CHRONIC ANTERIOR PITUITARY DYSFUNCTION FOLLOWING TRAUMATIC HEAD INJURY: PROSPECTIVE STUDY IN HOSPITAL SULTANAH AMINAH JOHOR BAHRU

BY

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LIST OF ABBREVIATIONS

1	AI	Adrenal Insufficiency
2	BOS	Base Of Skull
3	CT	Computed Tomography
4	FSH	Follicular Stimulating Hormone
5	GH	Growth Hormone
6	LH	Leutinizing Hormone
7	NB	Neurobehavioural
8	PTHP	Post Traumatic Hypopituitarism
9	SAH	Subarachnoid Hemorrhage
10	SF 36	Short Form-36 Questionnaire
11	T4	Thyroxine
12	TSH	Thyroid Stimulating Hormone
13	TBI	Traumatic Brain Injury

ABSTRAK

Latar Belakang dan Objektif

Kecederaan otak traumatik (TBI) berkaitan dengan peningkatan morbiditi, kematian dan kecacatan jangka panjang. Endokrinopati selepas kecederaan kepala sering berlaku dan kebanyakan pesakit mengalami endokrinopati yang tidak didiagnosis lebih awal dan tidak dirawat. Endokrinopati setelah TBI menyebabkan gangguan perlakuan dan kualiti hidup. Terdapat pelbagai endokrinopati setelah-trauma yang dilaporkan berkisar antara 10-58%. Tujuan kajian ini adalah untuk menentukan kejadian kekurangan pituitari anterior kronik pada pesakit dengan kecederaan otak traumatik. Setelah itu menentukan faktor risiko dan kesan terhadap kualiti hidup pesakit.

Kaedah

Ini adalah kajian prospektif di Hospital Sultanah Aminah Johor Bahru. Seramai 105 pesakit yang pernah mengalami kecederaan kepala di masukkan kedalam penyelidikan ini. Kriteria kemasukan adalah pesakit dengan kecederaan kepala traumatik, berusia 18 hingga 65 tahun dan mempunyai sejarah trauma 3 bulan sebelum pendaftaran. Kriteria pengecualian adalah pesakit kecederaan otak traumatik dalam keadaan vegetatif kronik dengan jangka hayat rendah, pesakit dengan diagnosis atau mengambil terapi penggantian hormon sebelum trauma, wanita hamil dan pesakit wanita dengan haid LH dan FSH tidak akan diambil. Penyiasat utama akan melakukan temu ramah dengan pesakit dan pesakit akan diajukan soalan untuk mengisi borang penyelidikan(36 soalan). Selepas itu, pengambilan sampel darah akan dilakukan. Data demografi lain akan diperlukan dari dokumen kemasukan ke wad.

Keputusan

Sebanyak 33 (31%) pesakit mengalami gangguan hormon anterior hipofisis. Mean umur adalah 36.97 ± 12.96 tahun dengan median 35 tahun. Dari 33 pesakit, 27 (32.5%) adalah lelaki dan 6 pesakit perempuan (27.3%). Disfungsi hipofisis anterior kronik juga dilihat pada lebih ramai pesakit dengan kecederaan kepala trauma berat sekitar 47.1%, berbanding dengan kecederaan kepala yang sederhana (8 pesakit, 38.1%) dan 2 mengalami kecederaan kepala ringan (5.6%). Tempoh mean selepas mengalami trauma adalah 10.3 bulan ± 1.79 dan mediannya adalah 11 bulan. Pituitari anterior kronik yang biasa dijumpai pada pesakit yang mendaftar dalam kajian pada 11 dan 12 bulan selepas trauma. Semua pesakit dengan disfungsi hipofisis mempunyai penemuan positif dalam pemeriksaan CT imej otak. Dari 33 pesakit, 22 mempunyai SAH di basal cistern dan 27 pesakit mengalami patah tulang tengkorak(basal). 52.1% pesakit menjalani pembedahan dan 8 pesakit tidak menjalani sebarang pembedahan. Dari semua 33 pesakit dengan disfungsi hipofisis anterior kronik, 84.8% melibatkan 1 paksi dan 5 (15.2%) pesakit lain mempunyai 2 paksi yang terlibat. Analisis regresi logistik binari mengkaji hubungan antara setiap pemboleh ubah dan menunjukkan bahawa keparahan kecederaan kepala ($p < 0.001$), jangka masa tinggal di hospital yang berpanjangan ($p = 0,014$), penemuan radiologi dari patah tulang tengkorak basal($p < 0.001$) , dan kehadiran perdarahan subarachnoid ($p < 0,001$) secara signifikan dikaitkan dengan disfungsi hipofisis anterior kronik. Terdapat perbezaan yang ketara yang dilihat pada markah borang penilaian SF36, di mana pesakit dengan disfungsi hipofisis anterior mempunyai nilai SF-36 min 56,3 ± 10,3. Ini menunjukan kualiti hidup yang lebih

teruk berbanding dengan pesakit kecederaan kepala tanpa ganggguan fungsi hipofisis.

