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Thyroid Hormone Profile in a Population of Nigerian Patients with Traumatic Brain Injury

Malomo T.A.[1], Rabiu T.B.[2], Udoh D.[3], Komolafe E.O.[4], Shokunbi M.T.[1]

[1]*Department of Surgery, College of Medicine, University of Ibadan, Ibadan, Nigeria,* [2]*Department of Surgery, Ladoke Akintola University Teaching Hospital, Osogbo, Nigeria.* [3]*Department of Surgery, University of Benin, Benin, Nigeria.* [4]*Department of Surgery, Obafemi Awolowo University, Ile Ife, Nigeria.*

Summary: Traumatic brain injury (T.B.I.) has an annual incidence of 200/100000. There is little or no information on neuroendocrine sequelae following T.B.I. in the Nigerian population. The purpose of the study is to evaluate the effect of T.B.I on the thyroid axis and relate it to outcome by outlining the change in thyroid axis of head injured patients. One hundred and fifteen patients were recruited with 85% male and 15% female. Of these patients, 71.7% presented within 24 hours of injury. The head injury was mild in 53%, moderate in 16% and severe in 31% of the patients. Serum T3 was high in 52.2%, low in 7.8% and normal in 40%. Serum T4 was high in 4.3%, low in 68.7%, and normal in 27%. Serum TSH was high in 16.5% TSH levels, low in 6.1% and normal in 77.4%. There was no correlation between the severity of head injury measured by the Glasgow coma score and patterns observed in the thyroid function test. With respect to outcome of head injury, serum T4 was low in patients who died or had persistent vegetative state (p=0.012). Traumatic brain injury in Nigerian patients is associated with an elevation of T3, low levels of T4 and normal TSH values. Death and persistent vegetative state were associated with low T4.

Keywords*:* Caffeine, ischaemia-reperfusion injury, cerebral ischaemia, neuro-inflammation, stroke.

**Address for correspondence*: temitayoshokunbi@gmail.com; Phone: +2348022912220

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INTRODUCTION

Traumatic brain injury is a major public health problem, with an annual incidence of 200/100000 (Bruns and Hauser 2003) in Africa. Passenger motor vehicular road traffic accident causes over 65% of traumatic brain injury in the African population(Adeolu *et al.*, 2005), and is a major cause of death(Hodgson, Stewart, and Girotti 2000), as well as physical, psychological, cognitive, behavioral and social morbidity(Salazar *et al.*, 2000).

Neuroendocrine sequelae have been described in traumatic brain injury. Studies have been carried out in increasing numbers which have shed light and have improved the understanding of traumatic brain injury induced hypopituitarism, low levels of cortisol has been identified predominantly as well as low levels of thyroid hormones (Olivecrona, Dahlqvist, and Koskinen 2013; Malekpour, Mehrafshan, and Saki 2012). These hormones are important in coping with stress of disease and injury, like traumatic brain injury. The prevalence of anterior pituitary dysfunction following traumatic brain injury ranges from 8% to 68%(Schneider et al. 2006) with that of thyroid hormone deficiencies ranging between 0 and 29% (Fernandez-Rodriguez and Bernabeu 2011)

Hypopituitarism secondary to traumatic brain injury has remained under-diagnosed(Ghigo et al., 2005; Gasco et al. 2012). This can be explained by the fact that the patients with traumatic brain injury can have the signs and symptoms of hypopituitarism masked by the head injury(Czirják, Rácz, and Góth 2012) and some of the hormone disorders are not life threatening, hence the index of suspicion is low.

Traumatic brain injury is of great importance in low- and middle-income countries which make up 70% of the global population(Krug et al. 2002; Rubiano et al. 2013; "Centers for Disease Control and Prevention. National Center for Injury Prevention and Control. Web-Based Injury Statistics Query and Reporting System" 2004) because trauma accounts for the largest percentage of potentially productive year of life lost. Proper management of head injury and recognition of prognostic factors is important for the quality of life of survivors.

