LIBRARY
Te Tumu Herenga
THE UNIVERSITY OF AUCKLAND

RESEARCHSPACE@AUCKLAND

http://researchspace.auckland.ac.nz

ResearchSpace@Auckland

Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage. http://researchspace.auckland.ac.nz/feedback

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form and Deposit Licence.

Note : Masters Theses

The digital copy of a masters thesis is as submitted for examination and contains no corrections. The print copy, usually available in the University Library, may contain corrections made by hand, which have been requested by the supervisor.

Traumatic Brain Injury in Early Childhood - Hypopituitarism and Grading Injury Severity

Dr Natasha Heather

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Medicine, The University of Auckland, 2012.

Abstract

Traumatic brain injury (TBI) is a very common childhood event. This thesis focuses on three research domains within early childhood TBI: the risk of hypopituitarism, programming of the hypothalamic-pituitary-adrenal (HPA) axis following abusive TBI, and the reliability of the Glasgow Coma Score (GCS) in the assessment of injury severity.

Hypopituitarism is proposed to be alarmingly common following TBI. The cornerstone of this thesis is a large clinical study of 198 children who sustained early childhood TBI, including 64 infants with abusive injuries. Consistent with the adult literature, initial tests identified potential hypopituitarism in a third of subjects. All children with subnormal results were carefully reviewed and followed longitudinally. Ultimately, there were no cases of true hypopituitarism. This reveals that permanent hypopituitarism is rare following early childhood TBI, whether the injury is accidental or inflicted. This highly significant negative study challenges evolving dogma, and strongly argues against the introduction of routine pituitary screening tests following childhood TBI.

Despite no cases of hypopituitarism, stimulated serum cortisol concentrations were lower in the inflicted as compared with accidental TBI group. This group difference was not seen in any other pituitary hormone axis, nor associated with TBI severity, and is likely to reflect environmental programming of the HPA axis. The metabolic and mental health consequences of the observed difference are unknown, and warrant further longitudinal studies.

GCS scores are widely used to define TBI severity, but may be a less reliable index of injury severity during early childhood. I performed a 10-year review of all early childhood TBI admissions to Starship Children's Hospital, and compared GCS scores to radiological injury and admission data. In addition, for those children followed in the hypopituitarism study, I correlated admission GCS scores to long-term disability. Severe GCS scores identified most cases of severe radiological injury in early childhood, and were good predictors of poor long-term outcome. However, young children admitted

to hospital with structural head injury and mild GCS scores also had an appreciable risk of long-term disability, and also warrant long-term follow-up.

Dedication and Acknowledgements

Most of all, I would not have been able to complete this work without the unwavering support of my husband, Jonathan. To Jonathan, Max and Theo – I've missed you, and you mean the world to me.

In addition, I would like to thank Professor Wayne Cutfield, my primary supervisor, for his intellectual input and infectious enthusiasm, as well as his expert guidance in the ways of academic medicine. I am also grateful to Christine Brennan, a fantastic research nurse whose caring nature and practical know-how was ideal for this work. I am very thankful to Associate Professor Paul Hofman for providing frank feedback on writing and presentations, and to Dr. Craig Jefferies for setting deadlines and keeping me motivated! In addition, I am indebted to Dr. José Derriak for his expert help in preparing manuscripts, and Dr. Andrea Graves for editorial assistance leading up to the submission of this thesis.

Table of Contents

Abstract ii

Dedication and Acknowledgements iv

List of Figures viii

List of Tables ix

List of Abbreviated Terms x

Co-authorship acknowledgement xi

Chapter 1. Overview 1

Chapter 2. Background 6

2.1. The pituitary gland 6

2.1.1. Pituitary structure 6

2.1.2. Pituitary regulation 9

2.1.3. Assessment of pituitary function 10

2.1.4. Hypopituitarism 16

2.2. Traumatic brain injury 19

2.2.1. Incidence of childhood TBI 19

2.2.2. TBI grading 20

2.2.3. Abusive TBI 24

2.2.4. Diagnosis of abusive TBI 25

2.2.5. Endocrine consequences of abuse 26

2.3. Hypopituitarism following TBI 28

2.3.1. Case reports 29

2.3.2. Autopsy data 31

2.3.3. Proposed mechanism of injury 32

2.3.4. Prevalence of hypopituitarism after TBI 33

2.3.5. Cross-sectional TBI data in adults 34

2.3.6. Longitudinal TBI data 40

2.3.7. Childhood TBI data 45

2.3.8. Risk factors for hypopituitarism 48

2.3.9. Data from clinical practice 51

2.3.10. Assessment guidelines 51

2.4. Summary and structure of this thesis 54

Chapter 3. Traumatic brain injury: Is the pituitary out of harm's way? 55

3.1. Preface 55

Publication: Traumatic brain injury: Is the pituitary out of harm's way? 56

3.3. Significance and contribution 61

Chapter 4. Permanent hypopituitarism is rare after structural traumatic brain injury in early childhood 62

4.1. Preface 62

Publication: Permanent hypopituitarism is rare after structural traumatic brain injury in early childhood 63

4.2. Particular issues 79

4.2.1. TBI severity within the cohort 79

4.2.2. Reliability of pituitary assessments 79

4.2.3. Timing of assessments 80

4.3. Significance and contribution 81

Chapter 5. Cortisol response to synacthen stimulation is attenuated following abusive head trauma 82

5.1. Preface 82

Publication: Cortisol response to synacthen stimulation is attenuated following abusive head trauma 83

5.2. Particular issues 91

5.2.1. Assessment of the HPA axis 91

5.3. Significance and contribution 91

Chapter 6. Glasgow Coma Scale and outcomes after structural traumatic head injury in early childhood 92

6.1. Preface 92

Manuscript: Glasgow Coma Scale and outcomes after structural traumatic head injury in early childhood 93

6.2. Particular issues 108

6.2.1. Inflicted head injury 108

6.3. Significance and contribution 108

Chapter 7. Summary and future directions 109

7.1. Summary 109

7.1.1. TBI and hypopituitarism 109

7.1.2. Early childhood TBI 110

7.1.3. Inflicted TBI 111

7.1.4. GCS and head injury severity 113
7.2. Future directions 114
7.2.1. TBI and hypopituitarism 114
7.2.2. Abuse and HPA dysfunction 116
7.3. Summary 116
Chapter 8. Appendices 117
8.1. Awards and abstracts 117
Awards and presentations 117
Submitted abstracts 117
8.2. Letter to prospective study participants 118
8.3. Copyright permissions 123
References 128

List of Figures

Figure 2.1. Blood supply to the pituitary gland..... 8
Figure 2.2. Regulation of GH production. 9
Figure 2.3. Suggested algorithm for pituitary assessment following moderate-severe traumatic brain injury. 53
Supplementary Figure 4.1. Flow chart of subject recruitment. 69
Supplementary Figure 4.2. Algorithm for GH assessment. 71
Supplementary Figure 4.3. Algorithm for ACTH assessment. 73
Figure 6.1. The association between GCS and AIS scores among children who suffered early childhood traumatic head injury..... 107

List of Tables

Table 2.1. GH stimulation tests in 472 normally growing children. 12
Table 2.2. Methods used to assess for secondary adrenal insufficiency. 14
Table 2.3. Clinical features of hypopituitarism. 17
Table 2.4. Causes of hypopituitarism. 18
Table 2.5. The Glasgow Coma Scale. 21
Table 2.6. Prevalence of hypopituitarism in adult TBI studies. 36
Table 2.7. Prospective studies of pituitary function after TBI. 41
Table 2.8 Prevalence of hypopituitarism in childhood TBI studies. 46
Table 2.9. Association between GCS and hypopituitarism. 49
Supplementary Table 4.1. Individual data for the 17 subjects with apparent ACTH deficiency. 75
Supplementary Table 4.2. Characteristics of two subjects diagnosed with precocious puberty. 77
Supplementary Table 5.1 Hormone profiles of the accidental and inflicted TBI groups. 89
Table 6.1. Demographics of the studied population. 105
Table 6.2 Hospitalization and ICU admission among children admitted to hospital with traumatic head injury 106
Table 6.3. Adverse long-term outcomes among children admitted to hospital with traumatic head injury. 106
Table 6.4. GCS scores and the prevalence of long-term disability among children admitted to hospital with traumatic head injury, with a radiological diagnosis more severe than a simple linear skull fracture. 107

List of Abbreviated Terms

Abbreviated Injury Score (AIS)

Adrenocorticotropin (ACTH)

Antidiuretic hormone (ADH)

Body mass index (BMI)

Coefficient of variation (CV)

Computer tomography (CT)

Confidence interval (CI)

Corticotropin-releasing hormone (CRH)

Cortisol binding globulin (CBG)

Diabetes insipidus (DI)

Follicle stimulating hormone (FSH)

Free thyroxine (free T4)

Free triiodothyronine (free T3)

Luteinising hormone (LH)

Glasgow Coma Scale (GCS)

Growth hormone (GH)

Growth hormone releasing hormone (GHRH)

Height velocity (HV)

Hypothalamic-pituitary adrenal axis (HPA axis)

Insulin-like growth factor 1 (IGF-1)

IGF binding protein 3 (IGF-BP3)

Insulin tolerance test (ITT)

Intensive care unit (ICU)

Intracranial pressure (ICP)

King's outcome score for childhood head injury (KOSCHI)

Magnetic resonance imaging (MRI)

New Zealand index of deprivation 2006 (NZDep2006)

Precocious puberty (PP)

Prolactin (PRL)

Socioeconomic status (SES)

Somatostatin (SRIF)

Standard deviation score (SDS)

Standard error of the mean (SEM)

Subdural haemorrhage (SDH)

Synthetic $ACTH_{1-24}$ (Synacthen)

Thyroid stimulating hormone (TSH)

Traumatic brain injury (TBI)

- Accidental TBI (TBI_A)
- Inflicted TBI (TBI_I)

Chapter 1. Overview

This thesis was designed to address an important clinical issue: the prevalence of hypopituitarism following abusive and accidental traumatic brain injury (TBI) in early childhood. Over the past decade, TBI studies in adults have reported that hypopituitarism is alarmingly common. However, this contrasts with experience from clinical practice, where hypopituitarism is considered a rare complication of TBI. The symptoms of hypopituitarism can be vague and insidious, and readily attributed to the cortical effects of TBI. However, undiagnosed hypopituitarism is likely to decrease quality of life and prolong recovery from TBI, as well as impair childhood growth and development. Undiagnosed hypopituitarism may be responsible for widespread morbidity following childhood TBI, and conversely, the prompt recognition and treatment of hypopituitarism has the potential for enormous benefit.

The first part of the literature review will outline the structure and function of the pituitary gland. The signs and symptoms of pituitary deficiency will be discussed, as well as the methods and pitfalls of hypothalamic-pituitary assessment. The aetiology and prevalence of hypopituitarism, as currently recognised, will also be reviewed.

The second section will outline the epidemiology of childhood TBI. TBI is both common and heterogeneous, and can be classified in functional or structural terms. The Glasgow Coma Scale (GCS) is commonly used to define TBI severity, but has significant limitations, particularly during early childhood. Shaken baby syndrome is a prominent cause of severe TBI in infancy which may place sufferers at high risk of pituitary injury, and the recognised endocrine consequences of child abuse will be discussed.

The final section will evaluate evidence linking hypopituitarism to TBI. Firstly, hypothalamic-pituitary damage is common after fatal TBI, with data suggesting a vascular mechanism of injury. More

recently, systematic studies have reported that hypopituitarism is also common amongst adults who survive TBI (Kelly, Gonzalo *et al*. 2000; Schneider, Kreitschmann-Andermahr *et al*. 2007). However, the reported prevalence is highly variable and risk factors poorly defined, and methodological weaknesses are likely to have lead to routine over-reporting. Despite these shortfalls, a number of expert groups now recommend routine pituitary assessment following moderate-severe TBI, as defined by GCS (Casanueva, Ghigo *et al*. 2004; Ghigo, Masel *et al*. 2005; Schneider, Stalla *et al*. 2006).

Despite a paucity of paediatric data, these recommendations have been extrapolated to include childhood TBI (Aimaretti, Ambrosio *et al*. 2005; Acerini, Tasker *et al*. 2006; Rose and Auble 2011). As a result, there is an urgent need for specific childhood prevalence data. Given the high frequency and heterogeneity of childhood TBI, these studies should also seek to identify high risk groups, such as specific injury types, age groups, or other early clinical indicators.

Therefore, at the outset of this thesis the specific aims were:

1. To determine the prevalence of permanent hypopituitarism after early childhood TBI.
2. To describe the differential risk of pituitary deficiency following abusive and accidental TBI.
3. To investigate the value of early clinical markers, such as the GCS and abnormalities on neuro-imaging, in predicting pituitary deficiency following early childhood TBI.