Kesimpulan

Prevalensi hipopituitarisme dianggarkan pada 31%. Tahap kecederaan kepala, , kemasukan ke hospital yang berpanjangan dan penemuan positif penilaian radiologi (kehadiran SAH dan patah tulang tengkorak basal) adalah faktor meningkatkan risiko menhidap hipopituitarisme. Disfungsi hipofisis anterior kronik pasca trauma juga berkaitan dengan kualiti hidup yang buruk seperti yang ditunjukkan oleh tanda SF36 yang rendah.

Kata kunci: disfungsi hipofisis anterior kronik, kecederaan otak traumatik, kualiti hidup, SF36.

Abstract

Background and Objective

Traumatic brain injury(TBI) is associated with increase morbidity, mortality and long term disability. Hypopituitarism following TBI is not rare and most patient had undiagnosed and untreated hypopituitarism. Association of post TBI hypopituitarism causing neurobehavioural and quality of life impairment. There are wide range of post-traumatic hypopituitarism (PTHP) has been reported ranging 10-58%. The aim of the study is to determine the incidence of the chronic anterior pituitary Deficiency in patients with traumatic brain injury. Subsequently determine the risk factor and the outcome of the patient with chronic anterior pituitary dysfunction.

Methods

This is the single centre prospective cross-sectional study where 105 traumatic head injury patients under Neurosurgical Department Hospital Sultanah Aminah, Johor Bahru follow up who fulfilled the inclusion criteria. The inclusion criteria were patient with traumatic head injury, age from 18 to 65-year-old and had history of trauma 3 month prior to enrolment. The exclusion criteria were traumatic brain injury patient in chronic vegetative state with low life expectancy, patient who diagnosed or taking hormonal replacement therapy prior to the trauma, pregnant woman and female patient with normal menses LH and FSH will not be taken. The primary investigator will do an interview with the patient and the patient will be asked question to complete questioner form (36 question). Subsequently, blood sampling will be done. Other demographic data will be required from the admission documents.

Results

A total 33 patients (31%) were noted to have anterior pituitary dysfunction. The mean age was 36.97 ± 12.96 years old with a median of 35 years old. Out of 33 patients, 27 (32.5%) were male and 6 patients were female (27.3%). Chronic anterior pituitary dysfunction also was seen in more patients with a severe traumatic head injury around 47.1%, a total of 23 patients sustained a severe head injury as compared to a moderate head injury (8 patients, 38.1%) and 2 sustained mild head injury (5.6%). The mean duration after the onset of trauma was 10.3 months ± 1.79 and the median was 11 months. Chronic anterior pituitary commonly found in the patient enrolled in the study at 11 and 12 months post-trauma. All patient with pituitary dysfunction had positive CT brain findings. Out of 33 patients, 22 had SAH at the basal cistern and 27 patients had a base of skull fracture. 52.1% of the patient underwent surgical intervention and 8 patients didn't undergo any surgical intervention. Out of all 33 patients with chronic anterior pituitary dysfunction, 84.8% involved 1 axis and another 5 (15.2%) patients had 2 axes involved. Binary logistic regression analysis studies the relationship between each of the variables and showed that severity of the head injury ($p < 0.001$), prolonged duration of hospital stay ($p=0.014$), radiological findings of a base of skull fracture($p <0.001$), and presence of SAH at basal cistern ($p<0.001$) was significantly associated with chronic anterior pituitary dysfunction There was a significant difference seen in SF36 marks, where the patient with anterior pituitary dysfunction has the lower SF-36 marks 56.3± 10.3.

Conclusion

The prevalence of hypopituitarism was estimated at 31%. Indicators of increased TBI severity, prolonged hospitalization and positive finding of radiological assessment (presence of SAH and base of skull fracture). Post traumatic chronic anterior pituitary dysfunction also related with poor quality of life as showed by low SF36 marks.

Keywords: chronic anterior pituitary dysfunction, traumatic brain injury, quality of life, SF36.

INTRODUCTION & LITERATURE REVIEW

Post-traumatic endocrine dysfunction has been reported as one of the complications of traumatic brain injury (TBI) which cause significant physical and mental effects in patient with traumatic brain injury. A majority of survivors of moderate or severe TBI have residual neurobehavioral deficits, depression, and poor quality of life. One hypothesis receiving much attention is that TBI- induced hypothalamic-pituitary dysfunction may contribute to poor quality of life in many TBI survivors.(Agha et al., 2004)

