Endocrine Surgery is often limited in surgery of thyroid gland, in Greece. However, the HPA axis disorders are very prominent in multi-trauma patients and in major abdominal surgery.

HPA axis disorders are more often in elderly, in cases with comorbidity and after brain injury. The commonest pattern of patient with acute disorder of the HPA axis is the multiple trauma with concomitant brain injury while the chronic HPA disorder we see mostly in surgery is in patients with extremely long duration of intra-Hospital stay and failure of recovery and exit from Hospital.

For programmed operations of major surgery in aged people, it is crucial to perform a pre-operative examination of the neurological status and to test the hormonal balance and the competence to respond endocrinologically in acute stress of long duration. Complex situations develop in patients with chronic alcoholism who undergo major operations or in patients with failure of the liver-spleen axis, who are in danger of sepsis.

Patients admitted in ICU receive noradrenaline as a rescue therapy and they may survive but may also lead to suffer consequently from a long-term dysfunction of the HPA axis. The same equals in various scenarios for patients with extended burns, cardiovascular operations and patients of old age with long-term infectious diseases or/and nutrition defects.

It seems that cellular stress, metabolic stress, systematic inflammatory response, sepsis and the syndrome of multiple organ dysfunction syndrome represent pathologic conditions that may relate with HPA axis failure, because HPA axis functions as a primitive survival machine for patients in danger Also, aged people, even if they are

not in critical status, have an altered function of HPA axis that should be taken into mind in major surgery and trauma.

Key-Words : HPA Axis, Surgery, ACTH, Adrenal Insufficiency, CRF

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Introduction

Hypothalamus -Hypophysis -Adrenals (HPA) axis is a theory of physiology, resistant in time, that explains physiologic and pathologic conditions that derive from neuroendocrine disorders.

The relation of general surgery and HPA axis is old. After a curative resection of adrenal tumors, causing Cushing syndrome, the surgeon should be able to respond to the needs of the recovering HPA axis. The hydrocortisone replacement therapy is necessary when a cortisol-secreting adrenal tumor is resected. Symptoms and signs of adrenal insufficiency are monitored for months. The patient is cured from hypercortisolism via this surgical operation, but the need for recovery of the HPA axis may reach the 22 months or more.¹ Normal adrenal function will be assessed with the response of adrenals to ACTH administration (ACTH stimulation test) and then the replacement therapy may be discontinued. The master organ that controls this homeostatic journey to HPA axis recovery is the brain.

The surgical patient taking glucocorticoids is another old chapter of general surgery. HPA axis is suppressed by chronic glucocorticoid therapy. If this patient needs to respond to a stress, like surgery, may not be able to respond, due to HPA axis failure. In the 1950s, the “stress dose” of glucocorticoids was established as a response to reports talking for HPA axis failure after surgery. The fear for the intra-operative adrenal crisis lead to protocols like 300 mg of hydrocortisone/ day for several days before and after the operation.²

The hypofunctional HPA axis is another option, in these cases, an extended pre-operative test should be conducted if the operation’s result depends on the adrenal sufficiency of the patient. For example, a

prospective study on patients undergoing disc surgery showed that chronically stressed patients are at a great risk of postoperative complications or/and failure of the operation due to reduced cortisol secretion postoperatively and the consequent synthesis of proinflammatory cytokines.³

The preoperative diagnosis of any HPA axis dysfunction, and the regulation of the axis is facilitated with glucocorticoid supplementation, which are administered in full conformity with the current guidelines for patients with adrenal insufficiency.⁴

Aim of this article is to outline the current frame into which a surgeon accomplishes a successful surgical laparotomy taking into mind any existing abnormality of the HPA axis of the patient.

Methods

For this reason, a search was conducted, without chronological limits, in the Pubmed Database, and a number of 20 articles were reviewed. The key terms for the search were HPA Axis, Surgery, ACTH, Adrenal Insufficiency and CRF.

Results

Primary adrenal insufficiency is caused by diseases of the adrenals. Secondary adrenal insufficiency may derive from pituitary or hypothalamic dysfunction or failure caused by tumors, irradiation, infiltration, trauma or surgery.⁵ Pituitary disease is a cause of secondary adrenal insufficiency, and includes any disease of the pituitary gland as trauma, tumors, vascular diseases, infectious diseases, infiltrative diseases, and other rare causes. Pituitary metastases may very rarely cause adrenal insufficiency.⁶

It has been found that patients with major depression with or without early life stress, have an impaired HPA axis response to stress in the adult life.⁷ Also, the cortisol awakening responses, the rapid increase in cortisol levels that reaches to a max. at 30–45 min after awakening in the morning are flattened in depression due to hormonal impairment.⁸ The level of this impairment has been found to be at the receptors of glucocorticoids and mineralocorticoids, and is found in stress-related psychiatric disorders.⁷

Iatrogenic adrenal insufficiency is caused by glucocorticoids in pharmacological doses.⁹ Suppression of the HPA axis derives from *supra-*

physiologic doses and long-term administration of glucocorticoid therapy.⁹ The real prevalence of this problem is not known.