This thesis is presented with publications, with the following chapters based on a series of manuscripts that have arisen from this work.

Chapter 3 is based on an expert commentary, “Traumatic Brain Injury – is the pituitary out of harm’s way.” This paper focuses on childhood TBI, and argues that current evidence does not support routine invasive pituitary assessment.

Chapter 4 is based on the publication of original data, “Permanent hypopituitarism is rare after structural traumatic brain injury in early childhood.” This is the first study to focus on a narrow age

range (0-5 years), and to include a large number of cases of abusive TBI. All subjects underwent comprehensive pituitary assessments in order to define the prevalence of true, clinically significant disease. Contrary to my expectations, the prevalence of hypopituitarism was low in both the accidental and inflicted injury groups. The significance and potential limitations of this negative study are discussed.

Chapter 5 is based on the publication, "Cortisol response to synacthen stimulation is attenuated following abusive head trauma." My original hypothesis was that the prevalence of hypopituitarism would be greater amongst children who suffered abusive as compared with accidental head trauma. However, the only group difference that I observed was the attenuation of stimulated cortisol concentrations (the "stress response") in the abused group. This paper provides an analysis of the possible aetiology and significance of this finding.

Chapter 6 is based on the manuscript "Glasgow coma scale and outcomes after structural traumatic head injury in early childhood." The cohort for the hypopituitarism study were selected on the basis of structural head injury rather than GCS, as the GCS was hypothesised to be an unreliable index of injury severity in early childhood. In order to test this, I reviewed early childhood head injury data from the Starship Children's Hospital Trauma Database over a 10 year period. Subsequent analysis confirmed that mild GCS scores were frequently associated with severe radiological markers of injury, as well as long-term disability, and the clinical implications of this are discussed.

Chapter 7 summarises the important findings of this thesis as well as future directions. The early childhood TBI hypopituitarism study answered a focused clinical question within a potentially high risk group. In the context of current recommendations, it is a highly significant negative study that is likely to impact the future management of large numbers of children with TBI. However, this is a relatively new area of enquiry, and important issues to be targeted by future research are outlined.

Author's Contributions

Chapter 3

This commentary is based on my own interpretation of the current literature. I wrote the first draft of the manuscript, incorporated comments from my supervisor, and produced the final draft.

Chapter 4

I assisted in the design of this study, and a successful grant application. I developed participant information sheets and wrote and defended the ethics application. I reviewed the notes of all potentially eligible subjects identified from two hospital databases. A research nurse assisted me with some subject recruitment and pituitary function assessments; however, I performed the majority of this work. Blood samples were analysed at LabPlus, the Auckland Hospital laboratory. I reviewed all results, communicated these with families, and arranged appropriate follow-up. I analysed the data with the help of a biostatistician, wrote the first draft of the manuscript, coordinated submissions from other contributors, and produced the final draft.

Chapter 5

It was apparent during the period of data collection that the likelihood of a subnormal response to Synacthen was greater amongst children in the inflicted TBI group. I assisted a statistician in analysing the pituitary function data, using injury group as a factor. The interpretation of this finding is my own; I wrote the first draft of the manuscript, incorporated comments from additional contributors, and produced the final draft.

Chapter 6

The concept behind this manuscript is my own. I reviewed early childhood head injury admission data from the Starship Children's Hospital Trauma database over a 10-year period, in addition to follow-up data previously collected from subjects in the hypopituitarism study. I analysed the data

with the assistance of a biostatistician, wrote the first draft of the manuscript, incorporated comments from additional contributors, and produced the final draft.

Summary and future directions

The summary and future directions are solely my work and consider the implications, short comings, and directions for future research based on my thesis. This Chapter incorporates customary minor comments on content and style made by my thesis supervisor.

Chapter 2. Background

2.1. The pituitary gland

Although the presence of the pituitary gland was recognised by early anatomists, it took centuries to elucidate the function of this essential organ (Toni 2000). In the 11th century AD, Galen proposed that nasal phlegm originated in the brain and was subsequently filtered in the pituitary gland (May 1968). As a consequence, the name "pituitary" is derived from the Greek word "ptuo" and Latin "pituita", both meaning "phlegm". The Galenic concept of pituitary function prevailed for an extended period, and was not formally refuted until 18th century (Toni 2000). Following this, the first description of pituitary hormone excess (acromegaly) was made in 1886 (Marie 1886), and hypopituitarism ("Simmonds disease") in 1914 (Simmonds 1914).

Over the past century, a number of developments have contributed to our understanding of the close relationship between the hypothalamus and pituitary. The hypothalamus was described anatomically in the late 19th century, and the neurovascular connections between the hypothalamus and pituitary described in the mid 20th century (Harris 1948; Greer 1951). Hypothalamic releasing and inhibitory factors were later identified in the 1950-60s, and Roger Guillemin and Andre Schally were awarded the 1977 Nobel Prize for Medicine for their pioneering work in this area (Guillemin 2011). However, our understanding of this complex regulatory unit continues to progress, and should still be considered incomplete.

2.1.1. Pituitary structure

The pituitary gland weighs approximately 600 mg in an adult, and 100 mg in a newborn (Thorner, Vance *et al*. 1992). It sits within the bony sella turcica at the base of the skull (see Figure 2.1) and is overlaid by the dural diaphragma sella, in close association to the optic chiasm. The pituitary stalk serves as an anatomical and functional connection between the gland and the base of the

hypothalamus. The pituitary gland is further divided into anterior and posterior lobes, as well as an additional (vestigial) intermediate lobe.

The anterior lobe is embryologically derived from Rathke's pouch. Hormone producing cells of the anterior pituitary have traditionally been divided on the basis of staining reactions; somatotropes and lactotropes are acidophilic, and the remainder are basophilic. Somatotrophs account for 35-45% of the gland, and are predominantly located in the lateral wings. They secrete growth hormone (GH), which stimulates the production of systematic insulin-like growth factor 1 (IGF-I), which in turn promotes growth and has metabolic effects. Lactotrophs account for 15-25% of cells; large cells are located throughout the gland and smaller cells clustered in lateral wings. They produce prolactin (PRL), which stimulates the production of breast milk. Due to their common origin, occasional mammo-somatotroph cells co-secrete both PRL and GH.

Basophilic cells include corticotrophs, which are clustered medially, and make up 20% of the gland. Corticotrophs secrete adrenocorticotropic hormone (ACTH), derived from pro-opiomelanocortin, which acts on the adrenal cortex to stimulate the secretion of cortisol and adrenal androgens. Gonadotrophs comprise a further 10-15% of cells, and are located laterally. They co-secrete luteinising hormone (LH) and follicle-stimulating hormone (FSH). In females, FSH stimulates ovarian follicle growth, and LH ovulation and luteinisation of ovarian follicles. In males, FSH stimulates spermatogenesis, and LH testosterone secretion. Thyrotrophs make up the final 5% and are situated antero-medially. Thyrotropin (TSH) stimulates the secretion of thyroid hormones, thyroxine (T4) and triiodothyronine (T3).

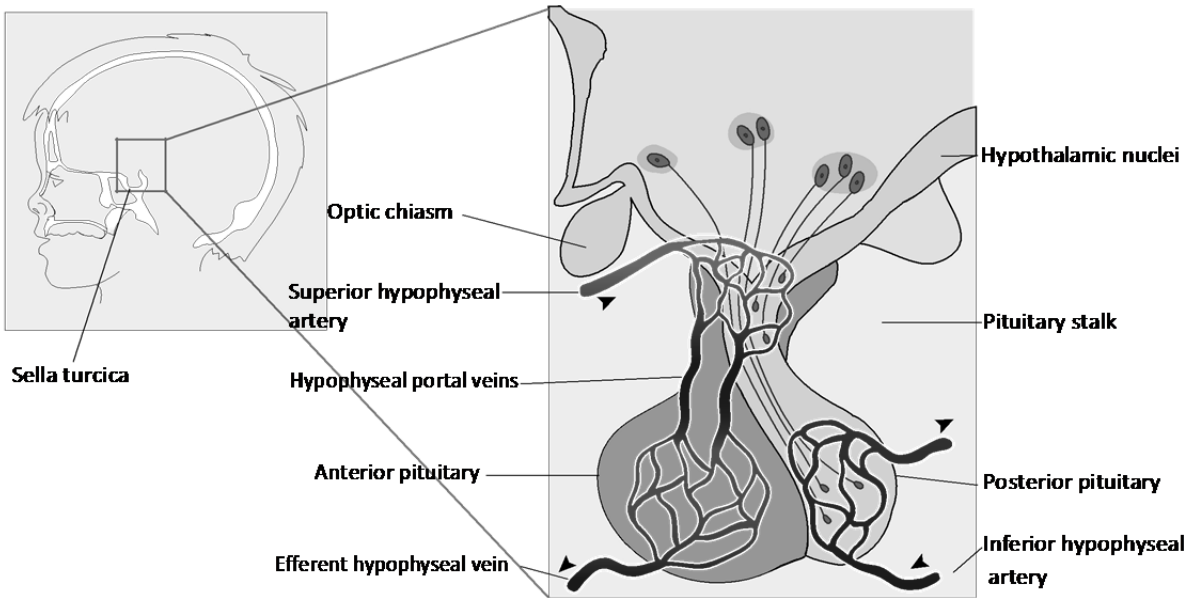
The posterior lobe is derived from neural ectoderm from the floor of the forebrain. Supraoptic and paraventricular hypothalamic neurons travel down the pituitary stalk, and make up the bulk of the posterior gland. Terminal axons store neurosecretory granules containing vasopressin (also known

as antidiuretic hormone, ADH), and oxytocin, which respectively promotes water retention at the renal collecting ducts, and stimulates milk ejection and contraction of the pregnant uterus.

2.1.1.1. Hypophyseal portal circulation

The pituitary circulation is of key relevance to this thesis. The entire gland is supplied by branches of the carotid artery, although a portal venous latticework forms a direct link between the hypothalamus and anterior pituitary (Figure 2.1). The portal veins form fenestrated capillary loops, which create a large vascular surface area, and greatly increase the ability of hypothalamic releasing factors to reach anterior pituitary sites. Superior hypophyseal vessels travel down the pituitary stalk as long hypophyseal veins and supply the majority of the anterior lobe, and short hypophyseal portal veins, which arise below the diaphragm sella, supply the remainder.

Figure 2.1. Blood supply to the pituitary gland.



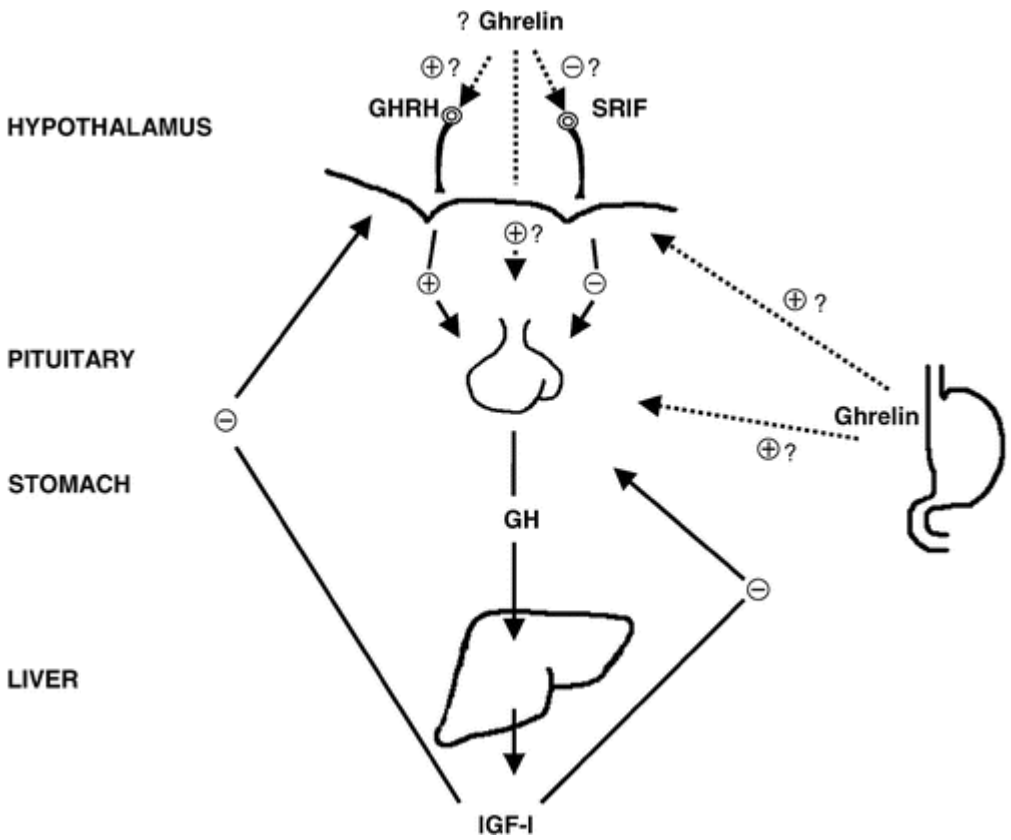
In contrast, the pituitary stalk and posterior lobe receive a direct arterial supply from middle and inferior hypophyseal arteries, and the posterior lobe is regulated through hypothalamic neural connections.

