

Management of Neuroendocrine Instability During Maintenance of Potential Organ Donors

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1. Introduction

Solid organ transplantation is the treatment of choice for patients with end-stage cardiac, pulmonary or liver disease. This form of surgical treatment has enjoyed increasing success, with better early and late survival for lung, liver and cardiac transplantation, while renal transplantation is both cost effective and improves the quality of life for the recipient receiving dialysis. The main limiting factor for this successful procedure is the shortage of suitable donor organs, resulting in longer waiting list for patients with a substantial risk of mortality before transplantation (Keegan M.T. 2009).

The majority of organs come from patients who suffered an acute neurologic injury, such as traumatic brain injury or cerebrovascular accidents, including spontaneous intracerebral bleeding and thrombosis that progresses to brainstem death. Unfortunately, not all brainstem dead patients become potential organ donors and organ are ultimately harvested from only 15-20% of individuals who satisfy organ donor criteria (Mascia et al 2010). Many reasons contribute to the paucity of donor organs, such as the sub-optimal critical care management of potential organ donors, lack of consent, logistical problems and the use of strict donor criteria (Mascia et al 2006).

In the present chapter we will discuss neuroendocrine alterations which occur in acute brain injured patients evolving to brain death. Since most of the data available has been collected in acute neurological patients with varying impairment of the conscious state, we will first summarize the pathophysiology, clinical signs, diagnosis and treatment of endocrine abnormalities in severe brain injury patients and then we will focus on the consequences of neuroendocrine alterations in brain dead subjects. These abnormalities contribute to the hemodynamic and metabolic instability of the potential organ donors and may affect organs availability for transplantation.

In severe acute brain injury patients evolving to brain death, hypothalamic-pituitary-adrenal insufficiency occurs in 30-50% (Behan et al 2008; Corneli et al 2007) of patients and a high prevalence of neuroendocrine deficiency is present in brain dead patients (Howlett et al 1989; Salim et al 2006). These endocrine alterations lead to metabolic abnormalities and hemodynamic instability with deleterious effects on these potential organ donors (Ullah et al 2006). Adequate organ donor management is therefore mandatory to prevent, reduce or reverse these alterations and to maintain the functional integrity of potentially transplantable organs. Since all donors are treated in intensive care units an optimal clinical management would be an integral component of intensive care medicine education and

practice. Nevertheless a substantial variability between medical centres and a consequent sub-optimal clinical management exists in the field of organ donors treatment (Mascia et al 2009). Regarding the neuroendocrine alterations most of the studies have been performed in neurological patients looking at the long term effects of these abnormalities.

When we treat acute neurological patients with a preserved conscious status who develop endocrine alterations such as anti-diuretic hormone depletion, details from the clinical history are collected, symptoms developed over time frame of weeks or even months are recorded, then clinical signs are identified and laboratory tests are required to confirm the clinical diagnosis. Finally a therapeutic strategy is implemented and the clinical prognosis is proposed according to the severity of symptoms and signs as well as the response to treatment. When we treat acute neurological patients with a severe impairment in the conscious state and endocrine alterations, the clinical history, symptoms and signs are not easily evaluated, although severe hemodynamic and metabolic alterations usually occur in a time frame of hours or few days. Laboratory tests are required to confirm the clinical diagnosis, a therapeutic strategies must be readily implemented and the severity of clinical status will have a prognostic value. When we treat potential organ donors with neuroendocrine alterations, clinical signs develop within minutes or few hours with a dramatic impairment in systemic hemodynamics and metabolism. Therefore, clinical diagnosis, laboratory test confirmation and implementation of the specific therapy are required in a time frame of minutes or few hours. Moreover, no prognostic evaluation is required, while hemodynamic stability and prompt correction of metabolic alterations are mandatory in order to guarantee an optimal organ perfusion and metabolic homeostasis for organ donation.

2. Neuroendocrine alterations in severe acute neurological patients

Several studies have demonstrated that brain injury such as traumatic brain injury (TBI) or subarachnoid hemorrhage (SAH) is a frequent cause of hypopituitarism, with an incidence that is much greater than previously reported.

First of all, we have to introduce a distinction between acute and prolonged critical illness in term of metabolic and neuroendocrine paradigms. The initial endocrine response consists primarily of an activated release of anterior pituitary hormone and peripheral inactivation of anabolic pathways. In the chronic phase there is a uniformly impaired pulsatile secretion of anterior pituitary hormones at least in part due to hypothalamic origin (Van den Berghe et al 1998), which is correlated with reduced activity of target tissue. However, this specific pituitary-dependent axis can be reactivated with preserved peripheral responsiveness. Another mandatory issue to underline is that there is sufficient data from the literature concerning long term effects at hypothalamic or pituitary level of TBI or SAH, while data regarding the short term effects of severe acute neurological injuries in terms of neuroendocrine activity are very scanty.