Several recent cohort studies have documented long-term hormonal dysfunction after TBI. Post traumatic hypopituitarism has been observed in 10-58% of patient. (Tolli et al, 2016). Collectively, these studies indicate that 25 to 40% of such TBI patients will develop chronic hormonal deficiencies. Commonly affected axes is the somatotroph and gonadotroph axes. (Tolli et al, 2016). 50.9% of TBI had at least one anterior pituitary hormone deficiency one year after TBI prospective study. Recent cross-sectional studies show that anterior pituitary dysfunction after traumatic brain injury is more common than expected, with a prevalence of 30–70% of hormonal abnormalities present after TBI. The frequency of chronic hypopituitarism (generally accepted as lasting at least 3 months) after TBI varies widely between the studies, most report a range of 15%–50%. (Tanriverdi, 2015). Schneider et al. showed that hypopituitarism is found in 56% of TBI patients at three months (Schneider et al. 2006)

TBI itself may impair cognition (concentration, memory, judgment and mood), movement abilities (strength, coordination and balance), sensation (tactile sensation and special senses, such as vision) and sexual function, leading to

important behavioural changes and consequences on daily living activities (Bondanelli, 2015). Hypopituitarism contributes to TBI-related mortality and functional and cognitive morbidity (Gray S ,2019). In fact, the post concussion syndrome, very common in 30% of patients in the short period after TBI, presents with headache, irritability, loss of memory and attention deficit, depression, fatigue and low working capability, symptoms also associated with pituitary hormones deficiency. (Lorenzo, 2005). This study is to determine the incidence of chronic anterior pituitary deficiency in Malaysian population, identify the risk factor and assess the quality of life.

2. STUDY PROTOCOL

This is the single centre prospective cross-sectional study where 105 traumatic head injury patients under Neurosurgical Department Hospital Sultanah Aminah, Johor Bahru follow up who fulfilled the inclusion criteria. The aim of the study is to determine the incidence of the chronic anterior pituitary Deficiency in patients with traumatic brain injury. The inclusion criteria were patient with traumatic head injury, age from 18 to 65-year-old and had history of trauma 3 month prior to enrolment. The exclusion criteria were traumatic brain injury patient in chronic vegetative state with low life expectancy, patient who diagnosed or taking hormonal replacement therapy prior to the trauma, pregnant woman and female patient with normal menses LH and FSH will not be taken.

Patient that fulfil the criteria of inclusion will be recruited and will be given research ID after consented to participate for the study. The primary investigator will do an interview with the patient and the patient will be asked question to complete questioner form (36 question). Subsequently, patients will be given

another date for blood sampling where they required to be fasted and sample taken 10cc around 8-9 am. All the blood samples will be sent to biochemistry lab and results will be interpreted based on the reference range. Any uncertainty or discrepancy will be consulted to the endocrinologist.

SF 36 questionnaire is a set of generic, coherent and easily administered quality of life measures. These measures rely upon patient self- reporting and widely utilized for routine monitoring and assessment of care outcomes in adult patient. This questionnaire is developed at RAND and RAND grants permission to use RAND 36- Item Short Forms Health Survey. No further written permission is needed for use of this health survey. Researcher will provide a credit line when printing and distributing this document acknowledging that is was developed at RAND as a part of medical outcome study.

Approval was obtained from the Medical Research & Ethics Committee of the Ministry of Health Malaysia and registered in the national register for clinical trials registration ID: NMRR- 20-1575-53747

Sample Size

Universal sampling was used in this study. Prior data indicate that the proportion of chronic anterior pituitary dysfunction in TBI is 0.14 (Carmen et al 2016). If the type I error probability and precision are 0.05 and 0.05, we will need to study 95 samples. With an additional of 10% dropout rate, the sample is 104.5. The final sample size will be 105.

This study was conducted over a period of 12 months from 1st October 2019 to 1st October 2020. The timeline of study is shown in Figure 1.

Declaration of Interest Conflict

There are no side effects on the participants as we are incorporating the standard operating procedure of management of severe head injury into this study protocol. The only procedure, blood investigation is not a routine investigation. The biochemical parameters required blood taking and cost for the investigation. No intervention done to the patient for this study. If the result was abnormal, patient will be informed and with their permission the patient will be referred to endocrinologist for further confirmatory investigation and treatment.

There may or may not be any benefits to study participant. Information obtained from this study will help improve the treatment or management of other patients with the chronic anterior pituitary dysfunction following traumatic head injury.

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki (2013) and the Malaysian Good Clinical Practice Guideline (2016). Approval was obtained prior to the initiation of this study. This is a prospective study and therefore patient consent is required during the blood taking and interview.

Names of subjects will be kept on a password-protected database and will be linked only with a study identification number during this research. The patient identification number instead of patient identifiers will be used on data sheets. All data will be entered into a computer that is password protected. Names of patients will not be disclosed, and all will be changed into identification number instead. On the completion of study, data in the computer will be copied to a USB drive and other softcopies will be erased while the hardcopy data will be kept and

locked in the office cabinet located in the Department of Neurosurgery, Hospital Sultanah Aminah Johor Bahru.