The exact mechanism and the pathophysiology of hypopituitarism and derangement of the thyroid hormones following traumatic brain injury is not well understood and several mechanisms have been

postulated (Maiya et al. 2008). A head injured patient may have other confounding factors that can mimic pituitary dysfunction for example the body's metabolic response to trauma. The drugs used in the early phases of trauma or acute illness may alter the metabolism of protein binding hormones resulting in false deficiencies. Thyroid hormone dysfunction has been described in severe trauma including burns and major surgery(Luo, Yu, and Li 2017; Sofianos et al. 2017), which reflected a decrease in the T4, T3 and free T3 and an increase in the TSH suggesting that the dysfunction is from the hypothalamic-pituitary axis. There is paucity of data on the effect of head injury on the thyroid hormone, with relation to severity of the head injury and relation of this to outcome of the injury.

Low levels of T3 and T4 have been described in severe head injury with no change observed in TSH and TBG. A poor outcome of heads injury was also observed with reduction in the levels of T4 (Malekpour, Mehrafshan, and Saki 2012; Shamaeva et al. 2012).

Whereas post-traumatic anterior pituitary dysfunction is a well-recognized entity, its frequency and potential impact on the outcome of head injured Nigerians has not been previously explored. A distinct feature of this population is that it consists mainly of the young population and middle-aged group that are still active with about 93.2% of its population below 54years (25-54years-30.1%, 15-24years 19.3%)("The World Factbook — Central Intelligence Agency" 2015).

MATERIALS AND METHODS

The study was a cross-sectional one carried out at the Department of Neurological Surgery, University College Hospital, Ibadan, Oyo State, Nigeria.

Study Population:
All patients with traumatic brain injury mild, moderate and severe, presenting at the Emergency Department of the University College Hospital, Ibadan and the Accident and Emergency Unit of the Ladoke Akintola University Teaching Hospital, Osogbo, during the study period (September 1st, 2014 – April 15th, 2015) were recruited into the study.

The patients were assessed: duration of trauma was noted, signs of head injury (altered sensorium, loss of consciousness, memory impairment, headaches, irrational talk and behavior, focal neurological deficits) were noted at presentation at the Emergency Department for eligibility to participate in the study without interrupting the planned care for the patient. Traumatic brain injury was classified using the post resuscitation Glasgow Coma Scale (GCS) score.

Mild: GCS score 13-15
Moderate: GCS score 9-12
Severe: GCS score <8.

Pregnant and breast-feeding women, patients on steroid therapy, patients on hormonal supplements, anti-androgen and anti-oestrogen, patients on thyroid supplements, patients with features of sepsis or burns and patients that had received any form of intervention prior to presentation were excluded from the study.
A sample size of 113 was calculated using the formula**:**
n = Z2 x. **(p)** x **(1-p)** / **C2**
where **n** =sample size, **Z** = Z value which is 1.96 for a 95% confidence level, **p** is percentage of patients with thyroid dysfunction following traumatic brain injury 8% (0.08), **C** is confidence interval in decimals 0.05), which is ideal for a descriptive study. A total number of 115 patients were recruited.

Blood Samples Collection and Handling
A large caliber vein was identified, usually at the cubital fossa, and the overlying skin was prepared with an ethanol-soaked cotton swab. The arm containing the infusion cannula was avoided. 5mls of venous blood was drawn with a 21G needle and a 5ml syringe. Samples were stored in a sterile plain bottle and kept in a refrigerator at 40C until serum was separated, usually within 48hours.

Serum was obtained by spinning the blood samples at 3600RPM in a centrifuge for 5 minutes and the supernatant removed and kept in a new sterile universal bottle. Serum samples were kept frozen at -20^0C while samples were being pooled, before analysis.