The first report of TBI-induced hypopituitarism was published in 1918 (Cyran 1918). Then several retrospective studies and case reports identified additional conditions of hypopituitarism following head injury (Altman and Pruzanski 1961; Edwards and Clark 1986; Kusanagi et al 2000). In particular, more than ten years ago Benvenga et al. confirmed the relationship between TBI and hypopituitarism (Benvenga et al 2000). These authors reported that in 70% of cases hypopituitarism was diagnosed within 1 year of injury. Indeed there are reports of patients with total, multiple or isolated hypopituitarism whose clinical history revealed the occurrence of TBI many years before the diagnosis.

Subarachnoid hemorrhage produces a pattern of deficits similar to that of TBI. Patients with aneurysmal SAH frequently present persistent physical, psychosocial, cognitive and emotional deficits similar to those of patients with untreated partial or complete hypopituitarism, even if clinicians do not normally relate these symptoms to pituitary insufficiency.

In the field of intensive care medicine, several studies show that critically ill patients with TBI frequently exhibited an abnormal pituitary hormonal response in the immediate post-injury period (Agha et al 2004b; Aimaretti et al 2004; Bondanelli et al 2005; Dimopoulou et al 2004). On the other hand, the critical illness itself has profound effects on the pituitary function (Van den Berghe and de Zegher 1996) that is characterized by protein hypercatabolism, preservations of fat depots and immune dysfunction. Since the anterior pituitary gland is the first regulator of human metabolism and immune function, the presence of an extensive interaction between these three players is not surprising. Interestingly, the critical illness may be associated with reduced levels of activity in the different pituitary axes, except for the corticotropic axis (Van den Berghe and de Zegher 1996). Furthermore, in the critical care scenario some therapeutic strategies such as the infusion of dopamine has been found to be associated with an impaired pituitary function, which has raised the hypothesis that dopamine may play a role in the pathogenesis of the pituitary dysfunction present in critical illness (Van den Berghe and de Zegher 1996).

2.1 Epidemiology

TBI-related hypopituitarism remains largely under-diagnosed, mostly due to the lack of awareness among physicians who take care of these patients. Indeed, considering the epidemiology of TBI (91–332/100,000 inhabitants all over the world) and the high risk to develop the most severe form of multiple or total hypopituitarism (at least 10–15% of patients), it has become more evident that many patients misdiagnosed hypopituitarism induced by brain injury may experience a poor quality of life and a low life expectancy.

The estimated incidence rates for SAH are between 10 to 25 per 100,000 per year. Morbidity and mortality in the acute phase are due to the pathophysiological changes related to the initial bleeding, such as the abrupt increase in intracranial pressure, impairment of cerebral perfusion and focal or global cerebral ischemia. In studies which included both SAH and TBI patients, an incidence different degrees of hypopituitarism was reported to be 27% and 47% respectively (Schneider et al 2007).

2.2 Pathophysiology

Pituitary function is at particular risk because of the vulnerable anatomic location of the gland within the sella turcica as well as its delicate infundibular hypothalamic structure and its fragile vascular supply (Kelly et al 2000). In several neuropathological studies haemorrhage, necrosis, and fibrosis of the pituitary gland and hypothalamus have been recorded after TBI or SAH. Stalk lesions can produce anterior-lobe infarction by damaging the portal blood supply (Daniel et al 1959; Kornblum and Fisher 1969). Hypothalamic lesions consisting of areas of ischemic necrosis, macro and micro-haemorrhages were noted in two-thirds of the patients who died shortly after SAH (Bondanelli et al 2006).

Growth hormonal deficiency is most often seen in patients with TBI since the growth hormone-secreting somatotrope cells are located in the wings of the pituitary gland and the vascular supply and oxygen they receive come out of the hypothalamic-pituitary portal vessels. Consequently, damage in this area impairs the blood and oxygen supply, resulting

in cell death. In contrast, the cells that secrete adrenocorticotropin hormone and thyroid-stimulating hormone are located ventrally in the more protected, medial portion of the pituitary, and they receive blood from the portal vessels and the anterior pituitary artery branch, which provides nutrients and oxygen to this area and to all the cells located in the sub-capsular part (Kelly et al 2000). However, data from literature show that the frequency of growth hormone deficiency and low cortisol levels are 15% and 46% respectively in TBI while in SAH the risk of hypopituitarism may be even higher (Agha et al 2004b; Aimaretti et al 2004; Casanueva et al 2004; Kreitschmann-Andermahr et al 2004).

Disorders of salt and water balance, in particular diabetes insipidus (DI) and the syndrome of inappropriate antidiuretic hormone secretion, are common complications in the acute phase of TBI (Kaufman et al 1993). Available information on the frequency of post-traumatic DI are mainly derived from retrospective data (Boughey et al 2004; Wong et al 1998), while few prospective studies have accurately defined the natural history of DI following TBI. In the first prospective study Agha and colleagues (Agha et al 2005) investigated the sequential posterior pituitary function after TBI and reported a frequency of early post-traumatic DI equal to 26%. Further studies reported a negative correlation between Glasgow Coma Scale and plasmatic levels of both osmolality and sodium, and a positive correlation between Glasgow Coma Scale and peak urine osmolality in the acute phase of TBI, suggesting that acute DI is associated with the severity of injury. Post-traumatic DI may result from inflammatory oedema around the hypothalamus or posterior pituitary, with recovery as the swelling resolves. It can also result from direct damage to the paraventricular and supraoptic hypothalamic neurones, the pituitary stalk or axon terminals in the posterior pituitary. These abnormalities may be either transient, if the supraoptic and paraventricular neurones form new vascular connections, or become permanent if gliosis occurs (Yuan and Wade 1991).