2.1.2. Pituitary regulation

The hypothalamus and pituitary form a tightly integrated unit dedicated to the homeostasis of diverse organ functions. The hypothalamus integrates neural and environmental information, and acts as an interface between the nervous and endocrine systems. It produces a range of stimulatory and inhibitory peptides, which entrain circadian rhythm and a pulsatile pattern of pituitary hormone release. Negative feedback loops allow further regulation, as both pituitary and peripheral hormones provide inhibitory feedback.

Figure 2.2. Regulation of GH production.

Reproduced with permission, from Anawalt and Merriam 2001.



Regulation of the GH-IGF-I axis can be considered as an illustrative example, as shown in Figure 2.2. GH secretion is largely controlled by the interplay between two hypothalamic peptides: growth hormone releasing hormone (GHRH) and somatostatin (SRIF) (Hindmarsh, Brain *et al*. 1991). In addition, ghrelin, a peptide derived from gastric mucosal cells, also stimulates GHRH and GH release

(Kojima, Hosoda *et al*. 1999). In turn, GH stimulates the production of a range of hepatic factors, including IGF-I, which is responsible for most of the growth promoting activities of GH (LeRoith and Buler 2001). IGF-I provides negative feedback to the hypothalamus and the pituitary, while GH inactivates hypothalamic GHRH and activates SRIF.

2.1.3. Assessment of pituitary function

In general, hypopituitarism is diagnosed based on the combination of a low concentration of peripheral hormones, paired with inappropriately low pituitary hormones. This basic method is used to diagnose TSH and gonadotropin deficiency. However, for other axes, pulsatile pituitary hormone release means that the assessment of basal levels provides limited information. As a result, the diagnosis of GH or ACTH deficiency is generally based on stimulation tests, as outlined below. However, it is important to recognise that provocation tests can lead to the over-diagnosis of hypopituitarism, and require careful interpretation.

2.1.3.1. GH assessment

During childhood, growth is the strongest measure of GH sufficiency, and clinical assessment subsequently based on auxology (Rosenfeld, Albertsson-Wikland *et al*. 1995). Laboratory assessments of GH status are reserved for poorly growing children, in whom there is a high index of suspicion. GH concentrations are typically low between secretory bursts, below the level of detection of assays, so that random basal levels are of limited value. Because of this, a range of GH provocation tests have been developed, and have been in widespread use now for over 50 years. However, GH stimulation tests do not provide a gold standard assessment of GH status (Rosenfeld, Albertsson-Wikland *et al*. 1995; Gandrud and Wilson 2004).

When GH treatment first became available in the 1960s, childhood GH deficiency was defined as a stimulated peak GH concentration of ≤3 ng/mL (Gandrud and Wilson 2004). Current diagnostic cut-offs for childhood GH deficiency are consensus-based with regional variance, so that a child may be diagnosed with GH deficiency with a peak GH of ≤10 ng/mL within Europe and the United States,

although the same child may not meet Australasian criteria of ≤5-7 ng/mL (Wyatt, Mark *et al*. 1995). Overall, it is likely that GH deficiency is over-diagnosed during childhood. This is supported by the observation that the growth response to treatment of children diagnosed with 'mild' or 'partial' GH deficiency is no greater than that seen in children with idiopathic short stature (Ranke, Lindberg *et al*. 2007). Furthermore, a large proportion of children diagnosed with idiopathic GH deficiency are found to have a normal level of stimulated GH when reassessed in adult life (Tauber, Moulin *et al*. 1997; Maghnie, Strigazzi *et al*. 1999). A commonly accepted adult definition of GH deficiency is peak GH <3 ng/mL in response to the insulin tolerance test (Ho 2007), reflecting the decrease in GH production during adult life.

Furthermore, assay variability strongly limits the interpretation of GH concentrations. Studies demonstrate that the variability in GH concentration reported from a single sample using different methods can exceed 100% (Morsky, Tiikkainen *et al*. 2005; Amed, Delvin *et al*. 2008). Initial GH assays were based on radioimmunoassay, which detected multiple isoforms and reported relatively high concentrations. Developments over the past decade include a move to sandwich type immunoassays, which employ monoclonal antibodies specific to 22kD GH, and the use of highly sensitive automated analysers (Bidlingmaier and Freda 2010). Furthermore, although assays were previously been standardised using reference preparations of different potency, there is a move to harmonise assays to the 98/574 preparation (Bidlingmaier and Freda 2010). As many of these factors would be anticipated to lead to lower reported GH concentrations, it is argued that the diagnostic cut-off for GH deficiency should also be reduced (Gandrud and Wilson 2004).

Furthermore, provocative GH tests discriminate poorly between GH deficient and normally growing children. In a landmark study, Ghigo *et al* described the response to GH provocation tests in a cohort of 472 normally growing children (Ghigo, Bellone *et al*. 1996). As described in Table 2.1 overleaf, a large proportion of normal children 'failed' provocation tests based on conventional criteria. Further, amongst a subgroup of 78 subjects who underwent two tests, the proportion who failed both tests

was greatly reduced (2.6-10%; Ghigo, Bellone *et al.* 1996). As a result of this work, failed response to at least two provocation tests is a widely accepted standard for the diagnosis of childhood GH deficiency (GH research society 2000).

Table 2.1. GH stimulation tests in 472 normally growing children.
Adapted from Ghigo, Bellone *et al*. 1996.

Stimuli for GH release	GH <7 ng/mL (%)	GH <10 ng/mL (%)
Glucagon	10	35
Clonidine	10.1	23.2
Arginine	12.6	32.9
Physical exercise	15.1	36.4
L-Dopa	23.6	36.4
Insulin tolerance test	23.7	49.1

In addition, pre-pubertal children are especially likely to 'fail' GH tests (i.e. produce a low GH response). This was first demonstrated by Marin *et al*; in a cohort of 84 normally growing children using a definition of GH peak <7 mcg/L, 61% of prepubertal children failed at least one provocative test, compared with 44% of those at Tanner stage 2, 11% at Tanner stage 3 and 0% at Tanner stage 4-5 (Marin, Domene *et al*. 1994). Conversely, estrogen priming increases GH response, and the ability to delineate GH deficient and sufficient children (Marin, Domene *et al*. 1994; Martínez A.S 2000). As a result, sex steroid priming is now widely used when performing GH provocation tests in pre-pubertal children, although there is no consensus for this practice (GH research society 2000).

BMI-dependant cut-offs have also been shown to increase the diagnostic accuracy of stimulation tests in adult subjects (Corneli, Di Somma *et al*. 2007), as obesity is associated with suppressed basal and stimulated GH concentrations (Scacchi, Pincelli *et al*. 1999). In childhood, there is a similar inverse relationship between BMI and GH peak (Stanley, Levitsky *et al*. 2009; Loche, Guzzetti *et al*.

2011), and it is clear that increasing BMI SDS, even within the normal range, leads to the over-diagnosis of childhood GH deficiency (Stanley, Levitsky *et al*. 2009).

In addition to GH concentration, serum growth factors can also be measured as a proxy for endogenous GH secretion. Serum concentrations of IGF-I and IGF-BP3 (the major serum carrier protein for IGF peptides) have the advantage of being relatively stable throughout the day, but must be interpreted with reference to age or pubertal stage-specific normative data. In particular, the normal range for IGF-I concentration is low in early childhood, with considerable cross-over between normal and GH deficient values (Ranke, Schweizer *et al*. 2004). IGF-I is also decreased in a number of disease states including malnutrition, hypothyroidism, renal failure and diabetes (Tamborlane, Hintz *et al*. 1981; Baxter, Brown *et al*. 1982; Soliman, Hassan *et al*. 1986), and is technically challenging to measure as it requires separation from high affinity binding proteins (Clemmons 2007).

Overall, both IGF-I and IGF-BP3 show relatively good specificity (67-98%), but poor sensitivity (55-75%), for the diagnosis of childhood GH deficiency (Juul, Holm *et al*. 1997). However, given that GH provocation tests were used as the gold standard, actual sensitivity may be greater than reported. Overall, although GH deficiency cannot be diagnosed based on growth factors alone, they provide useful supportive information.

2.1.3.2. Assessment of ACTH

The hypothalamic-pituitary-adrenal (HPA) axis is similarly difficult to examine, with no true gold standard that can be applied. Secondary adrenal insufficiency has an estimated prevalence of 150-280 per million, and is most often iatrogenic, due to prolonged therapeutic steroid administration. (Arlt and Allolio 2003). Symptoms of adrenal insufficiency, such as fatigue, anorexia and weight loss, are typically vague and insidious, but also include life-threatening adrenal crises. HPA tests are by necessity interpreted in a conservative manner, as missed cases (i.e. false negative results) can have fatal consequences.

ACTH secretion follows a pulsatile, diurnal rhythm, and has an in-built capacity for further increase in response to physiological stress. Furthermore, serum ACTH concentrations fluctuate widely and are highly unstable, so that random ACTH measurements have limited diagnostic value. It is generally accepted that morning cortisol concentrations <100 nmol/L are highly suggestive of adrenal insufficiency, whereas those >500 nmol/L demonstrate an intact HPA axis (Arlt and Allolio 2003). However, levels between these values are inconclusive, so that adrenal insufficiency can only be excluded by further, dynamic assessment. The pros and cons of commonly used adrenal function tests are outlined in Table 2.2 below. In addition to this, it is important to recognise that cortisol assays measure total cortisol, of which approximately 80% is bound to cortisol-binding globulin (CBG). There are wide inter-individual (influenced by estrogen and BMI), and intra-individual (e.g. in response postural change) variations in CBG concentration, which may confound basal and stimulated cortisol assessments (Dhillo, Kong *et al*. 2002; Davidson, Bolland *et al*. 2006).

Table 2.2. Methods used to assess for secondary adrenal insufficiency.

Test	Normal response	Comments
Early morning serum cortisol	Cortisol >500 nmol/L, (100-500 indeterminate).	Impact of timing, stress, possible confounders of estrogens and obesity.
Glucagon stimulation test	Cortisol >450 nmol/L.	Can be used for both GH and ACTH. Poor reliability.
Standard dose synacthen (250 mcg)	Cortisol >500-600 nmol/L.	Only suitable in prolonged ACTH deficiency. Low sensitivity.
Low dose synacthen (1 mcg)	Cortisol >500 nmol/.	Only suitable prolonged deficiency. Greater sensitivity but lower specificity than standard dose. Dose delivery difficulties.
Insulin tolerance test (ITT)	Cortisol >500-550 nmol/L.	Tests the entire HPA axis. Unpleasant, labour intensive.
Overnight metyrapone	11-deoxycortisol >200 nmol/L or 11-deoxycortisol plus cortisol >450 nmol/l.	Interrupts negative feedback. Oral absorption may be limited.

Direct stimulation of the adrenal with synthetic $ACTH_{1-24}$ (Synacthen) is a rapid and safe way to assess adrenal cortisol reserve. However, the test is only valid after a prolonged period of deficiency, as it is dependent on adrenal atrophy. Intravenous Synacthen can be administered at any time of day, and the cortisol response assessed at 30 and 60 minutes (Weintrob N 1998). The standard dose (250 mcg) is supra-physiological, and the false negative rate unacceptably high (in some series up to 65%; Arlt and Allolio 2003; Kazlauskaite, Evans *et al*. 2008). Conversely, the low dose test (1 mcg) is more physiologic but, whilst it has greater sensitivity and diagnostic discrimination, specificity is lower (Dickstein, Shechner *et al*. 1991; Kazlauskaite, Evans *et al*. 2008). Furthermore, the low dose test requires accurate dilution, and small but significant amounts can adhere to equipment (Murphy, Livesey *et al*. 1998); both of these factors can lead to false positive test results (i.e. falsely suggesting disease in normal subjects). Glucagon has the advantage that it can be used to stimulate both GH and ACTH, although it is a relatively weak stimulus of the HPA axis (Bottner, Kratzsch *et al*. 2005; Berg, Meinel *et al*. 2010).

