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Anterior Pituitary Gland Dysfunction following Mild Traumatic Brain Injury

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Declaration

This thesis has been composed by myself and the work has not be submitted for any other degree or professional qualification. All included publications are my own and work that I have done in collaboration with others. My contribution and those of the other authors have been attributed as appropriate.

John Emelifeonwu

Contribution to PhD

The research question for this PhD was proposed by Professors Andrews and Strachan and Mr Statham, who all supervised the project. Together, we wrote the ethics application and applications to research and development. We also created the PitSTOP study protocol and the questionnaires for the survey which was distributed amongst British and Irish neurosurgeons. I organised and carried out patient recruitment with the support of the Emerge research team who are based in the emergency department of the Royal Infirmary of Edinburgh. I authored the included papers with the support from the acknowledged collaborators.

Abstract

Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide. Many sufferers never return to their pre-injury level of function and have life-long health and socioeconomic problems that limit their daily activities. In the last two decades there has been renewed interest in whether post-TBI anterior pituitary dysfunction (PTPD) contributes to morbidity.

The PhD focuses on patients with mild TBI (mTBI). My aims are to explore the scientific evidence for PTPD including its prevalence in the TBI population and how it is currently managed by Neurosurgeons in Great Britain and Ireland. I also performed a prospective, feasibility study to determine if a larger study of the acute and long-term effects of isolated mTBI on anterior pituitary function was deliverable. Pilot data are presented in this thesis.

Our systematic review demonstrated that PTPD occurs in one-third of patients 12 months after TBI and we found disparities in surveillance practices across the UK and Ireland. We demonstrated in our feasibility study that 44% of patients have abnormal anterior pituitary hormone activity in the first 7 days following mTBI and 20% of patients who were followed up at 6 months had evidence of PTPD. We found no evidence that PTPD occurs as a result of structural damage to the anterior pituitary gland, suggesting other, yet to be determined factors play a role. A large, prospective, multi-centre study is needed to better understand the pathophysiology and incidence of PTPD.

Lay Summary

In the past 4 decades, there have been great advances in the way we treat people that suffer traumatic brain injuries (TBIs). These advances mean that more people are surviving after a TBI. The most common type of TBI is the least severe for, mild TBI or mTBI. MTBI is the focus of this thesis. Many survivors of mTBI do not return to the level of function they were at before the TBI. For example, many people are unable to do the type of work and social activities they did before the TBI because of the disabilities they sustained. Many mTBI sufferers may have structural damage to their brains that explain their disability, but others do not have any obvious structural problems to explain their ongoing symptoms and disabilities.

In the last 2 decades, there has been resurgence in the theory that some people may damage their anterior pituitary gland during their initial injury and that this may account for at least some of the symptoms in patients that have ongoing problems. The anterior pituitary is the front part of a pea-sized organ that sits under the brain and is one of the most important organs for homeostasis (balancing hormones in the body). The hormones secreted by the anterior pituitary control a range of functions from ability to concentrate and libido to metabolic rate and energy levels. Problems with anterior pituitary hormone secretion can be treated with replacement hormones. This is significant in the management of patients following TBI as treatments are readily available.

There were 3 main aims in this project. The first of which was to determine how common anterior pituitary dysfunction is after TBI. I did this by performing a review of the literature. Secondly, I designed a study to prospectively research the incidence of anterior pituitary dysfunction in patients with mild forms of TBI. Finally, I used the study design to conduct a feasibility study to determine whether the design protocol is workable. The results of this feasibility study gave information about how commonly anterior pituitary dysfunction occurs in patients with mild forms of TBI.

I found that one-third of patients develop anterior pituitary dysfunction when they are tested one year or more following TBI. I also found that UK and Irish neurosurgeons have very different ways of monitoring patients because of the lack of guidelines. Finally, I found that the protocol I designed was feasible and the results showed that one third of patients with mild forms of TBI developed anterior pituitary gland dysfunction when tested at 6 months even though there was no structural damage to their pituitary gland. This shows that anterior pituitary problems are common after mTBI and a large study is now needed to work out how common it is and exactly what causes it.

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I would like to dedicate this thesis to everyone who's love, attention, care and unconditional support has been the catalyst for everything I have achieved. Florence, my little girl who has taught me that the pursuit of happiness needn't be arduous. To Alison, Mum, Dad, Nonso, Nnamdi, Chiedu, Alisa and Eloka. Thank you! To my illiterate grandparents whose hard work made sure I would not suffer the same fate. To Prof Andrews and Mr Statham for the opportunity and the support throughout. I am forever grateful. Thank you! To Miranda, Julia, Polly, Adam, Rachel and Mia and the rest of the Emerge team. Thank you! To Prof Strachan and Sister Dillon at the metabolic clinic. To the medical students who helped with projects. Last, but not least, I would like to thank the patients whose patience made this thesis possible.

CHAPTERS

Table of Figures

Tables

Introduction

1.1. Traumatic brain injury definition

Traumatic brain injury (TBI) is defined as an alteration in brain function caused by an external force. It is a major public health issue that affects between 150 and 300 people per 100000 in Europe, 229 per 100000 in England and in Scotland, approximately 65 people per year die from TBI[1] [2] [3]. TBI is a leading cause of death and disability among young people and has significant socio-economic consequences including unemployment and loss of independence[4]. The disease burden is significant.

According to the demographics and clinical assessment working group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health[5], "alteration in brain function" can be one (or more) of the following:

- Any period of loss of or decreased consciousness
- Any loss of memory for events immediately before or after the injury
- Neurological deficits
- Alteration in mental state at the time of injury. This includes confusion, disorientation or slow thinking

The severity of TBI is assessed by the post-resuscitative neurological status of the patient. The most commonly used assessment of neurological status is the Glasgow Coma Scale (GCS), which consists of the sum score of three components: assessments of patients' eye opening, verbal and motor responses in relation to

verbal or painful stimuli (figure 1).The minimum GCS score possible is 3 and the maximum is 15. A post-resuscitative GCS of 13-15 is usually considered a mild TBI, a GCS score of 9-12 is considered moderate and a GCS score of 3 to 8 is considered a severe TBI.

Mild TBI (mTBI) constitutes approximately 80% of all TBIs and is the focus of this PhD thesis. It was once thought that there were no long term consequences for most patients that suffer a mTBI. However, we now know that approximately 15% of these patients develop persisting physical, cognitive and emotional symptoms. Headaches are the most common, however other symptoms include fatigue, concentration and memory problems, irritability and anxiety. These symptoms are often non-specific and can persist for months or years following mTBI. They are often diagnosed under the umbrella term post-concussion syndrome (PCS).

PCS describes a cluster of symptoms that occur for longer than a few days (usually 2 weeks) following mTBI. These include headache, dizziness, irritability, difficulty concentrating, memory problems, fatigue, visual disturbances, sensitivity to noise, judgment problems, depression, and anxiety. These symptoms can also occur following all severities of TBI but only persist in a small number of patients.There is ongoing debate as to whether the symptoms are non-organic (psychological) or organic (neurological). One potential organic cause for PCS is post-TBI pituitary dysfunction (PTPD), specifically anterior pituitary dysfunction. In the last two decades, there have been several reports that PTPD occurs in a significant proportion of cohorts that are followed up long term. Two meta-analyses have both

concluded that approximately one-third of patients develop PTPD after TBI. The symptoms of anterior pituitary dysfunction overlap those of PCS**.** It is therefore conceivable that some patients diagnosed with PCS have neuroendocrine dysfunction. It has been hypothesised that up to 7% of all cases of hypopituitarism may be related to TBI[6].

There are a number of hypotheses about how pituitary function may become dysfunctional following TBI. Firstly, the neuroendocrine theory suggests that PTPD may be a maladaptive physiological process: the hypothalamo-pituitary-adrenal (HPA) axis is activated following TBI (and other stressors) and leads both to an increase in serum cortisol and disruption of its usual diurnal rhythm. Similarly, hyperprolactaemia may occur. These acute responses, which are often accompanied by suppression in the other hypothalamic-anterior pituitary (HP) axes, usually normalise over time. PTPD could be due to an abnormally sustained response of the pituitary gland to TBI.

A second theory suggests that the pituitary gland's location within the sella turcica, makes it susceptible to injury either at the time of TBI through direct impact on the bony sella or through compression during subsequent oedema. Furthermore, the anterior pituitary gland is supplied by branches of the hypophyseal portal vessels which, according to the vascular theory of PTPD, are also vulnerable to shearing during the acceleration and deceleration of the brain at the time of TBI**[7].** There have been numerous radiological and histopathological reports of damage to the pituitary and hypophyseal vessels in patients who succumb from TBI.[8 9 10]. It seems likely that

this mechanism of PTPD is more significant in moderate and severe TBIs than in mTBI.

Finally, the autoimmune theory, postulates that circulating anti-hypothalamic antibodies (AHAs) and antipituitary antibodies (APAs), develop following TBI and may play a role in the pathogenesis of PTPD. Tanriverdi and colleagues found APAs in 45% of TBI patients followed up over 3 years compared to none in age- and sex-matched control groups and found that patients with APAs were more likely to have PTPD[11]. However these findings are yet to be repeated by other researchers.

PTPD is potentially reversible with hormone replacement and it is therefore important that affected patients are identified and treated appropriately. Testing all TBI sufferers is not feasible because of the financial and time costs involved. The function of the anterior pituitary gland is assessed by checking the serum concentrations of the efferent hormones of the HP axes which are circulating growth hormone, thyroid hormones, cortisol, prolactin and the sex hormones testosterone, follicle stimulating hormone and leutinising hormone. Whilst the circulating concentrations of most of these hormones are closely regulated within a narrow range, cortisol and growth hormone concentrations vary throughout the day and therefore the function of the hypothalamo-pituitary somatotrophic (HPS) and the HPA axes are best checked with stimulation tests where hormone levels (cortisol or growth hormone) are checked prior to, and sometime after intravenous administration of agents that stimulate their release.

Assessing these two axes is therefore invasive, time-consuming and expensive. Less invasive methods for assessing adrenal function include single measurement serum cortisol assays and salivary cortisol. However, serum cortisol is the protein bound hormone rather than the free hormone. As a result its concentration depends on transport proteins like albumin and cortisol-binding globulin, the concentrations of which can be variable. By contrast, early morning salivary cortisol is a non-invasive method of assessing adrenal function, which unlike serum cortisol is not influenced by binding proteins and therefore is more reflective of the bioactive free hormone. However, its accuracy in diagnosing adrenal insufficiency remains to be fully established. Similarly, the value of serum insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) as less invasive methods of diagnosing growth hormone deficiency is contentious as they can be normal in patients with undisputed growth hormone deficiency[12].

Most of the evidence on PTPD comes from studies on patients with moderate and severe TBI. My PhD aims to determine the relationship between mTBI and PTPD. These patients are usually managed by non-specialist and are therefore rarely followed up and the outcomes from these patients are less clear. The current guidelines recommend that patients with mTBI should be screened if they present with symptoms of hypopituitarism.

1.2. Aims of PhD

The main aims of my PhD are:

1. Determine the prevalence of PTPD 12 months or more following TBI as described in contemporary literature
2. Determine the current surveillance practices for PTPD in the UK and Ireland
3. Design a study protocol to determine the prevalence of PTPD in patients with mTBI
4. Perform a feasibility study aimed at determining the prevalence of PTPD in patients with mTBI

1.3. Hypothesis

Some patients with mild TBI (mTBI) develop a consequent anterior pituitary dysfunction.

1.4. Methods

I will first explore the current literature on PTPD by performing a systematic review on the prevalence of PTPD in patients a year or more following TBI. This systematic review will allow me to explore the hypothesis that PTPD affects patients with mTBI as well as patients with moderate and severe TBI. I then sent out a questionnaire to members of the Society of British Neurosurgeons (SBNS), whose membership includes neurosurgeons based in the UK and Ireland to determine current surveillance practices.

The main part of the PhD involved designing a protocol for a study to determine the how mTBI affected pituitary function acutely and to determine the prevalence of PTPD 6 months following TBI. I then conducted a feasibility study using this protocol

and focusing only on patients with mTBI. This feasibility study allowed me to determine the prevalence of PTPD 6 months after TBI in patients with mTBI. The data from patients screened and recruited for this study allowed me then to determine the characteristics and short-term outcomes of patients presenting to the emergency department with mTBI.

All major components of the PhD have been published or submitted for publication. This is in keeping with the University of Edinburgh thesis guidelines point 1.12 “it is in the interest of candidates to include any relevant published papers in their thesis. When published paper are to be included as a thesis chapter these must include an introduction and conclusion and be bound into the thesis at the appropriate point. These should either be by the bookbinder, as a chapter, an appendix or an electronic copy”.

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Papers included in this thesis

1. Prevalence of Anterior Pituitary Dysfunction Twelve Months or More following Traumatic Brain Injury in Adults: A Systematic Review and Meta-Analysis.
   Emelifeonwu JA, Flower H, Loan JJ, McGivern K, Andrews PJD. *Brain Inj.* 2018;32(5):675-677.
2. A national survey of clinical practice of surveillance for post-traumatic brain injury hypopituitarism in the United Kingdom and Ireland.
   Emelifeonwu JA, Wiggins AN, Andrews PJD. Emelifeonwu JA, Wiggins AN, Andrews PJD. *Br J Neurosurg*. 2020 Feb;34(1):20-23.
3. Characteristics and short-term outcomes of patients presenting with mild traumatic brain injuries (mTBIs)
   Emelifeonwu JA, Tominey S, Pewsey J, Pickering A, Flower H, Andrews PJD (Submitted)
4. Anterior hypothalomo-pituitary dysfunctions occur in acute mild Traumatic Brain Injuries without evidence of structural damage to the pituitary gland
   Emelifeonwu JA, Strachan M, Statham PF, Farrell A, Andrews PJ (Submitted)
5. Should we check for anterior pituitary dysfunction in all traumatic brain injury patients?
   Emelifeonwu JA, Strachan M, Carson A, Andrews PJD (Submitted)

Exploring the knowledge landscape: Part 1

Paper One

Prevalence of Anterior Pituitary Dysfunction 12 months or more following Traumatic Brain Injury in Adults – A systematic review and meta-analysis

Introduction: In order to explore the current knowledge on pituitary dysfunction following TBI, I conducted a literature review. There have been reports that *de novo* anterior pituitary dysfunction can occur several months after TBI, even in patients in whom anterior pituitary function had previously been normal. I therefore focused on reporting the prevalence of pituitary dysfunction 12 months or more after TBI.

Prevalence of Anterior Pituitary Dysfunction 12 months or more following Traumatic Brain Injury in Adults – A Systematic review and Meta-analysis

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Keywords: traumatic brain injury; hypopituitarism; pituitary dysfunction

Prevalence of Chronic Anterior Pituitary Dysfunction 12 months or more following Traumatic Brain Injury in Adults – A systematic review and meta-analysis

Abstract

The objective of this study is to systematically review clinical studies that have reported on the prevalence of chronic post-traumatic brain injury anterior pituitary dysfunction (PTPD) 12 months or more following traumatic brain injury (TBI). We searched Medline, Embase and Pubmed up to April 2017 and consulted bibliographies of narrative reviews, selected articles and conference proceedings. We included cohort, case-control, and cross-sectional studies enrolling at least five adults with primary traumatic brain injury in whom at least one anterior pituitary axis was assessed at least 12 months following TBI. We excluded studies in which other non-traumatic brain injuries were indistinguishable from TBI. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) score. We also considered studies that determined growth hormone deficiency (GHD) and adrenocorticotrophic hormone (ACTH) reserve using provocation test to be at low risk of bias. Data were extracted by four independent reviewers and assessed for risk of bias using a data extraction form. We performed meta-analyses using random effect models and assessed heterogeneity using the I^2 index. We identified fifty eight publications, of which 29 (2,756 participants) evaluating prevalence of anterior pituitary dysfunction at least 12 months following TBI were selected for meta-analysis. Twelve of these were deemed to be at low risk of bias and therefore 'high quality' as they had NOS scores greater than 8 and had used provocation tests. The overall prevalence of at least one anterior pituitary hormone dysfunction for all 29 studies was 32% [95% CI 25 – 38%]. The overall prevalence in the 12 'high-quality' studies was 34% [95% CI

27 – 42%]. We observed significant heterogeneity that was not solely explained by the risk of bias. Studies with a higher proportion of participants with mild TBI had a lower prevalence of PTPD. Our results show that approximately one third of TBI sufferers have persistent anterior pituitary dysfunction 12 months or more following trauma. Future research on PTPD should differentiate between mild and moderate/severe TBI.

Keywords: Pituitary dysfunction, traumatic brain injury, anterior pituitary gland, brain trauma

Introduction

Traumatic Brain injury (TBI) is common, affecting between 90 and 250 people per 100,000 Worldwide. It is the leading cause of death and disability among young adults[1] and has significant socio-economic consequences including unemployment and loss of independence. Many sufferers also have long-standing physical and psychological symptoms that affect their rehabilitation and ability to re-engage socially[2]. These medical problems are commonly diagnosed under the umbrella term post-concussive syndrome (PCS) and are seldom investigated by specialists. Some of these patients will have 'organic' pathologies that remain undiagnosed[3]. One example is posttraumatic hypopituitarism (PTHP) or more accurately, posttraumatic pituitary dysfunction (PTPD) (as hyperprolactinaemia occurs more commonly than hypoprolactinaemia). PTPD was first reported over a century ago[4] but in the last two decades, a number of studies have attempted to understand the condition better including its prevalence and the risk factors for developing PTPD[5 6 7].

A decade ago, a meta-analysis of 14 studies (1137 patients) determined the prevalence of chronic PTPD to be 27.5% (95% confidence interval [CI], 22.8%-28.9%)[8]. This would make TBI by far the commonest cause of pituitary gland dysfunction. However, in this meta-analysis, there was non-selective inclusion of studies that had used different methods to assess pituitary function. Furthermore, there was no attempt to assess risk of bias of the included studies. Consequently, the reported prevalence of pituitary hormone deficits in the included studies varied considerably from negligible to nearly 50%. The lack of robust inclusion and

exclusion criteria for the studies included in Schneider and colleagues' meta-analysis has made their findings difficult to interpret and the clinical significance of PTPD still divides opinions. Finally, there are reports of spontaneous resolution within a year in some patients with PTPD whilst other authors have reported that patients sometimes develop spontaneous PTPD up to one year following TBI[9 10 11]. It follows that meta-analyses of prevalence statistics for PTPD should take into account this propensity for late spontaneous resolution and the risk of late development of PTPD following TBI.

Aims

Primary Aim

The primary aim of this meta-analysis is determine the prevalence of chronic anterior PTPD at least 12 months following TBI. We compared the differences in prevalence of anterior PTPD at 12 months or more between studies at high risk of bias and studies at low risk of bias. Risk of bias was determined using the Newcastle-Ottawa Score (NOS) and whether primary provocation testing was used for assessing GHD and ACTH reserve.

Secondary Aim

Our secondary aim was to determine the extent that TBI severity, determined by Glasgow Coma Scale (GCS) of participants, influenced the overall prevalence of anterior PTPD at 12 months or more.

Methods

Criteria for considering studies for this review

This review was performed following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group guidelines[12]. Studies were considered for inclusion if they were observational studies with case–control or cohort designs. Only papers written in English were considered for inclusion. Case series, descriptive reports and grey literature (unpublished abstracts) were excluded from the analysis. Participants in the studies were mostly adults (≥17 years old) that had sustained a TBI and were prospectively followed up with pituitary function blood tests. Papers reporting on PTPD in children were only included if the results from included children formed a small proportion (less than 10%) of the overall study population. The primary outcome measure was the prevalence (proportion) of PTPD at 12 months.

Definition of PTPD, Study selection and Quality assessment

PTPD was defined as dysfunction of at least one anterior pituitary hormone mostly manifesting as hormonal deficit but also as over- or under-production of prolactin at least 12 months following a TBI. The quality of included studies (and risk of bias)

was assessed using a modified version of the Newcastle-Ottawa scale (NOS) (supplementary appendix 2)[13]. The NOS assesses the quality of each study using a star system. Studies with NOS of 8 and above were considered to be at low risk of bias. Studies were considered to be at high risk of bias and therefore 'low quality' if the NOS was lower than 8. High risk of bias was indicated if there were no clear inclusion and exclusion criteria for participant selection, when volunteer sampling strategies were used, or when details surrounding clinical features and management of TBI relied on retrospective data or on patient recollection of events. Studies were also considered to be at high risk of bias when growth hormone deficiency (GHD) and secondary hypoadrenalism were primarily measured using baseline tests instead of dynamic (provocation) tests. Acceptable provocation tests for GHD included glucagon stimulation test, insulin tolerance test, growth hormone release hormone and arginine infusion test and growth hormone releasing hexapeptide-6 (GHRP-6) test, whereas acceptable provocation tests for secondary hypoadrenalism included short synacthen test (SST) or corticotrophin releasing hormone (CRH) test. Studies in which baseline GH or Insulin-like growth factor-1 (IGF-1) and cortisol were done as screening tests prior to a full provocation test were considered at high risk of bias.

For all other pituitary axis hormones (thyrotropin, gonadotrophin and prolactin) dysfunction was defined as follows: secondary hypogonadism in men was defined as basal free testosterone values below the normal range defined by the study group with or without normal or low values of gonadotrophins. In women, hypogonadism was defined as the development of menstrual disorders or amenorrhoea following TBI or as basal value of oestradiol below the cut-off defined by the study team

(typically, this was ≤ 0·08 nmol/l). Secondary hypothyroidism was suggested by a free T4 value less than the cut-off defined by the authors in presence of normal or low TSH values. Studies were included if they reported on the prevalence of PTPD despite this not being the primary objective of the study but if there was enough information about patient selection to meet our inclusion criteria[14].

Search strategy for identification of studies

Sources of published data included electronic databases Pubmed, MEDLINE and Embase (inception to April 2017) and written in the English language. Bibliographies of review articles were checked for additional studies not identified by the electronic search. The MEDLINE search strategy was a variation of the strategy previously reported by Lauzier and colleagues[15].

Studies selection

Four authors (JE, KM, HF, JL) independently screened titles and abstracts and the full articles were retrieved for relevant studies and reviewed to determine their suitability for final inclusion. Reviewers were not blinded to the authors' names or affiliated institutions. Articles were selected for inclusion based on the pre-defined selection criteria. The output of all searches was exported into Microsoft Excel and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[16] statement was followed at all three stages (figure 1). Disagreements were resolved by consensus.

When an article reported on several types of brain injuries only TBI data were used. We omitted articles in which TBI data were indistinguishable from other types of brain injury such as blast injuries[17 18], subarachnoid haemorrhage[19] or chronic subdural haematoma[20] and data related to repetitive brain injuries for example in relation to long-term involvement in contact sports[21 22].

Data extraction and statistical analysis

Data including patient demographics, injury severity, cause of TBI and prevalence/proportion of PTPD in the cohort were extracted using a data extraction form. R Studio, version 3.4.1, was used for statistical analysis. A random effects model in the metafor package was used to calculate pooled prevalence estimates with 95% CIs. Heterogeneity was assessed using the I^2 measure with significance set at $p < 0.05$.

Patient involvement

There were no patients involved at any stages of setting up or executing this research. There was also no patient involvement in the analysis of results and writing up the final manuscript. The results of this study have not been made available to any patient groups.

Results

Our initial search identified 1655 publications. A flow diagram of the selection process is presented in Fig. 1. A total of 418 duplicate publications were removed, and of the remaining 1237 original articles, 1160 were excluded as irrelevant to the study objectives based on their titles and abstracts. A total of 58 full-text articles were reviewed and 29 articles that did not meet the selection criteria were excluded[23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51] (table 1). Ultimately, 29 studies met the inclusion criteria. Twelve studies were deemed to be at low risk of bias with NOS ≥ 8 and provocation testing used for GHD and ACTH reserve[52 53 54 55 56 57 58 59 60 61 62 63]. The median age of patients in the 29 studies was 37.45 years and the median time to testing following TBI was 19.5 months (table 2). The median GCS of participants at the time of injury was 8 (range 4 to 12). Information about the cause of TBI was available for two-thirds of participants and the commonest causes of TBI were road traffic accidents (53%), falls (28%) and assault 6%). There were 17 studies determined to be at high risk of bias (table 2).

Primary aim - Prevalence of anterior PTPD at 12 months or more after TBI

The 29 included studies had 2756 participants (67% males). The overall prevalence of any chronic anterior PTPD (more than one hormone deficiency) was 31.86% [95% CI 25.25– 38.46%] (**Figure 2)**. Using a fixed effects model the I^2 was 95.89%. The prevalence of individual hormone deficiencies for all 29 studies at 12 months are shown in table 2. The mean ages of the cohorts in the twelve studies (1112 participants) deemed to be at low risk of bias ranged from 31 – 53 (median 35.76) and the median time from TBI to testing for pituitary function was 18 months. Growth hormone deficiency was the most common individual hormone deficiency at 12 or

more months following TBI with a mean of 22% (range 2.7% to 63.6%) and hypo- and hyperprolactinaemia were the least common with averages of 3.6% (range 0 to 14.3%) and 4.8% (range 0 – 11.8%), respectively. Hypogonadism was the second most common deficiency (average 10.2%; range 0-28%), followed by secondary hypoadrenalism (10%; range 0 – 43%) and hypothyroidism (6.2%; range 0-22%).