Finally, pituitary function is impaired in 50% of patients with primary brain tumors, as a consequence of surgery and radiotherapy. Hypopituitarism in patients with primary brain tumors often includes severe growth hormone deficiency. However, the efficacy of treatment of hypopituitarism in patients with primary brain tumours has never been demonstrated (Schneider et al 2006).

2.3 Clinical signs and symptoms of hypopituitarism

In acute neurological patients with a preserved conscious level hypopituitarism is associated with a number of non-specific signs and symptoms. Fatigue is a major symptom (Kreutzer et al 2001; LaChapelle and Finlayson 1998) although this symptom may also be related to TBI. Other signs, symptoms and laboratory abnormalities include decreased lean body mass with increased body fat and dyslipidaemia, reduced exercise tolerance and muscle strength (Carroll et al 1998), DI (Edwards and Clark 1986), decreased thyroid-stimulating hormone and free tyroxine levels and adrenal insufficiency (Benvenega et al 2000; Carroll et al 1998; Lieberman et al 2001), amenorrhea/infertility, erectile dysfunction and hyperprolactinaemia (Benvenega et al 2000; Cytowic et al 1986), diminished cardiovascular function, impaired cognitive function, memory loss, decreased concentration, mood disturbances, increased anxiety and depression, irritability, insomnia (Deijen et al 1996; Howlett et al 1989; Leon-Carrion et al 2001) and a feeling of social isolation (Carroll et al 1998). A deficiency of growth hormone produces metabolic effects in different organs with consequences in both physical and emotional areas. These signs and symptoms of hypopituitarism are the same in hypopituitary patients after TBI. These symptoms and signs of hypopituitarism are also

present in TBI in the sub-acute phase. The overlap of clinical manifestations due to the sequelae of TBI or to the presence of hypopituitarism induced by trauma may result in a sub-optimal rehabilitation of TBI patients with hypopituitarism.

Traditionally, the onset of DI was considered a useful indicator of hypopituitarism because it is routinely attributed to pituitary insult. However, reports of the incidence of DI following brain injury vary widely, with Benvenga et al. (Benvenga et al 2000) reporting as many as 30% of cases compared to Aimaretti et al. (Aimaretti et al 2004) who reported only 5.5%. In a recent retrospective study, the incidence of severe hypernatremic cases of DI was 2.9% but the incidence of less severe forms seems to be much higher. Agha et al, in a retrospective study reported an incidence of 21.6% in the immediate period following TBI, which was related to the severity of the traumatic insult but not related to the development of anterior pituitary abnormalities (Agha et al 2004a). The discrepancy between anterior and posterior pituitary altered function has been recently confirmed in a prospective study which reported a high incidence of DI (26%) (Agha et al 2004a).

Likewise, reports on the incidence of hyperprolactinaemia, another marker of hypothalamus-pituitary derangement, following brain injury vary even more dramatically (Aimaretti et al 2004; Benvenga et al 2000; Lieberman et al 2001). While these findings provide evidence that TBI is associated with derangement of the hypothalamus-pituitary unit, it underscores the fact that a full endocrinologic assessment is necessary to determine the extent of the hormonal alterations after TBI and the need for a global endocrine evaluation. Aimaretti and co-workers (Aimaretti et al 2005) in a multicentered study prospectively investigated the risk to develop hypopituitarism in brain injured patients. Pituitary function was evaluated in 100 patients with TBI and in 40 patients with SAH after 3 and 12 months to evaluate the incidence of hypopituitarism and the effect of pituitary deficits on outcome one year after the brain injury. The 3 month study showed some degree of hypopituitarism in 35% of TBI patients. Total, multiple and isolated deficits were present in 4, 6 and 25% respectively. DI was present in 4%, secondary adrenal, thyroid and gonadal deficit was present in 8, 5 and 17%, respectively. Severe growth hormone deficiency was the most frequent pituitary defect (25%). In SAH patients some degree of hypopituitarism was reported in 37.5%. Multiple and isolated deficits were present in 10 and 27.5% respectively. DI was present in 7.5%, secondary adrenal, thyroid and gonadal deficits was present in 2.5, 7.5 and 12.5%, respectively. Severe growth hormone deficiency was the most frequent defect (25%). The 12 months retesting demonstrated that some degree of hypopituitarism was still present in 22.7% of the TBI patients. Total hypopituitarism was always confirmed at 12 months while multiple and isolated hypopituitarism was confirmed in 25%, DI was present in 2.8%. In SAH after 12 months retesting hypopituitarism was present in 37.5% with multiple or isolated deficits in 6.2 and 31.3% respectively. No multiple deficits were confirmed at 12 months but in 2 patients new deficits were diagnosed. It is important to note that 30.7% of SAH with isolated deficits at 3 months displayed normal pituitary function at 12 months and the most common deficit was severe growth hormone deficiency in both TBI and SAH.