Although there is no true gold standard for assessing the integrity of the HPA axis, reference tests are based on the response to a strong stimulus (e.g. insulin induced hypoglycaemia) or an interruption to negative feedback (i.e. the metyrapone test). The insulin tolerance test (ITT) invokes hypoglycaemia, a potent stimulus at all levels of the HPA axis. However, the ITT test is rarely used in childhood as it is unpleasant with attendant risks, including several reported deaths (Shah, Stanhope *et al*. 1992). Metyrapone inhibits the adrenal enzyme 11β-hydroxylase, and the conversion of 11-deoxycortisol to cortisol, and thus interrupts negative feedback. Concordance between ITT and metyrapone tests is high (Staub, Noelpp *et al*. 1979; Fiad, Kirby *et al.* 1994).

The original metyrapone test involved regular dosing over 24 hours (750 mg orally every four hours), and necessitated overnight admission (Liddle, Estep *et al*. 1959). The short metyrapone test is a convenient adaptation; metyrapone (30mg/kg) is given orally at midnight, with cortisol and 11-deoxycortisol measured the following morning (Fiad, Kirby *et al.* 1994). Like the ITT, metyrapone

tests may precipitate adrenal crises. In addition, variable oral absorption of metyrapone can lead to inadequate inhibition and invalid results (as evidenced by a non-suppressed serum cortisol, >200 nmol/L) (Fiad, Kirby *et al.* 1994).

2.1.4. Hypopituitarism

Hypopituitarism is a rare condition that describes deficiency in one or more pituitary hormones. Pituitary failure may be complete (panhypopituitarism) or isolated (affecting a single hormone axis). There has been just one population-based study of hypopituitarism, within which the overall prevalence was 45.5 per 100,000, and the incidence 4.2 per 100,000 per year, increasing with age (Regal, Páramo *et al*. 2001). The prevalence of GH deficiency amongst school-aged children is estimated to be 1:3,000-4,000 (Vimpani, Vimpani *et al*. 1977; Lindsay, Feldkamp *et al*. 1994). However, this is most frequently isolated GH deficiency, which is likely to be an over-diagnosed condition.

The clinical syndrome of hypopituitarism was first described by Simmonds in 1914, who reported a 46-year old woman with amenorrhea, weakness, and signs of rapid aging following an episode of puerperal sepsis, who was later found to have a very small pituitary gland at autopsy (Escamilla and Lisser 1942). The signs and symptoms of hypopituitarism are those of peripheral hormone insufficiency, and are summarised in Table 2.3 overleaf. Importantly, hypopituitarism is essentially a treatable condition, achieved through replacement of peripheral hormones.

During childhood, hypopituitarism has a profound effect on growth and development. In contrast, the symptoms of adult-onset hypopituitarism can be relatively vague and non-specific, although quality of life is invariably decreased. Furthermore, large studies have demonstrated that mortality is also increased, predominantly due to accelerated vascular disease (Sherlock, Ayuk *et al*. 2010). The rate of death from adrenal crisis is not known, but can been extrapolated from GH treatment databases, where children often have multiple pituitary hormone deficiencies. US data following

children treated with GH from the 1960s to 1990s reveals a three to four fold increase in mortality, of which >10% had a course consistent with adrenal insufficiency (Mills, Schonberger *et al*. 2004).

Table 2.3. Clinical features of hypopituitarism.
Adapted from van Aken and Lamberts 2005.

Hormone deficiency	**Clinical Features**
ACTH	Chronic: fatigue, pallor, anorexia, weight loss. Acute: adrenal crisis (dizziness, nausea, vomiting, hypotension).
TSH	General: tiredness, weight gain, cold intolerance, constipation, hair loss, dry skin, hoarseness, cognitive slowing. Childhood: short stature, mental retardation.
LH and FSH	Men: loss of libido, mood impairment, impaired sexual function, loss of facial, trunk and scrotal hair, decreased muscle mass, osteoporosis. Women: loss of libido, oligo/amenorrhoea, infertility, osteoporosis, premature atherosclerosis. Children: delayed puberty.
GH	General: decreased muscle mass and strength, central obesity, fatigue, decreased quality of life, impaired attention and memory, premature atherosclerosis. Children: growth retardation.
ADH	Polyuria, polydipsia.

2.1.4.1. Aetiology of hypopituitarism

The aetiology of hypopituitarism is outlined in Table 2.4 overleaf. Based on population studies, pituitary tumours are by far the most common cause of adult-onset hypopituitarism (Regal, Páramo *et al*. 2001). Traumatic brain injury (TBI) has traditionally been considered a rare cause of hypopituitarism (Escamilla and Lisser 1942), although this view has been challenged in recent years. Recent data suggests that hypopituitarism due to TBI may, in fact, be very common, although largely unrecognised (Kelly, Gonzalo *et al*. 2000; Schneider, Kreitschmann-Andermahr *et al*. 2007). Proponents argue that the neurological effects of TBI either mask the subtle signs of hormone deficiency, or cause physicians to falsely attribute symptoms to the cortical effects of TBI (Schneider,

Aimaretti *et al*. 2007). The evidence linking TBI to hypopituitarism will be discussed in detail within section 3 of this literature review.

The aetiology of childhood hypopituitarism is varied and can be either congenital or acquired. GH deficiency is most frequently labelled as idiopathic, which is likely to be an over-diagnosed condition. The Pfizer International Growth (KIGS) database contains information on >62,000 children treated with recombinant GH from 1987 to present. In a recent review, nearly half of cases were idiopathic, and just 141 cases were attributed to TBI (McDonald, Lindell *et al*. 2008). Given the very high proportion of cases for which the aetiology is unclear, it is possible that TBI could play a greater role than previously recognised. Furthermore, the excess frequency of breech deliveries amongst children with congenital hypopituitarism (68% vs. 4%) suggests that hypopituitarism may also be caused by traumatic births (Maghnie, Larizza *et al*. 1991).

Table 2.4. Causes of hypopituitarism.
Adapted from Schneider, Aimaretti *et al*. 2007.

Congenital:
Pituitary transcription factor defects (e.g. HESX1, PROP1, POU1F1)
Pituitary hypoplasia or aplasia
Acquired:
Pituitary tumours (adenomas)
Non-pituitary tumours (e.g. craniopharyngiomas, gliomas, metastases)
Iatrogenic (neurosurgery, radiotherapy)
Pituitary apoplexy (within tumour, Sheehan's)
Empty sella syndrome
Infiltrative disease (haemochromatosis, granulomatous disease)
Infections (abscess, hypophysitis, meningo-encephalitis)
TBI, including perinatal trauma
Subarachnoid haemorrhage, stroke
Psychosocial dwarfism
Unknown:
Idiopathic

2.2. Traumatic brain injury

Traumatic brain injury (TBI) is a very common event at all ages. It is the leading cause of death and disability amongst young adults, particularly males (van Baalen, Odding *et al*. 2003), and the most common cause of trauma death during childhood (Hiu Lam and Mackersie 1999). In developed nations approximately 180 children per 100,000 are admitted to hospital with TBI each year (Parslow, Morris *et al*. 2005).

2.2.1. Incidence of childhood TBI

Most TBI incidence studies are cross-sectional and based on a description of hospital admissions. These provide highly conservative estimates as the majority of TBI cases are mild and do not present to hospital (Corrigan, Selassie *et al*. 2010). Therefore, prospective whole population studies offer a major advantage to in terms of greater injury catchment.

Recent data from a New Zealand cohort, followed from birth to early adulthood, demonstrates that the incidence of TBI is actually 10-fold higher than normally assumed (McKinlay, Grace *et al*. 2008). In this study researchers evaluated the incidence of TBI amongst all people born in the Christchurch region in 1977. The 1265 participants represented 97% of those eligible, with 79% of the original cohort followed to age 25 years. For this study, the minimum case definition of TBI was a blow to the head for which medical attention was sought and a diagnosis of concussion given. Investigators conducted prospective interviews at regular periods to identify health events, which were then verified by review of medical records.

Overall, a third of the cohort had sustained a TBI by 25 years, 10% of TBI was classified as severe, and a third of those with TBI had sustained multiple events (McKinlay, Grace *et al*. 2008). The annual incidence of TBI was 1,750 per 100,000 per year overall (McKinlay, Grace *et al*. 2008), i.e. 10-fold higher than the incidence reported by studies based on hospital admissions (Kraus, Rock *et al*. 1990;

Hawley, Ward *et al*. 2003; Parslow, Morris *et al*. 2005; McKinlay, Grace *et al*. 2008). This is likely to reflect both to the inclusive definition of TBI and comprehensive method of data collection.

In addition, the epidemiology of childhood and adolescent TBI varies considerably with age. Overall, teenagers aged 15-20 years have greatest risk of TBI (TBI incidence 2.4/100 per year), with more than twice the TBI rate of school-aged children (Kraus, Rock *et al*. 1990; McKinlay, Grace *et al*. 2008). From 15-20 years, the most frequent causes of TBI are contact sports, motor vehicle accidents, and assaults (Kraus, Rock *et al*. 1990; McKinlay, Grace *et al*. 2008). Males have higher rates of TBI at all ages, but this trend is particularly marked during adolescence (Kraus, Rock *et al*. 1990; McKinlay, Grace *et al*. 2008). Young children, less than five years old, are also at relatively high risk of TBI (1.9/100 per year, as compared with 1.1/100 for school aged children) (McKinlay, Grace *et al*. 2008). Falls are the most common reported cause of early childhood TBI, although abusive TBI is also common and likely to be under-reported (Kraus, Rock *et al*. 1990; Duhaime, Alario *et al*. 1992).

2.2.2. TBI grading

TBI is a highly heterogeneous condition, and injury severity can be defined in either functional or anatomical terms. The widely used Glasgow Coma Scale (GCS) provides a simple functional assessment, but carries significant limitations and may be less reliable during early childhood.

2.2.2.1. Glasgow Coma Scale

In 1974, Teasdale introduced the GCS as a objective scale for impaired consciousness following head injury (Teasdale and Jennett 1974). The GCS comprises three aspects that are independently measured; best motor and verbal response, and the stimulus required for eye opening (Teasdale and Jennett 1974), see Table 2.5 overleaf. This simple test was designed to be performed repeatedly at the bedside, in order to facilitate objective communication about TBI patients and help detect deterioration.

Over the years, GCS scores have also become widely used to define TBI severity, with the initial hospital post-resuscitation score generally used for this purpose. According to consensus, a total score of <9 denotes severe TBI, 9-12 moderate TBI and 13-15 mild TBI (Rimel, Giordani *et al*. 1982). Amongst cases of severe TBI, the motor sub-score contains the majority of GCS information (Ross, Leipold *et al*. 1998; Healey, Osler *et al*. 2003) and is therefore proposed as a simpler assessment (Meredith, Rutledge *et al*. 1995; Al-Salamah, McDowell *et al*. 2004; Fortune and Shann 2010). However, both total GCS and motor scores have a weak and inconsistent association with survival, functional outcome and anatomical TBI (Demetriades, Kuncir *et al*. 2004; Foreman, Caesar *et al*. 2007; Marmarou, Lu *et al*. 2007).

Table 2.5. The Glasgow Coma Scale.
(Teasdale and Jennett 1974)

Score	Eye opening	Best verbal response	Best motor response
1	None	None	None
2	To pain	Incomprehensible	Extending
3	To speech	Inappropriate	Flexing
4	Spontaneous	Confused	Withdrawal
5	-	Orientated	Localising
6	-	-	Obeying

2.2.2.2. Validity of the GCS

There are a number of barriers to determining GCS in a repeatable and reproducible manner. For example, scores can be confounded by pre-hospital interventions, intoxication, extra-cranial injuries, a variable interval to assessment after TBI, and observer effects.

Common interventions such as pre-hospital intubation, heavy sedation or neuromuscular paralysis can all mask neurological responses, as can patient factors such as cardio respiratory instability, intoxication or seizures. In view of this, Marion *et al.* recommended that severity scores should be

determined in hospital 1-2 hours after injury, following resuscitation and 10 minutes later than the half-life of any sedating or paralyzing agent used (Marion and Carlier 1994). However, these principles are not easily achieved in clinical practice. In an Italian study of 753 consecutive TBI patients admitted to intensive care, 90% were evaluated in presence of confounding factors (Stocchetti, Pagan *et al*. 2004).

Furthermore, a number of studies have assessed the inter-observer reliability of assigned GCS. Although scoring is highly reliable amongst stable, severely impaired subjects (Teasdale, Knill-Jones *et al*. 1978) it is less reliable in emergency settings, amongst moderately impaired subjects and inexperienced users (Menegazzi, Davis *et al*. 1993; Gill, Reiley *et al*. 2004).