To determine the influence of study quality on prevalence of PTPD, we compared the overall prevalence of studies at high risk of bias with the overall prevalence of studies at low risk of bias. The combined prevalence of PTPD at 12 months or more following TBI in the 12 studies deemed at low risk of bias (1112 participants) was 34.05.% [95% CI 26.5. – 41.6%]. The rate of PTPD varied considerably from 5.4% to 75%. There was also significant statistical heterogeneity: using a fixed effects model the I^2 was 86.5% (see figure 2). TBI severity was reported in 11 of the 12 studies and of these, only 16.4% of the included participants had a mild TBI (total of 920 participants; 67% male). The median GCS at the time of injury for participants in these 12 studies was 8. The commonest reported causes of TBI were road traffic accidents (54%) and falls (23%). The most common hormone deficiency in these 14 studies was GH deficiency (22.8%), followed by secondary hypoadrenalism (12%) and secondary hypogonadism (8.6%). Secondary hypothyroidism was uncommon as were hyper- and hypo-prolactinaemia. Individual hormone deficiencies with confidence intervals are listed in table 3. Seventeen studies (1644 participants; 67.6% male) were deemed to be at high risk of bias either because they had not used provocation tests to determine GHD or ACTH reserve or because they had an NOS score below 8 [64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80]. We divided these 17 studies into 2 groups for comparison: those determined to be at high risk of bias based on

NOS < 8 (5 in total) and those that did not use provocation tests for GHD and secondary hypoadrenalism (9 in total). Three studies had both an NOS < 8 and had not used provocation testing in their primary assessment of pituitary function[64 65 80]. The overall prevalence of PTPD in these 17 studies was 30.3% [95% CI 20.3-40.3%). Using a fixed effects model the I^2 was 97.54%. There was no statistical difference between the overall prevalence of the 'high' and low quality studies (p=0.77). Studies with NOS scores of 7 had a lower overall prevalence of PTPD at 12 or more months compared to studies with NOS of 8 (24% vs. 35%) but this difference did not reach statistical significance (p = 0.12). There was also no statistically significant difference between the overall prevalence of PTPD reported for studies that used primary provocation tests versus studies that did not (p=0.72).

Finally, we calculated the overall prevalence of more than one hormone dysfunction at 12 or more months following TBI for all 29 studies. This overall prevalence dropped significantly to 6.7% [CI 0.45 to 8.8%] (figure 3).

Secondary aim - Influence of injury severity

To determine whether injury severity as determined by GCS influenced the reported prevalence of chronic anterior PTPD at 12 months, we divided all 29 studies into studies in which at least 50% of participants had suffered a mild TBI (GCS 13-15) and studies in which less than 50% of participants had suffered a mild TBI. Nineteen of the 29 studies[35 36 37 38 39 40 41 42 43 44 45 46 48 49] had less than 50% of participants with mild TBI (greater proportion with moderate and severe TBI) and 5 had more than 50% participants with mild head injury (lower proportions with moderate and severe TBI)[28 46 47]. Five studies did not report the injury severity of participants. The overall

prevalence of PTPD was higher for studies in which less than 50% of included participants suffered mild TBI (31.7%; 95% CI 24.8 – 38.7%) compared to the group in which more than 50% of participants suffered mild TBI (20.6% ;95% CI 3.5%-37.6%). However, this difference did not reach statistical significance (p=0.44)(figure 4).

Discussions

In our meta-analysis we compared the overall prevalence for PTPD 12 months following TBI reported for studies at low risk and studies at high risk of bias. We found a similar overall prevalence in both groups. The overall prevalence of deficit of at least one anterior pituitary hormone in both groups were 29% and 31.2% respectively, suggesting that a significant number of TBI sufferers are at risk of developing anterior PTPD at least one year following TBI. This prevalence rate is comparable to previous meta-analyses by Schneider and colleagues and more recently Lauzier and colleagues[8,15]. Schneider and colleagues were criticised for not differentiating between studies at high and low risks of bias, particularly the different methods that were used to test GHD and secondary hypoadrenalism. Our results however suggest that this did not make a difference to the overall prevalence of approximately one-third. The prevalence of PTPD was however influenced by injury severity and the greater the number of patients with mild TBIs in a cohort, the lower the prevalence of PTPD.

Although the clinical significance of chronic anterior PTPD remains controversial, untreated hypopituitarism may contribute to the neurobehavioral problems suffered by many TBI patients, which may ultimately affect rehabilitation in TBI sufferers. Hormone-replacement therapy in these patients may improve these symptoms.

Although several groups have provided guidelines for screening[81], there is little evidence that surveillance is widespread. As with previous meta-analyses, the limitations were the heterogeneity of studies on PTPD as well as the relatively small number of participants in the existing studies. This meant that despite our attempts to reduce bias by stratifying study quality using the NOS score, there remained significant bias in the studies used for the meta-analysis. We used the random-effects model in our analyses to allow for the heterogeneity of variance between studies. The I^2 for the studies with high NOS and that used provocation test was 94% and I^2 for studies the others was 90%. This makes it difficult to formulate a unified 'one-size-fits-all' surveillance guidance. A prospective, large study is required to develop surveillance guidelines in the future.

Our secondary objective was to determine whether injury severity affected prevalence of chronic anterior PTPD. We dichotomised all studies reporting on prevalence of PTPD at 12 months into studies in which greater than 50% of included participants had a mild TBI (GCS 13 – 15) and studies in which the proportion of participants with mild TBI was less than 50%. The overall prevalence of chronic anterior PTPD was higher in the group with less patients with mild TBI but this difference did not reach statistical significance (32% vs. 21%, pp=0.44). This suggests that injury severity may have a greater influence on the occurrence of chronic PTPD than the pituitary function test methodology or study quality. This is an important point because it suggests single baseline assessments of pituitary function may be as good an assessment as of pituitary function in this cohort as provocation studies which are difficult to implement in research participants because they are time consuming.

The association between PTPD and TBI severity has previously been suggested. Schneider et al demonstrated an association between injury severity and higher prevalence of chronic PTPD. In their meta-analysis, 35.5% of participants who had suffered a severe TBI (GCS ≤ 8) developed chronic PTPD compared to 16.8% of participants that had suffered a mild TBI. Interestingly the prevalence of PTPD in participants that had suffered a moderate TBI (GCS 9-12) was 10.9%[8]. Likewise, Lauzier and colleagues reported an association between increased injury severity and increased risk of anterior pituitary disorders with a risk ratio of 1.91 [95% CI, 1.17-3.13] for patients with non-mild vs. mild TBI. The influence of injury severity is corroborated by our results. However, there was insufficient data to explore the extent of this influence further. Future studies will need to differentiate between mild and non-mild TBI to reduce the study bias. Alternatively, an individual patient meta-analysis could be performed to better establish the relationship between injury severity and PTPD.

The strength of this meta-analysis is that it is the first meta-analysis on chronic anterior PTPD that takes into account the quality of the studies reporting on PTPD and the differences in the methodologies used by each study. We used a comprehensive search strategy, included new studies and have increased the body of literature summarised since the last review[15]. Despite these efforts, we have found significant inter-study heterogeneity. A large, multi-centre, prospective study is required to better inform clinical practice.

PRISMA Flow Diagram

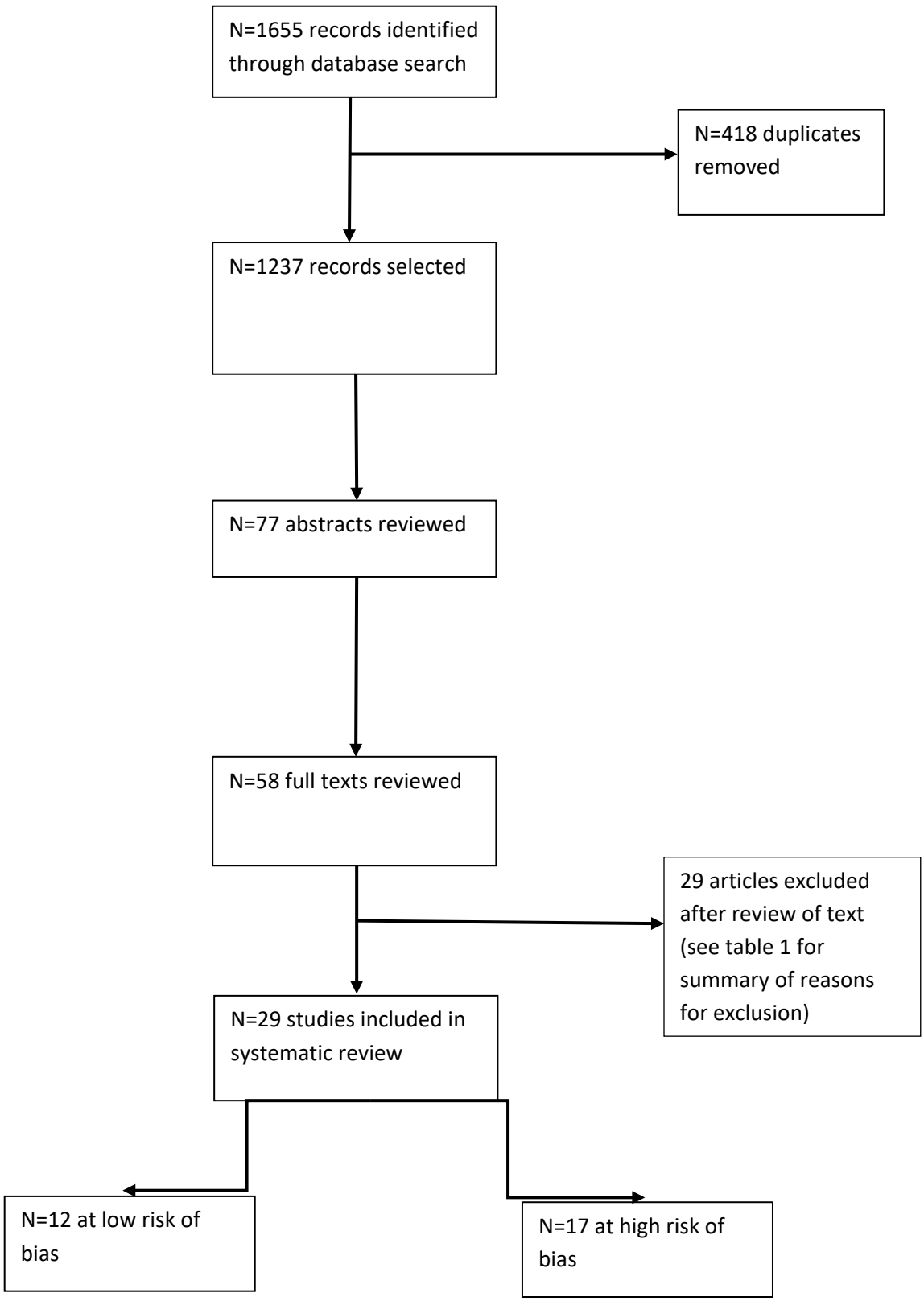

Figure 1. Study selection process

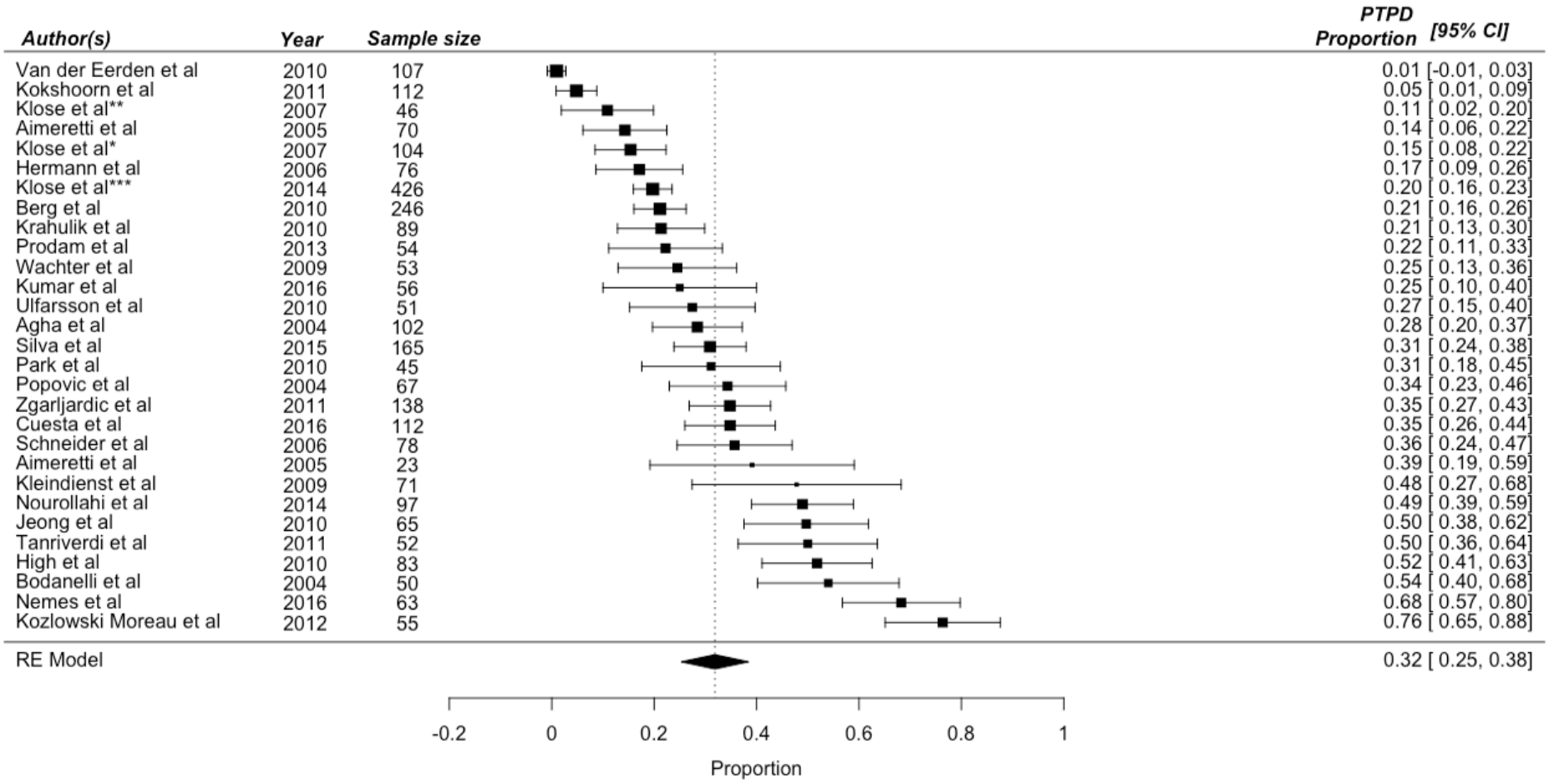

Figure 2. Overall prevalence rate with 95% confidence intervals of at least one pituitary hormone dysfunction 12 months or more following TBI for the 29 studies included in meta-analysis

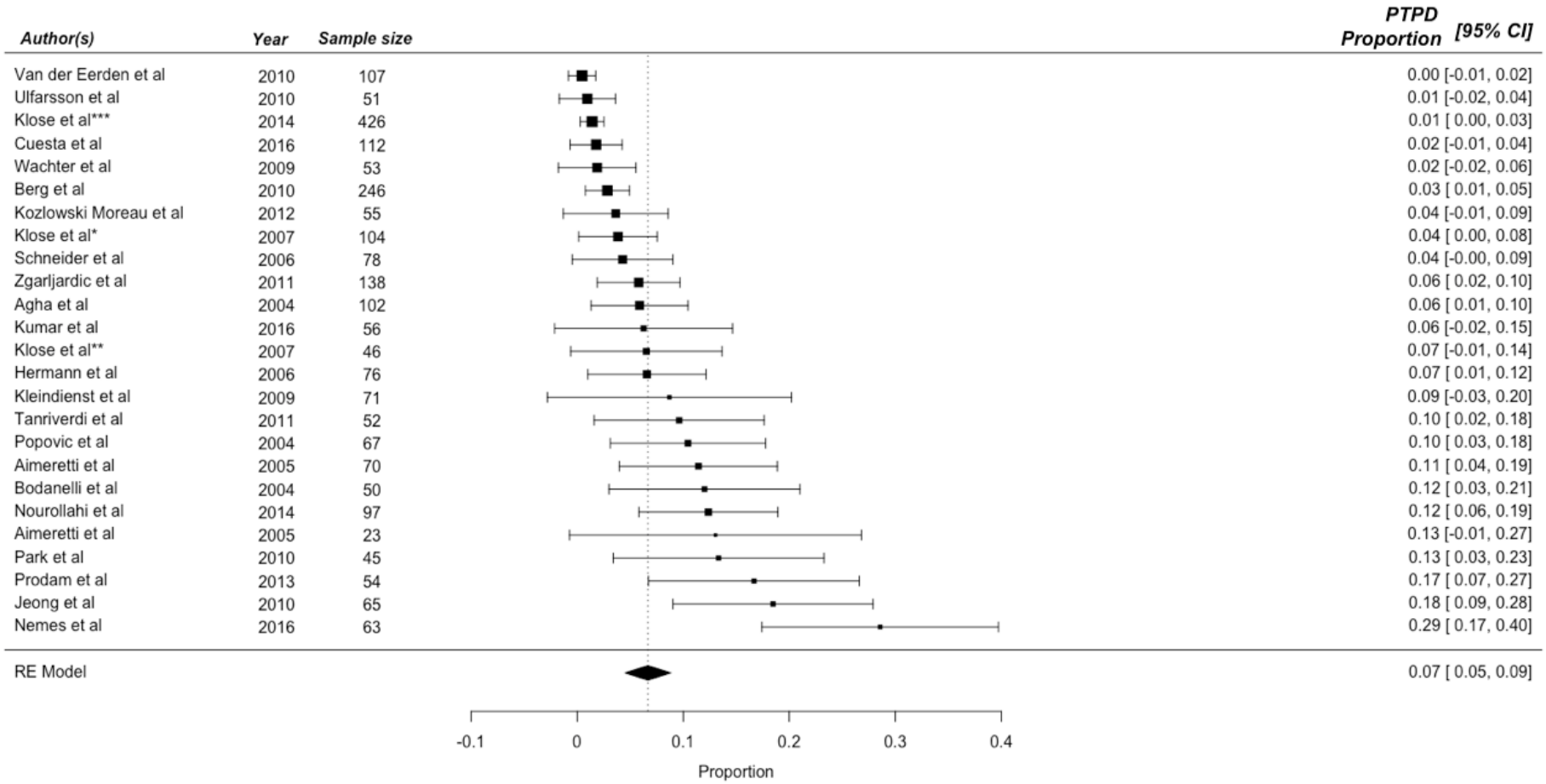

Figure 3. Overall Prevalence with 95% confidence intervals of more than one anterior pituitary hormone dysfunction 12 or more months following TBI

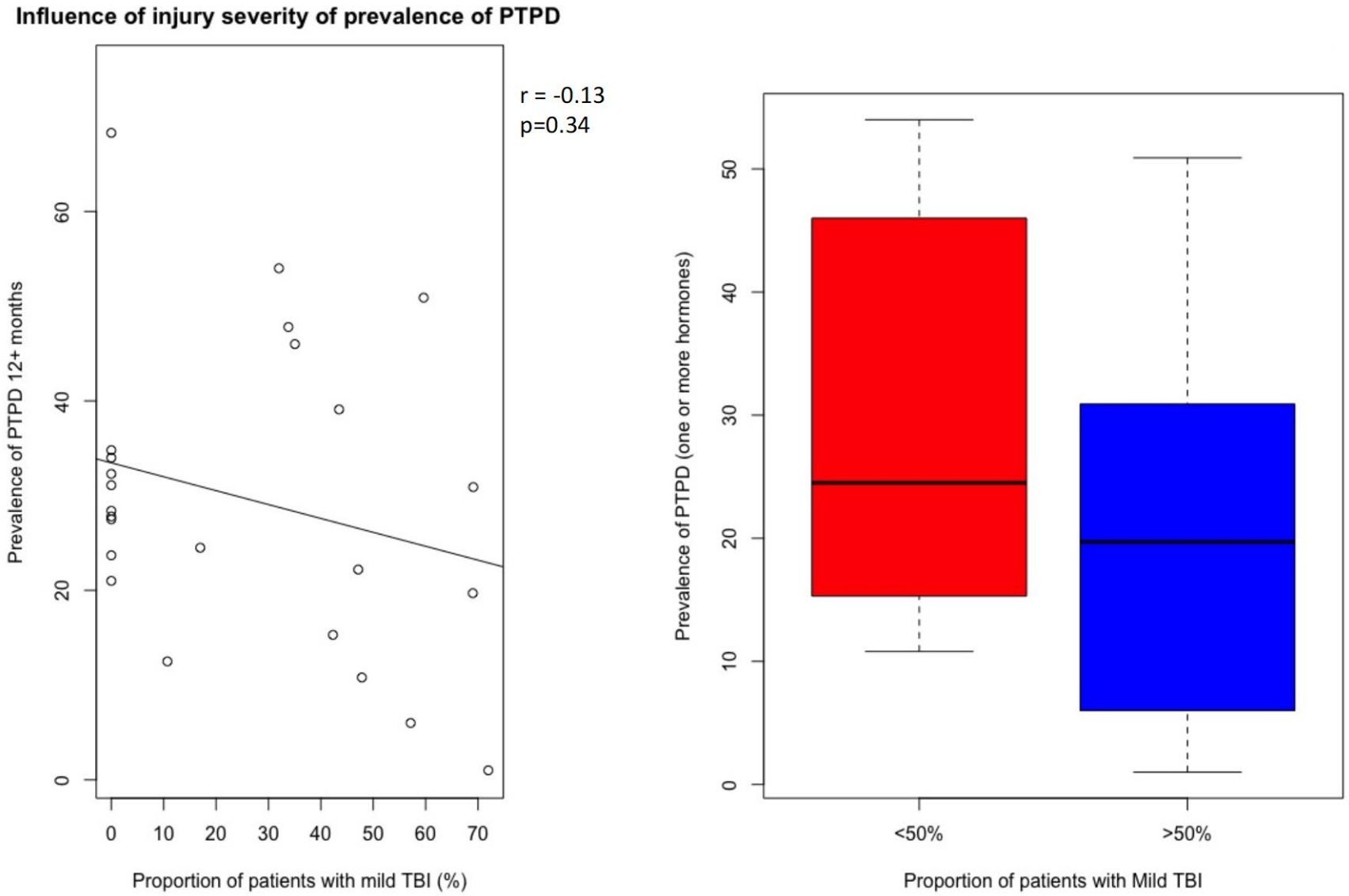

Figure 4. Influence of injury severity on prevalence of PTPD. Studies with more participants with mild TBI had a lower prevalence of PTPD.