Trauma affects, dramatically, the neuroendocrine response of the HPA axis, and it has been found that amygdala play a prominent role in healthy humans.¹⁰ According to Cacciaglia et al, a structural reorganization happens in amygdala when the brain is exposed to stress. In animal models, it has been found that it is both a neuronal hypertrophy and an increase in the volume of the nuclei of amygdala.¹⁰ To assess the HPA axis sensitivity Cacciaglia used the dexamethasone suppression test.¹⁰ They measured significant differences in chronic stress, current stress and anxiety.

Li M, et al recommends that all patients with traumatic brain injury who are treated with continuous sedation should be monitored for adrenal insufficiency carefully.¹¹ On the fifth day after injury, the mean baseline cortisol and simulated cortisol levels were significantly lower in the mechanical ventilation plus sedation group compared with patients with sedation alone or mechanical ventilation alone. Furthermore, hypoxemia on admission and shock were associated with the development of adrenal insufficiency.¹¹

The HYPRESS randomized clinical trial showed the effect of hydrocortisone on development of shock among patients with severe Sepsis. Interestingly, their findings do not support the use of hydrocortisone in this group of patients.¹²

Systemic inflammatory response syndrome (SIRS) is altered in patients with an acute brain injury. This inflammatory condition is started and expanded due to the secretion of important inflammatory mediators like interleukin (IL)-1 beta, IL-6 and tumour necrosis factor (TNF) alpha. In critical patients without brain injury, a compensatory anti-inflammatory response syndrome (CARS) controls the development of SIRS. However, in patients with acute brain injury immunosuppression is the only result of anti-inflammatory response, and the Multiple Organ Dysfunction Syndrome (MODS) may derive as a consequence. MODS is followed with significant mortality. This means that the intact HPA-axis as well as the sympathetic nervous system efferent limbs provide negative feedback for the production of inflammatory mediators. In brain injury, this function fails due to HPA-axis insufficiency.¹³

DISCUSSION

It has been found that a combination of prednisone with psychotherapeutic treatment and citalopram may provide better therapeutic effects in depression patients with hypocortisolism after traumatic brain injury.¹⁴ Depression after traumatic brain injury is closely related with hypothalamic-pituitary -adrenal (HPA) axis insufficiency.¹⁴

A study by Neigh et al, showed that cardiac arrest and cardiopulmonary resuscitation dysregulates the hypothalamic-pituitary-adrenal axis.¹⁵ Furthermore, there is a gradual increase in CRF(1) receptor binding in the hypothalamus and other regions, as well as a transient decrease of both CRF(1) and CRF(2A) receptors in the hippocampus.¹⁵ The CRF system is related with primitive reactions and is related to survival.¹⁶ There are many publications for the potential use of CRF peptide antagonists, which are suggested as agents to reinvigorate stress/anxiety affected "anatomy systems" in order to boost their efficacy.¹⁷ These data are in conformity with the theory that a stress response can take place with the participation of higher brain areas or may be simple, and in that latter case, an evaluation of the situation is not needed by the subject.¹⁸ In elderly, with or without neurocognitive dysfunction, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis may contribute to aging-related depression and cognitive deficits. *Aging of the HPA-axis* has also been associated with declining physical performance, possibly due to sarcopenia.¹⁹

The acute Hypothalamic-pituitary-adrenal response in traumatic brain injury with and without extracerebral trauma was examined by Llompart-Pou JA et al.²⁰ The researchers found that adrenal insufficiency was present in 23,6% of cases, and there was primary and secondary mechanism for this complication. Higher risk was reported in patients with low plasma ACTH levels (< 9 pq/ml) and in patients with hemorrhagic shock. However, in aged people, the data are complex, and the published studies have various results.

Conclusions

HPA axis is not any more an old theory of no interest. Current studies examine surgical diseases and HPA-axis disorders as closely related conditions, and thanks to the tremendous discoveries in the CRF system pharmacological research, there is a perspective for the introduction of

new pharmacologic agents in clinical practice, that will act both at peripheral and central sites, where CRF receptors have been discovered.

Conflict of Interest: None.

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