TITLE PAGE

Chronic Anterior Pituitary Dysfunction following Traumatic Head Injury: Prospective Study In Hospital Sultanah Aminah Johor Bahru

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3.2 Abstract

Background and Objective

Traumatic brain injury(TBI) is associated with increase morbidity, mortality and long term disability. Hypopituitarism following TBI is not rare and most patient had undiagnosed and untreated hypopituitarism. Association of post TBI hypopituitarism causing neurobehavioral and quality of life impairment. There are wide range of post-traumatic hypopituitarism (PTHP) has been reported ranging 10-58%. The aim of the study is to determine the incidence of the chronic anterior pituitary deficiency in patients with traumatic brain injury. Subsequently determine the risk factor and the outcome of the patient with chronic anterior pituitary dysfunction.

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A total 33 (31%) were noted to have anterior pituitary dysfunction. The mean age was 36.97 ± 12.96 years old with a median of 35 years old. Out of 33 patients, 27 (32.5%) were male and 6 patients were female (27.3%). Chronic anterior pituitary dysfunction also was seen in more patients with a severe traumatic head injury around 47.1%, a total of 23 patients sustained a severe head injury as compared to a moderate head injury (8 patients, 38.1%) and 2 sustained mild head injury (5.6%). The mean duration after the onset of trauma was 10.3 months ± 1.79 and the median was 11 months. Chronic anterior pituitary commonly found in the patient enrolled in the study at 11 and 12 months post-trauma. All patient with pituitary dysfunction had positive CT brain findings. Out of 33 patients, 22 had SAH at the basal cistern and 27 patients had a base of skull fracture. 52.1% of the patient underwent surgical intervention and 8 patients didn't undergo any surgical intervention. Out of all 33 patients with chronic anterior pituitary dysfunction, 84.8% involved 1 axis and another 5 patients had 2 axes involved. Binary logistic regression analysis studies the relationship between each of the variables and showed that severity of the head injury ($p < 0.001$), prolonged duration of hospital stay ($p=0.014$), radiological findings of a base of skull fracture($p <0.001$), and presence of SAH at basal cistern ($p<0.001$) was significantly associated with chronic anterior pituitary dysfunction There was a significant difference seen in SF36 marks, where the patient with anterior pituitary dysfunction has the lower SF-36 marks 56.3± 10.3.

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Keywords: chronic anterior pituitary dysfunction, traumatic brain injury, quality of life, SF36.

3.3 Introduction

Traumatic brain injury is the leading cause of death and disability in young adult with the consequences ranging from physical disabilities to long term cognitive, behavioural, psychological and social defect. These long-term consequences make traumatic brain injury a public health problem. Based on the head injury's census of Neurosurgical department, Hospital Sultanah Aminah, about 998 cases and 982 cases of head injury in respective 2016 and 2017 for adult population. Out of the 998 cases of head injury cases, severe head injury comprises 335 cases and moderate head injury comprise of 102 cases. For 2017, there are 324 cases for severe head injury and 98 cases for moderate head injury.

Hypopituitarism is defined as the total or partial loss of anterior and posterior pituitary gland function that is caused by pituitary or hypothalamic disorders. A variety of diseases may cause hypopituitarism and, accordingly, this disorder can be divided into two types depending on its cause primary and secondary cause. Traumatic head injury is one of the common cause for

secondary hypopituitarism. The incidence of hypopituitarism after a TBI seems to be more frequent, ranging 30-70%. (Kim, 2015)

Post-traumatic endocrine dysfunction has been reported as one of the complications of traumatic brain injury which cause serious physical and mental effects in patient with traumatic brain injury. A majority of survivors of moderate or severe TBI have residual neurobehavioral (NB) deficits, depression, and/or poor quality of life. One hypothesis receiving much attention is that TBI- induced hypothalamic-pituitary dysfunction may contribute to poor quality of life in many TBI survivors(Behan and Agha, 2007). Given the pituitary gland's confinement within the sella and tethering to the hypothalamus by the infundibulum, the neuroendocrine axis is susceptible to primary mechanical insults and secondary insults from hypotension, hypoxia, anemia, and brain swelling(Agha *et al.*, 2004).

Several recent cohort studies have documented long-term hormonal dysfunction after moderate or severe TBI. Collectively, these studies indicate that 25 to 40% of such TBI patients will develop chronic hormonal deficiencies, with the somatotroph and gonadotroph axes being most commonly affected and the thyrotrophin and corticotrophin axes being affected less frequently. A study prospective study showed that 50.9% of TBI had at least one anterior pituitary hormone deficiency after one year of TBI. Recent cross-sectional studies show that anterior pituitary dysfunction after traumatic brain injury is more common than expected, with a prevalence of 30–70% of hormonal abnormalities present after TBI(Dusick *et al.*, 2012).