Authors	**Reason for not using**
Abadi et al[23]	Less than one year follow up
Agha et al[24]	Less than one year follow up
Aimeretti et al[25]	Less than one year follow up
Alavi et al[26]	Less than one year follow up
Bavisetty et al[27]	Less than one year follow up
Baxter et al[28]	Less than one year follow up
Bondanelli et al[29]	Replicated data
Bushnik et al[30]	Retrospective data
Englander et al[31]	Retrospective data
Guilano et al[32]	Retrospective data
Hannon et al[33]	Less than one year follow up
Ioachimescu et al[34]	Retrospective data
Izzo et al[35]	Retrospective data
Kelly et al[36]	Less than one year follow up
Kelly et al[37]	Less than one year follow up
Kopczak et al[38]	TBI data indistinguishable from other forms of HI
Kreber et al[39]	Retrospective data
Krewer et al[40]	TBI data indistinguishable from other forms of HI
Leal-Cerro et al[41]	Retrospective data
Leon-Carron et al[42]	Less than one year follow up
Lieberman et al[43]	Retrospective data
Marina et al et al[44]	Replicated data
Mossberg et al[45]	Less than one year follow up
Pavlovic et al[46]	Retrospective data
Srinivasan et al[47]	Retrospective data
Tandon et al[48]	Less than one year follow up
Tanriverdi et al[49]	Replicated data
Tanriverdi et al[50]	Replicated data

Wilkinson et al[51]	TBI data indistinguishable from other forms of HI

Table 1. Studies excluded from meta-analysis

Authors	Year	Sample size	NOS	Dynamic test
Studies at low risk of bias				
Agha et al[52]	2004	102	8	Yes
Cuesta et al[53]	2016	112	8	Yes
High et al[54]	2010	83	8	Yes
Jeong et al[55]	2010	65	8	Yes
Kleindienst et al[56]	2009	71	8	Yes
Klose et al*[57]	2007	104	8	Yes
Klose et al**[58]	2007	46	8	Yes
Nourollahi et al[59]	2014	97	8	Yes
Schneider et al[60]	2006	78	8	Yes
Silva et al[61]	2015	165	8	Yes
Ulfarsson et al[62]	2010	51	8	Yes
Zgarljardic et al[63]	2011	138	8	Yes
Studies at high risk of bias				
Aimeretti et al[64]	2005	23	7	No
Aimeretti et al[65]	2005	70	7	No
Berg et al[66]	2010	246	8	Mixed
Bodanelli et al[67]	2004	50	8	Mixed
Hermann et al[68]	2006	76	8	Mixed
Kozlowski Moreau et al[69]	2012	55	8	Mixed
Kumar et al[70]	2016	56	8	Mixed
Nemes et al[71]	2016	63	8	Mixed
Popovic et al[72]	2004	67	8	Mixed
Prodam et al[73]	2013	54	8	Mixed
Wachter et al[74]	2009	9	8	Mixed
Klose et al***[75]	2014	426	7	Mixed
Kokshoorn et al[76]	2011	112	7	Mixed
Krahulik et al[77]	2010	89	7	Mixed

Park et al[78]	2010	45	7	Mixed
Tanriverdi et al[79]	2011	52	7	Mixed
Van der Eerden et al[80]	2010	107	7	No

Table 2. Studies included in meta-analysis

Hormone dysfunction	**Overall prevalence (%) [95% CI]**
Growth hormone deficiency	19.1% [11.5 – 26.6]
Secondary Hypoadrenalism	8.9% [4.1 – 13.8]
Secondary Hypogonadism	6.2% [2.9 – 9.4]
Secondary Hypothyroidism	1.2% [0.4 – 1.9]
Hyperprolactinaemia	1.7% [0.6 – 2.8]
Hypoprolactinaemia	1.2% [0.4 – 1.9]

Table 3. Overall prevalence rates with 95% confidence intervals of individual hormone dysfunction in studies at low risk of bias

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Medline search strategy

1. head trauma OR head injury OR head injuries OR brain trauma OR brain injury OR brain injuries OR cerebral trauma OR cerebral injury OR cerebral injuries OR craniocerebral trauma OR craniocerebral injury OR craniocerebral injuries OR tbi OR traumatic brain injury OR traumatic brain injuries OR brainstem trauma OR brainstem injury OR brainstem injuries OR Craniocerebral Trauma OR brain edema OR brain hernia OR intracranial hypertension OR Brain Edema OR Intracranial Hypertension

2. pituitary gland OR hypophysis OR hypophysis function OR pituitary hormone OR adenohypophysis hormone* OR neurohypophysis hormone* OR pituitary hormone-releasing hormone* OR pituitary function test* OR pituitary disease OR hypophysis disease OR neuroendocrine disease OR hypothalamus hypophysis system OR hypothalamus OR hypothalamus function OR hypothalamus hormone* OR hypothalamus lesion* OR hypothalamus disease OR pituitary-adrenal system OR hypothalamus hypophysis adrenal system OR hypophysis adrenal system OR adrenal cortex hormone* OR adrenocorticotropic hormone* OR hydrocortisone OR corticotropin release OR corticotrophin release OR corticotropin blood level OR corticotrophin blood level OR corticosteroid blood level OR pituitary-adrenal function test* OR corticotropin test* OR adrenal insufficiency OR corticosteroid therapy OR hypothalamus hypophysis gonad system OR progesterone OR progesterone

congeners OR estradiol OR estradiol congeners OR testosterone OR testosterone congener* OR androgen* OR androgen blood level OR estrogen* OR estrogen blood level OR progestin* OR androstenol* OR follitropin release OR follitrophin release OR follitropin blood level OR follitrophin blood level OR gonadotropin release OR gonadotrophin release OR gonadotropin blood level OR gonadotrophin blood level OR gestagen blood level OR luteinizing hormone blood level OR luteinizing hormone release OR hypogonadism OR hypogonadotropic hypogonadism OR ovary insufficiency OR estrogen deficiency OR androgen deficiency OR estrogen therapy OR androgen therapy OR hypothalamus hypophysis thyroid system OR thyroid hormone* OR thyroid hormone blood level OR thyrotropin release OR thyrotrophin release OR thyrotropin blood level OR thyrotrophin blood level OR thyroid function test* OR euthyroid sick syndrome* OR hypothyroidism OR diabetes insipidus OR vasopressin release OR vasopressin blood level OR insuline-like growth factor* OR growth hormone release OR growth hormone blood level OR somatomedin C OR growth hormone deficiency OR prolactin synthesis OR prolactin release OR prolactin blood level or hyperprolactinemia OR Pituitary Diseases OR Pituitary Hormones OR Pituitary Hormone-Releasing Hormones OR Diagnostic Techniques, Endocrine OR Hypothalamus OR Pituitary-Adrenal System OR Adrenal Insufficiency OR Adrenal Cortex Hormones OR Gonadal Steroid Hormones OR Androgens OR Estrogens OR Progestins OR Androstenols OR Hypogonadism OR Euthyroid Sick Syndromes OR Hypothyroidism OR Thyroid Hormones OR Insulin-Like Growth Factor 1

3. #1 and #2

Conclusion

The systematic review confirms that PTPD is a common and significant clinical entity and that full assessment of pituitary function should be considered in the chronic phase of recovery from TBI to detect anterior pituitary deficiency, which is reversible and may improve outcomes.

Exploring the research background: Part 2

Paper 2: A national survey of clinical practice of surveillance for post-traumatic brain injury hypopituitarism in the United Kingdom and Ireland

Introduction:

Having established in my systematic review that one-third of patients with TBI followed up with pituitary testing had evidence of anterior pituitary dysfunction, I performed a survey of surveillance practices amongst neurosurgeons in the UK and Ireland.

A national survey of clinical practice of surveillance for post-traumatic brain injury hypopituitarism in the United Kingdom and Ireland

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Acknowledgements: None

Keywords: Posttraumatic hypopituitarism, TBI, surveillance, pituitary

ABSTRACT

Background: Traumatic brain injury (TBI) is the most common cause of death and disability in young adults in industrialised countries. Post-TBI hypopituitarism (PTHP) is thought to occur in one-third of patients, however the natural history and predictive factors are not fully understood and as such guidelines for surveillance vary. The aim of this study was to assess the variations in current surveillance practices across the Neurosurgery Centres within the United Kingdom.

Methods: A questionnaire was developed following discussions with an expert panel and distributed to members of the Society of British Neurosurgeons (SBNS), by email and printed copy, to survey surveillance practices for PTHP. The questionnaire primarily aimed to determine how commonly screening was performed and the clinical parameters used to guide these surveillance practices.

Results: There were 45 responders representing Neurosurgery units in regions of England, Scotland and Ireland. The majority of participants (86.7%) considered PTHP to be a problem but only 25% (11/45) routinely screened for PTHP. There was wide variation in the criteria used to determine which patients were screened.

Conclusions: Our survey suggests that few Neurosurgeons routinely screen for PTHP and those that do use a wide variation of clinical parameters to guide surveillance practice. A UK-wide prospective cohort study may help identify patients at risk of developing PTHP.

Introduction

Traumatic brain injury (TBI) is a significant public health problem worldwide, with an overall incidence in Western countries of 200–235 cases per 100,000 individuals annually[1]. It is the leading cause of death and disabilities worldwide amongst young people under 40 years old. There are also significant health and socioeconomic consequences, with many sufferers developing chronic physical and mental health problems that prevent them from working or re-engaging socially after their injuries. There have been many advances made in supportive rehabilitation but very few therapeutic interventions that effect outcomes in patients recovering from TBI. One potential therapeutic avenue is diagnosis and treatment of post-TBI hypopituitarism (PTHP).

PTHP was first described over a century ago[2] and in the last 2 decades there has been a renewed interest in its clinical implications with two meta-analyses concluding that PTHP occurs in approximately one-third of TBI patients that are followed up long term[3,4].The risk factors for developing PTHP are less clear and this has made guidelines for surveillance difficult to establish. Our aim in this study was to survey the surveillance practices of Neurosurgeons in the United Kingdom (UK) and Ireland.

Method

An online questionnaire survey was designed using Google Survey and the contents of the questionnaire were informed by discussions with an expert panel that included a consultant neuro-intensivist, a consultant endocrinologist and a consultant neurosurgeon. After approval by the academic committee of the Society of British Neurological Surgeons (SBNS), the questionnaire was emailed to its members,

including consultants and trainees. To encourage members' participation, they were offered the possibility to be entered into a draw for a £50 gift voucher. The survey was open between 13th April 2017 and 19th June 2017 and an email reminder was sent after one month. There were a total of 11 questions designed to determine the region of the UK in which the responder worked and the surveillance practice of the responder. Nine questions focused on surveillance practice (see Table 1).

Results

Forty-five UK and Irish Neurosurgeons from 25 neurosurgery centres completed the questionnaire with broad regional representation (Table 2). Two-thirds of responders were consultant Neurosurgeons. There are approximately 600 SBNS members.

When asked whether participants considered PTHP a clinical problem, the majority of responding Neurosurgeons (86.7%) answered 'yes' (8.9% considered PTHP a major clinical problem, 37.8% considered it a moderate clinical problem and 40% considered it a minor problem), while only 6.7% did not consider PTHP to be a clinical problem. A small number (6.7%) answered 'I don't know' (Figure 1(a)). Furthermore, just over half (56.6%) of responders thought that evidence of pituitary dysfunction should be routinely assessed in patients that suffer TBI (Figure 1(b)). 13% of those who thought that evidence of pituitary dysfunction should be routinely checked provided clinical scenarios that should prompt pituitary screening. These included: "if there is [evidence of] sphenoidal basal fractures", "if able to" and "only for moderate and severe TBIs". Despite these responses, the majority of Neurosurgeons (76.1%) did not routinely check pituitary function in patients presenting with TBI (Figure 1(c)).

What clinical parameters prompt screening?

All participants answered the question “how do you decide which patients to screen?” Of these, 50% answered “I don’t routinely screen”, 34.8% answered “I only screen if there are clinical features suggestive of PTHP” and 15.2% answered “I screen based on clinical severity”. None of the participants screened based on duration of stay in hospital (Table 1). Most of the participants that checked pituitary function based on injury severity used more than one clinical markers of injury severity. The most commonly used severity parameter was admission Glasgow Coma Scale (GCS) (80%) and the neuro-imaging findings (46.7%). Duration of loss of consciousness and duration of post-traumatic amnesia were less commonly used (see Table 1).

Timing of screening

The most common timing for screening was between one and six months following TBI (28%). Only 16% and 8% of participants that routinely screened did so within one month and within one week of TBI, respectively. Nearly One-quarter (24%) of the participants did not have a specific interval during which they routinely screened patients.

What screening tests are performed?

When a surveillance pituitary function test was performed, the most commonly tested pathways were the pituitary-adrenal axis (92%), the pituitary-thyroid axis (76%) and prolactin levels (40%). Male and female sex hormones were tested by 36% and 32%

of participants that routinely screened, respectively and the pituitary-somatotropic axis or pituitary-growth axis was tested by 32%. Only 5 participants responded to the question about what GH axis test they performed: 3 stated that they checked Insulin-like Growth Factor-1 (IGF-1), one stated that they did a GH stimulation test (but did not specify which) and the 5th responder did not know what tests were routinely done for GH axis.

Discussion

Although subjective and with only a relatively small number of participants, our survey highlights the variations in the perceived clinical importance of PTHP and the surveillance practices amongst Neurosurgeons in the UK and Ireland. We found that while the majority of Neurosurgeons agreeing that PTHP is an important clinical problem, only approximately one-quarter routinely screen patients and of those that do, the clinical parameters that prompt screening and the post-injury interval to screening also varies considerably. These variations in clinical practice are likely due to the lack of widely accepted guidelines. Over the years, there have been several attempts to influence surveillance practice[5] including the recent guidelines issued by the British Neurotrauma Group[6]. However, the influences of such guidelines remain uncertain because none have been able to identify any definitive clinical or radiological risk factors attributed to the development of PTHP and as such it is difficult to know which patients to screen. The high incidence of TBI globally and in the UK, would make blanket surveillance of all patients financially and logistically impossible.

One difficulty with research into the prevalence and risk factors for PTHP is that there are disparities in the methodologies used by different researchers to diagnose PTHP. For example, some researchers have tested for secondary hypoadrenalism and growth hormone deficiency (GHD) with stimulation blood tests whilst others have used baseline blood tests only. There have also been differences in the intervals to surveillance, ranging from 3 months to 12 months. This has meant a wide variation in the reported prevalence of PTHP. Two meta-analyses have concluded the overall prevalence of PTHP to be 27.5% and 30%. However, reports of an association between PTHP and higher severity TBIs[7,8] or with certain imaging characteristics such as in patients with base of skull fractures[9].

In the recently published British Neurotrauma Group guidelines, screening for PTHP was recommended at 3 to 6 months for patients admitted for 48 hours or more following TBI or those who have symptoms suggestive of 'pituitary dysfunction' or in patients who are symptomatic 12 months or more following TBI. This recommendation is congruous with the reports that in serially followed up patients, PTHP appears to be a dynamic problem during which early pituitary dysfunction may resolve, whilst in other patients, pituitary dysfunction may present late and as such late development of PTHP (6 months or more after TBI) may be missed. However, one potential difficulty with the screening recommendations of the British Neurotrauma Group guidelines, which the group highlighted, is that many of the symptoms of hypopituitarism overlap with the cluster of symptoms that can occur after TBI and which are commonly referred to under the umbrella term post-concussion syndrome (PCS). Screening based on patients' symptoms may therefore lead to over-screening in patients with persistent PCS symptoms. A prospective study that aims to identify the risk factors for developing PTHP may help solve this

problem. Nonetheless, the British Neurotrauma group guidelines are a comprehensive set of guidelines for PTHP surveillance for UK based neurosurgerons

Finally, it should be noted that because the majority of studies on PTHP have recruited patients with moderate and severe TBIs, guidelines based on such studies cannot be extrapolated to patients that suffer mild TBI. As the majority of TBI sufferers are those that sustain a ‘mild’ TBI, such guidelines therefore have limited scope in influencing surveillance practices for patients with mild TBI. A large, prospective study is needed to determine the prevalence of PTHP in patients with all types of TBI including mild TBI, and to help formulate appropriate guidelines for these patients.

The main limitation of our study is that there were only a small number of responders and therefore the results are not reflective of the practices of all Neurosurgeons in the UK and Ireland. Additionally, most of the responders were neurosurgeons practicing in Scotland (where the authors also practice) and as such our findings could be skewed towards Scottish practice rather than the UK as a whole.. The overall picture is further affected by our questionnaire design which allowed participants who do not routinely screen patients to answer subsequent questions about how patients are screened. Furthermore, patients with acute neurotrauma are not always directly managed by neurosurgeons in some hospitals and likewise, neurosurgeons may not be involved in the long-term management of this patient group. This indicates that the overview of practice we have highlighted in this study may not be an accurate reflection of the clinical practices across all specialists involved in the rehabilitation of TBI patients. It may be prudent to repeat the survey

amongst other clinicians such as rehabilitation physicians, in order to get a better idea of surveillance practices.

Conclusion

In summary, our study shows that despite guidelines, the surveillance practices for PTHP vary considerably in the UK and Ireland amongst neurosurgeons. These variations are in part due to the ongoing debate about the clinical significance of PTHP. Given the health and socioeconomic burden of TBI, a UK-wide study is needed to define the prevalence of PTHP, its risk factors and to help formulate evidence-based recommendations for surveillance practices.

Table 1. The nine questions about surveillance practices and corresponding responses.

Questions about surveillance practices for PTHP	Responses (proportion of responders)
Do you consider PTHP a problem?	No (6.7%) Yes, minor (40%) Yes, moderate (37.8%) Yes, Major (8.9%) I don't know (6.7%)
2. Do you think that evidence for PTHP should be routinely checked?	Yes (56.6%) No (17.4%) I don't know (26%)
3. Do you routinely check pituitary function in patient with TBI?	Yes (76.1%) No (23.9%)
4. If your answer [to question 3] is yes, how do you decide which patients to check?	I don't routinely screen patients (50%) I screen patients that are in hospital for longer than a certain period I screen patients based on injury severity

Questions about surveillance practices for PTHP	Responses (proportion of responders)
	(34.8%) I only screen if there are clinical features suggestive of PTHP (15.2%)
5. If you screen based on duration of hospital stay, please state threshold duration	0%
6. If you screen based on injury severity, which criteria do you use?	Admission GCS (80%) Imaging (46.7%) Duration of loss of consciousness (20%) Duration of posttraumatic amnesia (33.3%)
7. If your answer [to question 3] is yes, when do you screen? (you may select more than one answer)	Within 1 week of TBI (8%) Within 1 month of TBI (16%) Between 1 and 6 months of TBI (28%) After 6 months (4%) Only if clinically indicated (28%) No specific routine (24%)
8. If your answer [to question 3] is yes, what tests do you perform? (you may select more than one)	Growth-hormone (GH) function (32%) Pituitary-adrenal pathway/axis (92%) Pituitary-thyroid pathway/axis (76%) Female sex hormone pathways/axes (32%) Male sex hormone pathways/axes (36%) Prolactin (40%)
9. Please state which test(s) you do for GH axis	IGF-1 (6.6%) GH stimulation test (2.2%) Don’t know (2.2%)

Table 2. Regions of the UK and Ireland represented by the 45 responders.

Region	Number of representatives
Ireland	2
Scotland	10
Northwest England	5
Northeast England	5
Yorkshire	2
West Midlands	4
East Midlands	2
East of England	1
Southeast England	4
Southwest England	1
South of England	1
Not stated	8

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Disclosure statement

The authors report no conflict of interest.

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9. Schneider M, Schneider HJ, Yassouridis A, et al. Predictors of anterior pituitary insufficiency after traumatic brain injury. Clin Endocrinol (Oxf) 2008;68:206–12.

Conclusion

In this article, we established that there was a wide-variation in surveillance practices across the UK and Ireland for post-TBI pituitary dysfunction.

4. **Pit**uitary dy**s**function following **t**raumatic brain injury: **O**utcomes and **P**revalence – A prospective feasibility study

4.1 Abstract

Background

The prevalence of post-traumatic brain injury pituitary dysfunction (PTPD) has been difficult to determine as has the pathogenesis. There is a need for better understanding of PTPD as it offers a potentially treatable cause of morbidity in traumatic brain injury (TBI) sufferers.

Methods

A pilot observational study was conducted to test the feasibility of a prospective study to determine how hormonal and structural responses of the anterior pituitary gland to TBI. Adults (> 17 years of age) who had recently suffered a TBI were eligible for inclusion if they did not have a prior endocrine disease or did not take any medications that affected the hypothalamo-pituitary axes. Participants were followed up with baseline anterior pituitary and magnetic resonance imaging (MRI) of their pituitary gland within a week of injury and further MRI and anterior pituitary function tests including stimulation tests for growth hormone and adrenocorticotropic hormone function six months after injury. Primary outcomes were the feasibility of participant recruitment, participant retention and assessment procedures.

Results

Between August 2017 and July 2018 (11 months), 926 patients were screened and 54 (5.8%) were recruited. Only 36 of the 54 recruited patients (66.7%) returned for the first visit. The median age of the returning patients was 38.5 years (IQR27.5-59.5 years) and there was an even distribution of female (58%) and male (42%) returners. Only 15 of the 36 patients who attended the first study visit returned for the second visit. The poor participant retention led to modification of the protocol from a four visit

study to a two visit study. All participants who were tested tolerated blood tests including stimulation tests and MRI imaging. No adverse events were reported by participants.

Conclusion

We adapted the protocol to reduce burden on participants. The results suggests that the trial methodology of the modified protocol are feasible for implementing an observational study of the prevalence and risks factors for PTPD.

Trial registration

www.isrctn.com ISCRTN71291784

Key messages

- What uncertainties existed regarding the feasibility?

  Prior to this pilot study, it was unknown whether it is possible to perform a prospective study to determine the prevalence and risks of developing anterior pituitary gland dysfunction after TBI.

- What are the key feasibility findings?

  Our results suggest that the trial methodology and interventions in the PitSTOP study protocol are feasible for implementing such a study in patients with mild TBI. We found a high attrition rate in this cohort and therefore adapted the protocol by reducing the number of visits to reduce the study burden on participants.

- What are the implications for the feasibility findings for the design of the main study?

The high attrition rate and low screened-to-recruitment ratio indicated that a large and multi-centre study is required to achieve the study objectives.

4.2. Introduction

Traumatic brain injury (TBI) is the “silent epidemic” of the 20th century. It is a major health problem worldwide [1]. Up to 250 people per 100,000 per year die or are hospitalised because of TBI and many more patients are discharged from emergency departments without input from specialists. Furthermore, TBIs disproportionately affect young people and is the leading cause of death and disability in patients under 40 years old in the United Kingdom, meaning that there are also significant socioeconomic consequences. In the United States, the direct and indirect costs of TBI are estimated at $ 56 billion [2]. In less developed countries, the incidence of TBI is higher and rapidly increasing [3]. In Scotland, the rate of continuous hospital stays as a result of TBI has been calculated as 446 per 100000 for men and 195 per 100000 for women [4]. This is higher than elsewhere in Europe and represents a significant and unique health challenge to the National Health Service in Scotland.

The majority of TBI patients are managed in and discharged from non-specialist centres with little or no scope for follow-up and as a result there are many patients with undiagnosed medical problems related to TBI that develop over days, weeks and months following TBI. One such chronic problem is TBI-related pituitary hormone dysfunction (post-TBI pituitary dysfunction or PTPD). It may affect as many as 25% of patients after TBI. The pituitary gland sits at the centre of the brain and is a major endocrine organ that regulates key homeostatic functions (the body’s balancing system) from basal metabolic rate to mental wellbeing and sexual function. Many of the symptoms of PTPD, especially the psychological disturbances such as cognitive impairment and chronic fatigue are difficult to differentiate from the

symptoms of post-concussion syndrome, which has become an umbrella term for many of these problems. Furthermore, the symptoms may develop several months after TBI, which further compounds diagnoses. Symptoms of PTPD are reversible with effective treatment and it is therefore important that affected patients are identified and treated appropriately. There has been very little progress made on post-event therapies in TBIs over the past two decades. Developing an effective screening tool for PTPD offers the opportunity to improve diagnoses, offer early treatments and improve the rehabilitation and recovery of many TBI patients.

The primary outcomes of this pilot study were to test the feasibility of the PitSTOP Study protocol and to inform a sample size calculation for the main study using the pilot phase data. The main questions

- Is it possible to consent patients after mild traumatic brain injury?
- What is the screened to consented ratio?
- Will consented patients return for subsequent visits including for stimulation tests of their anterior pituitary function which requires fasting from midnight and an MRI scan of brain?
- Can pituitary anatomy including vascular anatomy be assessed using our bespoke MRI image sequences?

4.3. Methods

Design and recruitment

This was a longitudinal, prospective observational study. Participants were recruited from the emergency department of the Royal Infirmary of Edinburgh over a 12-month period (figure 1). Patients who present to the emergency department with a history of TBI were eligible for recruitment.

The inclusion criteria were:

1) Primary traumatic Brain Injury (TBI) including multi trauma with a post resuscitation Glasgow Coma Scale score or 13 to 15 (mild TBI)
2) patients aged ≥ 17 years at the time of TBI
3) Informed consent obtained from participant

The exclusion criteria were:

1) Patients with a pre-existing endocrine diagnosis
2) Morbidly obese patients with BMI > 35
3) Unlikely to survive for the next 24 hours in the opinion of the Intensive care or Neurosurgical team treating the patient
4) Patients with known epilepsy
5) Patients on medications that are known to affect the hypothalamic-pituitary axis
6) Patients who are not able to consent

Research Ethics

This study was approved by the Lothian Ethics of Medical Research Committee (Reference number: **17/SS/0043**). All participants provided written informed consent prior to participation in this research.

Participant characteristics

Information on patient demographics age, gender, ethnicity, mechanism of injury, current medications, Glasgow coma score (GCS) and co-morbidities were collected at baseline.

Data sources and measurements

Once recruited, the participants were initially to be followed up for up to 12 months with three planned visits (Figure 1). However, poor participant retention necessitated protocol modification with revised protocol requiring 2 visits over 6 months. There were therefore 2 stages:

1. Recruitment and baseline assessments (Day 0 to 7 after the TBI)

Participants had fasting early morning (between 8am and 10am) blood tests for anterior pituitary hormones levels within 7 days of TBI. These included serum levels of cortisol, insulin-like growth factor 1 (IGF-1), testosterone, thyroxine (fT4), thyroid stimulating hormone (TSH), oestradiol. Some participants had an MRI scan of their pituitary gland with the following sequences being performed.