These data indicate that pituitary function may improve over time and that hypopituitarism is transient in most cases and would reflect effective repair of the hypothalamic-pituitary damage induced by brain injuries.

Considering the topic of this chapter it is important to note that the acute phase is characterized by a high incidence of hypopituitarism as sign of the acute brain damage in the hypothalamic pituitary area.

2.4 Diagnosis

Diagnosis of hypopituitarism due to brain injury does not differ from that of hypopituitarism due to other causes. Test of pituitary hormones function and their target glands should be always performed.

Diabetes insipidus is demonstrated by the presence of massive dilute urine volume (>3 L/24 h) with low urine osmolality (<300 mmol/kg) (Aimaretti et al 1998a; Aimaretti et al 1998b; Lamberts et al 1998; Lissett CA 1996).

Secondary adrenal insufficiency is demonstrated by early-morning (at 9:00 am) cortisol concentrations less than 30 $\mu\text{g/L}$ (or < 100 pmol/L) and morning ACTH below upper reference range, associated with another pituitary deficit (Aimaretti et al 1998a; Aimaretti et al 1998b; Lamberts et al 1998; Lissett CA 1996).

Secondary hypothyroidism is demonstrated by low free thyroxine (<8 ng/l) concentrations with normal or low thyroid-stimulating hormone levels (Aimaretti et al 1998a; Aimaretti et al 1998b; Lamberts et al 1998; Lissett CA 1996).

Secondary hypogonadism is demonstrated by: (1) in premenopausal women low estradiol levels (<20 pg/ml) with normal or low follicle-stimulating hormone and luteinizing hormone levels; (2) in men by low testosterone levels (<3 $\mu\text{g/L}$) with low or normal follicle-stimulating hormone and luteinizing hormone levels (Aimaretti et al 1998a; Aimaretti et al 1998b; Lamberts et al 1998; Lissett CA 1996).

GH deficiency is demonstrated by peak growth hormone response to growth hormone releasing hormone + arginine below 16.5 $\mu\text{g/L}$ (3rd centile limit of normal growth hormone response). A peak growth hormone response below 9.0 $\mu\text{g/L}$ (1st centile limit) indicates severe growth hormone deficiency (Aimaretti et al 1998a; Ghigo et al 2001; Lamberts et al 1998). Insulin-like growth factor-I levels were considered with respect to the 25th centile age-related normal limits (Aimaretti et al 1998a; Ghigo et al 2001; Hartman et al 2002; Lamberts et al 1998). From an endocrinological point of view, TBI patients in coma or in vegetative state should not be evaluated. The reason is that no data are now available showing that an early diagnosis and appropriate replacement for the different forms of hypopituitarism can be of any benefit for patients in such extreme conditions.

Therefore endocrinologists should perform a neuroendocrine assessment in: 1) patients who develop an acute form of hypopituitarism in the early phases after TBI (i.e. DI and electrolyte abnormalities in particular) 2) patients with abnormalities in the brain imaging techniques like hemorrhagic lesions (on CT or MRI scan). Although a neuroendocrine assessment is not a priority in severe neurological patients, an optimal hemodynamic management of severe brain injured patients is crucial to guarantee adequate perfusion to the brain during the repair process. Therefore, a prompt diagnosis and treatment of anti-diuretic hormone, cortisol and insulin depletion in severe brain injured patients may play a relevant role in stabilizing hemodynamic and electrolyte abnormalities. When these patients evolve to brain death hemodynamic stability remains a crucial part of the clinical management to optimize peripheral organ perfusion.

2.5 Therapeutic strategy

2.5.1 Who

The severity of TBI or SAH has been suggested as a risk factor for the development of hypopituitarism. Although some discrepancies are present in the literature, the degree of severity of the brain lesion is considered a limiting factor for treatment of endocrine abnormalities. Kelly et al. (Kelly et al 2000) identified Glasgow coma scale scores < 10 ,

diffuse brain swelling on initial CT and hypotensive or hypoxic insults as significant predictors for the development of hypopituitarism. Bondanelli et al. (Bondanelli et al 2004) confirmed that hypopituitarism was more prevalent in TBI patients with low Glasgow coma scale although the CT scan abnormalities based on the Marshall classification did not predict the development of pituitary abnormalities. Indeed, Lieberman et al (Lieberman et al 2001) and Aimaretti et al. (Aimaretti et al 2004; Aimaretti et al 2005) did not confirm any correlation between Glasgow coma scale and pituitary dysfunction. Because of these discrepancies regarding the risk factors for pituitary abnormalities after TBI, it is difficult to identify which patients should be screened for these alterations. However it is well known that: 1) hemodynamic instability (hypotension and low cerebral perfusion) and electrolyte abnormalities may affect neurological outcome after TBI; and 2) pituitary abnormalities may have a relevant impact on hemodynamic and metabolic homeostasis. Therefore, in order to guarantee the optimal clinical management of severe brain injured patients it is wise to plan a basic screening test for the presence of endocrine abnormalities after TBI.

