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Endocrinal Abnormalities Following Head Injury

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Abstract: Severe head injury still continues to be a great challenge and outcome is still depressing. Hence, many other aspects get neglected in severe head injury. The marked improvement in life support measures for patients following traumatic brain injury has kept more patients alive after injury than was true earlier. Neurosurgeons and the family members of the patients of head injury are often happy by the mere fact that the person survives severe head injury. The assessment of pituitary function is an infrequent consideration in the acute or long-term management of patients sustaining traumatic brain injury. Surprisingly, hormonal abnormality is also reported following minor head injury as well. Recently there is a lot of interest in evaluation of endocrine problems in survivors of severe head injury. In fact quality of life can be improved by proper hormonal replacement.

Keywords: endocrinopathy, head injury, hormone replacement.

Introduction

Despite of numerous case reports of patients with posttraumatic endocrinal disturbances[1-5], prospective studies or even large retrospective studies dealing with trauma induced pituitary dysfunction are not available. Severe cranio-cerebral trauma very often results in persistent deficits and invalidity. The chronic neurobehavioral problems and quality of life complaints plague many patients of severe head injury, which are often strikingly similar to those of patients who have adult onset hormone abnormalities[6]. Cyran[7] first made the association between head injury and development of hypopituitarism. Since then till the last decade of the last century, sporadic case reports of endocrine abnormality following head injury have appeared[7]. Pituitary function studies are infrequently considered in acute stage or even in long term management of patients with traumatic brain injury, even though it is almost a well-known fact that severe head injury is of considerable risk to pituitary function. Earlier autopsy studies had demonstrated anterior pituitary necrosis in as high as one-third fatal head injured patients[8-10]. However, inspite of development of neuroimaging and well established laboratory for neuroendocrinal assessment and histopathological evaluation, the incidence, clinical significance and degree of risk due to endocrinal deficits, in head injured patients are not well known.

Pathogenesis of Endocrinal abnormalities

The exact incidence of pituitary dysfunction following head injury is not known. The endocrinal problem could result either due to pituitary or from hypothalamic damage following the head injury. No doubt, pituitary is highly vulnerable due to its location in sella turcica, its vulnerable blood supply and delicate infundibular hypothalamic structures. In contrast to the low incidence of clinical dysfunction, autopsy reports indicate a higher incidence of pituitary lesions (30-33%) in fatal cases of head injury[8,9]. Daniel et al[2] reported hypopituitarism in 40% of patients with moderate and severe head injury[9]. Kornblum and Fischer reported demonstrated pathological lesions secondary to trauma in 62% of pituitary glands [10]. Capsular hemorrhage was the most common finding on histopathology being detected in upto 50-59% cases[10-11]. Anterior lobe infarcts have been reported to occur in about 13-22% of cases[10-11]. No report of posterior pituitary infarct is available, as its blood supply is not affected in head injury patients unlike anterior lobar supply. The confinement of the pituitary gland in the sella turcica by the diaphragma sellae makes the stalk as well as the infundibulum, vulnerable to the shearing strain. Subsequent swelling of the gland is limited by the diaphragma sellae, which has only a small circular opening serving as a passage for the pituitary stalk. As it swells, the fragile long hypophyseal vessels, resulting in anterior pituitary infarction[10]. Hormone abnormalities may exist even in the absence of pituitary lesions, suggesting the active involvement of other areas of the brain in regulating the hormonal milieu of the body. It is generally believed that pituitary dysfunction following head injury is by and large due to diffuse swelling, hypotension or hypoxic insult[12-13]. However, primary pituitary damage is well described[7-9]. Prior to CT scans most of the evidences were autopsy based. In autopsy studies pituitary abnormality is recorded in almost 75%[10]. The significant primary abnormalities includes capsular hemorrhage in over 50%, followed by posterior lobe and stalk hemorrhage in 30% and 20% cases approximately.

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Next to the hemorrhages, necrosis is another important finding. The common site of necrosis is anterior lobe

Table1: Pathology in pituitary gland following head injury

Primary	Hemorrhage	Capsular	50-55%
		Posterior Lobe	30
		Stalk	15
	Necrosis	Anterior pituitary	20%
		Posterior pituitary	0%
		Stalk	3%
Secondary	-	- Hypoxia - Oedema	
Direct stalk injury		Rupture of stalk Transection of stalk Stalk hemorrhage	

followed by pituitary stalk Table1..