- sagittal 3D T2-weighted
- sagittal 3D SPGR/MPRAGE T1-weighted
- sagittal 3D T2 Fluid-Attenuated Inversion Recovery (FLAIR)
- gradient echo and / or axial 3D Susceptibility Weighted Imaging (SWI)

2. Follow-up visit 1 (6months +/- One month after TBI)

Fasting, early morning anterior pituitary hormone profile was repeated including stimulation tests to access growth hormone (GH) and adrenocorticotropic hormone (ACTH) function [5]. Participants who had an MRI scan during the recruitment visit had the same sequences repeated. Participants were asked at this stage to complete an extended Glasgow Outcome Score (GOSE) questionnaire [6].

3. Follow-up visit 2 (12 months +/- one month following TBI)

During this visit, participants complete the same assessments as visit 2.

Sample size

Our targeted sample size was 100 participants. As this was a pilot study, a formal sample size calculation was not conducted. A sample of 100 participants was chosen because it was felt this would be a large enough sample to allow an accurate assessment of the feasibility of recruitment, retention, outcome measure completion, and testing the capacity for accommodating research blood tests and neuroimaging.

Feasibility Outcomes

1. Primary outcomes: Recruitment and retention

   The primary outcomes were to assess the recruitment and retention rates. Recruitment was defined as the number of new patients that consented to take part in the study and retention was the proportion of recruited patients who completed the subsequent visits.

2. Secondary Outcomes: Assessing assessments

   The secondary was to assess whether the blood sampling and stimulation tests could be achieved without adverse effects and whether our bespoke MRI sequences could diagnose structural changes to the pituitary gland in TBI patients. As recommended for pilot studies, we set criteria for acceptable completeness of assessments and we considered a >80% completion of assessments without adverse events as acceptable [7].

Data analysis

Descriptive statistics were used to summarise recruitment, retention, data completion and baseline characteristics. Means and standard deviations (SDs) were used to summarise normally distributed continuous variable and medians and interquartile ranges (IQRs) to summarise non-normally distributed continuous variables. Percentages were used to summarise categorical variables.

4.4. Results

A total of 926 patients were screened over 12 month. Participant baseline characteristics are presented in Table 1.The median age for this cohort was 63 years (IQR43-81years).

Feasibility measures

1. Primary outcomes: Recruitment and retention

Fifty four participants were recruited over the 12 month period. This was a screening to recruitment ratio approximately 1 in 17. The most common reasons for failure to recruit were potential participants were missed by the research team (33%) and because potential participants excluded because they had a normal CT head (26%) (figure 3). There was an attrition rate of 72.2% with only 15 of the 54 completing the 6 month follow-up. Eighteen of the recruited patients (33.3%) were excluded after the first visit because of incomplete data or blood sets. Therefore, only 36 of the 54 were eligible for follow up at 6 months. Of these 36, the attrition rate was 58%.

2. Secondary outcomes: Assessments

    a. Recruitment and baseline assessments (Day 0 to 7 after the TBI)

All recruited participants returned for their first blood test appropriately fasted. Therefore participant completion of this first assessment was 100%. However, there were technical problems with processing the blood tests in 18 of 54 participants (33.3%) and therefore these patients were excluded from subsequent visits which dropped completion of this assessment to 66.6%. There was 100% completion of the MRI scans for participants recruited to have MRI. The planned sequences provided a detailed examination of the pituitary gland and permitted analysis of structural damage. Baseline information was successfully competed for all participants at this stage.

b. Follow-up visit 1 (6 months +/- One month after TBI)

Fifteen of the 36 participants who were eligible for inclusion in the second stage of the study attended. Assessment during this stage required participants to have been fasted from midnight the night before and also required patients to have intravenous cannulation and stimulation testing, which included intravenous injections of synacthen, growth hormone, release hormone, and arginine and serial serum samples every 30 minutes for three hours. All participants completed this process and there were no adverse effects. All participants were able to undergo assessment as day cases and none required hospital admission as a consequence of the assessments. The GOSE was completed by all 15 participants.

Assessment fidelity

All assessments were conducted as per the study protocol including all blood tests and MRI imaging with 100% consistency. Eighteen blood tests were processed

incorrectly leading to exclusion of these patients from the study. This was not within the control of the study team. Finally, a lack of resources led to modification of the protocol occurred after the first few patients were recruited and the third study visit was omitted. As this occurred after implementation of the pilot study, 0% of patients completed this assessment.

4.5. Discussions

Our results suggest that a large, prospective study to evaluate the prevalence and risk of PTPD that aims to recruit patients from the emergency department is feasible. One in 17 patients agreed to recruitment into the study from a moderate sized emergency department and nearly 1000 patients were screened. The pilot study has highlighted the low retention rate in this patient cohort. Positively, the pilot study demonstrated strong treatment fidelity with 100% of treatment components and study assessments delivered in alignment with the study protocol for all participants that attended the study visits.

Limitations

1. High attrition

The high attrition rate from the first to second visit is an important feasibility outcome that will have to be addressed in the design of a future definitive study. Attrition rates are influenced by patient specific factors and study design factors. Patient factors associated with loss to follow-up in TBI include low socioeconomic and ethnic minority status, education, injury severity and substance abuse [8,9,10]. These

attributes are prevalent in TBI populations (table 1). It is therefore difficult to design a study that excludes these patients as the results could not be extrapolated for the general TBI population.

One solution, which we adopted during the pilot study, is to reduce the number of follow-up visits. Our decision to omit the third visit was, in part, directed by the difficulties we encountered whilst trying to organise follow up for patients at this stage of the pilot study. A future definitive study will have just a single follow up visit. There is no consensus on the optimal timing of assessments in TBI [11]. However, there is clear evidence that the longer the duration between assessments, the higher the attrition rates. There is also evidence that *de novo* pituitary dysfunction can occur up to one year following TBI [12]. Therefore a reasonable strategy for a definitive study is a single follow up at 12 months after TBI.

2. No control group

Another criticism of the pilot study was the lack of a control group. There remains uncertainty about the clinical significance of post-TBI anterior pituitary dysfunction [13]. One way to improve on the evidence is to conduct a prospective study that includes a control group of non-TBI trauma patients. This would improve the validity of the study and its results. Therefore, definitive future study must have a pre-defined control group who are put through the same assessments as the main study group.

3. Neuroimaging group

We did not specify how the participants that had MRI scans were selected. This was done at random during this pilot phase but will need to be more explicit in the definitive study.

4.6. Conclusion

The lessons learnt from the pilot study have allowed us to modify the PitSTOP protocol to better suit the patient demographic. The results of this pilot study also suggest that it is feasible to implement a fully powered case-controlled study to evaluate the prevalence and risk of anterior pituitary dysfunction in patients with mild TBI.

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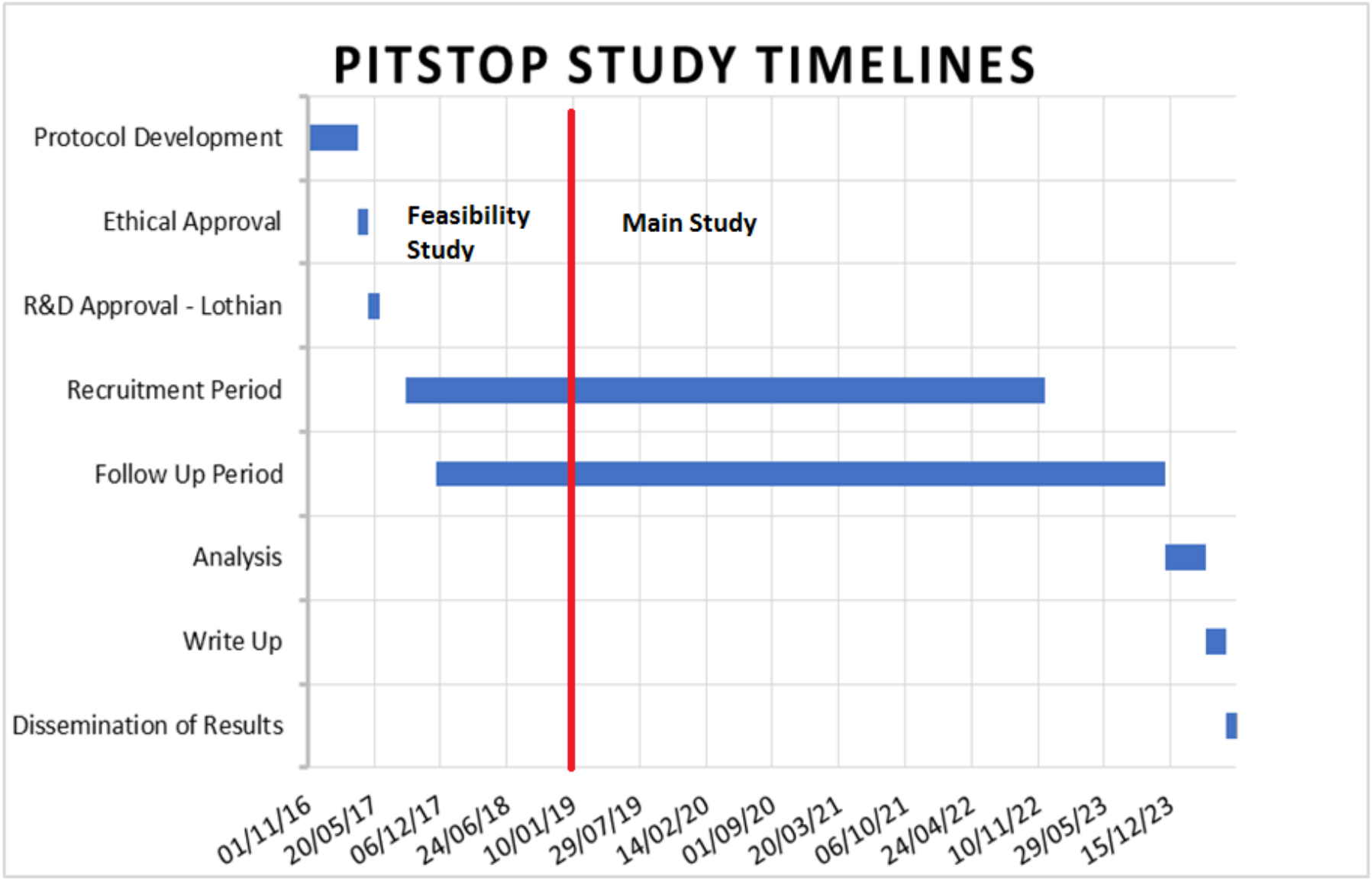
PITSTOP STUDY TIMELINES
Protocol Development
Ethical Approval
R&D Approval - Lothian
Recruitment Period
Follow Up Period
Analysis
Write Up
Dissemination of Results
Feasibility Study
Main Study
01/11/16
20/05/17
06/12/17
24/06/18
10/01/19
29/07/19
14/02/20
01/09/20
20/03/21
06/10/21
24/04/22
10/11/22
29/05/23
15/12/23

Figure 1. The GANTT chart above shows the overall timeline for the full PitSTOP Study. A line has been added to show the end of the proposed Feasibility Study.

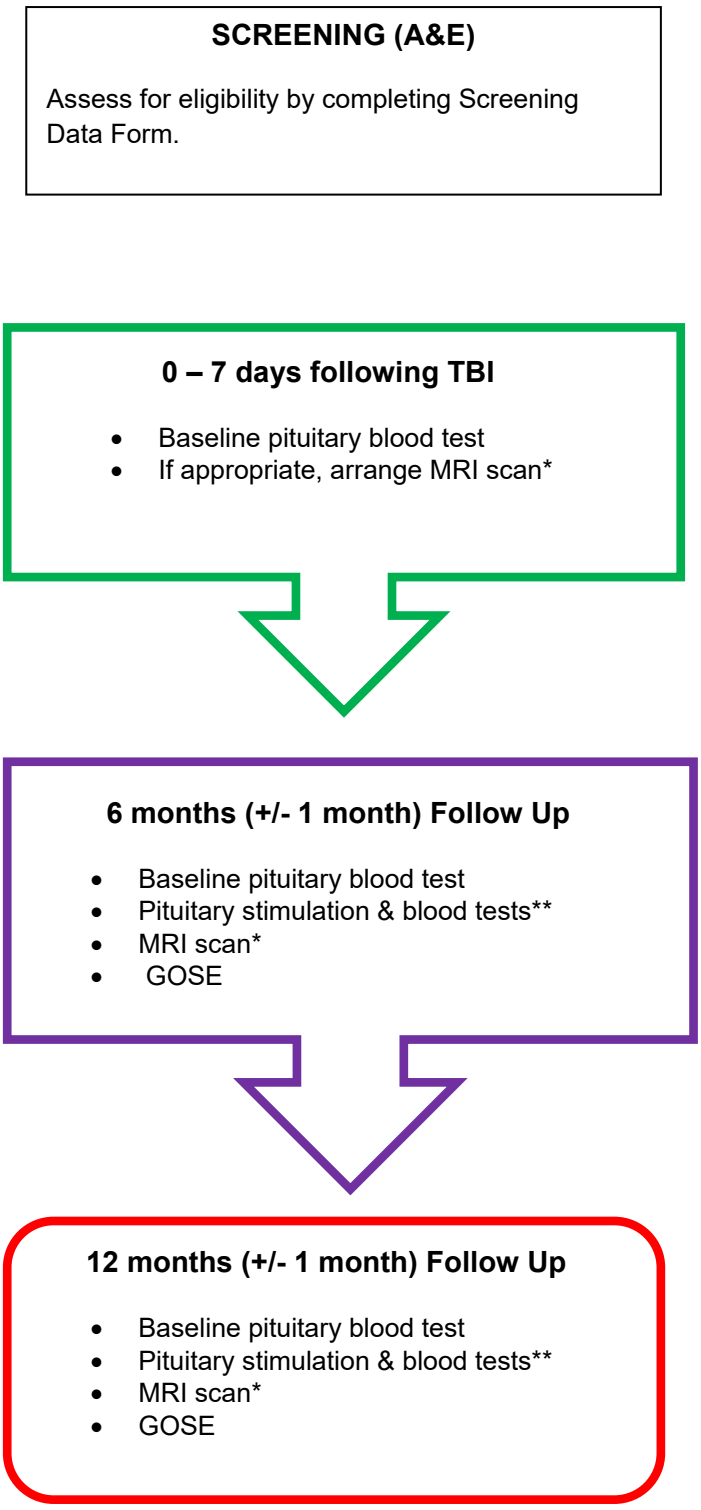

Figure 2. Proposed patient flow for PitSTOP participants

* 20 consecutive patients will be offered an MRI brain scan across each of the 3 study stages. A total of 20 MRIs will be performed

** Stimulation blood tests for growth hormone deficiency (GHD) and secondary hypoadrenalism

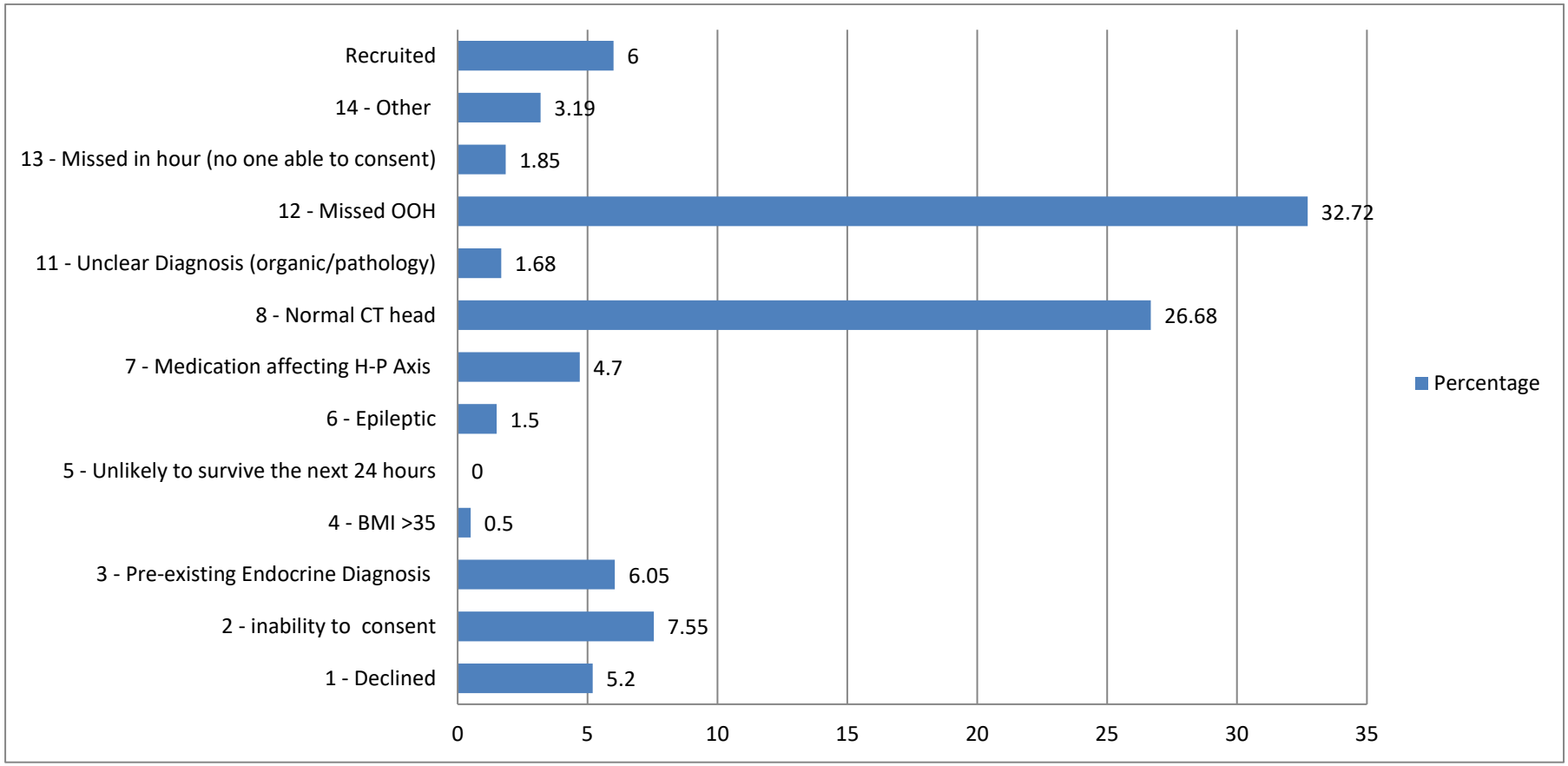

Figure 3. Bar graph of PitSTOP participant recruitment. Top bar represents recruited patients and the rest represent reason participant was not recruited

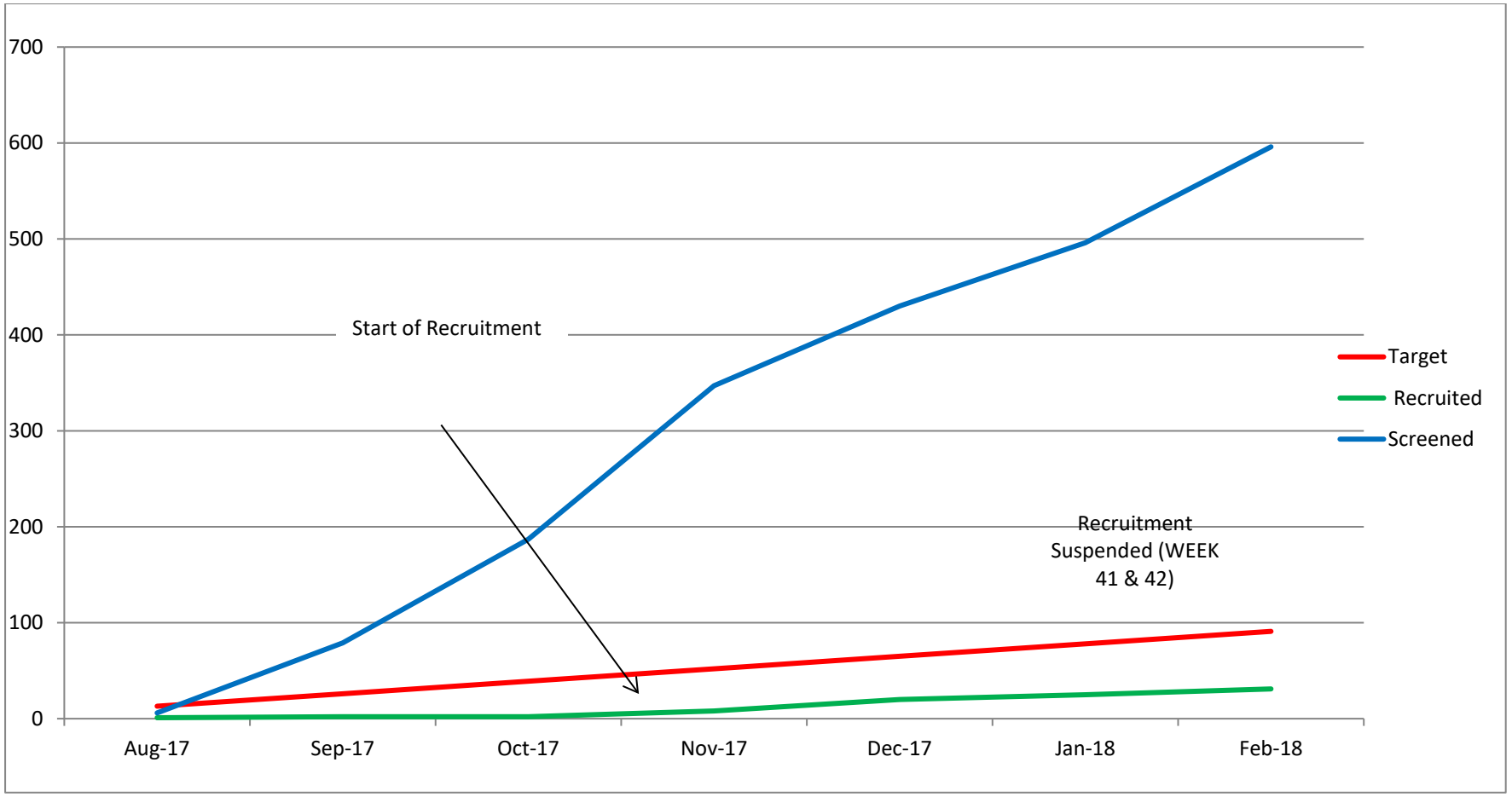

Figure 4. Line graph of proportion of screened to recruited patients for the PitSTOP study

		Number of participants	Percentage
Gender			
	Female	336	36%
	Male	377	41%
	Missing	213	23%
Mechanism of Injury			
	Assault	93	10%
	Collapse	43	4.6%
	Fall	489	52.8%
	RTA	26	2.8%
	Sports	19	2%
	Missing	282	30.5%
GCS			
	13	13	1.4%
	14	133	14.4%
	15	500	54%
	Missing	280	30.2%
SIMD			
	1	72	7.8%
	2	125	13.5%
	3	106	11.4%
	4	99	10.7%
	5	157	16.9%
	Missing	367	39%

Table 1. Characteristics of screened patients in the PitSTOP Pilot study

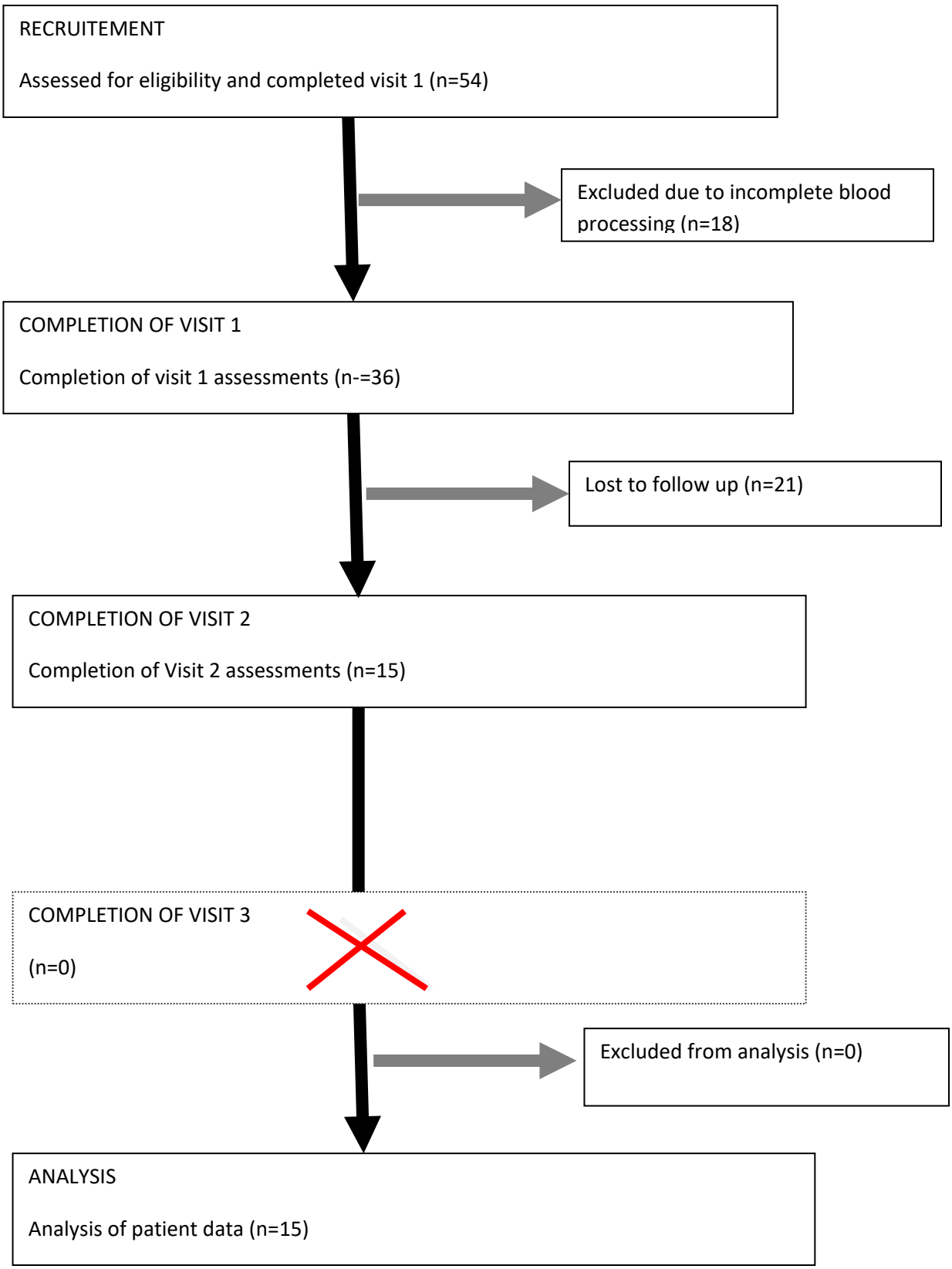

Figure 5. Adapted recruitment flow chart for PitSTOP Pilot

Outcomes from Pilot Study: Part 1

Paper Three

Characteristics of patients presenting with mild traumatic brain injuries (mTBIs): Is it time we considered mTBI a different clinical entity to moderate and severe TBI? (submitted)

Introduction:

In order to better characterise traumatic brain injury (TBI) and to identify the most effective research approaches for mild TBI, we conducted a study to determine the demographics and short-term outcomes in these patients. Information from this study helped to inform the PitSTOP protocol design.