Undiagnosed hypopituitarism might lead to life-threatening hormonal crisis, and until now it has not clear whether hormonal replacement might lead to

additional benefit in post- traumatic rehabilitation due to positive effects on cognition and body composition(Schneider *et al.*, 2006)

In a study, hormonal assessments in a very early phase after TBI (mean 12 days after trauma) indicated a substantial prevalence of pituitary deficiencies. However, in this early phase, it is not clear whether these hormonal changes are specifically due to brain trauma or are an unspecific reaction to critical illness. The frequency of chronic hypopituitarism (generally accepted as lasting at least 3 months) after TBI varies widely between the studies, most report a range of 15%–50% (Tanriverdi and Kelestimur, 2015).

The pathophysiology of anterior pituitary hormone deficiency following TBI remains incompletely understood, but current evidence has indicated a role is played by both direct mechanical injury and injury from hypotension, hypoxia, anaemia and brain swelling causing restriction of flow in the long hypophyseal portal vessels. Support of this concept comes from autopsy studies where up to one-third of patients with a fatal head trauma had anterior pituitary gland necrosis(Dusick *et al.*, 2012)

The clinical picture depends on the severity of hypopituitarism and the number of deficient anterior pituitary hormones. The clinical presentation seen in hypopituitarism varies from very subtle findings, which are often not discovered unless a very careful medical history and physical examination have been undertaken, to life-threatening conditions in which patients are seen in the emergency department because of severe manifestations of pituitary failure, such as adrenal crisis, severe hypotension, hypoglycemia and hypothyroidism. Because the mild/subtle manifestations due to hypopituitarism could result from different causes, most patients with hypopituitarism remain undiagnosed and

thereby untreated. (Tanriverdi and Kelestimur, 2015)

The data regarding the natural history of TBI-induced hypopituitarism are extremely limited. In a prospective study covering five years, GH deficiency was found to be the most common pituitary hormone deficit at one, three and five years following TBI. It was also reported that most of the pituitary hormone deficiencies improved over five years, but a substantial number of patients still had hypopituitarism at the fifth year. Some patients, although rarely, may develop new onset hypopituitarism or pituitary dysfunction may worsen over the years (Tanriverdi and Kelestimur, 2015; Krewer *et al.*, 2016).

In contrast, in patients with TBI-induced hypopituitarism, the presenting symptoms are often related to deficient anterior pituitary hormones only. Thus, the clinical picture in patients with hypopituitarism due to TBI is apparently related to the severity of pituitary hormone deficiencies. Current data suggest that isolated GH deficiency is probably the most common anterior pituitary hormone deficiency(Tanriverdi *et al.*, 2006; Tanriverdi and Kelestimur, 2015). Among the clinicoradiological parameters, diffuse axonal injury and basal skull fracture were found to be associated with increased prevalence of TBI-induced hypopituitarism(Tanriverdi and Kelestimur, 2015).

The Endocrine Society Clinical Practice Guidelines published in 2016 provides recommendations for the diagnosis of hypopituitarism. The guideline recommends measuring serum cortisol levels at 8 - 9 am as the first-line test for diagnosing central adrenal insufficiency (AI). A cortisol level < 3 µg/dL is indicative of AI and a cortisol level > 15 µg/dL likely excludes an AI diagnosis. For central hypothyroidism, a free T4 level below the laboratory reference range

in conjunction with a low, normal, or mildly elevated TSH in the setting of pituitary disease is usually confirmatory. In males with suspected hypogonadism, it is recommended to measure the serum testosterone, FSH, and LH in the absence of acute/subacute illness and before 10 am (after an overnight fast) combined with a serum prolactin (PRL) level. In the presence of oligomenorrhea or amenorrhea, it is recommended to measure serum estradiol (E2), FSH, and LH. Clinicians should exclude other causes of menstrual irregularities related to impaired ovulation. For postmenopausal women, the absence of high serum FSH and LH is sufficient for a diagnosis of gonadotrope dysfunction (provided the patient is not on hormone replacement therapy(Krewer *et al.*, 2016).

The 36-Item Short Form Health Survey questionnaire (SF-36) is a very popular instrument for evaluating Health-Related Quality of Life. The SF-36 Health Survey has been shown to yield reliable scores for scales measuring eight dimensions of health status and for summary measures of physical and mental health components. The SF-36 measures eight scales: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). This questionnaire is developed at RAND as a part of the medical outcome study. RAND grants permission to use RAND 36- Item Short Forms Health Survey. No further written permission is needed for use of this health survey. Researcher will provide a credit line when printing and distributing this document acknowledging that is was developed at RAND as a part of medical outcome study(*36-Item Short Form Survey (SF-36)* | *RAND*, 2004).

Andelic et al. used the SF-36 to examine QoL of patients after TBI. They found that all dimensions were affected in their patients (Andelic *et al.*, 2009). Another study showed the results of the SF-36 after 6 months indicate a better QoL for patients with treated Post Traumatic Hypopituitarism than for patients after TBI without endocrinological impairment, although this discrepancy is not statistically significant (Nourollahi *et al.*, 2014).