In an autopsy study, Kornblum and Fisher in 1969[10], had reported anterior pituitary necrosis in 35% patients of fatal head injuries those who had survived longer than 12 hours. Necrosis patterns always corresponds to the blood supply of the long hypophyseal portal veins. Long portal veins pass through diaphragma sella, where they are vulnerable to mechanical compression from swollen brain and swollen pituitary gland[2,8,10]. Long hypophyseal portal veins supply 70% blood to anterior pituitary. The somatotrophs and gonadotrophs are laterally placed, hence more frequently involved[3]. This anatomical arrangement very well explains the long-term hormonal insufficiency. Direct stalk injury in form of stalk transection and stalk hemorrhage also lead to immediate and long term hypopituitarism[1, 13-15]. This can result due to fracture of the sella turcica[1]. With the advent of CT and MRI it is possible to demonstrate rupture of the pituitary stalk[4-14,15.] Hypothalamic injury also can lead to hypopituitarism following severe head injury. By and large these patients do not survive long enough to have long term hypothalamic problems. Masol J et al[16] described hypothalamic lesions in closed head injury patients. Recently, with improved imaging such lesions are more frequently diagnosed radiologically[6, 12,14.] Traumatic SAH with or without vasospasm also contribute to hypothalamic and pituitary dysfunction.

Trauma causes the T3 to fall, but T4 usually remain normal or is marginally elevated (euthyroid sick syndrome/non thyroid illness/low T3 and normal T4 syndrome)[17-18]. TSH values are found to be higher amongst survivors as compared to those who succumb to their injuries. According to Chiolero et al significant lower serum TSH values are present amongst non-survivors[19]. TSH has been shown to reduce biological activity due to impaired receptor binding in cases of severe traumatic brain injury[20-21].

Severe catabolic response with marked tissue wasting seen in head injury patients is attributed to higher ACTH levels seen[22]. Abnormally elevated levels of cortisol have been seen as late as four months after head injury[22]. Stimuli from the injured area traverse the peripheral nerves, ascend through the spinal cord and brain stem to integrating centers in the reticular formation and limbic areas, where these impulses may or may not be modified by stimuli descending from the cerebral cortex. Impulses are then transmitted to the median eminence where corticotrophin releasing factor is liberated. These traverses to the anterior pituitary through hypothalamic hypophyseal portal vessels and in turn releases ACTH that is then transmitted into the systemic circulation to the adrenal gland and stimulates secretion of cortisol[23]. Rinnai, in a series of head injured patients who did not present with clinical evidence of endocrine dysfunction or abnormal basal excretion of urinary 17-hydroxysterioids, showed that about one third of patients in his group demonstrated limited ACTH reserve as measured by response to metyrapone[24]. The author found that those with limited ACTH reserve had been unconscious for a longer time than those who gave a normal response to metyrapone. Patients who succumb to injury demonstrate a poor rise in cortisol levels as compared to survivors.

A paradoxical growth hormone response is seen in traumatized patients (GH increases post glucose in severe head injury with normal GH response in less severe injury patients)[25]. In studies of CSF of comatose patients following head injury, results indicate increased turnover of nonadrenaline, serotonin and dopamine[26]. All these transmitters exert a positive effect on GH secretion and could favor a paradoxical response[27]. According to a recent report by Bondanelli et al, GH levels were found to be normal in severe head injury evaluated at least one month after leaving the ICU, when their nutritional stutus had improved[28]. Basal prolactin increases following head injury and suggests hypothalamic damage[18,27,29-30]. Edward and Clark in their review on posttraumatic hypopituitarism reported elevated prolactin (4 of 12 female patients developed galactorrhoea) [3]. As the lactotrophes which secrete prolactin, are located in the periphery of the gland, anterior pituitary necrosis could occur with destruction of other pituicytes but leaving the lactotrophes relatively intact[31]. Few authors have reported low basal prolactin levels with an absence of response to TRH, indicating damage to lactotrophes with extensive anterior pituitary necrosis[3,19].

Hypogonadism associated with transient increase in LH concentration falling to subnormal levels with an exaggerated response to exogenous GnRH stimulation is

seen in head injury patients[3,18,,32]. Hypogonadism after trauma could be due to primary gonadal dysfunction with increased levels of catecholamines and cortisol having a direct suppressive effect on Leydig cells[33, 34]. In a series of 99 patients of severe head injury seen at our institute (of which 59 survived and were evaluated for hormonal abnormalities subsequently), elevation of cortisol followed by prolactin was the most common hormonal derangement followed by elevation of GH, TSH, LH and FSH and suppression of %T3. There was a statistically significant temporal trend (over 6 months) in T4, cortisol and GH ($p < 0.05$). Fatal outcome was directly related to LH and gonadotrophin elevation and inversely related to TSH elevation ($p > 0.05$). (Table 2)

Table 2: Trends of hormone abnormality seen in severe head injury patients[56].