Characteristics of patients presenting with mild traumatic brain injuries (mTBIs): Is it time we considered mTBI a different clinical entity to moderate and severe TBI?

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Keywords: CT-scan; head injury; mild traumatic brain injury; outcome; demographics

Characteristics of patients presenting with mild traumatic brain injuries (mTBIs): Is it time we considered mTBI a different clinical entity to moderate and severe TBI?

Abstract

Background:

Little is known about the demographic and clinical characteristic differences of patients suffering mild TBI (mTBI)

Objective:

To determine the demographics and short-term outcomes of patients presenting to the emergency department with significant mild traumatic brain injuries (mTBI) that met the SIGN guidelines for CT brain imaging.

Methods:

Prospective study of consecutive trauma admissions to a level 1 trauma hospital. We compared differences in mechanism of injury, injury severity and 30-day outcomes between different groups including between male and female patients, different age groups and different socioeconomic groups for a final total of 709 patients.

Results:

The average age of patients was 63 years and 47% of patients were female. There was a male predominance in younger patients, but this disappears by the middle ages and the number of elderly female patients exceeded the number of elderly male patients. Young patients were more likely to be from lower socioeconomic areas, whilst older patients were more likely to be from more affluent areas. The median

length of stay in hospital was 0 days and patients intoxicated with alcohol were discharged earlier than those not intoxicated. There was only one death and therefore a mortality of 0.14% in this cohort

Conclusions:

The demographics, injury characteristics and outcomes for mTBI are different to moderate and severe TBI. mTBI should be considered a different disease entity with different management strategies.

Introduction

Major trauma is the leading cause of death and disability of people under 40 years old (1) and in this age group, traumatic brain injury (TBI) is prevalent. TBI has been described as a “silent epidemic” that affects approximately 1.5 million people a year in England and Wales each year (2). In the last 4 decades, protocol-driven treatments of acute TBI, such as the Advanced Trauma Life Support (ATLS) and National Institute for Health and Care Excellence (NICE) protocols (3,4), have improved outcomes and reduced mortality for patients who sustained moderate and severe TBIs (5,6,7). But these patients form only 10-20% of TBI patients. Patients with mild TBI (mTBI), usually defined as a post-resuscitation Glasgow Coma Score (GCS) of 13 to 15, are much more prevalent (8,9). We know less about the epidemiology and outcomes of mTBI due to differences in patient pathways across different hospitals and because only few patients are followed up by specialists (10).

In the last decade, several large scale, multisite studies have been set up to address this historic oversight (11). Protocols such as those provided by NICE and the Scottish Intercollegiate Guidelines Network (SIGN) have also been modified to help with decision making in the acute management of mTBI such as in determining which patients should have imaging of their brains and which ones should be observed in hospital (12). But these guidelines have a limited role in the overall management. There needs to be a better understanding of this patient group and their clinical needs. The objective of this study was to describe the demographics, clinical characteristics and short-term outcomes of patients that present to the emergency department with mTBI and that met the SIGN guidelines for CT brain

scan. We describe gender, age and socioeconomic differences and assess the length of stay, ICU/HDU admissions and 30-day readmissions for this patient group.

Methods

Study design

Our analyses are based on individual patient data from the **Pit**uitary dy**s**function in **T**BI: **O**utcomes and **P**revalence (PitSTOP) feasibility study (currently unpublished). In this study, patients presenting within a week of sustaining an isolated mTBI to the emergency department at the Royal Infirmary of Edinburgh, Scotland, were screened and when suitable, recruited for follow up pituitary function tests within one week and six months following mTBI. We defined mTBI as an alteration in brain function, or other evidence of brain pathology, caused by an external force and resulting in a post-resuscitation GCS of 13 to 15 (13). Eligible patients were adults (≥17 years old) that met the SIGN guidelines for a CT scan of the brain following TBI (12).

We collated data on gender, age, Scottish Index of Multiple Deprivation (SIMD) rankings, mechanism of injury and whether alcohol was involved, results of CT scan, length of stay (LOS) in hospital (days), admissions to high dependency or intensive care units. The SIMD ranking is a measurement of material deprivation that is based on an administratively collated data and is created using seven different domains to score geographies in Scotland on their relative deprivation. These are income, health, crime, employment, education, access and housing. The overall SIMD rank is a weighted sum of the 7 domains (14). These domains are used to rank populations (determined using postcodes) into deprivation quintiles or deciles. We divided our

patient populations according to SIMD quintiles with 1 being the most deprived and 5 being the least deprived.

Each patient's GCS and the clinical indication for CT brain was determined by and documented by their responsible emergency department physician. CT brain imaging was categorised according to Marshall CT Classification based on the report provided by an independent consultant radiologist with no affiliation to the research study. The Marshall CT classification categorises injuries as different levels of diffuse lesions, based on basal cistern compression and midline shift, or focal lesions, depending on whether lesion volume exceeds 25 cm (table 1) (3,15). This classification is still considered a "gold standard" for TBI classification as components of the Marshall CT classification have been shown to contribute to outcome prediction in TBI (16). The mechanism of injury was determined from the description in the medical records as: a fall, road traffic accident, assault, sport and recreational activity, collapse or other cause (not defined). Simple cross-tabulations and percentages were used to describe the study demography, injury mechanisms and features of the care such as CT Marshall Score and duration of admission.

Statistics

Descriptive data are presented as medians (with interqauntile ratios (IQRs). Differences between groups and between subgroups, such as different injury severities, were analysed using non-parametric tests (chi-square, Wilcoxon or Kruskal–Wallis). Relationships between variables were analysed with the Spearman rank correlation coefficient. All statistical analyses were performed using R, version

3.2.2 (R Foundation for Statistical Computing). Exact significance levels are given for values in the range 0.01–0.05, whereas <0.01 represents significant levels less than 0.01. P values above 0.05 are considered statistically not significant (NS).

Ethical Approval

This study was approved by local Caldicott Guardian (reference number 18173). It was determined that anonymised patient data could be collected and stored without specific patient consent. All data arising from this study were stored on NHS servers. The computers on this network have restricted physical access; data are stored under coded filenames and the local network has secure password access restricted to only the research team. Patients included in the PitSTOP study were consented separately (data currently unpublished). Data from those patients are also included in this study.

Patient and public involvement

Patients were not involved in the design of this study, the choice of the outcome measures, or analysis of the data or dissemination.

Results

Age of presentation and the influence of gender

Between April 2017 and July 2018, a total of 1092 patients were screened as part of the PitSTOP study. There was incomplete data on 383 patients and these patients

were omitted from our final analysis. Ultimately, 709 patients (335 females and 374 males) were included for analysis. There was a significant difference between the age of presentation for female and male patients ($p<0.01$). The median age of presentation for women was 73 years (IQR 50 to 85 years) and the median age for men was 50 years (IQR 32-74 years). The overall median age of presentation for men and women was 63 years (IQR 38-81 years). The number (and proportion) of patients in each age group (categorised according to decade of life) are shown in table 2. Octogenarians were the largest age group represented and constituted 23% of all patients. The number of patients in this group was nearly double the second biggest group, which were patients in their twenties (13.9%). Septuagenarians were the third largest age group represented (13.8%).

There was a bimodal distribution of age of presentation for both men and women. For men, the two peaks of the bimodial curve were at 30 and 60 years. For women there was a small peak at 20 years

and then a much larger peak at 70 years. This was much larger than the second peak seen for men. Before the age of 50, there was a male predominance in patients presenting with mTBI. This predominance lessened as the age of presentation increased until the age group 50-59 years, when there was an equal number of male and female patients. In septuagenarians, octogenarians and nonagenarians, the proportion of female patients presenting with mTBI exceeds male patients. The female representation in these groups was large enough to counter the male predominance in younger age groups such that the overall female proportion in all age groups (47%) was almost the same as males **(figure 1)**.

Mechanism of injury in each age group

The most common causes for mTBI were falls and assaults, accounting for 69% and 14%, respectively. Road traffic accidents (RTAs) and collapses (of unknown origin) occurred less frequently **(table 2).** Generally, the proportion of patients presenting with assaults decreased with age whilst the proportion presenting as a result of a fall increased with age. Approximately one-third of patients under 30 years presented following an assault whilst nearly one-fifth of octogenarians (the largest group represented) presented following a fall. The proportion of patients presenting following a sports injury followed a unimodal distribution which peaked in the age group 30 to 39 years old. The highest incidence of RTAs were seen in patients less than 30 (14%) and in patients between 50 and 59 years old (10%) **(table 2).**

Injury severity

a. *Marshall CT score*

The majority of patients a Marshall CT score of 1 (649 patients; 92%) or 2 (50 patients;7%). There were no gender differences between CT Marshall scores (p=0.73). The median lengths of hospital stay for patients with Marshall CT groups 1 and 2 were 0 (IQR 0-1 days) and 2 days (IQR 1-2 days). The median LOS for patients with CT Marshall score 3 and 4 were 23 days (IQR 12.5-87.5 days) and 6 days (IQR 4-22.5 days). One patient had a CT Marshall score of 5 and was hospitalised for 33 days and three patients had a CT Marshall score of 6. One died and the other two were in hospital for an average of 18 days.

b. *Fractures*

There were a total of 34 (4.8%) skull fractures (19 facial fractures and 15 cranial vault fractures). There were 3 patients (0.42%) with associated cervical spine fractures. Two of these were odontoid peg fractures. Patients with no skull fractures (median age = 64 years (IQR 39-82 years) were significantly older than patients with fractures (median age 43 (IQR29-73; p<0.01). The median LOS for patients with c-spine fractures (9 days) was longer than for all without c-spine fractures.

Anticoagulation and antiplatelet medications

There were 253 patients (35.7%) patients on antiplatelet or anticoagulation medication. The proportion of females on these mediations (42.8%) was higher than

the proportion of males (28.7%; p<0.01). The proportion of patients on these medications increased with age **(table 2).** The median age was significantly higher for patients on anticoagulation or antiplatelets. The median age for patients on these medication was 80 years (IQR 71-87 years) compared to a median age of 46.5 years (IQR 71 to 87 years) for patients not on these medications (p<0.01). The medications included clopidogrel (28.1%), Apixiban (23.3%), aspirin (21.7%) and warfarin (18.6%). There was no difference in the median LOS between patients on anticoagulation or antiplatelets and those that no were not on these medications (median number of days = 3 days (IQR2-18 days) vs 2 days (IQR 2-4); p=0.06). There was also no difference in median Marshall CT score for patients on anticoagulation &/or platelets and patient not on these medications.

Socioeconomic status

The proportion of female and male patients in each SIMD quintile were similar. There were 13.3% patients from SIMD quintile 1 (44% females, 56% males); 21.4% from quintile 2 (49% females and 51% males), 18.7% from quintile 3 (44% females and 56% males), 17.8% from quintile 4 (49% females and 51% males) and 28.7% from quintile 5 (52% females and 48% males). Generally, the average age of patients increased with SIMD. There was a higher proportion of young patients in SIMD quintiles 1 and 2 (most deprived) and a higher proportion of older patients in SIMD 4 and 5 (figure 3).

Influence of alcohol

Alcohol intoxication (patient reported alcohol use immediately prior to TBI) was recorded in 27.5% of patients. Patients in whom alcohol involvement was recorded were significantly younger than those in whom alcohol involvement was not recorded (46.3 years vs 65.7%; p<0.01). Alcohol involvement was recorded in two-fifths to half of patients up to 70 years old. The proportion of patients who were intoxicated with alcohol then falls markedly **(table 2).** Alcohol involvement was significantly less likely with female patients than with male patients: one-fifth (20.4%) of female patients compared with nearly two-fifths (37.7%) of male patients were intoxicated at the time of presentation (p<0.01). LOS was shorter for patients in whom alcohol involvement was recorded compared to those in whom alcohol involvement was not recorded (1.58 days compared to 4.24 days, p<0.01).

Length of stay in hospital, thirty day readmissions and death

The median LOS was 0 days (IQR 0-2 days). There were no difference in the median length of stay between male and female patients (p=0.4) or between patients from different social status (p=0.8). There was a weak correlation between age and LOS. The correlation coefficient was 0.11 [95% confidence interval 0.07 – 0.15] (p<0.01) **(figure 4)**. Sixty percent of patients were discharged on the same day of admission and 84% of patients were discharged within 2 days of admission. Only 74 patients (10.4%) were admitted for longer than 7 days. No patient was referred to a specialist clinical neurosciences service following discharge.

There were 99 (14%) readmissions within 30 days of initial discharge. The majority of these were due to planned outpatient follow up appointments with specialists for management of associated injuries such as maxillofacial surgery for those who sustained facial fractures and follow up with physicians for patients who had unexplained collapses. The highest rates of readmissions were seen in patients in their 70s and 80s. There was only one death; a death rate in this cohort of 0.21%. The patient was an 84-year-old who took Apixaban and whose SIMD quintile was 3. She presented with a post-resuscitation GCS of 14 and a Marshall CT score of 6 (a subdural haematoma that was not evacuated). She died several days after discharge from the emergency department.

Discussion

TBI is often considered a disease of young men. However, our findings have highlighted that this is not the case for mTBI. We have shown that mTBI, unlike severe and moderate TBI, affects older patients more than younger patients; approximately 62% of patients with mTBI that met the SIGN guidelines for CT brain were 50 years or older. We have also found that above the age of 50, the male predominance typically described for TBI, disappeared and there was a female predominance. There was an approximately 50:50 split of male and female patients in the 50-59 and 60-69 age groups. As with moderate and severe TBIs, the mechanism of injury changes as patients get older with younger patients more likely to be assaulted or involved in RTAs and older patients more likely to present due to frailty, following falls and collapses. Unlike severe and moderate TBIs, the proportion

of patients presenting as a result of RTAs was small. This has previously been demonstrated by others and corroborates the lower impact trauma usually reported in mTBIs (17,18). It also explains the low mortality of mTBI compared with the high mortalities seen with moderate and severe TBIs (19).

One explanation for the average age of patients included is that the SIGN guidelines for CT brain imaging recommend scanning all patients over the age of 65 years with any loss of consciousness or amnesia and all patients on anticoagulation and with neurological deficits. Such measures, designed to identify elderly patients at risk, inevitably lead to a disproportionately higher number of elderly patients getting CT brain imaging.

It is interesting that younger patients that sustain mTBI are more likely to be from less affluent areas and the opposite is true for older patients. The reason for this is unclear but it may be that young people in less affluent areas are more prone to high risk behaviours than their counterparts in more affluent areas and conversely, older patients from affluent areas may be more likely to keep their independence for longer and therefore be more prone to falls and accidents. Furthermore, people in more affluent socioeconomic geographies live longer and therefore are likely to have a higher proportion of elderly representatives that less affluent areas.

Alcohol played a role in approximately one-third of presenting patients and was twice more likely to have played a role in male patients than in female patients. A similar proportion of alcohol involvement and male predominance has been reported for

moderate and severe TBIs (20). Alcohol use is a known risk factor for all types of injures and mTBI is seemingly no different (18). Patients in whom alcohol involvement was recorded were in hospital, on average, half the number of days of patients in whom alcohol involvement was not recorded. Presumably, this is because younger patients were more likely to be intoxicated and are discharged from emergency departments once they become sober.

None of the patients in our cohort were referred to a specialist head injury service after discharge. One possible reason why our understanding of mTBI has been extrapolated largely from moderate and severe TBI research is that many patients with mTBI are managed in and discharged from emergency departments and do not get seen by or followed up by experts and therefore very little is known about the outcomes for these patients. In a recently study, Nelson and colleagues reported that over 80% of mTBI sufferers reported a functional impairment at 12 months and that approximately half of mTBI sufferers reported functional limitations. However, most did not receive follow up care after discharge from the emergency department (21). This seems to be commonplace in many emergency departments across Europe (11).

Nelson and colleagues also demonstrated in their study that patients with acute intracranial findings were more likely to suffer neuropsychological sequalae. It may be that patients with Marshall CT classification >1 are at greater risk of complications and should be admitted for longer and perhaps should be offered follow up after discharge. We found no evidence of this practice in our cohort but there was also no

evidence that higher Marshall CT scores was associated with increased readmissions within 30 days of discharge. It should be noted that the Marshall scale was designed as a predictive tool for patients with moderate and severe TBIs that were likely to develop raised ICP. It is therefore has limited used in mTBI.

One potential challenge with mTBI research and the clinical approaches to these patients is that they are numerous. mTBI is a common diagnosis and constitutes approximately 80% to 90% of TBIs. The true prevalence is not known because a number of patients either do not present to hospital or do not get a diagnosis of TBI. It would be difficult to offer follow up to all patients presenting with mTBI and more pragmatic measures and guidelines for follow up are needed to in order to make the economics of patient follow up viable. An example of this is the emerging evidence that some TBI sufferers develop anterior pituitary gland dysfunction that is undetected and that may contribute to long term neuropsychological symptoms (22). It would be economically and logistically difficult to offer every patient presenting to the emergency department with mTBI pituitary function tests and also to ensure that all patients with abnormal pituitary results are seen by an appropriate specialist. Further research is needed to identify those patients at risk and to help formulate surveillance guidelines.

Limitations

One limitation of this study is the inclusion of only mTBI patients that met the SIGN guideline's clinical threshold for a CT scan of their brain. Whilst this was a pragmatic

criteria designed to ensure that “trivial” TBIs were not included, it is likely that some patients with significant injuries that presented to the emergency department did not meet the criteria for brain imaging and therefore were not included. Consequently our findings may not be an accurate reflection of outcomes of mTBI patients. Secondly, although it was not part of our objective, there was perhaps a missed opportunity to follow these patients up for long term outcomes (> one month). Recently, published data suggests that patients with CT-positive mTBI are more likely to report difficulties with activities of daily living. With so few large series on this patient group, additional information about long term outcomes would have been a useful contribution to the current literature.

Conclusions

Despite its limitation, the data presented is one of the largest cohorts on this patient group. We have shown, prospectively, that the patient characteristics of mTBI are different to the traditional understandings of TBI that has largely been determined in patients with moderate and severe TBI. There is a potential danger of extrapolating the results from the research focused on moderate and severe TBIs to this patient group. Researchers and clinicians should view mTBI as a different clinical entity to severe and moderate TBIs and further research is needed to better understand the long-term consequences of mTBI.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Figures

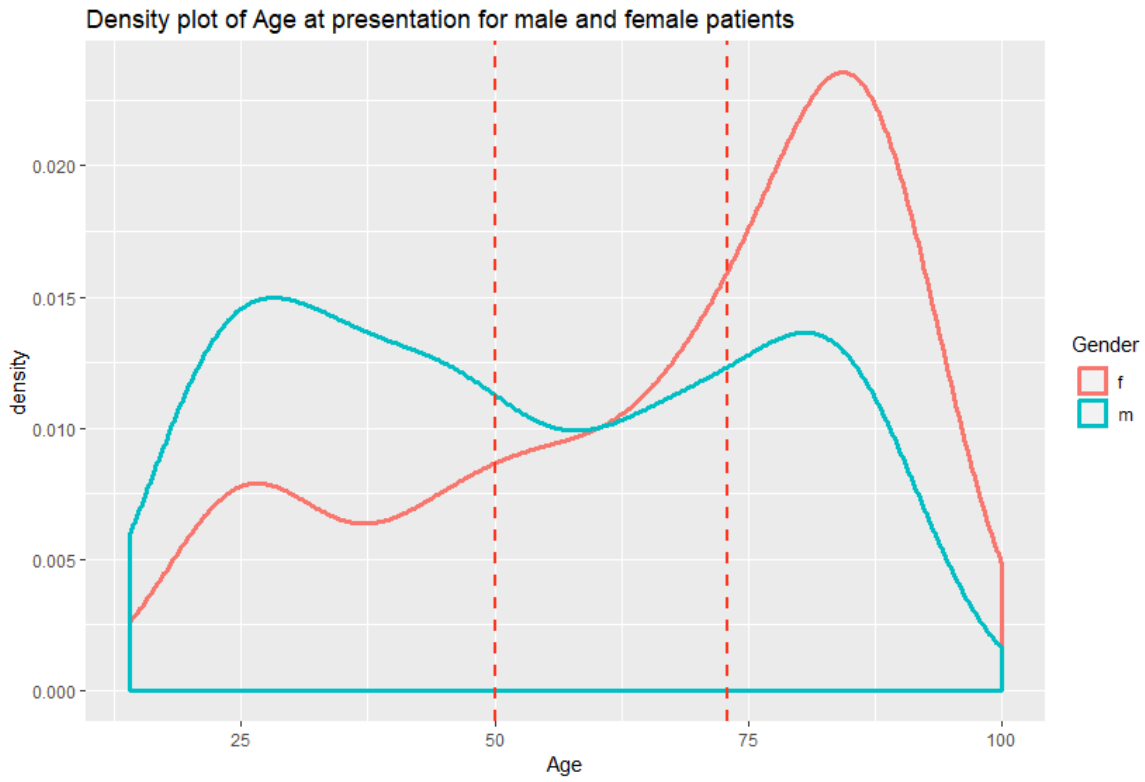

Figure 1. Density plot of age distribution for female and male patients. The proportion of female TBI patients becomes equal to males by their mid-50s and subsequently overtakes the proportion of male TBI sufferers