2.5.2 When

It is well known that hormonal secretion from the pituitary is altered immediately following TBI (Chiolero and Berger 1994). However, because of the use of drugs, metabolic abnormalities, and functional alterations, a condition of hypopituitarism is difficult to assess (Dimopoulou et al 2004). Agha et al. (Agha et al 2004a) examined the prevalence of anterior and posterior pituitary dysfunction in the acute (7–21 days) phase following TBI. The authors identified adrenocorticotropin hormone deficiency and posterior pituitary dysfunction as the main abnormalities which required immediate replacement therapy. In the recovery phase, Aimaretti et al. (Aimaretti et al 2004; Aimaretti et al 2005) established that early diagnosis of pan-hypopituitarism is always confirmed at one year and thus treatment is required at the time of diagnosis. In the chronic phase, Bondanelli et al. (Bondanelli et al 2004) observed a high prevalence of growth hormonal deficiency and hypogonadotrophic hypogonadism but not corticotrophic and posterior dysfunction.

2.5.3 How

To date there are no conclusive data on this topic in severe brain injured patients. In cases with a clear indication of hormonal deficiency, the treatment should be conducted by an endocrinologist as defined by the international guidelines. DI, adrenal insufficiency, thyroid dysfunction and hypogonadism should be treated along with appropriate follow up.

Diabetes insipidus The general goals of treatment are the correction of pre-existing water deficits and reduction in ongoing excessive urinary water losses; however, the specific therapy varies with the clinical situation. Ambulatory patients with DI and normal thirst have little body water deficit and may be helped from relief of the polyuria and polydipsia that disrupt normal activities. In contrast, comatose patients with or without DI are unable to drink in response to thirst, and in these patients progressive hypertonicity may be a life-threatening situation. A variety of anti-diuretic agents have been used to treat central DI, but desmopressina is the treatment of choice for this disorder. Desmopressina is an anti-diuretic hormone analogue, which particularly useful because it has a much longer half-life than anti-diuretic hormone and is devoid of the pressor activity of anti-diuretic hormone at vascular V1 receptors. Desmopressina is generally administered orally (60–120 µg every 8–

24 hours), but can be given parenterally in acute situations (1–2 mg intravenously, intramuscularly or subcutaneously). For both oral and parenteral preparations, the increase of the administered dose generally has the effect to prolong the duration of anti-diuresis rather than increasing its magnitude; consequently, altering the dose can be useful to reduce the required frequency of administration. Synthetic anti-diuretic hormone (Pitressin) can also be used to treat central DI, but its use is limited by a much shorter half-life, requiring frequent doses or a continuous infusion, and carries a side effect of increased blood pressure due to vasoconstriction.

Secondary adrenal insufficiency Conventional treatment is represented by 10–25 mg of hydrocortisone per day (2–3 doses per day) or 25–37.5 mg of cortisone acetate. It is essential to use the lowest possible dose. In stress situations (psycho-emotional, surgery, transient diseases, infections etc.) the dose should be increased to 25–50 hydrocortisone per day or 50–75 mg of cortisone acetate or if reduction of intestinal absorption is expected parenteral hydrocortisone 100–50 mg should be administered.

Secondary hypothyroidism L-thyroxine is considered the drug of choice. The usual replacement dose is age-dependent and varies from 1.3 µg/kg (< 60 yrs) to 1.1 µg/kg (> 60 yrs). The most common route of administration is oral, even through nasogastric tube, but in acute situations when this is not possible, parenteral administration can be used (50–300 µg/daily iv). Because thyroid hormone replacement increases the rate of metabolism of glucocorticoids, which can lead to an adrenal crisis, replacement therapy should begin after hydrocortisone substitution has been initiated.

Hypogonadism In male patients testosterone substitution (testosterone gel 25–50 mg/day or testosterone undecanoate 1000 mg every 3 months) returned bone and muscle mass, sexual function and haematocrit to normal levels.

In pre-menopausal female patients sex hormone substitution (20–35 µg ethinyl oestradiol or oestradiol valerate 2–4 mg/day plus progesterone unless hysterectomised) can return libido, well being and bone mass to normal levels. In post menopausal women sex hormone therapy is not indicated because a significant increased risk of cardiovascular and neoplastic diseases.

3. Neuroendocrine alterations in brain dead patients

Brain death results from damage to the brain stem with a complete irreversible loss of its function. This devastating insult to the brain stem is immediately followed by a “sympathetic storm”. In addition, brain death causes significant endocrine alterations involving the hypothalamic-pituitary axis and triggers an inflammatory reaction. The catecholamine storm, the endocrine disturbances and the systemic inflammatory reaction represent the first insult with consequential organ insufficiency and metabolic derangement (Avlonitis et al 2003). Sub-optimal management of potential organ donors leading to a further impairment of the cardiovascular and respiratory function represents an additional damage to potentially transplantable organs (Fisher et al 1999; Venkateswaran et al 2009a). Any intervention in each of these three phases in order to prevent or treat these insults may have an impact on the functional outcome of transplanted organs (figure 1). In this prospective a prompt recognition and treatment of neuroendocrine alterations represent one of the possible therapeutic strategies able to optimise organ availability for transplantation.