The study aims to evaluate out the incidence of the chronic anterior pituitary deficiency in patients with traumatic brain injury in the Neurosurgical department, Hospital Sultanah Aminah, Johor Bahru and to identify predictive factors that increase risk of chronic anterior pituitary deficiency after traumatic brain injury and to assess the quality of life patients with chronic anterior pituitary dysfunction.

3.4 Methodology

3.4.1 Research design

This is a prospective study. Approval was obtained from the Medical Research & Ethics Committee of the Ministry of Health Malaysia and registered in the national register for clinical trials registration ID: NMRR-20-1575-53747.

3.4.2 Research location and duration

Data from patients who fulfilled the inclusion criteria from the Hospital Sultanah Aminah Johor Bahru and treated for traumatic head injury during the period of October 2019 to October 2020, were obtained and analysed. Neurosurgery Department of HSAJB is Southern Malaysia's neurosurgery centre where it consists of Brain suite with 2 operating theatres, 10 bed Neuro HDU and

3 neurosurgery wards. Based on the head injury's census of Neurosurgical department, Hospital Sultanah Aminah, about 998 cases and 982 cases of head injury in respective 2016 and 2017 for adult population. Hospital Sultanah Aminah was chosen for this study because it is a tertiary centres where neurosurgical services are led by consultant neurosurgeons and supporting team by the endocrinologist in assisting treatment of head injury with hypopituitarism.

3.4.3 Study population

All patients who sustained traumatic head injury who were admitted to HSAJB and fulfilled the inclusion and exclusion criteria were included in the study. The inclusion criteria for patients in this study were patients with traumatic head injury, age between 20- 60 years old and had history of head injury 3 month prior to enrolment into the study. Patient who had traumatic head injury in chronic vegetative state with low life expectancy, was diagnosed or taking hormonal treatment prior to the trauma and pregnant woman will be excluded from the study.

3.4.4 Method of research

Patient will be selected and will be given research ID after consented for the study. For patient with good cognitive function who understand Malay or English will fill up a questionnaire on their own. Estimated time to fill up the questionnaire is 10- 20 minutes. If they unable to complete the questionnaire on their own, Primary investigator will explain the question to the respondent or caretaker. Primary investigator will fill up the form based on the answer given. Subsequently they will be given an appointment date for blood taking at next clinic

appointment within 2 week's time. The result from the questionnaire will be converted to 100-mark scale via calculator provided by RAND.

For the blood investigation, patient is required to be fasted and sample to be taken at 8- 9 am in the morning. Venipuncture done, 10 cc of blood sample taken and kept in 2 sodium heparinized bottle and 1 plain tube. The sample which is serum cortisol, LH, FSH, T4 and TSH will be sent to biochemistry lab and processed. Investigation for growth hormone was excluded in this study. The result of the hormonal level will be reviewed by primary investigator and under guidance of the endocrinologist (table 1). Their admission record will be traced, and clinical data will be taken. The radiological imaging was recorded based on official radiologist report.

3.4.5 Statistical analysis

The data analysis will be done using the SPSS version 26 statistical software. Descriptive date will be expressed as mean ± standard deviation (SD) unless otherwise stated. Frequency test will be used to determine the incidence of the Chronic Anterior Pituitary Deficiency in patients with Traumatic Brain Injury and the outcome (quality of life). Other parameters such as age, gender, severity of traumatic head injury, length of stay, duration post trauma, mode of treatment and radiological findings were put into the binary logistic regression analysis to determine the relationship of the parameters with chronic anterior pituitary deficiency.

3.5 Results

3.5.1 Demographic and Clinical Characteristic

A total of 105 patients who sustained a traumatic head injury was fulfilled the inclusion criteria and were enrolled in the study. Clinical characteristic of the patients included is summarized in Table 2. Of 105 patients 83 (79%) patients were male and 22 (21%) were female. The age distribution of patients showed 62.9 % were young adults (18-40 years old) and 39% were middle-aged adults (41-60 years old). The mean age was 36. 91 ± 12.42 years old. The patient was enrolled in the study around 9.88 ± 2.29 month after the trauma, with the minimum duration was 6 months and the maximum duration was 15 months after the trauma. A total of 48 (45.7%) patients sustained a severe head injury, 21(20%) patients sustained a moderate head injury and 36 (34.4%) patients with a mild head injury. 58.1% (61) of the patient had positive CT Brain findings meanwhile 44% had negative CT Brain findings. Out of 105 patients, 48 patients underwent surgical intervention. 22 patients (21%) undergo decompressive craniectomy, 21 patients (20%) undergo craniotomy and 7% had intracranial pressure probe inserted. Around 53 (50%) of the patient had 1 to 14 days stay in the hospital, meanwhile, only 5 patients (4.8%) had prolonged hospital stay for more than 30 days. We also observed that the mean for the SF36 was 70 ± 13.13 with the highest marks was 90 and the lowest was 30. Of this group of patients, there were 33 patients (31.4%) developed chronic anterior pituitary dysfunction and 72 (68.6%) of the patient had no abnormality.