2.2.2.3. GCS in early childhood

Importantly, GCS is designed for use in an adult population and may be less reliable in young, children. In particular, the target verbal response may be beyond a young child's developmental stage. However, although various childhood adaptations have been described, none have achieved widespread acceptance. Perhaps as a result of the perceived complexity and decreased value, coma scores may be poorly documented following early childhood TBI (Falk, Cederfjäll *et al*. 2005).

Simpson presented the first simplified paediatric version of the GCS in 1991, recognising that responses should be related to age appropriate normative behaviour (Simpson, Cockington *et al*. 1991). This adaptation has been validated as showing a lower disagreement rate than standard GCS scores in early childhood (Yager, Johnston *et al*. 1990). In Australasia, a similar verbal modification is used, but has not been validated (Browne, Cocks *et al*. 2001). Limited data suggests that the predictive value of severe scores during childhood GCS are similar to that reported amongst adult TBI populations (Lieh-Lai, Theodorou *et al*. 1992; Ducrocq, Meyer *et al*. 2006). However, these studies have been performed in children of all ages, and there is very little data that can be used to

assess the reliability of early childhood scores over a range of injury severity (Holmes, Palchak *et al*. 2005).

2.2.2.4. Structural TBI

The widespread use of acute computerised tomography (CT) scans following TBI offers an alternative method of injury classification. A description of structural TBI is likely to be more objective than functional assessments, particularly in early childhood. As would be anticipated, "complicated" mild TBI (GCS 14-15 but with intracranial abnormalities) carries a worse outcome than "uncomplicated" mild TBI (Williams, Levin *et al*. 1990). However, although a grading scale based on structural severity is an appealing concept, these are not widely used in clinical practice.

The Marshall scale is a specific TBI grading scale, based on the initial CT head scan, which focuses on the presence of mass lesions or oedema (Marshall, Marshall *et al*. 1991). However, Marshall scores have less prognostic value than individual CT characteristics, such as the presence of traumatic subarachnoid haemorrhage (Maas, Hukkelhoven *et al*. 2005; Maas, Steyerberg *et al*. 2007). Furthermore, criteria are based on adult volume and distances, and have not been adapted for childhood TBI.

The Abbreviated Injury Scale (AIS) is a consensus-derived anatomical scoring system that was intended as a standardised system to describe the diverse injuries that can result from motor vehicle accidents (States 1971). The AIS dictionary contains a large number of possible injuries, divided into six anatomical regions. Individual injuries are ranked on a "threat to life" scale of 1 to 6 (1 being mild, 2 moderate, 3 serious, 4 severe, 5 critical, and 6 not survivable), where the AIS score reflects the worst structural diagnosis within each region (States 1971). The total injury severity score is a composite score derived from the three most severely injured regions.

For TBI, the head region AIS score is typically graded based on the findings of an acute computerised tomography (CT) scan, but can also be defined as a result of structural lesions that are directly

visualised (including intra-operatively or during an autopsy). A score of 1 indicates a relatively minor injury, for example an isolated scalp contusion or abrasion, and a score of 2 may indicate a simple skull vault fracture or cranial nerve injury. Scores of 3 generally reflect intra-cranial injury, e.g. small cerebral contusion or subarachnoid haemorrhage, but could also indicate a basal skull fracture. Scores of 4-5 denote more severe intra-cranial injury, such as extensive cerebral contusions, subdural haematoma or diffuse axonal injury. Although a score of 6 is considered non-survivable, it is scored based on the anatomical diagnosis (e.g. brain stem transection) rather than outcome.

In adult TBI populations, head region AIS scores show a better or similar correlation with mortality and functional outcome than the GCS (Demetriades, Kuncir *et al*. 2004; Foreman, Caesar *et al*. 2007; Timmons, Bee *et al*. 2011). The AIS includes specific consensus-derived adaptations for childhood TBI, although these have not been validated in large childhood populations (Association for the Advancement of Automotive Medicine, 1998). Overall, AIS scores are predominantly used in comparative injury research, and are seldom applied in clinical practice.

2.2.3. Abusive TBI

Abusive injuries are the most common cause of fatal TBI in infancy (Billmire and Myers 1985). A conservative estimate of the incidence of abusive TBI in New Zealand is 19.6 per 100,000 infants per year (Kelly and Farrant 2008). However, whilst this best estimate is consistent with international reports (Barlow and Minns 2000), abusive TBI is likely to be grossly under-recognised and under-reported throughout the world (Reece and Sege 2000; Runyan 2008).

In the early 1970s, Caffey introduced the concept that violent, intentional shaking of an infant could lead to serious head injury (Caffey 1972; Caffey 1974). The mechanism behind the “shaken baby syndrome” has since been substantiated by confessions from caregivers, as well as radiological and biomechanical studies, and the most widely accepted hypothesis is of violent, repetitive episodes of acceleration/deceleration that may be exacerbated by impact (Duhaime, Christian *et al*. 1998; Case,

Graham *et al*. 2001). Common features of abusive TBI include the young age of victims (median age 2.2 months) (Barlow and Minns 2000), and the presence of subdural and/or retinal haemorrhage (Feldman, Bethel *et al*. 2001; Keenan, Runyan *et al*. 2003). There is often evidence of previous episodes of TBI, as demonstrated by old subdural haemorrhages (SDH) (Jenny, Hymel *et al*. 1999). In some cases there is also clear evidence of impact to the head, in the form of scalp bruising or skull fracture (Duhaime, Alario *et al*. 1992).

Infants have increased susceptibility to TBI, which occurs as a result of several anatomical features. Firstly, the weight of a young child's head is proportionately great; an infant's head comprises 10-15% of total body weight compared with 2-3% for an adult (Case 2008). In addition, infant neck muscles are poorly developed and the skull base shallow, allowing greater head movement in response to acceleration-deceleration forces (Case 2008). Furthermore, the large number of neurons without glial or dendritic connections, small axonal size and paucity of myelination all reduce the threshold for cortical shearing injury (Case, Graham *et al*. 2001; Case 2008). In addition, the skull is relatively thin and pliable, and the subarachnoid space relatively thin (with a reduced buttressing capacity), so that impact forces are transferred more effectively across an infant's head (Gean 1994; Case 2008).

Limited research also suggests that outcomes are poor following abusive TBI. The reported mortality varies from 10-30%, with 30-50% of survivors left with significant cognitive or neurological deficits, and less than 30% making a full recovery (Jayawant, Rawlinson *et al*. 1998; Barlow, Thomson *et al*. 2005). Furthermore, amongst missed cases where infants have been returned to the same setting, there is a high mortality from further abuse (Jenny, Hymel *et al*. 1999).

2.2.4. Diagnosis of abusive TBI

In clinical paediatrics, it is extremely important to differentiate abusive from accidental TBI. Abuse that is witnessed or confessed can be considered as definite; however, this history is seldom

available. The diagnosis is therefore based on history and examination, a thorough social evaluation, and targeted radiological assessment looking for intra-cranial injury and occult fractures.

"Red flags" for inflicted TBI include no history of trauma given, a history that changes over time or between caregivers, or one that is inconsistent with the injury or with an infant's developmental age (Duhaime, Christian *et al*. 1998; Hettler and Greenes 2003; Bechtel, Stoessel *et al*. 2004). When no history of trauma is given for infants who present with intra-cranial haemorrhage, the positive predictive value for abusive rather than accidental TBI is very high (0.92-1.0) (Hettler and Greenes 2003). Additional associated findings include retinal haemorrhages, and injuries outside the head (e.g. external bruising, genital injuries, rib or metaphyseal fractures) (Duhaime, Alario *et al*. 1992; Duhaime, Christian *et al*. 1998). In New Zealand, TBI cases that are classified by a multi-disciplinary Child Protection teams as definitely or possibly consistent with abuse are referred to the statutory authorities, and these medical opinions typically validated by statutory authorities (Kelly, MacCormick *et al*. 2009).

2.2.5. Endocrine consequences of abuse

Although the pituitary effects of abusive TBI have never been systematically assessed, historical data suggests that extreme neglect or abuse can lead to growth failure. More recent data suggests that childhood abuse may program the HPA axis, and contribute to an increased lifetime risk of depression (Heim, Newport *et al*. 2008).

2.2.5.1. Psychosocial dwarfism

In the 1960s, Powell described a series of children with emotional deprivation simulating hypopituitarism, termed "psychosocial dwarfism" (Powell, Brasel *et al*. 1967). In this seminal report, all subjects (13 children, aged 3-11 years) were referred with extreme short stature (Powell, Brasel *et al*. 1967). Growth acceleration was dramatic upon removal from the home environment (height velocity 2-3 fold expected), and sustained over several years. The authors proposed that growth failure was caused by "psychic factors" that had inhibited GH release (Powell, Brasel *et al*. 1967).

The children in Powell's series underwent detailed medical investigations, including pituitary function assessments both during the periods of growth failure and recovery (Powell, Brasel *et al*. 1967). In all subjects, the initial stimulated GH response met strict diagnostic criteria for deficiency, and spontaneously normalised upon removal from the dysfunctional environment. The majority of children were also ACTH deficient, as evidenced by an abnormal response to metyrapone. Interestingly, in the majority of cases (80%), metyrapone tests remained abnormal after growth recovery had occurred, although no explanation was given for this persistence.

More recently, Skuse reported a similar case series of children with psychosocial short stature (n=30), and suggested a further division into hyperphagic and anorexic subgroups (Skuse, Albanese *et al*. 1996). All of the children in Powell's series had marked symptoms of polyphagia and polydipsia, although only one subject appeared malnourished (Powell, Brasel *et al*. 1967). The weight gain that occurred alongside catch-up growth was often relatively mild, and, in several cases growth failure immediately recurred upon returning home, despite adequate nutrition. Therefore, although malnutrition can simulate hypopituitarism, emotional deprivation is likely to be an independent causative factor.

2.2.5.2. Traumatic hypopituitarism

In addition, Miller *et al.* reported three cases of permanent hypopituitarism following abusive TBI (Miller, Kaplan *et al*. 1980). All subjects were diagnosed with abusive TBI with subdural haemorrhage during infancy, and re-presented with growth failure during mid-childhood. All three were found to have multiple anterior pituitary hormone deficiencies (GH, TSH, ACTH, possibly gonadotropins). Although the appearance of the pituitary gland was grossly normal on CT, the children were thought to have acquired pituitary injury, and permanent hypopituitarism, as a result of their abusive TBIs.

2.2.5.3. The HPA axis

Acute stress leads to activation of the HPA axis, and increased production of adrenal cortisol (Selye 1936). Although the short-term benefits of additional cortisol include the increased availability of

energy substrates and greater cardiovascular tone, prolonged or excessive exposure is associated with immune suppression and adverse metabolic effects (Sapolsky, Romero *et al*. 2000). Depression is also associated HPA hyperactivity (Gold, Goodwin *et al*. 1988), and child abuse is proposed to program the HPA axis and increase susceptibility to depression (Heim, Newport *et al*. 2008).

There is increasing evidence that abuse during childhood can lead to a persistently altered stress response throughout later life. In several studies, adults with a history of abuse demonstrate decreased HPA feedback inhibition (Heim, Mletzko *et al*. 2008; Carpenter, Tyrka *et al*. 2009). Similarly, suicide victims show greater methylation of hippocampal glucocorticoid receptors (which would lead to decreased negative feedback) than non-abused suicide victims (Heim, Mletzko *et al*. 2008; McGowan, Sasaki *et al*. 2009). However, although the lifetime risk of depression is greatly increased following childhood abuse, careful longitudinal data is needed in order to determine the temporal relationship between HPA dysfunction and depression.

Childhood HPA challenge studies amongst abuse victims have been very small (n=15-30), and report variable results. For example, in different studies the response to CRF stimulation was either increased or decreased (De Bellis, Chrousos *et al*. 1994; Kaufman, Birmaher *et al*. 1997; Heim, Newport *et al*. 2001). This apparent contradiction may relate to current environment, as Kaufman reported that ACTH hyper-responsiveness was only seen within a sub-group still living in high stress environments (Kaufman, Birmaher *et al*. 1997). Furthermore, these small studies have had limited ability to account for the key biological factors (age, gender, pubertal status) which impact serum cortisol concentrations.

2.3. Hypopituitarism following TBI

Over the past decade, a series of studies have reported that hypopituitarism is common following TBI (Kelly, Gonzalo *et al*. 2000; Lieberman, Oberoi *et al*. 2001; Schneider, Kreitschmann-Andermahr *et al*. 2007). Although there is no doubt that TBI can lead to hypopituitarism, the variable reported

rates (5-69%; Lieberman, Oberoi *et al*. 2001; Kokshoorn, Smit *et al*. 2011) carry very different implications. An important clinical question is whether routine pituitary assessment should be performed following TBI, and, if so, which patients are at sufficient risk to warrant screening tests. This chapter will review the current evidence that hypopituitarism may be a common, unrecognised complication of TBI, and outline the many areas of uncertainty within emerging data. Furthermore, the majority of studies have been performed in adults, so that the childhood risk is poorly defined.