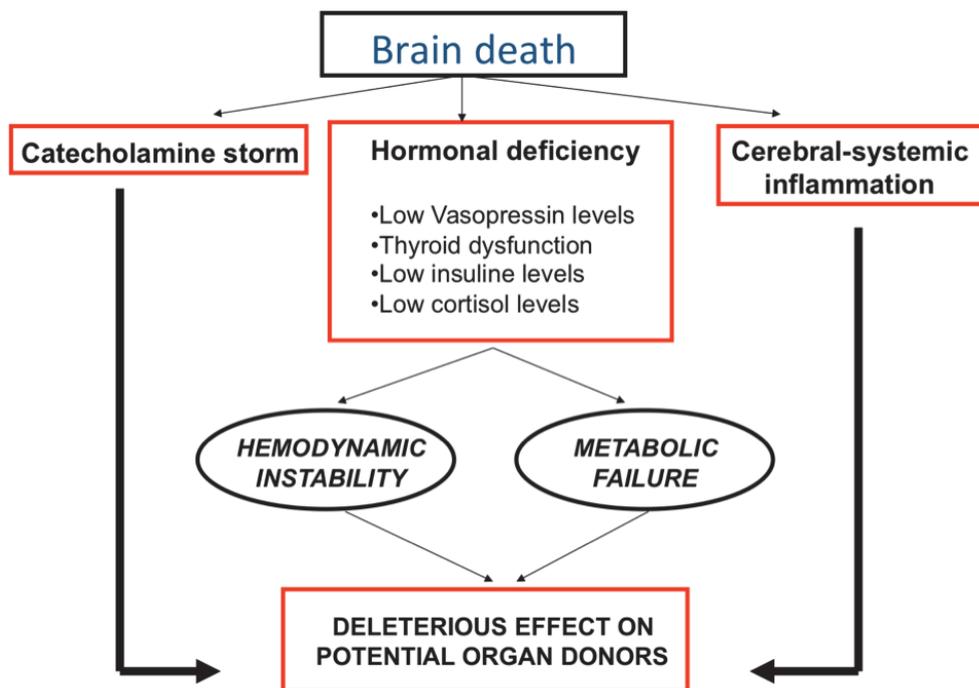


Fig. 1. Pathophysiology of hormonal deficiency in brain death and its implication on organ donors maintainance

3.1 Pathophysiology

Brain death has an important impact on endocrine function leading to profound metabolic abnormalities and hemodynamic instability with deleterious effects on the potential organ donors (Chamorro et al 2009; Smith 2004). The most important endocrine disturbances are a reduction in anti-diuretic hormone secretion, thyroid dysfunction, reduction in adenocorticotrophic hormone and insulin levels (Ullah et al 2006). In experimental animal models of brain death, the pituitary gland hormones vasopressin and adenocorticotrophic hormone decreased significantly after 15 and 45 minutes of brain death respectively (Bittner et al 1995). Circulating triiodothyronine, thyroxine, glucagons and insulin concentrations were significantly reduced within a few hours after brain death (Bittner et al 1995; Chen et al 1996). The significant reduction in circulating concentrations of stress hormones was associated with a severe hemodynamic instability (Chen et al 1996; Hing et al 2007; Novitzky et al 2006). In a prospective randomized experimental study of brain death, Hing et al. showed that hormonal replacement therapy including triiodothyronine, methylprednisolone, vasopressin and insulin reduced norepinephrine requirements and improved hemodynamics and cardiac function (Hing et al 2007).

An interesting study by Ishikawa et al. (Ishikawa et al 2009) compared, in autoptic cases, morphological results as well as endocrine function in brain death (within 24 hours post mortem), acute death (< 3 h) and delayed death (survival time 4-51 days). Histology and electronic microscopy of pituitary gland were performed and blood as well as cerebrospinal

fluid levels of adrenocorticotropin hormone, growth hormone and thyroid-stimulating hormone were measured. Morphological and microscopic studies revealed partial necrosis of central anterior lobe but preservation of its periphery, autolysis in the hypothalamus, swelling of mitochondria and dilation of smooth endoplasmic reticulum and golgi apparatus suggesting that pituitary is preserved without blood supply after brain death but the integrity of hypothalamus pituitary axis is lost. Regarding pituitary secretion, no peculiar findings were demonstrated after brain death different from cases of delayed death. In fact, serum adrenocorticotropin hormone levels were similar to the clinical reference values in both brain death, acute or delayed death cases, while serum growth hormone, cerebrospinal fluid growth hormone and adrenocorticotropin hormone levels were lower in brain and delayed death than in acute cases and serum thyroid-stimulating hormone levels were comparable in both brain death and delayed death cases (Ishikawa et al 2009).

