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Hypothalamic-pituitary axis disorder – "the puppet master" of multiple organ dysfunction in brain-dead patients

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One of the most revolutionary discoveries of modern medicine was organ transplantation, as it brought hope and healing in cases that seemed incurable. Best outcomes in organ transplantation are related to a rigorous tissue typing and an appropriate immunosuppressant therapy that allowed a longer survival rate for recipients [1]. The management of the potential brain-dead donor is a complex one that involves several well-defined stages: early identification of potential donors, brain death determination, maintaining vital functions, and graft transplantation.

Brain death determination is synonymous with irreversible anatomical and functional injury to the entire brain and brainstem. This process involves a major alteration of the hemodynamic and hormonal homeostasis. Hypothalamic irreversible injury is followed by a profound normothermia dysregulation. The aggressive inflammatory response after brain death occurrence is responsible for capillary leakage and refractory hypotension [2]. Clinical diagnostic tests that assess brain death include brain stem areflexia, apnea, and cerebral unresponsiveness, linked with a known, irreversible cause of coma [3].

A better understanding of the pathophysiology in such cases is mandatory for a successful graft transplantation and a lifesaving procedure. This issue highlights the fact that despite the lack of a current pattern for monitoring and treating brain-dead patients, all the therapy should be directed towards optimal organ perfusion pressure [2,4]. This condition is essential for maintaining a mitochondrial aerobic metabolism, being well known that mitochondrial dysfunction is the main mechanism involved in multiple organ dysfunction occurrence and death [5].

The "puppet master" of this complex and challenging intensive care pathology remains the hypothalamic-pituitary axis, due to its two major functions: thermoregulation and hormonal homeostasis. More than obvious, the attention of the intensivist should be focused on the major hemodynamical changes in order to maintain an adequate perfusion pressure. The irreversible damage of the hypothalamic-pituitary axis is responsible for the occurrence of a vicious circle leading to multiple organ dysfunctions.

In terms of hemodynamic instability, for brain-dead patients it is well known that the cardiovascular changes are divided in two phases: the first one, known as the catecholamine storm, is due to a marked increase of the sympathetic tone, and the second one, the cardiovascular collapse, due to the depletion of catecholamines and vasodilation [1,6]. Hypotension occurs because of hypovolemia, myocardial dysfunction, inadequate fluid repletion or restriction, use of diuretics or depletive treatment for previous cerebral edema, hyperosmolar therapy, third space losses, hemorrhage and/or diabetes insipidus. The severe inflammatory response occurred shortly after the irreversible loss of brain function is responsible for a marked vasoplegia, capillary leak and left ventricular dysfunction [7]. The alterations in hormonal production and regulation secondary to the cessation of blood supply of the hypothalamic-pituitary axis causes hypothyroidism and hypocortisolism and the lack of antidiuretic hormone. This hormonal impairment is a major contributor to the worsening of the hemodynamic instability, forming a vicious circle [8].

Antidiuretic hormone deficiency leads to diabetes insipidus associated with polyuria, hypernatremia, hypokalemia, hypocalcemia, hypophosphatemia and hypomagnesaemia. Hyperosmolality secondary to the urinary massive free water loss induces proinflammatory cytokine responses. Hypernatremia plays an important role by impairing hepatic gluconeogenesis

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and lactate clearance, responsible for acidosis and a decrease in left ventricular contractility. High serum natrium levels can induce rhabdomyolysis and consequent acute renal failure, that can affect the renal function of the donor with serious consequences on the kidney transplant recipients [9, 10,11].

Another particularity of brain-dead donors is related to the occurrence of hypothyroidism as a consequence of hypothalamic-pituitary injury. The thyroid hormones act on almost every cell in the body, and are responsible for increasing basal metabolic rate, stimulating protein synthesis, and increasing the body's sensitivity to catecholamines [12,13]. This emphasizes their importance related to the normal function of the cardiovascular system since thyroid hormones increase the automaticity of the pacemaker cell, followed by an increase in chronotropy and inotropy. At vascular level, they are related to the smooth muscle relaxation and vasodilation [12,13].

In brain-dead patients, the most common changes in thyroid hormones are low serum triiodothyronine (T3) and elevated reverse T3, leading to what is generally known as "low T3 syndrome" that increases and maintains hemodynamic instability [12].

Hypothalamic–pituitary injury occurring after brain death can lead to adrenal insufficiency. The inability of the adrenal glands to adequately respond to stress cause a drop in circulating cortisol levels. Hormonal combination therapy including immunosuppressive doses of corticosteroids is suggested for donors presenting low left ventricular ejection fraction [11].