3.5.2 Chronic Anterior Pituitary Dysfunction

Table 3 showed the clinical comparison of the patient with anterior pituitary dysfunction with the patient without pituitary dysfunction. Out of 105 patients, 33 were noted to have anterior pituitary dysfunction. The mean age was 36.97 ± 12.96 years old with a median of 35 years old. Out of 33 patients, 27 (32.5%)

were male and 6 patients were female (27.3%) who developed anterior pituitary dysfunction. The difference in gender is not a risk factor to develop chronic anterior pituitary dysfunction (p-value 0.637). Chronic anterior pituitary dysfunction also was seen in more patients with a severe traumatic head injury around 47.1%, a total of 23 patients sustained a severe head injury as compared to a moderate head injury (8 patients, 38.1%) and 2 sustained mild head injury (5.6%).

The mean duration after the onset of trauma was 10.3 months ± 1.79 and the median was 11 months. Chronic anterior pituitary commonly found in the patient enrolled in the study at 11- and 12-months post-trauma. All patient with pituitary dysfunction had abnormal CT Brain findings. Out of 33 patients, 22 had SAH at the basal cistern and 27 patients had a base of skull fracture. 52.1% of the patient underwent surgical intervention and 8 patients didn't undergo any surgical intervention. The most procedure done was decompressive craniectomy, followed by craniotomy and ICP probe insertion.

Univariate logistic regression analysis (Table 4) studies the relationship between each of the variables and showed that severity of the head injury ($p < 0.001$), prolonged duration of hospital stay ($p=0.014$), radiological findings of a base of skull fracture($p <0.001$), and presence of SAH at basal cistern ($p<0.001$) was significantly associated with chronic anterior pituitary dysfunction. This indicates that the severity of the head injury, prolonged hospitalization, and the radiological findings were the factors associated with developing chronic anterior pituitary dysfunction after trauma. 23 of the patients had a base of skull fracture and another 31 had subarachnoid hemorrhage present in their basal cistern. Both of these parameters are a significant predictor for developing chronic anterior

pituitary dysfunction. The odd ratio of developing anterior pituitary dysfunction if the patient had a base of skull fracture is 4.32 with 95%CI (1.781,10.497). The odd ratio for patients with subarachnoid hemorrhage at the basal cistern was 3.33 with 95%CI (1.401,7.932). We also observed that all the patients that had pituitary dysfunction had prolonged stays in the hospital (84.8%) compared to the patients without pituitary dysfunction. There was a significant difference seen in SF36 marks, where the patient with anterior pituitary dysfunction has the mean SF-36 marks 56.3± 10.3 as compared with no pituitary dysfunction 77.74± 7.73.

Out of all 33 patients with chronic anterior pituitary dysfunction, 84.8% involved 1 axis and another 5 patients had 2 axes involved. Table 5 showed the most affected hormone by head trauma is the gonadotroph (54.5%) axis followed by thyrotrophin (42.4%) and corticotrophin (18.2%) axis. A single hormonal defect was the most prevalent abnormality in 28 patients followed by the 2 axes in 5 patients, but no patient was diagnosed with three-axis dysfunction.

3.6 Discussion

Traumatic brain injury defined as a change in brain function or other evidence of brain pathology caused by external forces and well recognized public health problem worldwide. In Malaysian own statistic, head injury was the fifth (7.86%) commonest cause of hospitalization. There were 250 patients who sustained traumatic head injury had been admitted to Neurosurgery Department Hospital Sultanah Aminah Johor Bahru in 2019.

Being the major referral and tertiary neurosurgical centre, Hospital Sultanah Aminah Johor Bahru serves as the only largest referral centre for a traumatic head injury cases in the entire state of Johor and Southern region of

peninsular Malaysia. 105 patients enrolled in the study. The high proportion of male in relation to females in the study is similar as other published studies. (Tanriverdi and Kelestimur, 2015; Yaseen, Al-Khaqani and Mansour, 2018). This is one of the prospective studies done in Southeast Asia that studies on the prevalence of chronic anterior pituitary dysfunction and the outcome of patients with the pituitary dysfunction.

31% of our patient had developed certain pituitary dysfunction, this observation is almost similar with previous study that were ranging between 15 to 60 %. A multicentred study showed 14.1% of their patient had diagnosed with post traumatic hypopituitarism(Krewer *et al.*, 2016). Another study, showed 60% out of their 28 patient had pituitary dysfunction(Yaseen, Al-Khaqani and Mansour, 2018). The studies by Aimaretti et all showed 35% of their traumatic head injury patient had at least one pituitary axis affected (Aimaretti *et al.*, 2007). Our study showed almost comparable result with the previous studies with similar inclusion and exclusion criteria.