Sample Analysis:
Samples were analyzed in batches of 50 using Enzyme linked immunosorbent assay (ELISA). Dialab GmbH Elisa (Austria) for T3, T4 and TSH were used for analysis. According to the test kit used, hormone values were described T3: high > 2.0ng/ml, normal 0.8- 2.0 ng/ml, low < 0.8ng/ml; T4: high > 161nmol/l, normal 58 – 161nmol/l, low < 58nmol; TSH: high > 4.7mIU/L, normal 0.5 – 4.7 mIU/L, low < 0.5mIU/L.

Statistical Analyses:
Categorical data were presented as frequencies and proportions while continuous data were represented as means and standard deviations. mean values were compared using Students T test. Point of significance was set as $P < 0.05$. The Data obtained were analyzed using IBM Statistical Package for Social Sciences version 22.

RESULTS

Most of the patients were between the ages of 21 and 40 years which was 51.3% of the total population sampled (*Table 1)* and the least represented were the elderly (10.4%). About fifty-three percent of the patients had mild head injury while 15.8% and 30.7% of the patients had moderate and severe head injury respectively. About fifty-two percent of the patients

had a high total T3 while only 7.8% had low T3. Conversely, only 4.3% of the patients had high T4 values while 68.7% of the patients had low T4. Most of the patients (77.4%) had normal TSH values (Table 2). The Glasgow Outcome Scale Extended shows that 46.5% of the patients fell into normal range while 24.2% died.

Table 1: Age distribution of the patients

Age in years	Frequency	Percentage
0-20	24	20.9
21 – 40	59	51.3
41 – 60	20	17.4
> 60	12	10.4

Table 2. Duration of trauma in hours prior to presentation.

Duration of trauma before presentation (Hours).	Frequency	Percentage
< 24	81	71.7
24 – 48	12	10.6
> 48	20	17.7

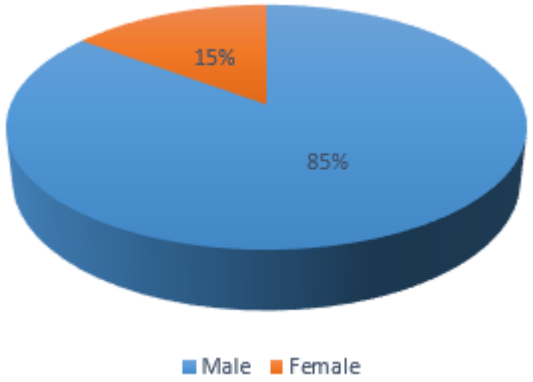

Fig 1: Sex distribution of the patients

Table 3 shows the result of cross tabulation of thyroid function test (in three variables: high, normal and low) with Glasgow Coma Scale (in three variables: mild, moderate and severe) of the patients. Total T3 was elevated in general amongst the sampled population 60%. Total T3 values was highest amongst patients with mild head injury (high T3 = 51.7%), and the decreases in severely head injured patients were noted (high T3 = 31.7%). Lowest values were however noticed in moderate head injury (high T3 = 16.7%). This observed difference was however not statistically significant (p = 0.945)

There was a general decrease in T4 levels with 78% of the sampled population having low T4 levels. The pattern noticed with Total T4 values showed high values in mild head injury (high T4 = 80%) and decreases in severe head injury (high T4 = 20%) while dipping to the lowest value in moderate head injury (high T4 = 0%), however all groups of head injured patients had a higher percentage of people in that group having low T4 whether mild, moderate or severe. This observed difference was not statistically significant (p = 0.664).

A higher percentage of the sampled population had normal TSH values across the different severity of head injured patients 80%. Amongst the patients with high TSH, those with severe head injury formed the bulk of the population.

There was a consistent decline in the percentages of patient with high T3, from normal patients with high T3 65.3% of that population, patients with moderate disability had high T3 in 6.1% of that population and patients with severe disability had high T3 in 2.0% of that population. Persistent vegetative state and death were the worst outcomes and were put together, only 2 patients in the total population were in persistent vegetative state and they eventually died. Fifty-two percent of the patient that died had high T3 while 48% of these patients had normal T3.