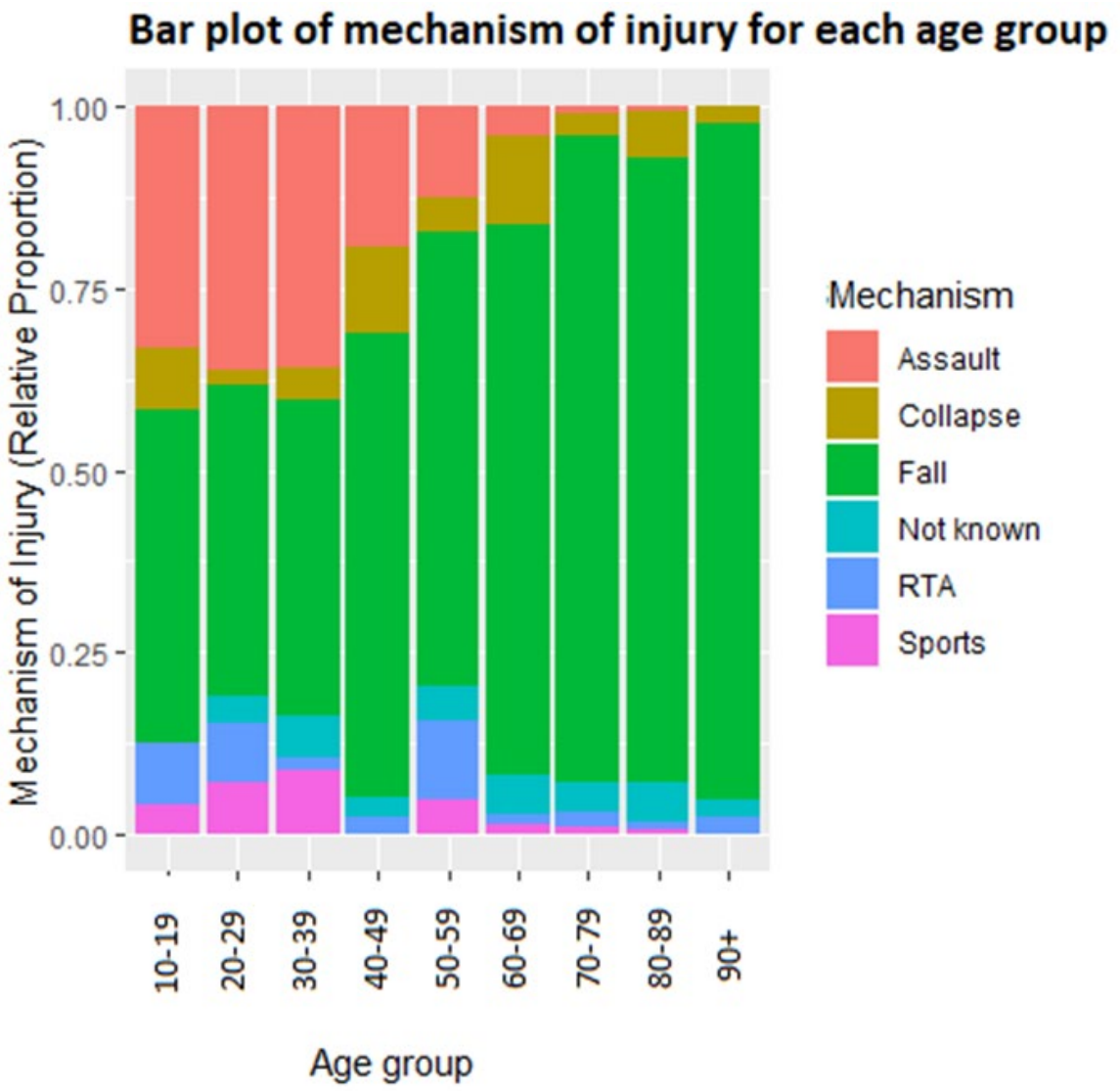

Figure 2. Bar plot of mechanism of injury for each age group

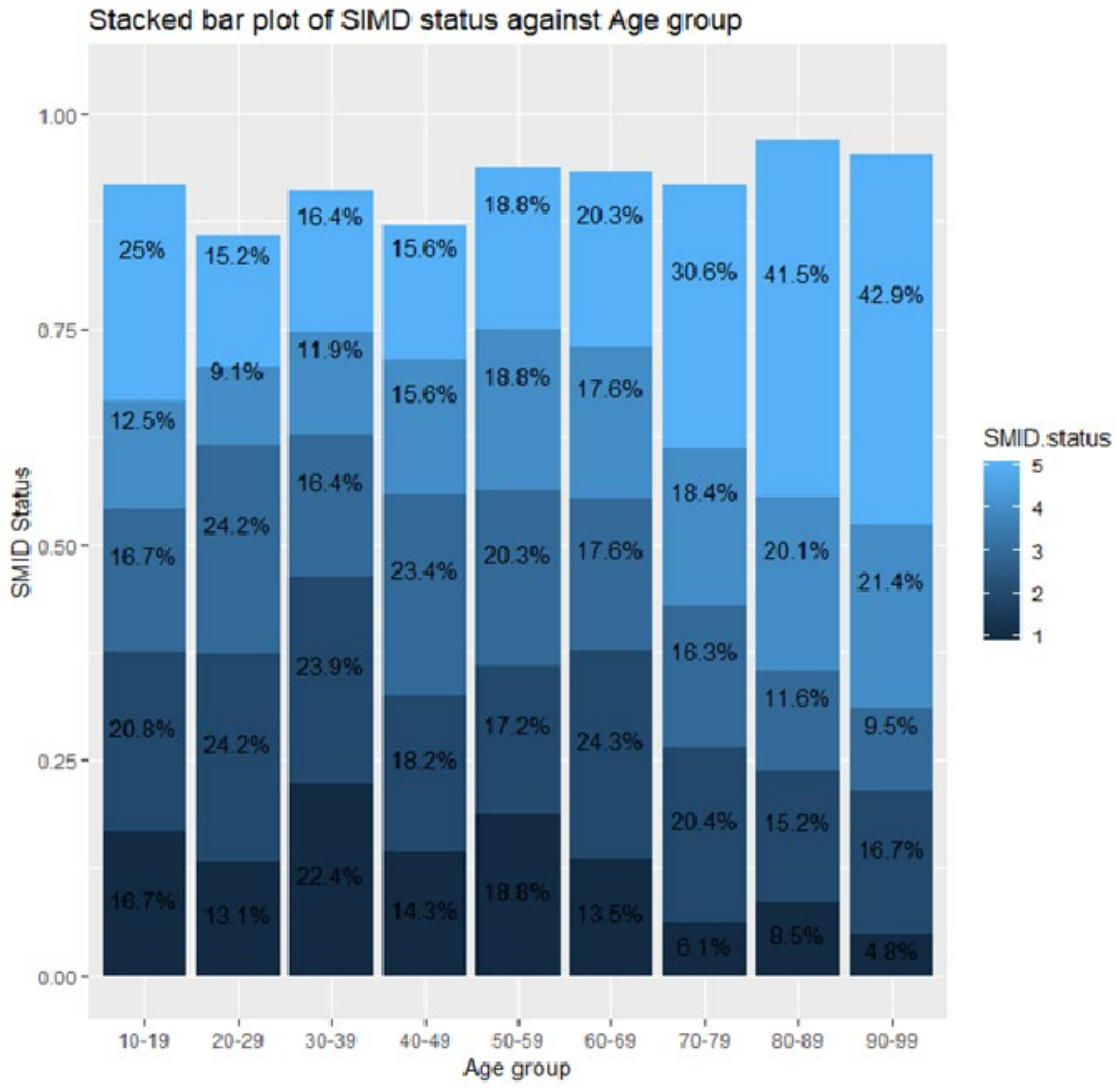

Figure 3. Bar plot of SIMD quintiles for each age group (Scottish Index of Multiple Deprivation (SIMD): from most deprived (1) toleast deprived (5))

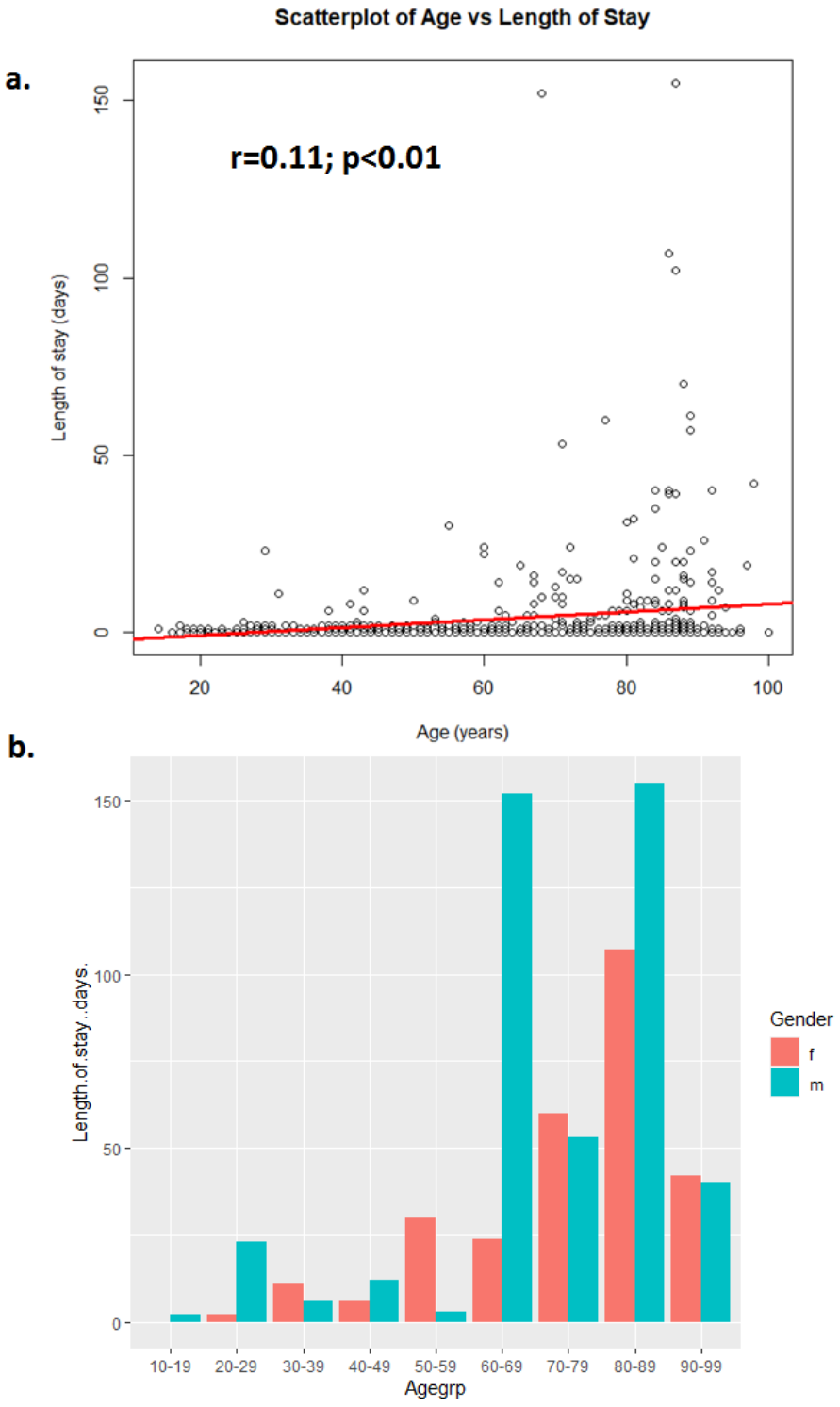

Figure 4. Scatter plot (a) and bar plot (b) of age against length of stay showing a weak but positive correlation (Pearson's r = 0.11)

Marshall CT Classification	Radiological features
I	No visible pathology
II	Midline shift of 0 to 5mm Basal cisterns remain visible No high or mixed density lesions > 25cm^3
III	Midline shift 0 to 5mm Basal cisterns compressed or completely effaced No high or mixed density lesions >25cm^3
IV	Midline shift >5mm No high or mixed density lesions >25cm^3
V	Any lesion evacuated surgically
VI	High or mixed density lesions >25cm^3 Not surgical evacuated

Table 1. Marshall CT classification for TBI

	Age Group								
	10-19	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	**90-99**
Number of patients (%)	24 (3.4%)	99 (13.9%)	67 (9.4%)	77 (10.9%)	64 (9%)	74 (10.4%)	98 (13.8%)	164 (23.1%)	42 (5.9%)
Number of female patients (%)	5 (20.8%)	34 (34.3%)	16 (23.9%)	27 (35.1%)	32 (50%)	35 (47.3%)	53 (54.1%)	99 (60.4%)	34 (80.9%)
No. of Assaults (% for age group)	8 (33.3%)	36 (36.36%)	24 (35.82%)	15 (19.48%)	8 (12.5%)	3 (4.05%)	1 (3.06%)	1 (0.61%)	0 (0%)
No. of Collapses (% for age group)	2 (8.33%)	2 (2.02%)	3 (4.48%)	9 (11.69%)	3 (4.69%)	9 (12.16%)	3 (3.06%)	1 (6.71%)	1 (2.38%)
No. of Falls (% for age group)	11 (45.83%)	42 (42.42%)	29 (43.28%)	49 (63.64%)	40 (62.5%)	56 (75.68%)	87 (88.78%)	140 (85.37%)	39 (92.86%)
Road traffic Accidents (% for age group)	2 (8.33%)	8 (8.08%)	1 (1.49%)	2 (2.60%)	7 (10.94%)	1 (1.35%)	2 (2.04%)	2 (1.22%)	1 (2.38%)
Sports injury (% for age group)	1 (4.17%)	7 (7.07%)	6 (8.96%)	0 (0%)	3 (4.69%)	1 (1.35%)	1 (1.02%)	1 (0.61%)	0 (0%)
Cause unknown (%)	0 (0%)	4 (4.04%)	4 (5.97%)	2 (2.60%)	3 (4.69%)	4 (5.41%)	4 (4.08%)	9 (5.49%)	1 (2.38%)
Alcohol involvement	11 (52.50%)	38 (38%)	28 (41%)	38 (49%)	26 (40%)	29 (39.20%)	15 (15.30%)	9 (5%)	1 (2.30%)
Anticoagulation/Antiplatelet use	0 (0%)	2 (2%)	3 (3%)	7 (8%)	12 (16%)	30 (37%)	66 (63%)	103 (56%)	29 (67%)
Proportion of HDU/ICU admission	0 (0%)	1 (1%)	2 (2.90%)	1 (1.29%)	1 (1.60%)	1 (1.35%)	1 (1%)	1 (0.60%)	0 (0%)
30 day admission	1 (4%)	13 (13%)	10 (15%)	9 (12%)	5 (8%)	12 (16%)	17 (17%)	30 (17%)	3 (7%)

Table 2. Demographic information and patient characteristics

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Conclusions

The results showed that mild TBI affected a different patient demographic to that reported for moderate and severe TBI. Unlike with moderate and severe TBI, mild TBI affected older patients. I also found that this patient group had a very short hospital stay. This study led to me altering the PitSTOP protocol to allow the first visit to occur within 7 days of TBI as I now knew that most patients were discharged on the same day and therefore an inpatient early morning, fasting blood test was not going to be possible for most.

Outcomes from Pilot Study: Part 2

Paper Four

Anterior hypothalomo-pituitary dysfunction occurs in mild Traumatic Brain Injuries without evidence of structural damage to the pituitary gland: Results of a pilot study

Introduction

During this feasibility study, all aspects of the PitSTOP protocol are tested with a focus on patients with mild TBI. The results of study will determine how workable the PitSTOP protocol is and whether it can be rolled out as a multi-centre study. We will also aimed to determine whether anterior pituitary dysfunction occurred in patients following mild TBI.

Anterior hypothalomo-pituitary dysfunction occurs in mild Traumatic Brain Injuries without evidence of structural damage to the pituitary gland: Results of a pilot study

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Andrew Farrell A,

Peter J Andrews

Abstract

Background:

The aims of this study are to examine the acute biochemical and radiological response of the anterior pituitary to acute mild traumatic brain injury (mTBI) and to determine the prevalence of post-TBI anterior pituitary dysfunction (PTPD) six months following mTBI.

Methods:

Patients presenting to the ED with mTBI (GCS 13-15) were screened with a fasting morning serum levels of cortisol, free thyroxine, TSH, prolactin, IGF-1 and sex hormones and an MRI scan of the pituitary gland within 7 days of injury and were followed up at 6 months repeat anterior pituitary blood test including stimulation tests and a repeat MRI.

Results:

A total of 36 patients completed baseline anterior pituitary hormone serum blood test. (within 7 days of mTBI). There was abnormal hormone activity in 44% (16/36). All had abnormalities in a single anterior pituitary axis and none had deficiencies in multiple axes. Only elevated serum cortisol correlated positively with injury severity on CT. Fifteen patients returned for follow up at 6 months and 3 (20%) were found to have PTPD. There was no association between anterior pituitary dysfunction and structural damage on MRI.

Conclusion:

Pituitary dysfunction occurs after mTBI and is not caused by structural damage of the pituitary gland.

Key words: traumatic brain injury, TBI, Pituitary dysfunction, anterior pituitary

Introduction

Traumatic brain injury (TBI) remains a leading cause of adult mortality and morbidity in the developed world[1]. Many sufferers do not return to their pre-injury level of function and quality of life because of ongoing physical or neuropsychological disabilities[2]. Some symptoms may be due to post-TBI anterior pituitary dysfunction (PTPD)[3 4]. PTPD is defined as evidence of anterior pituitary dysfunction attributable to TBI and occurring at least 3 months following TBI. This is distinct from anterior pituitary hormone changes that occur in the days following TBI[5 6 7 8 9]. Several meta-analyses have concluded that PTPD occurs in approximately one-third of TBI suffers[4 10 11]. It has been difficult to determine whether abnormal pituitary function following acute TBI is pathological or is an appropriate adaptive response to the injury and whether it predisposes to PTPD. The mechanism of PTPD is also unclear and there are several hypotheses including direct damage to the anatomically vulnerable pituitary gland from the primary injury[12 13] and secondary insult due to oedema, haemorrhage or hypotension[14 15]. These hypotheses have been largely extrapolated from post-mortem studies of patients who died from TBI and there are only a small number of studies that have used magnetic resonance imaging (MRI) to assess the pituitary gland of patients that suffered acute TBI. For example, Maiya and colleagues demonstrated pathological changes in the pituitary gland during the acute phases following moderate and severe TBI[16] and Zheng and colleagues demonstrated, using apparent diffusion coefficient (ADC) MRI imaging, that microstructural damage occurred in the pituitary of patients with all severities of TBI[17].

Most studies on PTPD have been focused on patients with moderate and severe TBI. These patients have serious and often catastrophic physiological insults which may include anterior pituitary dysfunction. Mild TBIs (mTBIs) damage brain cells and trigger the same damage associated molecular patterns (DAMPS) seen in moderate and severe injuries without necessarily triggering the same systemic responses seen in moderate and severe TBI[18]. It can therefore be hypothesised that the anterior pituitary response to isolated mTBI may reflect the true response to TBI without being confounded by the global and systemic responses to injury that occur in moderate and severe TBIs.

Some of the long-term consequences of TBI are due to DAMPS occurring during the acute phase of the injury which may persist or progress. There have been suggestions that screening for PTPD should be offered to patients who sustain "complex" mTBI; defined as intercranial bleed, brain swelling or skull fracture on initial computerised tomography (CT) scan. Therefore, the aims of this study are firstly to determine how mTBI affects the structure and function of the anterior pituitary gland acutely, secondly to prospectively determine the prevalence of PTPD at 6 months following mTBI, and finally to establish whether acute pituitary hormone changes predispose patients to PTPD.

Material and methods

Patients

This study reports on individual patient data from the **Pit**uitary dy**s**function in **T**BI: **O**utcomes and **P**revalence (PitSTOP) feasibility study. In this study, patients presenting within 7 days of sustaining an isolated mTBI to the emergency department (ED) at the Royal Infirmary of Edinburgh, Scotland, were screened and when suitable, recruited to have baseline serum test of anterior pituitary gland function and MRI scan of their pituitary gland within one week of injury. They were then followed up at six months with stimulation (growth hormone and adrenocorticotropic axes) and baseline (all other axes) testing of anterior pituitary gland function, and a further MRI scan of their pituitary gland. We defined mTBI as an alteration in brain function, or other evidence of brain pathology, caused by an external force and resulting in a post-resuscitation Glasgow Coma Scale (GCS) score of 13 to 15[19]. We kept patient selection criteria broad; eligible patients were adults (≥17 years old) that met the National Institute for Health and Care Excellence (NICE) guidelines for a CT scan of the brain following TBI[20].

We collated data on gender, age, body mass index (BMI), mechanism of injury and results of CT scan. Each patient's GCS and the clinical indication for CT brain was determined by and documented by their responsible ED physician. CT brain imaging was categorised according to Marshall CT Classification[21]. For analysis, all patients

who had evidence of haemorrhage or skull vault or base of skull fractures on CT scans were deemed to have a ***'complex'*** mTBI, in order to differentiate from those whose index scans were normal (non-complex mTBIs)[22]. The mechanism of injury was determined from the description in the medical records as: a fall, road traffic accident, assault, sport and recreational activity, collapse, or other cause (not defined). Simple cross-tabulations and percentages were used to describe the study demography, injury mechanisms and features of the care such as CT Marshall Score and duration of admission.

Many medications can affect pituitary function including several medications used in the acute setting. For example, opiates act with varying potency at three types of receptors (gamma, kappa and mu) and have varying effects on the pituitary gland. Most research has focused on opioid-induced hypoginadism but emerging evidence suggests that they can also cause adrenal insufficiency. Other commonly used medications including antidepressants, antipsychotics, antihistamines, and proton-pump inhibitors can raise prolactin levels. A list of medications that may affect HP-axes were approved by an endocrinologists and patients on these medications were excluded for the study. We used the following exclusion criteria:

1) Patients with a pre-existing endocrine diagnosis

2) Morbidly obese patients with BMI >35

3) Unlikely to survive for the next 24 hours in the opinion of the intensive care or neurosurgical team treating the patient

4) Patients with known epilepsy

5) Patients on medications that are known to affect the hypothalamic-pituitary axis

6) Patients who are not able to consent

Written informed consent was sought from all participants recruited to the study.

Serum Hormone Measurements

Anterior pituitary dysfunction was defined as the presence of single or multiple anterior pituitary axes deficiencies. These were based on the normal serum concentrations of hormone as defined by our local laboratory and include:

1. serum prolactin level 60-500mIU/L (22 ng/ml)
2. gonadotropin deficiency was defined for women as secondary amenorrhea or a menstrual disorder with a blood oestradiol level below 20 pg/ml and normal or low gonadotropin levels and for men as a blood testosterone level below 10 nmol/L with normal or low gonadotropin levels.
3. Thyrotropin deficiency was defined as a low free thyroxine (T4) level with normal or low thyroid-stimulating hormone (TSH) levels.
4. Acute corticotropin deficiency was defined as a blood cortisol level below 138µg/dl. To determine corticotrophin deficiency at 6 months, a short synacthen test (SST) was performed: 250µg of synacthen was administered intravenously and cortisol levels were checked before and after 30 minutes. Cortisol level of <430 nmol/L were regarded as deficient.
5. Growth hormone (GH) axis was assessed after acute TBI using baseline insulin-like growth factor 1 (IGF-1) levels. Normal levels were between 72 and 259µg/L GH axes at 6 months was investigated with GH releasing hormone (GHRH) + Arginine test. During this test, GHRH, 1µg/kg, was administered by

bolus injection, immediately followed by infusion of an arginine solution (0.5g/kg) over 30 minutes. Serum GH was measured at baseline, 30, 60, 90, 120 and 150 minutes. The following cut-off levels were used to diagnose GH deficiency (GHD): for patients with a BMI < 25 a peak GH < 11.5ng/L, for BMI of 25–30 a peak GH < 8.0ng/L, and for patients with BMI > 30 a peak GH < 4.2ng/L.

MR Imaging Protocol

MRI scans have greater soft tissue contrast allowing for better visualisation of the pituitary gland than CT imaging. Therefore, a T2w whole brain volume and T1w and T2w saggital and coronal views of the sella region were acquired. All participants were imaged using a Siemens Magnetom Prisma 3 T clinical scanner (Enlangen, Germany). Images were loaded onto the hospital PACS system and interpreted by a consultant radiologist (AF).

Statistical Analysis

Patients' data were expressed as median (interquartile ranges) if non Gaussian distribution or mean ± SEM if Gaussian. Normally distributed values between two variables were compared by unpaired Student's *t* test, with a 95 % confidence interval (CI), whereas the Mann–Whitney U test was performed for non-parametric data. The chi square test or variance analysis was used to compare categorical data. Correlations were tested with Pearson test. Statistical significance was considered when the *P* value was <0.05. All the statistical analyses were carried out using R, version 3.2.2 (R Foundation for Statistical Computing).

Ethical approval

The studies that provided data for evaluating this protocol were approved by the Lothian Ethics of Medical Research Committee (REC **17/SS/0043**) and the NHS Lothian R+D Office (2017/0146), and conducted according to the principles expressed in the 1964 Declaration of Helsinki. All patients gave written informed consent to be included in the study.

Results

A total of 54 patients consented for inclusion in the study. A complete anterior pituitary profile was not completed in 17 patients; these patients were omitted from the final analysis as well as 1 patient who did not return for blood tests. A total of 36 patients (21 female and 15 males) were included in the final analysis. The median age for this cohort was 38.5 years (IQR27.5-59.5 years) and the median BMI was 24 (IQR 22-27). There were 28 patients (80%) that presented with mTBI following a fall, 4 patients (11.4%) following an RTA and 2 patients (5.7%) that presented following an assault. Two patients (5.7%) presented following sports injuries. Three patients had a post resuscitation GCS of 13, 6 patients had a post resuscitation GCS of 14 and 27 patients had a post resuscitation GCS of 15.