Single hormonal defect was far more common than combined hormonal deficiencies, a common observation found by us and other authors like Lieberman et al*.,* where he found 51% versus 17% for single versus combined deficiencies (Lieberman *et al.*, 2001), another study found 28.5% versus 4.5% ((Krewer *et al.*, 2016)) and Tanriverdi et al*.* 41% versus 10%, respectively(Tanriverdi and Kelestimur, 2015), which are in concordance with our findings. Most of the investigators had found that GH deficiency is the most prevalent pituitary endocrine defect after TBI, as Tanriverdi et al*.,* 44%(Tanriverdi and Kelestimur, 2015) Aimaretti et al*.,* 18.6%(Aimaretti *et al.*, 2007); Klose et al*.,* 15% followed by gonadal axis then the thyrotrophin axis(Klose *et al.*, 2007).

However in this study did not include growth hormone, we had the gonadal axis as the most common axis affected followed by thyrotropin and corticotrophin.

Given the hypothesis of developing post traumatic hypopituitarism is related to the primary mechanical insults of the sella turcica and secondary insults from hypotension, hypoxia, anemia, and brain swelling, the aim of this study is to find out the risk factor of developing anterior pituitary dysfunction and the outcome of the patient with chronic pituitary dysfunction. Severity of the head injury is one of the risk factors of developing pituitary dysfunction. As seen in the Schneider's series the prevalence of pituitary dysfunction in cases of severe, moderate, and mild TBI were 35.3%, 10.9%, and 16.8%, respectively(Schneider *et al.*, 2006). Our study showed slightly high prevalence compare to the case series 47.1%. This is likely due to the high incidence of severe head injury in our study. The severity of the head injury related with the radiological finding, brain swelling and midline shift which supported the pathophysiology of developing hypopituitarism post traumatic head injury.

Finding of the association between radiological findings and the development of pituitary dysfunction was the aim of previous studies. Yang *et al*. found that basal skull fracture was more significantly associated with pituitary dysfunction than ICH(Yang *et al.*, 2016). Similarly, our studies showed that the base of skull fracture was a risk factor of developing pituitary dysfunction. We also found that having a subarachnoid bleed at the basal cistern also raised the risk of developing anterior pituitary dysfunction (70.5%). In study by Kelly et al showed, 40% patients had SAH at the cistern developed pituitary dysfunction(Kelly *et al.*, 2000). The study by Yaseen, Klose and Schneider also showed that prolonged hospital stay are one of the contributing factors of pituitary

dysfunction(Schneider *et al.*, 2006; Klose *et al.*, 2007; Yaseen, Al-Khaqani and Mansour, 2018). In study by Yaseen did mention regarding increased prevalence of pituitary dysfunction for patients with prolonged ICU stay however was not studied by our paper.

Post-traumatic endocrine dysfunction has been reported as one of the complications of traumatic brain injury which cause serious physical and mental effects in patient with traumatic brain injury. A majority of survivors of moderate or severe TBI have residual neurobehavioral (NB) deficits, depression, and/or poor quality of life. One hypothesis receiving much attention is that TBI- induced hypothalamic-pituitary dysfunction may contribute to poor quality of life in many TBI survivors. In individuals with moderate-to-severe TBI, almost 70% of the individuals attained good functional recovery on early follow-up (3-month) and 30% still have a poor functional outcome(Agha *et al.*, 2004). However with pituitary hypopituitarism, showed marked reduction in quality of life as compare to traumatic head injury population without hypopituitarism. this is consistent with other study such as Andelic et al. who also used the SF-36 to examine QoL of patients after TBI where they found that all dimensions were affected in their patients(Andelic *et al.*, 2009). Study by Nourollahi et al also supports that post traumatic hypopituitarism further deteriorates the already impaired quality of life after traumatic brain injury(Nourollahi *et al.*, 2014)

3.7 Study Limitations

The main limitation of the study is unable to do a full array of pituitary profile especially the growth hormone. Our patients only had the level of cortisol, T4, TSH, LH and FSH measured. Growth hormone study was not available in the

study centre; thus growth hormone was not included in the study. Subsequent study with full pituitary profile and early intervention of treatment should be done to see the response of the patient towards the treatment of pituitary dysfunction. Longer duration of the study also will give more information and to study the risk factor of chronic pituitary dysfunction. Furthermore, this study only involved a single centre, which the result doesn't show the overall picture of pituitary dysfunction in the entire region. Hence a multicentred study should be conducted in the future with only single TBI group study which is either severe, moderate or mild with fixed time for blood test and outcome assessments.

3.8 Conclusion

The prevalence of hypopituitarism was estimated at 31%. Indicators of increased TBI severity, prolonged hospitalization and positive finding of radiological assessment (presence of SAH and base of skull fracture). Post traumatic chronic anterior pituitary dysfunction also related with poor quality of life as showed by low SF36 marks. Despite SF 36 is not a specific measurement tools for post traumatic hypopituitarism, it can be used as screening tools prior to invasive screening such as blood taking. Therefore early detection and intervention can be done to improve the quality of life of post traumatic patients.

3.9 References

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