Hormone	Post trauma days	No. of patients trauma	Min. level	Max. level	Mean	Std. Deviation	P value
T3	D-0	59	.75	1.64	1.126	.19721	NS
	D-15	54	.85	2.00	1.205	.2149	
	D-90	51	.50	1.70	1.165	.2266	
	D-180	48	.53	8.40	1.289	.0731	
T4	D-0	59	4.5	14.0	8.017	1.983	**P<0.05**
	D-15	54	4.0	13.0	7.417	1.868	
	D-90	51	4.7	12.0	7.713	1.356	
	D-180	48	3.2	11.0	7.368	1.447	
TSH	D-0	59	.4	16.0	3.390	3.271	NS
	D-15	54	.5	12.5	3.211	2.607	
	D-90	51	.5	12.0	3.073	2.370	
	D-180	48	.8	11.0	3.141	2.076	
PRL	D-0	59	5	76x	18.47	11.56	NS
	D-15	54	2.3	76	19.80	12.35	
	D-90	51	3	66	19.13	14.00	
	D-180	48	4	35	16.25	8.64	
CORTISOL	D-0	59	60	472	275.6	88.18	**P<0.01**
	D-15	54	50	476	260.6	96.76	
	D-90	51	18	440	224.2	93.37	
	D-180	48	40	395	165.3	97.59	
GH	D-0	59	.3	18	3.273	3.537	**P<0.01**
	D-15	54	.1	14	3.496	3.251	
	D-90	51	.3	12	2.248	2.513	
	D-180	48	.2	12	1.622	1.937	
LH	D-0	59	2	125	8.81	16.38	NS
	D-15	54	2	20	6.4	3.912	
	D-90	51	2	22	5.559	3.371	
	D-180	48	2	14	5.238	2.596	
FSH	D-0	59	2	35	5.558	5.897	NS
	D-15	54	2	13	5.14	2.28	
	D-90	51	2	13	4.39	1.54	
	D-180	48	3	14	5.03	1.90	

*Data of head injury patients seen at institute: 59/99 surviving patients (17-60 yr. age group) admitted within 24 hrs of severe head injury (GCSÍ 8). Patients with history of endocrine abnormalities, those suffering from pulmonary/metabolic disorders excluded[56].

Clinical problem

Clinical problem in head injury varies from acute stage to chronic problems. In acute stage there is likely have cortisol and ADH deficiency which can manifest persistent hypotension in absence of any obvious cause as patients can not withstand stress in presence of acute pituitary failure. Diabetes insipidus (DI) is not uncommon in severe head injury. Failure of posterior pituitary leads to fall of plasma ADH resulting in DI. This can be diagnosed as patients pass large volume of urine, which is of low specific gravity, of high serum Osmolality and low urinary Osmolality [15-16]. Syndrome of inappropriate ADH secretion in severe head injury is not rare and can be diagnosed on the biochemical parameters of serum and urine. Pituitary dysfuctions are also reported in minor or moderate headinjury[3]. Ziaber et al[35] reported Plasma cortisol and beta-endorphin abnormality in minor head injury.

Diabetes insipidus is an important clinical problem in severe headinjury[15, 16,36]. In addition to DI, SIADH is not uncommon[37]. These clinical problems are also to be differentiated from patients with cerebral salt wasting (CSW). In these patients, serum sodium is low and 24 hours urinary sodium secretion is very high. For above reasons only, a careful electrolyte balance should be monitored in severe head injury patients upto 2 weeks[37]. Electrolyte and plasma osmolality abnormalities are more frequent in patients with diabetes mellitus and chronic alcoholism.

Clinically, significant hypogonadism is not uncommon in major head injury[32, 34,38]. The hypogonadism could be transient[34] or long term. Clark et al[32] in 1988 reported 33 male patients with major head injury in whom total free testosterone was significantly lower on 3rd day. However, persistent hypogonadism was only reported in 5 of these 21 patients in whom the tests were performed between 3-6 months after injury. They suggested repeated endocrinal assessment in patients with severe head injury. Woolf et al in 1986[34] reported transient hypogonadism following head injury. They included both severe and moderate head injury patients. They studied 31 male patients in whom testosterone and other hormonal assessments were performed shortly after injury and on the 4th day. They observed good correlation between severity of head injury and sex hormone abnormalities. Precocious puberty is another rare problem following severe headinjury[39]. The precise mechanism is not still clear. Some authors have hypothesized extrahypothalamic involvement.