A. <u>Acute anterior pituitary response to mTBI</u>

Sixteen patients (44.4%) had at least one anterior pituitary axis dysfunction in the first week following mTBI. This included 6 patients (16.7%) with abnormal IGF-1, of

which 5 were elevated and one was low, 5 patients (13.8%) with hypogonadism, 5 patients (13.8%) with hypercorticolsaemia, one patient (2.8%) with hyperprolactaemia and one patient (2.8%) with low thyroid function.

The median age for patients with acute anterior pituitary hormonal abnormalities was 33 years (IQR 26.5-43.5 years) compared to 45.5 years (IQR 29-67.5 years) for those with normal hormone profile and the median BMI for patients with abnormal and normal hormone profiles were 24.5 and 24, respectively. There were no significant differences in age or BMI for patients with abnormal and normal pituitary profiles (p=0.67 and 0.66, respectively). There were also no differences between the proportions of participants with “complex” and non-complex mTBIs**.**

Elevated cortisol levels

Serum cortisol levels are usually elevated as a response to stress. Five patients (13.8%) had elevated cortisol levels in the first week following TBI. Four of the five were patients who had sustained mTBI following falls. One patient had a sports injury. Four of the 5 were female. There was no difference between BMIs of patients with elevated serum cortisol (BMI 22[IQR 21-24]), compared to patients with normal serum cortisol concentrations (24.5 [IQR 22-27.5] (p=0.29). There was also no difference in mean ages for the two groups (38.8 years (elevated cortisol) vs 45.8 years; p=0.57).

The median serum cortisol concentration for the cohort was 379.5nmol/L (IQR 277.5 to 503.5nmol/L). Patients with complex mTBIs had a significantly higher median cortisol concentration than patients without complex mTBI (462nmol/L vs. 351.5nmol/L; p=0.035). However, there were no differences in serum cortisol concentrations between female and male patients (p=0.14), patients with normal and abnormal pituitary profile (p=0.4) or between the different mechanisms of injury (p=0.38). There was an inverse correlation between post resuscitation GCS and serum cortisol concentration, but this was not significant. There was no significant correlation between age and cortisol concentration and no correlation association between BMI and cortisol concentration.

Somatotrophic-IGF-1 axis

IGF-1 levels were available for 32 patients. Six patients (18.75%) had an abnormal somatotrophic axis; five had elevated IGF-1 levels and one male patient had a low concentration. Four of the six had suffered a mTBI following a fall, one had an RTA and one was assaulted. There was no difference in the mean ages (43.1 years (abnormal GH) vs. 45.4 years; p=0.8) or BMI (p= 0.26) between the patients with a normal and abnormal somatotrophic axis (Table 1). There was no significant difference in the mean IGF-1 concentrations between patients with and without complex mTBIs (p=0.47).

Gonadotrophic axis

Sex hormone assays were available for 32 patients (13 female and 19 male). Nine patients (28.1%) had hypogonadism. All were male and therefore 47.4% of males in this cohort had hypogonadism. Males were therefore significantly more likely to suffer hypogonadism post mTBI than female patients **(p=0.01).** There were no differences in the ages (p=0.26) and BMIs (p=0.1) of patients with and without hypogonadism and there was also no difference in the proportions of patients with and without complex mTBIs in each group.

Thyrotrophic axis and prolactin

Thirty-six patients had blood tests to check the thyrotrophic axis. Only one female patient had serum tests compatible with hypothyroid. The same patient had a raised serum prolactin and was the only participant with abnormal serum prolactin levels. This patient was subsequently found to be taking oral contraceptive pill that affected both these pathways and was subsequently excluded from the study. No patient had an abnormality in these pathways.

MRI Changes to the pituitary in acute mTBI

Thirteen patients (9 females and 4 males) consented to having MRI imaging within a week following mTBI. Four of the 9 female patients had an abnormal pituitary axis (one had 2 abnormal axes) and all 4 males had an abnormal axis (3 had hypogonadism and one had a raised IGF-1). The gross structures of the anterior pituitary in all patients scanned were normal and there was no evidence of structural anterior pituitary gland damage.

B. Chronic anterior pituitary response to mTBI

Fifteen of the 36 patients (42%) returned for follow up anterior pituitary testing at 6 months including stimulation tests for growth hormone axis and secondary hypoadrenalism. Three (20%) of the 15 returning patients (2 female and one male) had evidence of anterior pituitary dysfunction. The male patient had evidence of hypogonadism which had persisted from the acute phase of injury and the two female patients had evidence of de novo secondary hypoadrenalism: one female patient aged 59 years had a baseline cortisol of 268nmol/L and a cortisol of 395nmol/L 30 minutes after stimulation. The other was 39 and had a pre stimulation cortisol of 185nmol/L and post stimulation cortisol of 415nmol/L. The mechanism of injury in all 3 patients was fall. The 59 year old female patient had a complex mTBI with a thin subdural haematoma on their index CT scan whilst the other two patients did not have any abnormalities on their index CT scan. There was no significant correlation between *complex* mTBI and PTPD. None of the three patients with PTPD had MRI imaging of their pituitary gland.

MRI pituitary at 6 months

Six of the 13 patients (46%) that had MRI scans within 7 days of mTBI returned for follow up imaging at 6 months. One patient, whose pituitary gland was normal at the time of injury, had loss of volume of pituitary at 6 months. This patient did not have corresponding biochemical evidence of anterior pituitary dysfunction. The rest of the patients imaged at 6 months had normal pituitary glands.

Discussions

There have been disagreements about the clinical significance of PTPD with different authors drawing different conclusions about the disease burden[23]. Our aims in this study were to determine the acute biochemical and structural response of the anterior pituitary gland to mTBI and the prevalence of PTPD at 6 months following mTBI. Our main findings are firstly that there was a high prevalence (44%) of abnormal serum concentrations of anterior pituitary hormone in the acute phase (within one week) of mTBI, secondly that PTPD occurred in one-fifth of patients followed up at 6 months including *de novo* PTPD in patients previously found to have a normal anterior pituitary function, and thirdly these changes occurred without associated structural changes on MRI. Only one patient had structural changes in their pituitary gland and this was not associated with abnormal hormone activity. To our knowledge, this is the first study that attempts to correlate the biochemical response of anterior pituitary with structural imaging of the pituitary gland in patients with acute mTBI.

We chose to study patients with isolated mTBI because moderate and severe TBIs are often associated with severe systemic responses that make it difficult to perform or interpret anterior pituitary function.

Pituitary (dys)function following acute mTBI

1. *Adrenal insufficiency*

Several studies have concluded that TBI induces adaptive changes in the HPA axis leading most commonly to hypercortisolaemia. However, most have focused on reporting the incidence of post-TBI hypopituitarism (PTHP) and in particular, the potentially life-threatening hypocortisolaemic[24]. The reported incidence of TBI-induced adrenal insufficiency varies widely amongst different studies because of the different diagnostic criteria and study protocols used. For example, the gold standard insulin-tolerate test is thought to be unsuitable in patients with head injuries because of the theoretical risk of seizure[15] and the synacthen (corticotrophin) test can be unreliable in the acute setting[5]. Only a small number of studies have reported on the acute changes in the HPA axis that occur following mTBI. One such study by Tanriverdi and colleagues reported that the HPA response to TBI was similar in patients with mTBI compared to those with moderate and severe TBI. The authors' definition of ACTH deficiency was similar to ours and in their cohort of 52 patients, 9.8% of participant with TBI had evidence of adrenal insufficiency. Similarly, Klose and colleagues performed stimulation tests in the first 12 days following TBI in a cohort that included 22 patients with mTBI. Two of the 22 mTBI patients (9.1%) had an insufficient 30 min cortisol response to ACTH stimulation.

In our cohort, none of the participants had hypocortisolaemia and 13.8% of participants had elevated serum cortisol levels. Hypercortisolaemia correlated positively with injury severity as determined by presence of haemorrhage or fracture on CT scan (*complex mTBI*). The other hormonal changes seen in the acute stages in our cohort occurred independent of age, BMI and mechanism of injury. Hypercortisolaemia in these patients is therefore likely due to physiological activation of the corticotrophin axis in response to stress[25]. Kleindeinst and colleagues found elevated levels of urinary free cortisol and cortisone on day-7 in 85% of patients tested, concluding that the normal circadian variation of cortisol is replaced by a more continuous secretion under severe stress[26]. Additionally, hypercortisolaemia in our cohort occurred without any structural damage to the pituitary gland on MRI scan suggesting it is physiological and not pathological. On this basis we found that in the setting of mTBI, acute adrenal insufficiency does not occur and there is no requirement for screening..

An alternative method for ascertaining HPA function would have been the use of salivary cortisol. Salivary cortisol secretion is a reliable indicator of free cortisol in plasma and salivary cortisol levels have been correlated with serum and 24-hour urine cortisol levels in children and adults. Cortisol secretion follows a daily circadian rhythm with a daily peat between 5am and 8am and lowest levels around midnight. Therefore, a single salivary cortisol collected at a standardised time of day for all participants would have been a less invasive method of determining HPA function. We however opted not to use salivary cortisol as it not as reliable as stimulation testing.

2. *Hypothalamic-pituitary-Gonadal Axis*

Nearly one-third (28.1%) of male participants in our cohort had low serum testosterone levels. Suppression of the hypothalamic–pituitary–gonadal axis is common after TBI and stress. It is thought that a decrease in the sex hormone pathways during stress is an adaptive means of energy conservation to deal with the acute stressor. A high prevalence of gonadotrophin deficiency has been reported for all severities of TBI, particularly in male participants. Low serum testosterone levels have been reported in up to 100% of male participants in the first few days following injury[27 28]. The degree of testosterone suppression correlates with injury severity, however in our cohort, there was no difference between participants with and without complex mTBIs. The significance of low testosterone levels in patients that have sustained mTBI remains unclear, however, it has recently been shown that suppression of the gonadotrophin pathways may be associated with post-traumatic stress diagnosis (PTSD)[29]. Only one of the 9 male participants with low testosterone in the acute phase had a persistently low testosterone level after 6 months. Given, the potentially detrimental health consequences of gonadal suppression, male patients should be screened for low testosterone acutely following mTBI.

3. Growth Hormone

Of the 5 patients with abnormal levels of IGF-1, 4 had elevated levels of IGF-1 in the first week following mTBI. Most studies that have examined IGF-1 expression in the days following TBI have reported a reduction in serum IGF-1 concentration[27 30 31 32]. Most of these were studies that included participants with moderate and severe TBI. In vivo animal studies have shown a negative correlation between serum IGF-1 levels and proportion of apoptotic cells in regions of the brain following trauma. It is

conceivable that elevate IGF-1 levels following mTBI may be a neuroprotective adaptive response[33]. Only one patient in our cohort had low serum IGF-1, suggesting that routine IGF-1 screening is unnecessary acutely following mTBI.

4. Thyroid and Prolactin

Serum concentrations of prolactin and thyroid hormones can be affected by stress including TBI[34 35]. There are varying reports on the significance of these pathways in the acute stages of TBI[36 37]. Only one patient had biochemical evidence of hypothyroid and hyperprolactinaemia acutely and this was likely a consequence of the oral contraceptive pill which was undisclosed at the time of recruitment. We did not find that these hormones were significantly affected by mTBI and therefore there is no evidence for routine screening acutely following mTBI.

Pituitary (dys)function at 6 months

The reported incidence of chronic pituitary dysfunction also varies considerably in the literature. Tanriverdi and colleagues, in a 3-year, prospective study, reported that 17% of 18 patients with mTBI in their cohort had PTPD. Of note, 15 of 18 patients (including all with PTPD) had *complex* mTBIs suggesting that patients with *complex* mTBI have a substantial risk[38]. By contrast, in the study by van der Eerden and colleagues, there was a low incidence of PTPD in patients who had stimulation testing a median of 13 months following mTBIs[39]. Only one patient was ultimately found to have evidence of anterior pituitary dysfunction representing less than 1% of patients followed up.. This study did not take into consideration the propensity for de novo, long-term anterior pituitary dysfunction in patients in whom anterior pituitary

function had previously been normal. Only patients with abnormal anterior pituitary baseline screening were followed up with stimulation tests month after their initial TBI. It is therefore likely that this study underestimated the prevalence of PTPD.

In our cohort, we found that 20% of the returning patients had PTPD at 6 months. Although the proportion of returning patients was small, this corresponds with the prevalence of PTPD reported in the three systematic reviews that have been written on the topic[4 10 11]. It is noteworthy that in our systemic review there was no statistical difference between the studies that had high proportions (>50%) of participants with mTBI and those with low proportions (<50%) of participants with mTBI. It therefore seems appropriate to conclude that a proportion of patients with mTBI go on to develop abnormal pituitary function months following mTBI.

The anterior pituitary response to mTBI: Pathogenesis of PTPD

Formulating a hypothesis on the pathogenesis of PTPD is relies on a clear understanding of the how the brain and the anterior pituitary gland responds to trauma and our study provides some insight. There are three main theories. Firstly, the vascular hypothesis proposes that the long hypophyseal vessels that supply the pituitary gland are particularly vulnerable to injury and since the anterior lobe of the pituitary gland receives its blood supply from these vessels, hormone dysfunction following trauma results from vascular compromise[40 41]. Secondly, the autoimmunity hypothesis suggests that the pituitary may be infiltrated by inflammatory cells released in response to or because of trauma[42]. Thirdly, the neuroendocrine theory suggests that altered hypothalamo-pituitary function caused by the impact of trauma may affect anterior pituitary function[43].

We have shown that anterior pituitary hormonal dysfunction, which is well documented in more severe forms of TBI, occurs in the first few days following mTBI and that this abnormal serum anterior pituitary biochemistry occurs without structural damage to the pituitary gland and without evidence of haemorrhage, necrosis, inflammation or ischaemic changes in the anterior pituitary gland. The biochemical result is an increase in potentially neuroprotective hormones (cortisol and IGF-1) and suppression in others (testosterone). This adaptive response is clearly selective as it is not proportional to the volume of the different cell types of the anterior pituitary. Approximately 50% of the cells of the anterior pituitary are somatotrophs that produce growth hormone (GH) and the prolactin-secreting lactotrophs and the corticotrophs each represent approximately 15% of cells. Gonadotroph cells represent only approximately 10% of the human anterior pituitary cell population and thyrotrophs are the least abundant cell type in the anterior pituitary, comprising approximately 5% of the total cell population. In our cohort gonadotrophin, somatotroph and corticotroph abnormalities were the most common. This suggests that the adaptive response of the anterior pituitary selectively involves these cell types. The precise mechanisms involved are still uncertain. A prospective, large and multi-centre study, perhaps with a higher resolution MRI imaging of the pituitary gland, is needed for a better insight of the pathogenesis of PTPD.

Study limitations

This study was conducted as a feasibility study with two main limitations. Firstly, only two-thirds of recruited patients retuned for initial blood tests and only 50% of the patients who had initial blood tests returned for follow up at 6 months. The study

highlights the difficulties of researching this group of patients who are typically young and in employment and therefore struggle to return for appointments. Secondly, not all patients received an MRI scan. MRI imaging for all patients would have added to the breadth of understanding of the morphological changes that may occur in the pituitary gland following mTBI. This study is also limited by the fact that only single basal hormone levels were assessed. Although pragmatic, single blood tests do not reflect the pulsatile secretory pattern of some anterior pituitary hormones. Finally, we did not perform stimulation tests acutely because of the documented risk of seizures, however stimulation tests would have better assesses the hypothalamic-pituitary axes.

Conclusion

Despite these limitations, we have demonstrated that the anterior pituitary's adaptive response to mTBI leads to over-activity in the acute stages of trauma leading to increased hormone production. We have also shown that PTPD, which is typically thought to affect patients with moderate and severe TBIs, also occur in patients with mTBI and surveillance guidelines in the future should take this into account. Despite this, there was a high rate of attrition in line with the well-known difficulties in follow-up in this patient group. This would make a larger study difficult to achieve.

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Conclusion

We showed in this feasibility study that the study protocol is workable and also found that some patients with mild TBI develop chronic anterior pituitary dysfunction. The protocol can therefore be used to conduct a large, prospective study.

Conclusion

Should we check for anterior pituitary dysfunction in all traumatic brain injury patients?

- **What you need to know?**
- There is uncertainty about the clinical significance of post-traumatic brain injury anterior pituitary dysfunction (PTPD)
- Studies suggest that up to one-third of patients that suffer traumatic brain injury (TBI) go on to develop anterior pituitary gland dysfunction but these studies are heterogeneous, use different methodologies and mostly recruit patients with the most severe forms of TBI Anterior pituitary dysfunction can be very difficult to diagnose in these patients. There should be a high index of suspicion particularly for patients with ongoing behavioural, mood and cognitive disturbances
- Patients with base of skull fractures should be considered at high risk of developing pituitary dysfunction

Acute imbalances of anterior pituitary gland hormones occur commonly in the first few days after traumatic brain injury (TBI). They usually resolve. Some patients develop long-term anterior pituitary dysfunction (3 or more months after TBI). Three meta-analyses have concluded that up to one-third of patients that suffer TBI go on to develop long-term post-TBI anterior pituitary dysfunction (PTPD) [1] [2] [3].

TBI has been described as a “silent epidemic”, and is one of the most common causes of death and disability in people under 40 years old[4]. Given the scale of TBI, this could make TBI the most common cause of anterior pituitary dysfunction. As anterior pituitary dysfunction is relatively easy to treat with hormone replacement, diagnosing and treating affected individuals is an important therapeutic intervention in the rehabilitation of TBI sufferers, many of whom never return to their pre-morbid function because of ongoing cognitive and neuropsychological problems[5].

What is the evidence of uncertainty?

Search strategy

We searched PubMed and the Cochrane Library for observational studies and randomised control trials of anterior pituitary dysfunction following TBI[33]. There is evidence that anterior pituitary dysfunction in these patients is dynamic up to a year after TBI: with resolution in some patients that develop pituitary dysfunction within a few months after TBI and late, de novo dysfunction, several months after injury in patients whose anterior pituitary had previously been normal. We therefore only included papers that tested pituitary dysfunction in adults (>17 years) on average a year or more following TBI. The Newcastle-Ottawa scale (NOS) was used to determine study quality. Studies that scored 8 or more were deemed to be at low risk of bias and studies with a score of less than 8 were deemed to be at high risk of bias.

What proportion of patients develop PTPD?

Our literature search identified 29 studies of which 17 were deemed to be at high risk of bias[6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22] and 12 were low risk of bias[23 24 25 26 27 28 29 30 31 32 33 34]. The overall prevalence of PTPD for the 12 studies at low risk of bias was 35% (fixed and random effect model) and the overall prevalence for the studies at high risk of bias was 28% (figure 1). The overall prevalence for all 29 studies was 29.1% [95% confidence interval 23.6% - 35.4%; I^2 89.2%]. There was considerable bias in the included studies. Most studies focused on patients with moderate and severe TBI (which form 10-20% of TBIs) that were mostly recruited from intensive care units and endocrinology clinics and the results may not be generalisable to the much larger mild TBI population. Also, the methods used to assess anterior pituitary function, particularly growth hormone and adrenocorticotrophin function, varied between studies.

When is the best time to check for PTPD?

The recent screening guidelines by the British Neurotrauma Group recommended that evidence of PTPD should be checked at 3-6 months following TBI if patients were initially admitted to hospital for more than 48 hours or if they experience symptoms suggestive of pituitary dysfunction[35]. This guidance, based on expert opinion, is one of the most extensive currently available. These recommendations take into account the observation that chronic anterior PTPD is a dynamic process, which can spontaneously resolve in some patients but also importantly that can develop late in others some months following TBI even if earlier testing for anterior PTPD had previously been negative. Of the 29 included studies included in our meta-analysis, 6 reported on the prevalence of PTPD when checked at 3 months

after TBI, and 2 reported on its prevalence at 6 months and at 9 months after TBI. A boxplot of the overall prevalence at these time intervals is depicted in figure 2. The overall prevalence of PTPD at 3 months was 34.1% [95% CI 24.6-44.9%; I^2 78.7%], the overall prevalence at 6 months was 26.4% [95% CI 15.2 – 41.7%; I^2 70%], the overall prevalence at 9 months was 23.4% [95% CI 17.1%-31.1%; I^2 0%]. Although there were no statistical differences in the overall prevalence between the groups, these figures seem to endorse the theory that resolution occurs in some patients over time (although the mechanism is unclear) and the increase in prevalence between 9 months (23%) and 12 months (35%) suggests that some patients develop late, de novo PTPD. The clinical implication, as highlighted in the British Neurotrauma group guidelines, is that early surveillance alone might miss some patients that develop late PTPD.

The criticism of the British Neurotrauma group guidelines, which the authors themselves noted, is that the symptoms of pituitary dysfunction overlap with those of post-concussion syndrome and it may be difficult to stratify suitability for screening on symptoms alone at 12 months or more.

What are the current surveillance practices amongst Neurosurgeons in the UK and Ireland?

In a survey of 45 Surgeons in England, Scotland and Ireland, the majority of participants (86.7%) considered PTPD to be a problem but only 25% (11/45) routinely screened for PTHP. There was also wide variation in the criteria used to

determine which patients were screened. This suggests that even amongst experts, there are disparities in surveillance practices across the UK.

What are the risk factors for chronic anterior PTPD?

It is important to consider potential risk factors for chronic anterior PTPD in order to better determine which patients should be screened. Six of the 29 authors included in the meta-analysis reported on the risk factors for developing PTPD[6 16 19 26 28 32]. In addition, we found 2 further studies that followed patients up for 9 months (both with a NOS score of 8) that reported on risk factors for chronic anterior PTPD[36 37]. We pooled the results of eight potential risk factors reported by the majority of these studies for the overall risk of developing PTPD. These risk factors included:

1. abnormal pupils at the time of TBI;
2. brain swelling on neuroimaging;
3. presence of cranial vault or facial fractures,
4. pre-resuscitation hypoxia or hypotension,
5. male gender,
6. mild TBI vs. non mild TBI,
7. moderate or severe TBI vs. non moderate or severe TBI and
8. presence of subarachnoid blood on neuroimaging.

Only the presence of fractures was significantly associated with the development of chronic anterior PTPD (RR 1.52[95% CI 1.03-2.24];p=0.03) (figure 3). However, we recently completed a study in which 36 participants with mild TBI were followed up for 6 months following injury and found that 20% of returning participants had

evidence of PTPD without any structural damage to their pituitary gland on MRI scan (unpublished). This suggests that patients with mild TBIs are also at risk.

What should we do in light of this research?

Ideally, all TBI sufferers should be screened for PTPD. However, this would be both costly and logistically difficult as follow up in this patient group[38]. In the absence of level one evidence, there has to be a pragmatic approach to surveillance. Firstly, chronic anterior PTPD should be borne in mind when dealing with patients who progress slowly during rehabilitation from TBI. Pituitary testing should be considered early (3 to 6 months) and late (at least 12 months) in these patients and in those that have symptoms suggestive of pituitary dysfunction. We recommend the surveillance algorithm of British Neurotrauma Group (figure 4) and would suggest that those with base of skull fractures may be at increased risk.

Screening blood tests should be done between 8am and 10am and should be done with the patient fasted (nothing to eat from midnight on the day of testing) unless contraindicated. The following blood tests should be done in all patients suspected of having PTPD:

- TSH and free T4
- Short-synacthen test (SST) or early morning cortisol, if SST not feasible

In addition, men and post-menopausal women should have their gonadotropic axis tested (including luteinising hormone (LH), follicle-stimulating hormone (FSH), testosterone, sex hormone-binding hormone and albumin). Premenopausal women

with regular menstrual cycles do not need an assessment of their gonadotropic axis. Posterior pituitary dysfunction may be assessed initially by asking about symptoms of thirst, polydipsia and polyuria.

Screening for somatotropic axis dysfunction (growth hormone) is more challenging; formal testing can be lengthy and in the case of insulin tolerance testing, be contraindicated in some patients with TBI. We would therefore suggest that patients suspected of having anterior pituitary dysfunction and in whom the above tests are normal, should be referred to the endocrinology clinic for consideration of growth hormone testing.

Recommendations for Future Research

Population

- Patients with mild TBI recruited from A&E as well as those with moderate and severe TBI.

Intervention

- Patients should be followed up prospectively for at least 12 months and stimulation tests should be used to test growth hormone and adrenocorticotrophin axes, when safe to do so

Comparisons

- hormone replacement therapy, particularly growth hormone and testosterone replacement, following TBI should also be considered.