Most studies suggest the use of methylprednisolone as the corticosteroid of choice to treat hypothalamic–pituitary–adrenal axis failure, which might be involved in maintaining hemodynamic instability, and to reduce inflammation, which could impair organ graft function. Due to poor evidence offered by randomized clinical trials, corticosteroid treatment in brain-dead donors is controversial, but it could be useful in cases of marked hemodynamic instability [14,15].

Temperature dysregulation, because of hypothalamus injury, is an inevitable situation, defined as a continuous reduction of the internal temperature, unless active correction is applied [15]. Disruption of the blood supply to the hypothalamus results in a loss of thermoregulatory control. The initial manifestation is hyperthermia, followed by hypothermia.

Hypothermia is defined as a core temperature of under 35°C. Other factors contributing to the occurrence of hypothermia in brain-dead patients are related to poikilothermia secondary to hypothalamic injury, large amounts of cold intravenous fluids or blood products, a decreased metabolic rate, and loss of temperature preservation mechanisms [16]. The negative consequences of hypothermia are activation of intravascular coagulation and organ damage that impair the survival and function of the graft [15].

Because the need for organ transplants is increasing, nursing of a brain-dead patient requires the intensivist to fight on multiple battlefronts, to provide longer and healthier lives for organ recipients. In order to battle the multiple organ dysfunction caused by brain death, doctors worldwide must understand the importance of the hypothalamic-pituitary axis and its functions. The "puppet master" must have a master puppeteer!

Conflict of interest

None to declare.

References

1. https://optn.transplant.hrsa.gov/learn/about-transplantation/history/
2. Anwar ASMT, Lee JM. Medical Management of Brain-Dead Organ Donors. Acute Crit Care. 2019;34(1):14-29. doi:10.4266/acc.2019.00430
3. Nair-Collins M, Northrup J, Olcese J. Hypothalamic-Pituitary Function in Brain Death: A Review. J Intens Care Med. 2014. 31. 10.1177/0885066614527410
4. Chamorro-Jambrina C, Muñoz-Ramírez MR, Martínez-Melgar JL, Pérez-Cornejo MS. Organ donor management: Eight common recommendations and actions that deserve reflection. Med Intensiva. 2017;41(9):559-568. doi:10.1016/j.medin.2017.01.012
5. Hahnenkamp K, Böhler K, Wolters H, et al., Organ-Protective Intensive Care in Organ Donors. Dtsch Arztebl Int. 2016;113(33-34):552-558. doi:10.3238/arztebl.2016.0552
6. Shemie SD, Dhanani S, The Physiology of Brain Death and Organ Donor Management. Ped Crit Care Med. 2014 Jan 28:497–518. doi: 10.1007/978-1-4471-6362-6_38.
7. Kuecuek O, Mantouvalou L, Klemz R, et al. Significant reduction of proinflammatory cytokines by treatment of the human brain dead donor. Transplantation. 2004; 78(2):197.
8. Mi Z, Novitzky D, Collins J, et al. The optimal hormonal replacement modality selection for multiple organ procurement from brain-dead organ donors. Clin Epidemiol.

2015;7:17-27.

9. Lindner G, Funk GC. Hypernatremia in critically ill patients. J Crit Care. 2013;28(2):216.e11-216.e2.16E20. doi:10.1016/j.jcrc.2012.05.001.
10. Opdam HI, Hormonal Therapy in Organ Donors. Crit Care Clin. 2019;35(2):389-405. doi:10.1016/j.ccc.2018.11.013.
11. Bajwa SJ, Haldar R, Brain death in ICU patients: Clinical significance of endocrine changes. Indian J Endocrinol Metab. 2014;18(2):229-231. doi:10.4103/2230-8210.129118
12. Buchanan IA, Mehta VA, Thyroid hormone resuscitation after brain death in potential organ donors: A primer for neurocritical care providers and narrative review of the literature. Clin Neurol Neurosurg. 2018;165:96-102. doi:10.1016/j.clineuro.2018.01.004.
13. Akbaş T, İbrahim EŞ, Ayhan Ö. Alterations in thyroid hormones in brain-dead patients are related to non-thyroidal illness syndrome. Endokrynologia Polska. 2018;69(5). DOI: 10.5603/EP.a2018.0056.
14. Kotsch K, Ulrich F, Reutzel-Selke A, et al. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial [published correction appears in Ann Surg. 2011 Aug;254(2):391]. Ann Surg. 2008;248(6):1042-1050. doi:10.1097/SLA.0b013e318190e70c.
15. Meyfroidt G, Gunst J, Martin-Loeches I, et al. Management of the brain-dead donor in the ICU: general and specific therapy to improve transplantable organ quality. Intensive Care Med. 2019;45(3):343-353. doi:10.1007/s00134-019-05551-y.
16. Anwar A.S.M.T., Lee J.M., Medical Management of Brain-Dead Organ Donors. Acute Crit Care. 2019;34(1):14-29. doi:10.4266/acc.2019.00430.