Neurobehavioral impact of hypopituitarism is significant. Chronic behavioral problem is recorded in significant number of patients with brain injury[40-44]. Both behavioral and cognitive defects are even notice one year following injury[40-42]. Saatman et al[44], in 1997 demonstrated

cognitive abnormality in experimental brain injury. It is generally believed that the deficiency of growth hormone or insulin like growth factor 1 deficiency results in neurobehavioral and cognitive deficit[43, 44]. Saatman et al[43] reported improvement in incongitive function by supplementing Insulin likes growth factor. Loss of memory, higher anxiety level, impaired motor skill and lower quality of life is also attributed to growth hormone deficiency[45, 46]. Sex hormone deficiency also lead to mood disturbances and behavioral problems.

Investigations

Both anterior and posterior pituitary functions are tested, when there is high degree of suspicion of hypopituitarism[47].

(a) Insulin tolerance test is a simple test to find out corticotrophin and somatotroph secretion by measuring GH and cortisol level.

(b) A TRH stimulation test is important to assess the level of TSH and prolactin.

(c) GnRH stimulation test is necessary to assess gonadotroph function. (Table 3)

Table 3: Hormonal assessment in Pituitary dysfunction diagnosis

Hormone	Test	Method	Adult hormone levels
GH	Insulin tolerance test	RIA	0-5 ng/ml
ACTH	Insulin tolerance test	RIA	9-50ng/ml
TSH	TRH stimulation	Immnochemo luminescence assay	0.4-4.2mu/L
Free thyroxin		RIA	5.5-11.5µ/dl
FSH	GnRH stimulation test	Fluroimmunometric assay	FHS-20-250pg/dl
Testosterone	GnRH stimulation test	RIA	298-1043ng/dl

Posterior pituitary function is not of less importance, realizing the problem of fluid electrolyte imbalance, problems of DI and SIADH. Hence, measurement of serum sodium, blood urea, nitrogen, Creatinine and Osmolatity of plasma and urine are important. In addition a regular check in urinary specific gravity and 24 hours urinary sodium excretion is also carried out to differentiate one from the other. Assessment of serum ADH level is also important[6].

Overall insufficiency of growth hormone is reported in 85% and of gonadotrophin in 95% cases. Approximately 30% patients develop DI during their illness.

Treatment of Hypopituitarism

No doubt endocrinal abnormality, be it in acute phase of head injury or chronic state requires careful evaluation and replacement therapy. In acute stage, patients with DI, or SIADH or cerebral salt wasting, need treatment to correct the deficiency. The treatment may be long term or short term depending on the need, in an individual patient. DDAVP nasal spray, arginine, vasopressin and pitressin injections are widely used.[6, 15,16]. Several studies dealing with GH deficient patients showed beneficial role of GH replacement, which included improved memory, attention, comprehension and vocabulary. Improvement also included general well being of mood and reduction in depression and anxiety state[47-48]. GH also helps in increasing muscle mass. Some authors have used Insulin like growth factor 1 and shown improvement in various cognitive functions[43-44].

Other important replacement therapy includes the deficiency of testosterone. Testosterone replacement in men helps in normalization of libido and sexual function, helps in bone formation and increases the muscle mass.[49-50]. Sex hormone deficiency in women is adequately treated with estrogen therapy, which improves their neurobehavioral and cognitive functions.

Cerebral salt wasting (CSW) occurs due to unregulated release of natriuretic peptide[51-55]. Patients present with persistent hyponatraemia, hypernatriuresis with hyperosmolar urine. In CSW, volume is depleted, hence volume is replaced with Na containing fluids and deranged haematocrit should be restored. Infusion of saline, plasma and blood is necessary depending on the need. Fludrocortisone acetate is the specific treatment for CSW[51-55], which helps in sodium retention with fluid and correct hyponatremia.

CONCLUSIONS

Endocrinal abnormality related problems in head injury are a neglected aspect. Overall, 40% of severe head injury patients develop either short term or long term endocrinal problems. Basic reasons may be hypothalamic or pituitary damage, may be primary or even secondary to hypoxia or hypotension. Both anterior and posterior pituitary gets involved. Pituitary stalk necrosis or avulsion can also occur. Elevation of cortisol followed by prolactin is the most common hormonal derangement followed by elevation of GH, TSH, LH, FSH, ADH and suppression of T3. GH and gonadotrophin deficiency is also to some extent responsible for long-term behavioral and cognitive problems. Diabetes Insipidus, inappropriate ADH secretion and CSW are quite frequent. The entire endocrinal problem needs proper

evaluation and adequate short term or long-term replacement to improve the overall outcome in-patients with both severe and minor head injuries.

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