Table 3: Thyroid function test /Glasgow coma scale

Variable	Glasgow Coma Scale			Total	Chi square	P value
	Mild	**Moderate**	**Severe**			
Total T3						
High	31 (51.7%)	10(16.7%)	19(31.7%)	60 (100%)	0.749	0.945
Normal	25(55.6%)	6 (13.3%)	14 (31.1%)	45 (100%)		
Low	5(55.6%)	2 (22.2%)	2 (22.2%)	9 (100%)		
Total T4						
High	4 (80%)	0 (0%)	1 (20%)	5 (100%)	2.390	0.664
Normal	17 (54.8%)	6(19.4%)	8 (25.8%)	31(100%)		
Low	40 (51.3%)	12(15.4%)	26 (33.3%)	78 (100%)		
TSH						
High	6 (31.6%)	4 (21.1%)	9 (47.4%)	19(100%)	5.814	0.214
Normal	50 (56.8%)	14(15.9%)	24 (27.3%)	88 (100%)		
Low	5 (71.4%)	0 (0%)	2 (28.6%)	7 (100%)		

Table 4. The relationship between thyroid function test values with Glasgow Outcome Score

Variable	Glasgow Outcome Score				Total	Chi square	P value
	Normal	**Moderate Disability**	**Severe Disability**	**PVS - Death**			
Total T3							
High	32(65.3%)	3(6.1%)	1(2.0%)	13(26.5%)	49(100%)		
Normal	25(59.5%)	3(7.1%)	2(4.8%)	12(28.6%)	42(100%)	5.578	0.427
Low	7(87.5%)	0(0%)	1(12.5%)	0(0%)	8 (100%)		
Total T4							
High	4(80.0%)	1 (20.0%)	0 (0.0%)	0 (0%)	5(100%)		
Normal	15(55.6%)	2 (7.4%)	2 (7.4%)	8 (29.6%)	27(100%)	5.166	0.523
Low	45(67.2%)	3 (4.5%)	2 (3.6%)	17 (25.4%)	67(100%)		
TSH							
High	8 (57.1%)	1(7.1%)	0(0%)	5(35.7%)	14(100%)		
Normal	52 (65.8%)	5(6.3%)	4(5.1%)	18 (22.8%)	79(100%)	2.508	0.868
Low	4 (66.7%)	0(0%)	0(0%)	2 (33.3%)	6(100%)		

Table 5: Thyroid function test amongst patients that died

Variable	Glasgow Coma Scale			Total	Chi square	P value
	Mild	**Moderate**	**Severe**			
Total T3						
High	1 (8.3)	2(16.7%)	9 (75.0%)	12 (100%)	2.294	0.318
Normal	2(18.2%)	0 (0%)	9 (81.8%)	11 (100%)		
Low	0(0%)	0 (0%)	0(0%)	0 (0%)		
Total T4						
High	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8.830	0.012
Normal	3 (42.9%)	1(14.3%)	3 (42.9%)	7(100%)		
Low	0 (0%)	1(6.3%)	15(93.8%)	16 (100%)		
TSH						
High	0 (0%)	1 (20.0%)	4 (80.0%)	5(100%)	2.476	0.649
Normal	3 (18.8%)	1(6.3%)	12 (75.0%)	16 (100%)		
Low	0 (0%)	0 (0%)	2 (100%)	2 (100%)		

Similarly, Total T4 values showed a consistent decline in percentages from normal patients (high T4 = 40%) to patients with moderate disability having high T4 in 20% of the population and none of the patients with severe disability and death had a high Total T4. Amongst the patient that died (worst outcome), 77% of them had low T4 while 23% had normal T4. While 70% of those with the best outcome also had normal T4. These observed differences were however not statistically significant (p = 0.527). In the same vein, Total TSH values showed a consistent decline in percentages from upper normal (high TSH = 42.9%) to upper severe (high TSH = 0%) and low values in lower severe (high TSH = 0%) and persistent vegetative state (high TSH = 0%). Total TSH in relation to death was distinct with high TSH values of 35.7%, normal TSH values of 21.5% and low T4 values of 33.3%. These observed differences were however not statistically significant (p = 0.963)

Based on the pattern observed that patients who died had deviation from the trend that was observed for other patients, the outcome severity of injury of patients that died was crossed with the thyroid function tests and T3 was either high or normal with no statistical significance (p= 0.318) T4 was low in 84% of patients with severe head injury and low in 50 % of patients with moderate head injury (p=0.012). The patients with mild head injury had normal T4. None of the patients that died had an elevation in T4 (Table 5).