2.3.1. Case reports

Hypopituitarism following TBI was first described in 1918 (Cyran 1918), just four years after the initial clinical description of hypopituitarism. Over the ensuing decades, TBI was considered to be a rare cause of hypopituitarism (Escamilla and Lisser 1942), with cases reported either individually or in small series.

By 2000, Benvenga had collated 367 cases of hypopituitarism following TBI (Benvenga, Campenni *et al*. 2000). Of this group, almost all were diagnosed with gonadotropin deficiency, and half with TSH and ACTH deficiency (44% and 53%, respectively). In addition, 30% had diabetes insipidus, and 24% GH deficiency. Prolactin deficiency (3.8%) was less common, although nearly half (48%) had hyperprolactinaemia, suggestive of hypothalamic injury. There is likely to have been strong selection bias to reported cases, in particular the very high prevalence of gonadotropin deficiency may reflect the fact that most cases were detected following the investigation of infertility, menstrual irregularity or erectile dysfunction.

Within Benvenga's series, by far the most common description was of a young adult male with TBI caused by a road traffic accident (Benvenga, Campenni *et al*. 2000). The male to female ratio within the series was 5:1, with 60% of injuries having occurred during early adulthood. Almost all cases (93%) were associated with coma or loss of consciousness, and the majority (55%) had skull

fractures. Amongst 76 cases where CT or MRI scans were reported, almost all (93%) had visible lesions in the pituitary or hypothalamus.

Of concern, although hypopituitarism was generally identified within the first year after injury, extensive delays (>5 years) were reported in 15% (Benvenga, Campenni *et al*. 2000). This suggests that patients and physicians had either overlooked the symptoms of hypopituitarism, or falsely attributed them to the cortical effects of TBI. In addition, there are several well documented cases of recovery from hypopituitarism, suggesting that significant transient hypopituitarism can occur following TBI (Eiholzer, Zachmann *et al*. 1986; Benvenga, Campenni *et al*. 2000; Agha, Ryan *et al*. 2005).

Five years ago, Acerini and colleagues collated the paediatric literature and reported a total of 20 cases of hypopituitarism following TBI (Acerini, Tasker *et al*. 2006). Overall, these highly selected case reports support the adult literature, indicating that permanent hypopituitarism can also occur following childhood TBI. The children in this series were aged 1-16 years at the time of diagnosis, with short stature and delayed puberty the most common presenting complaints. In contrast to the relatively low frequency of GH deficiency amongst adult case reports, GH deficiency was very common (85%). Most of the children had multiple hormone deficiencies, with gonadotropin, TSH and ACTH deficiencies also very common (80%, 75% and 55%, respectively). Like the adult literature, structural hypothalamo-pituitary abnormalities were frequent, especially pituitary stalk transection (Yamanaka, Momoi *et al*. 1993; Barbeau, Jouret *et al*. 1998; Benvenga, Vigo *et al*. 2004).

In addition, it is likely that those with recurrent episodes of TBI are at increased risk of hypopituitarism. Hypopituitarism has been reported amongst athletes (e.g. boxers, football players) with a history of relatively mild TBI events, for which no medical attention was sought (Kelestimur 2005; Ives, Alderman *et al*. 2007). Similarly, as discussed in section 2.2.3 and included within

Acerini's childhood case series, shaken babies are often injured repeatedly, and so may be at high risk of hypopituitarism.

2.3.2. Autopsy data

Traumatic infarction of the anterior lobe of the pituitary gland was first described in 1959 (Daniel, Prichard *et al*. 1959). In this report, five patients with fatal TBI (survival for 3-9 days) had massive necrosis of the anterior pituitary, attributed to transection of the pituitary stalk. Of note, four of these cases had sustained basal skull fractures involving the mid-cranial fossa.

Following this report, several large autopsy series have demonstrated that hypothalamic-pituitary damage is common following fatal TBI (Ceballos 1966; Kornblum and Fisher 1969; Crompton 1971). Pituitary injury is found in the majority of cases (64-86%) (Ceballos 1966; Kornblum and Fisher 1969), and includes capsular haemorrhage or vascular injury to the stalk, anterior or posterior gland. Only one study systematically examined for hypothalamic lesions, and reported haemorrhage or necrosis in 42% of cases, also associated with basal skull fractures (Crompton 1971).

Amongst these large series, ischaemic necrosis of the anterior pituitary was found in up to 35% of fatal TBI (Kornblum and Fisher 1969). The area of necrosis corresponds to the blood supply of the long hypophyseal portal vessels, consistent with injury to the small perforating blood vessels. Furthermore, Kornblum noted that the rate of injury was far greater following motor vehicle accidents than penetrating gunshot wounds or impact injuries, which may reflect vascular shear injury from greater displacement of the brain within the skull (Kornblum and Fisher 1969).

However, there are likely to be a number of differences between the pathophysiology of fatal and non-fatal TBI. High intracranial pressure and cerebral herniation, as well as severe hypotension and hypoxaemia, are all common amongst non-survivable TBI, and each could contribute to the hypothalamo-pituitary lesions described (Dusick, Wang *et al*. 2008). Interestingly, a recent autopsy series found that massive necrosis of the adenohypophysis (>50%) was primarily found in subjects

who survived for >24 hours, implying that secondary brain injury plays a strong contributory role (Salehi, Kovacs *et al*. 2007).

2.3.3. Proposed mechanism of injury

The mechanism of pituitary injury has not been clearly established, and vascular, traumatic and auto-immune hypotheses are proposed (Yuan and Wade 1991; Dusick, Wang *et al*. 2008; Tanriverdi, De Bellis *et al*. 2008). However, as outlined below, the primary injury mechanism is likely to be vascular.

Firstly, the anatomy of the pituitary gland makes it particularly vulnerable to vascular injury. The gland is suspended on a stalk, and potentially mobile. Long hypophyseal vessels travel down the stalk and supply the anterior pituitary via a latticework of portal vessels (Figure 2.1). These small perforating vessels are vulnerable to shearing injury from acceleration-deceleration forces. Furthermore, pituitary enlargement on MRI (likely representing oedema) is common in the first week after TBI (Maiya, Newcombe *et al*. 2008), and atrophy and perfusion defects in the chronic phase (Schneider, Samann *et al*. 2007). Lastly, the hierarchy of hormone failure corresponds to the anatomy of the gland, with somatotrophs and gonadotrophs (located in the vulnerable vascular territory of the long hypophyseal portal system) most often reported as deficient following TBI (Dusick, Wang *et al*. 2008). In contrast, corticotrophs and thyrotrophs, found in the more protected territory of the short hypophyseal portal system, are less frequently implicated.

Direct mechanical trauma at the level of the hypothalamus, pituitary stalk or gland is another potential mechanism. The pituitary is cushioned by cerebrospinal fluid and cerebral tissue and is therefore relatively protected from direct trauma. Of note, both hypothalamic and pituitary injuries are associated with basal skull fractures, particularly through the sella (Crompton 1971; Kelly, Gonzalo *et al*. 2000), which are likely to reflect greater local forces at impact. However, hypothalamic lesions are common in post-mortem series but not on MRI scans of survivors,

suggesting that most individuals who sustain a major hypothalamic injury die (Crompton 1971; Schneider, Samann *et al*. 2007). Stalk disruption is an uncommon complication of TBI, although it is well recognised in both case reports and autopsy series, and leads to massive anterior lobe infarction (including empty sella) and posterior lobe denervation (Yuan and Wade 1991).

In a small prospective study, anti-pituitary antibodies were reported to be associated with pituitary deficiency three years after TBI (Tanriverdi, De Bellis *et al*. 2008). Based on this finding as well as limited longitudinal data suggesting that pituitary deficiency can evolve following TBI (Aimaretti, Ambrosio *et al*. 2005), the authors postulated that hypopituitarism may be a progressive, inflammatory disorder (Tanriverdi, De Bellis *et al*. 2008). However, it could also be argued that the appearance of antibodies is a marker of damage, as opposed to a direct pathogenic mechanism.

2.3.4. Prevalence of hypopituitarism after TBI

Almost all systematic studies have reported that hypopituitarism is common following TBI, however the reported prevalence of hypopituitarism varies greatly (5-69%, Table 2.6; Lieberman, Oberoi *et al*. 2001; Kokshoorn, Smit *et al*. 2011). This dramatic variability is due to various methodological factors, including differences in patient selection, duration of follow-up, methods of assessment and the diagnostic cut-offs used to define hypopituitarism. As a result, the rate of true, clinically significant hypopituitarism following TBI is unclear.

It is also important to note that the overwhelming majority of data comes from adult cohorts. Despite marked differences in the types of TBI that occur during childhood, there is very little paediatric data, and none that is specific to early childhood. As a result, the prevalence of hypopituitarism following childhood TBI is largely unknown, and predictions are almost entirely extrapolated from adult data. In the following sections, I will firstly review the adult TBI literature, both cross-sectional and longitudinal, followed by the smaller body of childhood data.

2.3.5. Cross-sectional TBI data in adults

2.3.5.1. Prevalence of anterior hypopituitarism

The first systematic study of pituitary function following TBI was published in 2000, and reported hypopituitarism in 34% of cases (Kelly, Gonzalo *et al*. 2000). Although this was a small study (consisting of just 22 subjects), the design was robust, and included stimulation tests and a matched control group. The second such study, based on 70 subjects recruited from a brain injury rehabilitation unit, reported that pituitary abnormalities were alarmingly common, affecting more than two thirds of subjects (Lieberman, Oberoi *et al*. 2001). All of these subjects were recovering from very severe TBI, and may therefore represent a group at particularly high risk of pituitary damage. However, it is evident that a number of clinically insignificant results were included in the total; such as low basal hormone levels paired with a normal response to stimulation tests, and elevated levels of prolactin likely due to medications. Despite short-falls, both studies suggested that hypopituitarism is common and under-diagnosed following TBI, and encouraged further investigation.

As outlined in Table 2.6, TBI studies over the past decade have continued to report a variably high rate of hypopituitarism. This table summarises cross-sectional studies in adult cohorts, where pituitary assessments were performed during the chronic phase following TBI (>6 months). In contrast to individual case reports, the vast majority of cases of hypopituitarism identified in these studies have been deficient in a single axis, most commonly GH (6-28%; Bondanelli, De Marinis *et al*. 2004; Leal-Cerro, Flores *et al*. 2005) or gonadotropins (0-22%; Kelly, Gonzalo *et al*. 2000; Lieberman, Oberoi *et al*. 2001), followed by TSH (1-22%; Lieberman, Oberoi *et al*. 2001; Agha, Rogers *et al*. 2004), and ACTH (0-13%; Agha, Rogers *et al*. 2004; Bondanelli, De Marinis *et al*. 2004). The weighting of hormone deficiencies also varies greatly; for example Lieberman reported that TSH deficiency was common but gonadotropin deficiency rare (Lieberman, Oberoi *et al*. 2001), and Agha that ACTH deficiency common but TSH deficiency rare (Agha, Rogers *et al*. 2004).

To date, the largest report comes from a multi-centre German registry of 1,242 TBI patients, which describes a very high prevalence of hypopituitarism (35-60%) within a clinical TBI database (Schneider, Schneider *et al*. 2011). The treating clinician was free to select the level of pituitary investigation. The majority of subjects (>85%) underwent basal assessments of pituitary function only, and 35% of this group were diagnosed with hypopituitarism, although it is somewhat surprising that this would occur in the absence of confirmatory dynamic tests of GH and ACTH. Further, there was an alarmingly high prevalence of hypopituitarism (60%) within the minority who underwent dynamic tests. The authors speculate that this group was selected by physicians as being high risk, however, it is also true that a variety of tests were allowed, including those with poor positive predictive value. Overall, it is highly likely that hypopituitarism was over-diagnosed in all groups. Furthermore, the paper does not describe whether some or all patients labelled with hypopituitarism went on to receive hormone replacement treatment. In view of the limitations of this recent large report, it has not been included in the summary Table 2.6 overleaf.

Table 2.6. Prevalence of hypopituitarism in adult TBI studies.