In observational clinical studies, an early depletion of arginine vasopressin and development of DI is present in almost 45-80% of brain death organ donors (Gramm et al 1992; Howlett et al 1989; Salim et al 2006). Arginine vasopressin is one of the most important endogenously released stress hormones. It is also named anti-diuretic hormone based on its effects on the distal tubule of the kidney. It is synthesized in the hypothalamus and released into the bloodstream from posterior pituitary. Vasopressin has several important physiological functions including water retention by the V2 receptors on the kidney and constriction by V1 receptors on vascular smooth muscle on the systemic and pulmonary circulation. In addition to its anti-diuretic action, vasopressin is important in maintaining arterial blood pressure during episodes of hypotension (Gordon et al 2010). In brain dead patients there is a deficiency of vasopressin levels in systemic circulation due to supraventricular and paraventricular hypothalamic nuclei ischaemia (Agha et al 2007) or pituitary stalk damage that disrupts the hypothalamic pituitary axis associated to a defect in the baroreflex-mediated secretion of vasopressin levels in systemic circulation (Chen et al 1999; Gordon et al 2010). Therefore, the depletion of vasopressin may contribute to the hemodynamic instability associated with diabetes insipidus. In brain dead patients, low dose arginine vasopressin infusion, in addition to treating diabetes insipidus, results in significant reduction of inotropic support and has been associated with good kidney, liver and heart graft function (Pennefather et al 1995). Comparing the treatment of brain-dead patients with epinephrine alone versus epinephrine plus vasopressin the authors obtained a prolonged hemodynamic stabilization in brain-dead donors treated with vasopressin (Yoshioka et al 1986). In brain dead patients without clinical signs of DI, Chen et al obtained a significant reduction in catecholamine doses (dopamine and/or norepinephrine) using arginine vasopressin at low dosage (0.04 to 1.0 U/min) with a significant increase in mean arterial pressure and better organ perfusion (Chen et al 1999). A complete weaning from catecholamine has been demonstrated in up to 40% of the donors with the use of vasopressin. Indeed a more extensive use of vasopressin as an alternative to norepinephrine has been suggested in a prospective randomised double blind trial (Venkateswaran et al 2009b).

Thyroid dysfunction is another event of brain death. This decrease of thyroid function is not caused by a primary failure of the thyroid or pituitary glands. It has been defined "sick euthyroid syndrome" and has also been described in cardiopulmonary by-pass. It is postulated that proinflammatory cytokines may play a role in inhibiting the conversion of thyroxine to the active form of thyroid hormone, and instead, convert it to the non-active

form, reverse- thyroid hormone (Ullah et al 2006). In an animal model of brain death, Novitzky et al. showed that levels of thyroid hormones were severely depleted (Novitzky et al 1988). In interventional clinical studies the following results have been reported: 1) administration of thyroid hormone to donor and recipient improved cardiac allograft function; 2) therapy with thyroid hormone reversed donor myocardial dysfunction, promoted hemodynamic stability and reduced inotropic support (Novitzky et al 1990; Salim et al 2001). However a randomized clinical trial in a small number of potential organ donors using low dose of thyroid hormone was unable to confirm the positive effect of hormonal therapy on cardiac function (Goarin et al 1996). Conversely, in pediatric patients following cardiac surgery triiodothyronine administration improved cardiac function (Bettendorf et al 2000). Therefore, there is still a considerable debate whether the sick euthyroid syndrome requires treatment.

Insulin levels fall after brain stem death, leading to a decrease in intracellular glucose concentration, the development of an cellular energy deficit, and a shift toward anaerobic metabolism and acidosis (Ullah et al 2006).

In brain dead patients there is also a significant decreases in cortisol levels that, in association with decreases in thyroid hormone, may contribute to the cardiovascular instability. The decrease in plasma cortisol may be associated with a decrease in the release of its stimulating factors adrenocorticotrophic hormone from the anterior lobe of the pituitary gland (Gramm et al 1992). High dose steroid administration has a beneficial role in attenuating the effects of pro-inflammatory cytokines released after brain death. Steroids significantly improved oxygenation and simultaneously increased lung recovery (Follette et al 1998). A beneficial effect is described also in cases of liver transplantation involving donor treatment with methylprednisolone (Kotsch et al 2008).

3.2 Therapy of neuroendocrine dysfunction in potential organ donors

Several studies have suggested that the use of Hormonal Replacement Therapy (HRT) in donor management may serve a crucial role in helping to maintain metabolic stability and prevent hemodynamic instability (Rosendale et al 2003b). Rosendale et al. showed an increase of the mean number of organs from HRT donors (22.5%) when compared to non-hormonal resuscitation donors, which led to a significant increase in organs transplanted per donor (Rosendale et al 2003a; Rosendale et al 2003b). HRT allowed substantial improvement in mean arterial pressure and consequently in organ perfusion, and left ventricular stroke work index combined with reduction in central venous and wedge pressure and a reduction of inotropic support (Wheeldon et al 1995).