DISCUSSION

Traumatic brain injury is a major source of economic burden as majority of people affected by this problem are in their active years as shown in the results with majority of affected patients being between the ages 21 – 40 years making up more than half of the respondents (Table 1). More males are affected than females since they engage in risky activities and take on jobs that expose them to the hazards of the road. This data is like what Benvenga et al observed in their series(Benvenga et al., 2000). In this series 24.2% of patients died. These deaths are economic losses to the relatives of the patients and the country.

A rise in the levels of T3 and a reduction in the levels of T4 with TSH being within normal levels was observed in this study. This is at variance with that of Malekpour et al (2012), in their series observed a reduction in T3 and T4 with T3 being more significant, however their study was on severely head injured patients (Malekpour, Mehrafshan, and Saki 2012), while this study focused on head injury in general, whether mild, moderate or severe. The pattern

observed with TSH being within normal limit is similar to the findings Malekpour et al (2012 and Shamaeva et al. (2012) When this pattern was compared with Glasgow coma score, in each group of head injured patients i.e. mild, moderate or severe, the percentage of patients with T3 higher than normal levels in each category remained the majority, while those with T4 lower than normal levels were also the majority across board in each group of head injured patients. Lieberman et al described a global reduction in freeT4 and TSH in a population group who had head injury and they were already past the acute phase, on rehabilitation however, in their series, they did not assay for T3(Lieberman, Oberoi, and Gilkison 2001). The observed elevation of T3 in these group of patients is like the finding by Cernak et al.(1999) who observed a rise in T3 within the first 5 days of head injury in patients with mild head injury however, a reduction in T3 was observed in severely head injured patients.

The changes in the levels of the thyroid hormone levels in the different spectra of head injury did not show statistical significance. Most studies reported a low T3, T4, and TSH especially in severely head injured patients. Chiolero et al (1988) reported such a finding in 35 severely head injured patients, this study also had a similar number of severely head injured patients presenting within 24 – 48 hours post trauma; however, the findings are different in these population.

Most studies compared the thyroid hormones with the severity of head injury. This study showed a pattern with outcome of head injury. Elevated T3 values was associated with upper normal Glasgow outcome score in 44.9% of respondents without statistical significance. The percentages reduced as the scale moves towards the poor outcomes up to persistent vegetative state.

T4 was reduced in most of the patients with head injury as noted earlier however the pattern was that a higher percentage of people with low T4 had an upper normal and lower normal Glasgow outcome score. These findings can also be explained by most of the patients had mild head injury, and they are expected to make significant recovery and have good outcomes at recovery. However, death in the Glasgow Outcome Score also showed a different pattern on evaluation of patients T4. This is in concordance with other studies previously carried out. The observed pattern of T3 which is different from what is previously documented is still a subject for investigation. The metabolic response to trauma may explain the elevated T3 and normal TSH (Desborough, 2000), but this would not explain the reduced T4 in this group of patients. Total T3 and Total T4 was assayed, however the active form of the thyroid hormones are the free unbound molecules. Hence assaying for both the bound and the free hormones may not give the exact picture of the response of the thyroid axis to the stress of head injury

In conclusion, traumatic brain injury in Nigerian patients is associated with an elevation of T3, Low levels of T4 and normal TSH values. The levels of the hormones assayed T3, T4, and TSH observed is not significant when compared with the severity of head injury. Low T4 is observed in patients with the worst outcomes of traumatic brain injury (death), using the Glasgow outcome score extended, while high and normal T3 levels is observed in this group of patients.

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