Outcomes

- risk factors for developing PTPD including patient factors and injury factors
- the optimal timing for surveillance

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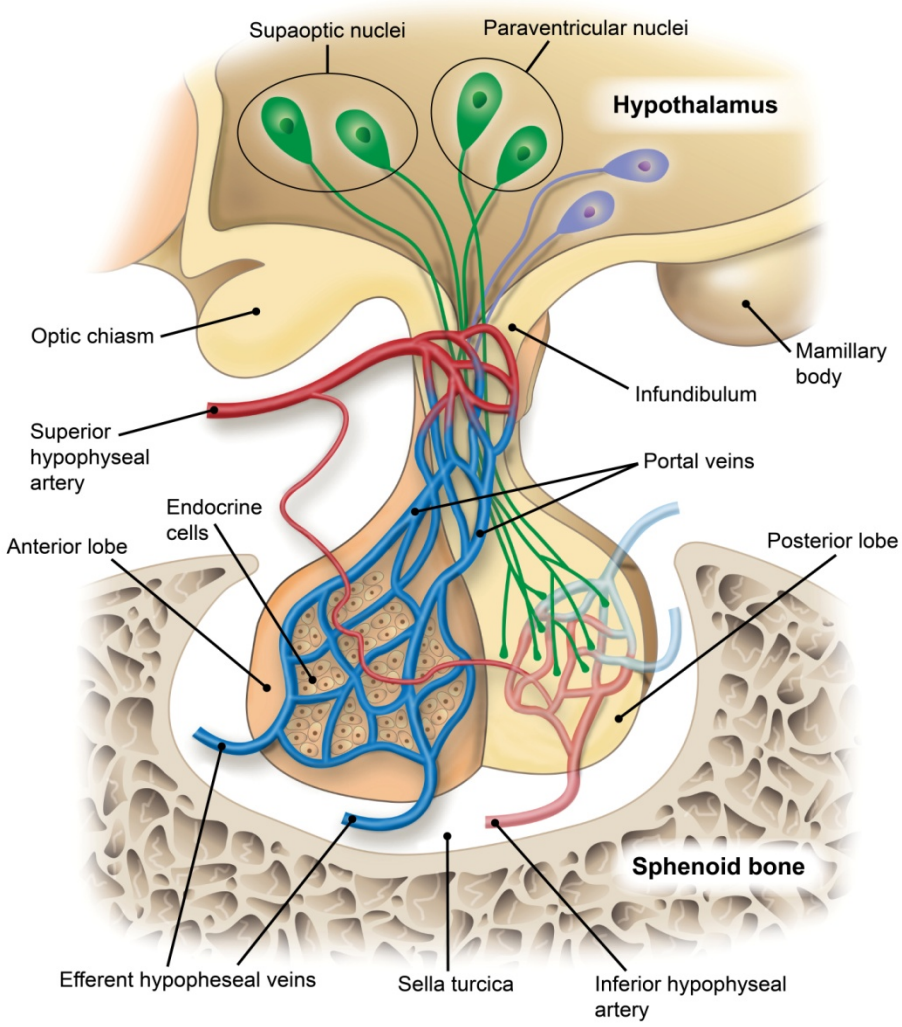
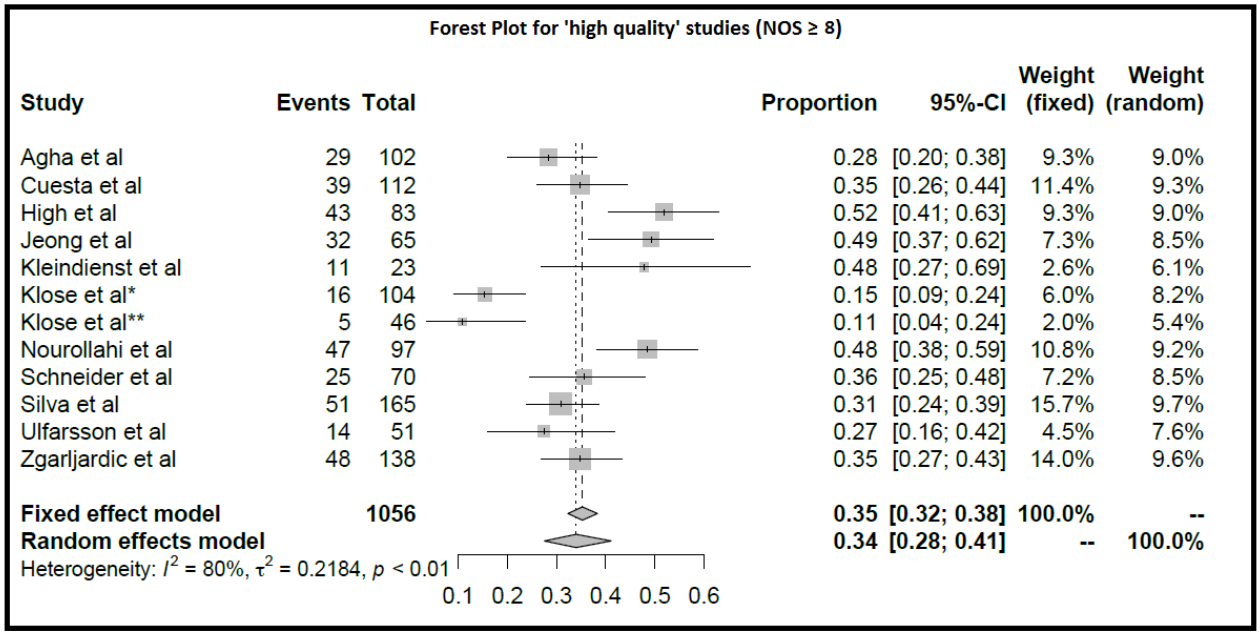


Figure 1. Location and blood supply of the pituitary gland within the sella turcica


Forest Plot for 'high quality' studies (NOS ≥ 8)
Study
Events
Total
Proportion
95%-CI
Weight (fixed)
Weight (random)
Agha et al 29 102 0.28 [0.20; 0.38] 9.3% 9.0%
Cuesta et al 39 112 0.35 [0.26; 0.44] 11.4% 9.3%
High et al 43 83 0.52 [0.41; 0.63] 9.3% 9.0%
Jeong et al 32 65 0.49 [0.37; 0.62] 7.3% 8.5%
Kleindienst et al 11 23 0.48 [0.27; 0.69] 2.6% 6.1%
Klose et al* 16 104 0.15 [0.09; 0.24] 6.0% 8.2%
Klose et al** 5 46 0.11 [0.04; 0.24] 2.0% 5.4%
Nourollahi et al 47 97 0.48 [0.38; 0.59] 10.8% 9.2%
Schneider et al 25 70 0.36 [0.25; 0.48] 7.2% 8.5%
Silva et al 51 165 0.31 [0.24; 0.39] 15.7% 9.7%
Ulfarsson et al 14 51 0.27 [0.16; 0.42] 4.5% 7.6%
Zgarljardic et al 48 138 0.35 [0.27; 0.43] 14.0% 9.6%
Fixed effect model 1056 0.35 [0.32; 0.38] 100.0% --
Random effects model 0.34 [0.28; 0.41] -- 100.0%
Heterogeneity: I^2 = 80%, τ^2 = 0.2184, p < 0.01
0.1 0.2 0.3 0.4 0.5 0.6

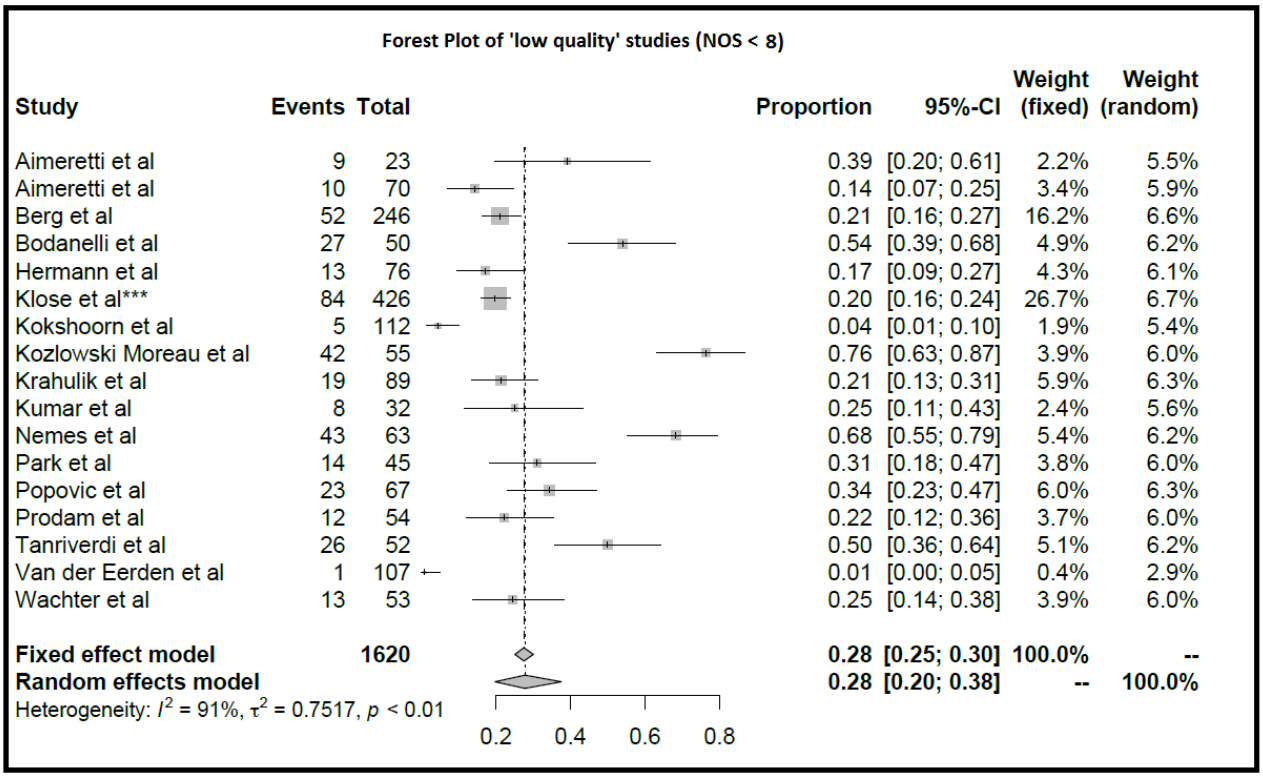

Forest Plot of 'low quality' studies (NOS < 8)
Study
Events
Total
Proportion
95%-CI
Weight (fixed)
Weight (random)
Aimeretti et al 9 23 0.39 [0.20; 0.61] 2.2% 5.5%
Aimeretti et al 10 70 0.14 [0.07; 0.25] 3.4% 5.9%
Berg et al 52 246 0.21 [0.16; 0.27] 16.2% 6.6%
Bodanelli et al 27 50 0.54 [0.39; 0.68] 4.9% 6.2%
Hermann et al 13 76 0.17 [0.09; 0.27] 4.3% 6.1%
Klose et al*** 84 426 0.20 [0.16; 0.24] 26.7% 6.7%
Kokshoorn et al 5 112 0.04 [0.01; 0.10] 1.9% 5.4%
Kozlowski Moreau et al 42 55 0.76 [0.63; 0.87] 3.9% 6.0%
Krahulik et al 19 89 0.21 [0.13; 0.31] 5.9% 6.3%
Kumar et al 8 32 0.25 [0.11; 0.43] 2.4% 5.6%
Nemes et al 43 63 0.68 [0.55; 0.79] 5.4% 6.2%
Park et al 14 45 0.31 [0.18; 0.47] 3.8% 6.0%
Popovic et al 23 67 0.34 [0.23; 0.47] 6.0% 6.3%
Prodam et al 12 54 0.22 [0.12; 0.36] 3.7% 6.0%
Tanriverdi et al 26 52 0.50 [0.36; 0.64] 5.1% 6.2%
Van der Eerden et al 1 107 0.01 [0.00; 0.05] 0.4% 2.9%
Wachter et al 13 53 0.25 [0.14; 0.38] 3.9% 6.0%
Fixed effect model 1620 0.28 [0.25; 0.30] 100.0% --
Random effects model 0.28 [0.20; 0.38] -- 100.0%
Heterogeneity: I^2 = 91%, τ^2 = 0.7517, p < 0.01
0.2 0.4 0.6 0.8

Figure 2. Forest plot of pooled proportions (and 95% confidence intervals [CI]) of anterior pituitary dysfunction one year or more following traumatic brain injury. Studies were separated into high and low quality based on the Newcastle-Ottawa score (NOS), which assesses the quality of non-randomised studies. The square boxes represent the reported prevalence for each study and whiskers represent 95% confidence interval. The diamonds represent the pooled proportions. Pooled proportions were calculated using 2 models. The large diamonds represent pooled proportions calculated with random effect model and the small diamond represent pooled proportions calculated using fixed effect model.

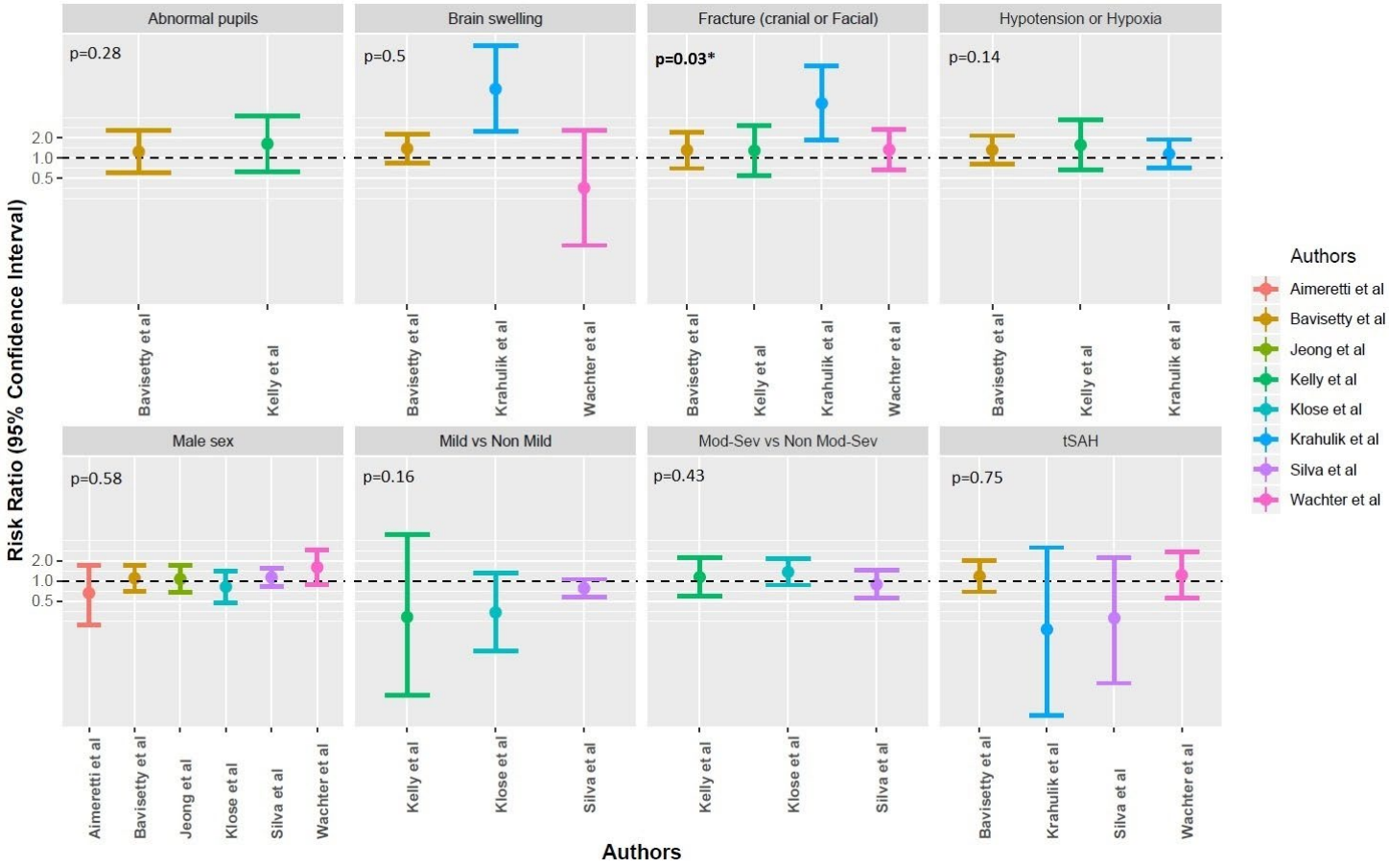
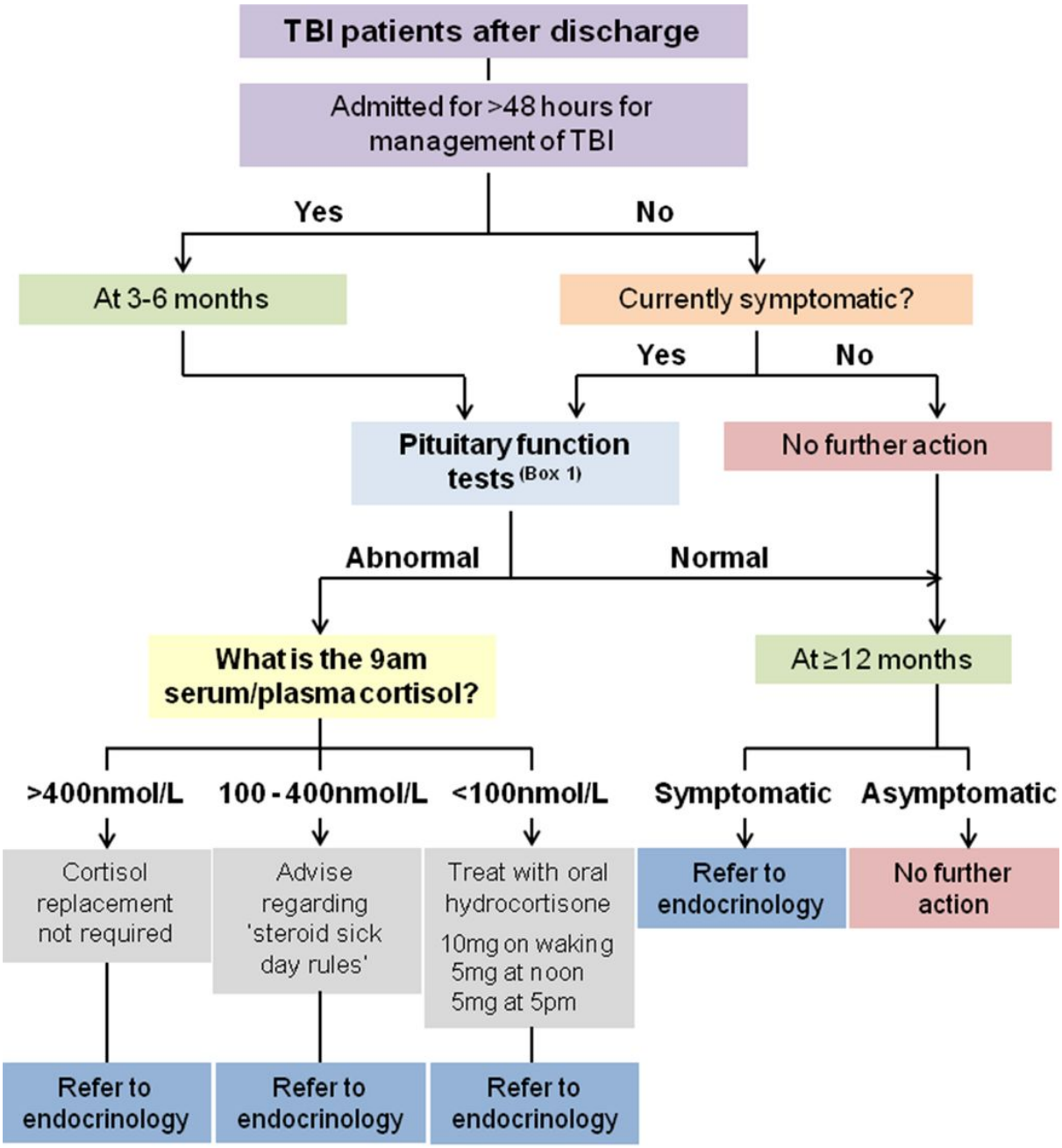


Figure 3. Forest plot of pooled risk ratios for reported risk factors for developing post-TBI anterior pituitary dysfunction. The solid circles are the risk ratios and the whiskers are the 95% confidence intervals (95%CI). Only the presence of fracture (cranial or facial) significantly increase the risk of developing anterior pituitary dysfunction.



* For patients receiving regular hydrocortisone replacement or 'sick day rules' cover, parenteral hydrocortisone will be required in the event of vomiting/diarrhoea when oral absorption is uncertain

Figure 4. Recommendations for screening for pituitary dysfunction in patients with traumatic brain injury (TBI) following discharge by the British Neurotrauma Group.

Conclusions

In this thesis, I conducted a systematic review that demonstrated evidence for anterior pituitary dysfunction following traumatic brain injury and a questionnaire that indicated variations in surveillance practices across the UK and Ireland. This suggested that there were uncertainties about the burden of disease. I therefore designed a study to address the research question “what is the prevalence of anterior pituitary dysfunction following traumatic brain injury?” and conducted a feasibility study to test all aspects of the study protocol. Whilst these objectives were met, there were problems along the way. These problems are listed here.

1. Defining anterior pituitary dysfunction

The definition of anterior pituitary dysfunction is unreliable when based solely on the serum concentrations of anterior pituitary hormones alone and in the absence of a pre-test probability of anterior pituitary hormone deficiency. This is because several factors including the physiological response to stress and trauma, seizures and some medications influence anterior pituitary hormone secretion. One solution to this problem could have been to have a control group of non-TBI trauma patients to compare anterior pituitary function. However, this would have been difficult to achieve with the resources available and may have been unreliable if a significant proportion of the control group were also found to have pituitary dysfunction. A second solution would have been to follow patients up in an endocrinology clinic with the involvement of an endocrinologist to determine each participant’s pre-test probability of anterior pituitary dysfunction prior to blood test. Although an endocrinologist was involved in interpreting the blood results, they were not involved in the clinical assessment of participants.

2. Sampling bias

The patients recruited to the PiTS study were those who presented to the emergency department. We also recruited patients being admitted to a single centre for the feasibility study. The majority of patients with mild TBI do not come to hospital and therefore would not be included in the PitSTOP study. The results are therefore not generalisable to mild TBI patients. I have dealt with this problem in the study my assuming that patients with the most 'severe' forms of mild TBI (in this case, those that meet the NICE guidelines for brain imaging) are at higher risk of developing pituitary dysfunction. Although there is currently no evidence for this assumption, it was a pragmatic solution as it would be difficult to obtain a population-based sample of patients with TBIs that are managed in the primary care setting or who do not attend hospital.

3. Sampling size and recruitment

Patient recruitment was difficult because for two reasons. Firstly, patients tended to present out of hours and we initially had no research support out of hours. Therefore, a large number of potential patients were missed during their hospital stay and not approached for inclusion. This was dealt with by changing the working patterns of members of the research team. The second problem was the very high proportion of patients who having consented for inclusion, failed to attend subsequent visits. Although we tried to reduce the burden on patients by reducing the number of visits, only approximately 56% of recruited patient came to the first visit and 28% attended the second visit. This was a difficult problem during the feasibility study because of the

limited resources, however one solution for future studies would be to incentivise patients financially or otherwise to attend research visits.

4. Data Collection and Lab interaction

Because the study team was small, we relied on the clinical and nursing staff to record participants' observations. However, we found that as many of the participants recruited to this study were generally well, many did not get a full set of clinical observations recorded and therefore missing data was picked up on a number of occasions by the trial team. This included discharge data such as discharge destination and sample times not being completed.

We also found that early on in the study blood samples were often mislabelled or were not completed because the clinical staff or the laboratory staff were unaware of the study. This resulted in a frustrating number of uncompleted sampling for patients who ultimately could not be included in the final analysis.

These problems were resolved by meetings which were organised to provide better information to all stakeholders including the clinical and nursing staff and the laboratory staff to ensure all were aware of the study. Due to the time critical nature of the study, we highlighted the need to prioritise and coordinate the recruitment process efficiently. Therefore, working with the multidisciplinary team closely was vital to capture patients between their investigations and assessments. Awareness and data capture improved with time.

We also developed techniques to ensure all data was captured to complete the CRF. For example, alert cards were placed in patient notes to alert the clinician to complete the clinician assessment.

5. Future directions

Despite the limitations, I was able to design and conduct, prospectively, a study which has shown that anterior pituitary dysfunction occurs in patients following mild TBI. I have also been able to prove that the PitSTOP protocol is workable and therefore the next stage is to apply for funding for the PitSTOP study. There are three main questions that need to be addressed:

1. How common is chronic anterior pituitary dysfunction following TBI?
2. Which TBI patients are at risk of developing anterior pituitary dysfunction?
3. What surveillance methods should be used to detect such patients?

A large prospective study using the PitSTOP protocol will answer these questions. Given that anterior pituitary dysfunction is potentially treatable with hormone replacement, this could represent a significant study in TBI research.