Source	Total Subjects	% *(n)* with pituitary deficiency	% *(n)* GH deficient	% *(n)* LH, FSH deficient	% *(n)* ACTH deficient	% *(n)* TSH deficient
Kelly, Gonzalo *et al*. 2000	22	36 (8)	18 (4)	22 (5)	5 (1)	5 (1)
Lieberman, Oberoi *et al*. 2001	70	69 (48)	10 (7)	0	7 (5)	22 (15)
Bondanelli, De Marinis *et al*. 2004	50	54 (27)	28 (14)	14 (7)	0	10 (5)
Aimaretti, Ambrosio *et al*. 2004	100	16 (16)	14 (14)	8 (8)	5 (5)	4 (4)
Agha, Rogers *et al*. 2004	102	29 (29)	11 (11)	12 (12)	13 (13)	1 (1)
Popovic, Pekic *et al*. 2004	67	34 (23)	15 (10)	9 (6)	8 (5)	5 (3)
Leal-Cerro, Flores *et al*. 2005	170	25 (42)	6 (10)	17 (29)	7 (11)	6 (10)
Herrmann, Rehder *et al*. 2006	76	24 (18)	8 (6)	17 (13)	3 (2)	3 (2)
Schneider, Schneider *et al*. 2006	70	36 (25)	10 (7)	20 (14)	9 (6)	3 (2)
Tanriverdi, Senyurek *et al*. 2006	52	50 (26)	38 (20)	8 (4)	19 (10)	6 (3)
Bushnik, Englander *et al*. 2007	57	93 (53)	66 (39)	14 (7)	60 (39)	19 (12)
Klose, Juul *et al*. 2007	104	15 (15)	15 (16)	2 (2)	5 (5)	2 (2)
Wachter, Gündling *et al*. 2009	55	24 (13)	2 (1)	15 (8)	2 (1)	5 (3)
Berg, Oeffner *et al*. 2010	246	21 (52)	5 (12)	9 (22)	1 (2)	12 (30)
Krahulik, Zapletalova *et al*. 2010	89	21 (19)	13 (12)	6 (5)	0	0
†Van der Eerden, Twickler *et al*. 2010	107	1 (1)	0	0	1 (1)	0
Kokshoorn, Smit *et al*. 2011	112	5 (6)	3 (3)	1 (1)	2 (2)	0
% Total (Range)		**29%**	**13%**	**10%**	**7%**	**6%**
% Range		**5-93%**	**0-66%**	**1-22%**	**0-60%**	**0-19%**
n	**1,442**	**420**	**186**	**143**	**107**	**93**

† The majority of subjects in this study had mild TBI, so that data have been excluded from total calculations.

2.3.5.2. Cohort factors

To a large degree, the wide variation in reported prevalence can be attributed to methodological factors. Firstly, most studies have been small (n<100), and recruitment rates low, leading to possible selection bias of symptomatic cases (Wachter, Gündling *et al*. 2009; Kokshoorn, Smit *et al*. 2011). For the most part, subjects have been identified following neurosurgical admission to a tertiary hospital, and can be assumed to have sustained relatively severe TBI. Exceptions to this include two studies which recruited subjects from residential rehabilitation units (Lieberman, Oberoi *et al*. 2001; Berg, Oeffner *et al*. 2010) and one that identified subjects (with predominantly mild TBI) from an Emergency Department (Van der Eerden, Twickler *et al*. 2010). As would be anticipated at these extremes, the rate of hypopituitarism was far higher amongst the severe (rehabilitation unit) as compared with mild (emergency department) ends of the spectrum of TBI severity.

In addition, subject selection criteria for the majority of studies have included moderate-severe GCS scores. As discussed earlier, this is a crude assessment of cognitive status which does not take into account the nature of the head injury, or the structural TBI evident on MRI or CT. More consistent incidence reports would be expected if subjects were homogenously selected based upon the form of head injury and structural changes.

Furthermore, whilst most studies have performed a uniform laboratory assessment on all participants, some have excluded those who are judged asymptomatic (Leal-Cerro, Flores *et al*. 2005; Wachter, Gündling *et al*. 2009). Not surprisingly, gonadotropin deficiency (for which symptoms are easily identified), is reported to be far more common than GH deficiency (for which symptoms can be vague and ill-defined) in these studies (Leal-Cerro, Flores *et al*. 2005; Wachter, Gündling *et al*. 2009).

2.3.5.3. Pituitary tests

Further limitations to these studies are those that are inherent to pituitary tests. As discussed in section 2.1.3, the accurate diagnosis of GH and ACTH deficiency is challenging, and should be based on the careful interpretation of dynamic tests. Few studies have performed repeat assessments in subjects with abnormal results, although where this has been done a high proportion of subjects have later been re-classified as normal (Herrmann, Rehder *et al*. 2006; Klose, Juul *et al*. 2007; Van der Eerden, Twickler *et al*. 2010). Furthermore, studies that have assessed matched control groups have also reported a number of false positive results (falsely suggesting hypopituitarism) amongst control subjects (Kelly, Gonzalo *et al*. 2000; Klose, Juul *et al*. 2007).

Although almost all studies have used dynamic tests to assess GH secretory reserve, interpretation is complicated by the use of different stimuli and diagnostic cut-offs. Studies that have used weak stimuli (e.g. glucagon or GHRH-GHRP-6) report higher rates of deficiency as compared with strong stimuli (e.g. GHRH-arginine or the insulin tolerance test) (Agha, Phillips *et al*. 2005; Tanriverdi, Senyurek *et al*. 2006; Ho 2007; Kokshoorn, Wassenaar *et al*. 2010). Similarly, studies with stringent diagnostic criteria (i.e. a relatively low GH peak as the diagnostic cut-off) report lower rates of deficiency (Lieberman, Oberoi *et al*. 2001; Agha, Rogers *et al*. 2004). In addition, studies that have based the diagnosis on two (failed) tests report lower rates of deficiency than those which have relied upon one (Agha, Rogers *et al*. 2004; Herrmann, Rehder *et al*. 2006; Klose, Juul *et al*. 2007; Berg, Oeffner *et al*. 2010).

Furthermore, few studies have considered the confounding effect of BMI on GH concentrations. Almost all studies have reported that BMI is higher amongst GH deficient subjects (Corneli, Di Somma *et al*. 2005; Kokshoorn, Wassenaar *et al*. 2010). Despite this observation, a minority have applied BMI dependant cut-offs (Schneider, Schneider *et al*. 2006; Berg, Oeffner *et al*. 2010; Kokshoorn, Smit *et al*. 2011). One author noted that, without consideration of BMI, the number of subjects labelled as “GH deficient” would have been five-fold higher (Kokshoorn, Smit *et al*. 2011).

Thus, failure to account for BMI is likely to have contributed to the over-diagnosis of apparent GH deficiency.

Similarly, studies that have relied upon basal morning cortisol concentrations to diagnose ACTH deficiency report the highest, and most variable, rates (0-60%, depending on the cut-off selected; Bondanelli, De Marinis *et al*. 2004; Bushnik, Englander *et al*. 2007). Again, where dynamic tests have been used, the choice of stimuli impacts on reported prevalence, with higher rates reported for synacthen or glucagon, as compared with insulin (Kokshoorn, Wassenaar *et al*. 2010). Conversely, very low rates have been reported in studies that begin assessment with a screening basal cortisol, and apply dynamic tests to a minority (Wachter, Gündling *et al*. 2009; Berg, Oeffner *et al*. 2010).

The timing of pituitary assessments has also occurred at variable intervals following TBI. In general, studies that have included assessments performed within the first 6 months after injury, during the period when transient pituitary suppression may occur, report higher rates of hypopituitarism (Lieberman, Oberoi *et al*. 2001; Berg, Oeffner *et al*. 2010). The longitudinal course of apparent hypopituitarism following TBI is discussed in more detail in section 2.3.6.

Thus, although almost all studies have reported that hypopituitarism is common after TBI, the methods of pituitary assessment have almost certainly led to widespread over-reporting. More recent studies report lower rates of hypopituitarism (around 15%, as compared with >30%), which is likely to reflect more stringent diagnostic criteria and a greater likelihood that those labelled with hypopituitarism have true disease. In order to advance our understanding, future studies should apply rigorous assessment criteria, and report confirmatory follow-up for those diagnosed with hypopituitarism.

2.3.5.4. Prevalence of diabetes insipidus

Diabetes insipidus (DI) has a dramatic presentation, and is therefore unlikely to be missed in clinical practice. Most cases of post-traumatic DI are transient, due to inflammatory oedema rather than

denervation (Yuan and Wade 1991). DI is associated with severe injury, and carries a poor prognosis (Outwater and Rockoff 1984). Barzilay reported an incidence of 6% early DI amongst 300 children with severe brain injury, following which diagnosis the mortality for DI patients was >85% (Barzilay and Somekh 1988). DI is also a part of "Turner's triad" of clinical signs that brain death has occurred (Staworn, Lewison *et al*. 1994).

Although permanent DI is common amongst TBI case reports (Benvenga, Campenni *et al*. 2000), it is rare (2-4%) in systematic studies (Aimaretti, Ambrosio *et al*. 2004; Klose, Juul *et al*. 2007). Most studies have relied on a combination of symptom review and assessment of early morning paired samples of serum and urine osmolality. Only one study to date has used screening water deprivation tests, which offer a highly sensitive assessment of ADH sufficiency, on all subjects (Agha, Thornton *et al*. 2004). In this study, DI was relatively common (7%), although only 2% met diagnostic criteria for complete deficiency. Of note, all subjects with either partial or complete DI were identified on symptom review, and only those with complete deficiency were offered treatment. Furthermore, there was no association between DI, either transient or permanent, and anterior pituitary dysfunction. As a result, only anterior pituitary deficiencies will be discussed in the following section.

2.3.6. Longitudinal TBI data

Transient hypopituitarism may delay recovery from TBI, and a number of groups have sought to define the prevalence and natural history of hypopituitarism in the first year after TBI (see Table 2.7 overleaf). With the exception of two small paediatric studies (total n<50) (Einaudi, Matarazzo *et al*. 2006; Kaulfers, Backeljauw *et al*. 2010), all prospective data comes from adult TBI populations.

In general, pituitary dysfunction in the acute phase mirrors that seen in critical illness, and does not predict later deficiency. Recovery occurs throughout the first year, so that hormone levels are generally stable (either deficient or sufficient) by 6 months. However, the interpretation of longitudinal data is complicated by the use of different tests at various time-points and difficulty in

defining "normal" pituitary function during this period. As with the cross-sectional data, these factors are also likely to have lead to the over-diagnosis of hypopituitarism.

Table 2.7. Prospective studies of pituitary function after TBI.

Source	Subjects*	Interval	GH	LH, FSH	ACTH	TSH
Aimaretti, Ambrosio *et al*. 2005	100/70	3 months	23%	17%	9%	6%
		12 months	11%	20%	7%	6%
Agha, Phillips *et al*. 2005	50/48	Days 7-20	18%	80%	16%	2%
		6 months	13%	23%	20%	2%
		12 months	10%	13%	19%	2%
Schneider, Schneider *et al*. 2006	78/70	3 months	9%	32%	19%	8%
		12 months	10%	20%	9%	3%
Tanriverdi, Senyurek *et al*. 2006; Tanriverdi, Ulutabanca *et al*. 2008	52/51/30	Day 1	20%	42%	10%	6%
		12 months	43%	3%	20%	6%
		36 months	23%	0%	7%	0%
Klose, Juul *et al*. 2007	52/46	Days 0-12	*not tested*	67%	4%	33%
		12 months	11%	2%	7%	2%
†Einaudi and Bondone 2007	30/26/20	Days 1-3	0		0	23%
		6 months	0		5%	0
		12 months	5%		5%	0
†Kaulfers, Backeljauw *et al*. 2010	27/25/24/21	1-5 weeks	0		0	4%
		3 months	0		0	24%
		6 months	13%‡		0	46%‡
		12 months	5%‡		0	8%

*Number of subjects at each time point.
†Paediatric cohorts; note that gonadotropin deficiency is not included as subjects were largely prepubertal.
‡ In this study, the level of assessment varied over time. An additional nocturnal GH and TSH study were performed at the third visit, and a GH provocation test on the fourth.

2.3.6.1. Acute phase

In the first weeks after TBI, pituitary abnormalities follow the typical response to critical illness. This includes peripheral inactivation, with low levels of thyroid and gonadal hormones, plus hypersecretion of GH in the presence of low IGF-I, and an activated HPA axis (Van den Berghe, de Zegher *et al*. 1998). This phase may be followed by a period of more generalised pituitary suppression, a characteristic response to prolonged, severe illness (Adamo, Drazin *et al*. 2009).

Initial pituitary tests have been variably performed on days 1-20 following TBI. Testosterone concentrations are almost invariably low (up to 80% of cases), and inversely related to TBI severity (Agha, Phillips *et al*. 2005; Tanriverdi, Senyurek *et al*. 2006; Klose, Juul *et al*. 2007). Low concentrations of TSH and/or free T3 and T4 are also frequent (up to 33%) (Tanriverdi, Senyurek *et al*. 2006; Klose, Juul *et al*. 2007) but often resolve quickly (Agha, Phillips *et al*. 2005). Low IGF-I is common (Tanriverdi, Senyurek *et al*. 2006), as is GH suppression (Agha, Phillips *et al*. 2005). However, these changes tend to resolve over the first year and are poorly associated with chronic hypopituitarism (Tanriverdi, Senyurek *et al*. 2006). Thus, the initial pituitary response following severe TBI is likely to represent the general physiological response to critical illness.