The selection of donors who are predicted to benefit from HRT was outlined at the Cristal City Consensus Conference Report (Rosengard et al 2002). After conventional management to adjust volume status, anemia and metabolic abnormalities, the guidelines recommended to perform an echocardiogram to rule out the structural abnormalities and document the ejection fraction. If the ejection fraction is less than 45%, a pulmonary artery catheter should be placed and HRT should be started. The four hormones commonly used are: methylprednisolone, triiodothyronine, arginine vasopressin titrated to obtain systemic vascular resistances of 800-1200 dynes/sec-cm) and insulin titrated to maintain blood sugar at 120 to 180 mg/dL (Rosengard et al 2002). However the use of HRT is not supported by a strong level of evidence. Clinical studies of HRT have been observational, retrospective, used non-matched controls and tested single hormonal replacement or a combination of

HRT but not the complete hormonal replacement advocated in the United Network for Organ Sharing guidelines (<http://www.ccdt.ca/english/home.html> ; Rosendale et al 2003a; Rosendale et al 2003b; Rostron et al 2008; Venkateswaran et al 2009a; Venkateswaran et al 2009b). In addition, the contribution of other changes in donor management such as invasive hemodynamic monitoring make it difficult to judge the relative contribution of combined hormonal resuscitation to the improvements in donor organs outcome reported in these studies. These observations have provided the foundation for prospective clinical trials to examine the efficacy and optimal timing of HRT. However, until these results are not available it remains prudent to reserve HRT for unstable donors requiring high doses of dopamine or with an ejection fraction of less than 45% (Rosengard et al 2002; Wood et al 2004; Zaroff et al 2002).

The diagnosis of DI in brain death patients does not differ from other clinical situations. DI must be differentiated from the polyuria induced by mannitol, hyperglycemia or diuretic agents. Assessment of diuresis (> 40 ml/kg body weight/day or 3000 cc/day), plasma (> 295 mOsm/kg) and urine (< 200 Osm/kg) osmolality and sodium levels (> 146 mEq/l) are key elements for its diagnosis (Mascia et al 2009). Plasma anti-diuretic hormone levels have little importance due to the poor reliability of the assay, the extreme high variability of anti-diuretic hormone plasma levels and the relatively long turn-around time (4-10 days) for results. The clinical goals are primarily based on the stabilization of the volume status by hypotonic fluid replacement with 5% dextrose or nasogastric water, serum sodium and osmolality and then on an adequate urine output. When urine volume loss are large, anti-diuretic hormone replacement therapy is required (Mascia et al 2009). A vasopressin infusion acts on the V1 and V2 receptors and induces vasoconstriction and anti-diuretic effects (Mutlu and Factor 2004). Low dose arginine vasopressin decreases serum osmolality and sodium levels, maintains blood pressure and reduces the need for vasoactive medications in potential organ donors, with no deleterious short-term or long-term effects on the function of the donated kidney to the recipient (Guesde et al 1998; Rosendale et al 2003a; Wood et al 2004). Intermittent treatment with synthetic analogue anti-diuretic hormone desmopressin can also be used. Synthetic analogue anti-diuretic hormone desmopressin was synthesized as a selective antagonist of vasopressin V2 receptors. In brain death patients synthetic analogue anti-diuretic hormone desmopressin is administered parenterally (1-2 mg intravenously, intramuscularly or subcutaneously); increasing the administered dose generally has the effect of prolonging the duration of anti-diuresis rather than increasing its magnitude (Wood et al 2004).

4. Conclusion

In conclusion, hypothalamic-pituitary-adrenal insufficiency occurs in 30-50% of patients after traumatic and non-traumatic brain injury and has a high prevalence in brain dead patients. These endocrine alterations lead to metabolic abnormalities and hemodynamic instability with deleterious effects on potential organ donors. To optimize clinical management of potential organ donors and therefore guarantee the availability of transplantable organs, recent guidelines advocate the use of standardized hormonal therapy (l-thyroxine, methylprednisolone, vasopressin and insulin). This replacement therapy is suggested to stabilize brain death patients who present hemodynamic instability unresponsive to standard cardiovascular treatment. Despite available experimental data and increased interest for HRT in the management of potential organ donors, there are no

prospective randomized controlled clinical studies testing combined HRT and examining its effects on donor cardiac function, hemodynamics and vasopressor requirements. Therefore in our opinion the HRT with particular attention to the antidiuretic hormone represents a valid component of the treatment choices to stabilize hemodynamics in potential organ donors. In the sub-group of brain death patients with a clear diagnosis of DI, the replacement therapy with low dose of arginine vasopressin is the treatment of choice.

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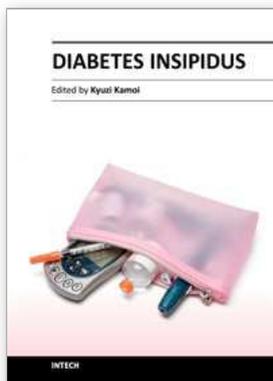
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The first chapter of the book reports on the management of Langerhans cell histiocytosis (LCH)-induced central diabetes insipidus and its associated endocrinological/neurological sequelae in the national survey. The next chapter addresses DI and head injuries. Next, the management of neuroendocrine instability during maintenance of potential organ donors is described. Organ transplants have gradually increased worldwide. To have maintenance of appropriate potential organs, AVP is needed. Furthermore, nephrogenic DI-the potential therapeutic drugs and analysis of membrane protein stability is the topic of the next two chapters, followed by new insights into the diagnosis and management of pregnancy-related DI. The seventh chapter reports on the problems with differential diagnosis in a case of central DI in a female patient with bipolar disorder. The lithium treatment usually resulted in nephrogenic DI. Finally, over the last years, the development of MRI imaging on the pituitary gland with the stalk and hypothalamus has advanced. The final chapter interprets imaging techniques in DI in detail.

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