HPA activation occurs as part of the adaptive stress response to TBI. As a result, cortisol concentrations are elevated in the first days to weeks after TBI, and correlate with greater injury severity (Klose, Juul *et al*. 2007). However, a variable degree of HPA activation, and decrease in cortisol binding globulin (CBG) (Hamrahian, Oseni *et al*. 2004), mean that the common definitions of adrenal insufficiency are not reliable (Klose, Juul *et al*. 2007). ACTH deficiency, and the inability to mount a stress response, can be life-threatening, so that the threshold for glucocorticoid replacement in this context is unclear (Cohan, Wang *et al*. 2005).

2.3.6.2. Recovery period

Over the first 6 months following TBI, there is a trend towards normalisation of pituitary function (Aimaretti, Ambrosio *et al*. 2005; Schneider, Schneider *et al*. 2006; Klose, Juul *et al*. 2007; Krahulik, Zapletalova *et al*. 2010). Isolated deficiency (especially involving GH or gonadotropins) often resolves, whereas deficiency in multiple hormones is more likely to persist (Aimaretti, Ambrosio *et al*. 2005). This suggests two different processes in play: the general response to critical illness (mimicking hypopituitarism) and genuine traumatic pituitary injury. In contrast, the onset of new deficiency after 3 to 6 months is rare, and may either represent evolving disease or false positive results.

Gonadal suppression is common and likely to normalise by one year (Agha, Phillips *et al*. 2005; Schneider, Schneider *et al*. 2006). Testosterone levels are inversely correlated with functional disability at all time points, and may therefore be viewed as an index of physical recovery (Klose, Juul *et al*. 2007). Although old age is reported as a risk factor for persistent suppression, it is likely that gonadotropin deficiency is over-diagnosed in older men (Agha, Phillips *et al*. 2005).

GH suppression is also relatively common in the months following TBI. Longitudinal studies have consistently demonstrated an increase in stimulated GH peak over the first year (Agha, Sherlock *et al*. 2005; Klose, Juul *et al*. 2007), and one small study reported further recovery between one and three years (Tanriverdi, Ulutabanca *et al*. 2008). New cases of GH deficiency appear rare after 6 months (Agha and Thompson 2006). In one report, persistent GH deficiency only occurred in overweight subjects aged >40 years, which may represent confounders as opposed to true cases (Schneider, Schneider *et al*. 2006).

Assessment of the HPA axis is complicated by the physiological transition from early activation to possible suppression. There appears little relationship between early cortisol levels and those at 6 to 12 months. Although some authors have reported that early ACTH deficiency is likely to persist, this

is not a consistent finding (Agha, Phillips *et al*. 2005; Schneider, Schneider *et al*. 2006; Klose, Juul *et al*. 2007). For example, in a study by Klose *et al*, mean stimulated cortisol levels were decreased 3 months after TBI, but at 6 months were equivalent to healthy controls (Klose, Juul *et al*. 2007). Therefore, it appears likely that many cases of presumed early ACTH deficiency are either due to transient suppression or false positive tests (suggesting disease in normal subjects).

Thyroid dysfunction is uncommon beyond the acute phase. TSH deficiency is usually seen alongside deficiency in multiple pituitary axes, and generally persists to 12 months. The reported prevalence of TSH deficiency is 2-8% at 3 months, (Agha, Phillips *et al*. 2005; Schneider, Schneider *et al*. 2006) and 2-6% at 12 months (Aimaretti, Ambrosio *et al*. 2005; Klose, Juul *et al*. 2007). In contrast to other hormone axes, TSH deficiency is uncommonly reported and more likely to represent true disease.

An important rationale for longitudinal TBI studies is to guide the optimal timing of pituitary assessment. Although early pituitary suppression is very common, it does not predict chronic hypopituitarism. It is also clear that screening for pituitary deficiency at 3 months would generate an unacceptably high number of false positive results. Conversely, new deficiencies are rare beyond 6 months, and deficiency that is present at 6 months is likely to persist. Therefore, screening for permanent pituitary deficiency should be deferred until at least 6 months.

Furthermore, the significance of transient pituitary suppression following TBI is unknown. Animal models suggest that GH deficiency may have a negative effect on early neuro-protective and repair processes. GH is a neuronal rescue factor for hypoxic-ischaemic brain injury, and IGF-I is involved in remyelination and oligodendrocyte protection (Ye and De Ercole 1999; Scheepens, Sirimanne *et al*. 2001). Therefore, transient GH suppression could be expected to impact TBI recovery, and this warrants further investigation.

2.3.7. Childhood TBI data

The few childhood TBI studies also describe a highly variable rate of hypopituitarism (5-61%) (Niederland, Makovi *et al*. 2007; Moon, Sutton *et al*. 2010). These studies have all been small, and include subjects aged from infancy to early adulthood. Due to the invasive nature of dynamic tests, childhood studies have placed a greater emphasis upon symptomatic screening. Importantly, no studies have provided follow-up data for those labelled with hypopituitarism.

As noted in the previous section, Einaudi *et al.* and Kaulfers *et al.* have both published small prospective TBI studies in children (Einaudi, Matarazzo *et al*. 2006; Kaulfers, Backeljauw *et al*. 2010). However, the total number of children assessed prospectively is small (n<50), and the data is difficult to interpret as the methods of assessment varied at different time points. For example, Kaulfers *et al.* performed additional overnight studies of GH and TSH at 6 months, with hypopituitarism defined as lower than expected hormone concentrations in any test performed (Kaulfers, Backeljauw *et al*. 2010). Not surprisingly, the rate of "deficiency" is also highest at 6 months, where it refers to a subnormal hormone either in the morning or overnight (see Table 2.7).

The reported prevalence of permanent hypopituitarism following childhood TBI is summarised in Table 2.8 overleaf. As with the adult literature, GH is the most commonly reported deficiency (0-42%; Niederland, Makovi *et al*. 2007; Moon, Sutton *et al*. 2010), followed by ACTH (0-34%; Kaulfers, Backeljauw *et al*. 2010; Moon, Sutton *et al*. 2010; Niederland, Makovi *et al*. 2007), and TSH (0-12%; Niederland, Makovi *et al*. 2007; Khadr, Crofton *et al*. 2010; Moon, Sutton *et al*. 2010). Gonadotropin status cannot be assessed amongst pre-pubertal subjects, however precocious puberty is reported in up to 14% (Kaulfers, Backeljauw *et al*. 2010). Overall, these studies have included three children known to have DI prior to assessment, (Poomthavorn, Maixner *et al*. 2008; Norwood, Deboer *et al*. 2010) and screening tests identified no new cases of DI.

Table 2.8 Prevalence of hypopituitarism in childhood TBI studies.

Source	Subjects *(n)*	% *(n)* pituitary deficiency	% *(n)* GH deficiency	% (n) ACTH deficiency	% *(n)* LH, FSH deficiency or PP*	% *(n)* TSH deficiency
Einaudi, Matarazzo *et al*. 2006	48	12 (6)	6 (3)	4 (2)	6 (3)	2 (1)
Niederland, Makovi *et al*. 2007	26	61 (16)	42 (11)	34 (9)	-	12 (3)
Poomthavorn, Maixner *et al*. 2008	54	17 (9)	7 (3)	11 (6)	6 (3)	6 (3)
Khadr, Crofton *et al*. 2010	33	39 (13)	21 (7)	24 (8)	0	0
Kaulfers, Backeljauw *et al*. 2010	21	28 (6)	5 (1)	0	14 (3)	10 (2)
Norwood, Deboer *et al*. 2010)	32	25 (8)	16 (5)	19 (6)	-	3 (1)
Moon, Sutton *et al*. 2010	20	5 (1)	0	0	5 (1)	0
% Total		**25%**	**13%**	**13%**	**6%**	**5%**
% Range		**5-61%**	**0-42%**	**0-34%**	**0-14%**	**0-12%**
n	**234**	**59**	**30**	**31**	**10**	**10**

*PP = precocious puberty

As outlined in Table 2.8, childhood TBI studies have been uniformly small, consisting of just 20-50 subjects. Further, the cohorts have included children of mixed ages (early infancy to late adolescence), with various injuries. Most have defined TBI in terms of GCS score, despite the limitations of childhood scores. Assessments have also been performed at variable intervals post injury (from 6 months to nearly 10 years). Small study size and the heterogeneous groups studied mean that this data cannot be used to predict the specific risk for defined patient groups.

It is difficult to recruit paediatric subjects into studies, and both parents and investigators seek to reduce invasive assessments. The largest childhood study to date (54 subjects), was made up of a combination of patients already known to have hypopituitarism, as well as TBI subjects screened for possible disease (Poomthavorn, Maixner *et al*. 2008). The latter were asked to complete a questionnaire, to which the response rate was <50%, and baseline blood tests were performed in

those with possible symptoms of hypopituitarism (<25% total). Similarly, in a UK study of children admitted to intensive care with TBI, <20% of eligible subjects were recruited (Moon, Sutton *et al*. 2010). Given that those with potential symptoms of hypopituitarism may be more motivated to take part, it is noteworthy that the authors reported a relatively low prevalence of hypopituitarism (5%).

As with the adult TBI studies, it is likely that GH deficiency has been widely over-reported. The best illustration of this is the study by Niederland *et al.*, who reported GH deficiency in 41% of subjects (Niederland, Makovi *et al*. 2007). Despite a mean interval of 3 years following TBI, there was no decrease in height SDS among those with apparent GH deficiency (Niederland, Makovi *et al*. 2007). In clinical practice, the diagnosis is made following observation of a period of poor growth. Studies that have performed GH tests on all subjects report the highest rates of deficiency (Niederland, Makovi *et al*. 2007; Khadr, Crofton *et al*. 2010; Norwood, Deboer *et al*. 2010). Conversely, the lowest rates are reported by studies that have used serial height assessments and IGF-I to select a group for subsequent assessment (Einaudi, Matarazzo *et al*. 2006; Poomthavorn, Maixner *et al*. 2008; Moon, Sutton *et al*. 2010).

As observed in the adult literature, there has been a lack of attention to possible confounders. Failed GH tests are particularly common among normal prepubertal and obese children (Marin, Domene *et al*. 1994; Stanley, Levitsky *et al*. 2009). Despite this, none of the childhood studies have used sex steroid priming in prepubertal subjects or interpreted GH tests with consideration of BMI. Furthermore, no studies have provided follow-up growth or treatment data for those labelled GH deficient. Similarly, studies that have relied on morning basal cortisol or relatively weak stimuli (e.g. glucagon) to assess the HPA axis report the highest rates of deficiency (Niederland, Makovi *et al*. 2007; Khadr, Crofton *et al*. 2010). As a result of the general limitations of pituitary tests, it is likely that both GH and ACTH deficiency have been over-reported.

Overall, although hypopituitarism is reported to be common following childhood TBI, the studies carry similar methodological weaknesses to the adult literature, and are considerably smaller. Thus, although pituitary dysfunction may carry a greater significance in childhood, the data should be interpreted with caution. In support of this, one author noted that, despite finding biochemical hypopituitarism in 25% of subjects, none of these cases were supported by clinical evidence of hypopituitarism (Khadr, Crofton *et al*. 2010). Furthermore, the risk within specific groups (e.g. adolescents, young children, abusive head injuries) has not been systematically addressed. Overall, the prevalence of hypopituitarism after childhood TBI is poorly described. Future studies should focus on specific groups, and include serial growth measurements to validate the diagnosis of GH deficiency.

2.3.8. Risk factors for hypopituitarism

Virtually all of the published studies evaluating pituitary function following TBI have concluded that pituitary hormone deficiency is a common occurrence; however the description of clinical risk factors has been far less uniform. In particular, although it is generally assumed that hypopituitarism is more likely to occur following severe TBI (as defined by GCS), this has not been consistently demonstrated.

As outlined in Table 2.9 overleaf, the majority of studies that have included subjects with a range of GCS scores have found no association between GCS category and hypopituitarism (Popovic, Pekic *et al*. 2004; Aimaretti, Ambrosio *et al*. 2005; Schneider, Schneider *et al*. 2006; Tanriverdi, Senyurek *et al*. 2006). It is possible that the relationship between GCS and hypopituitarism has been masked by low numbers of subjects with mild scores, as well as the over-diagnosis of hypopituitarism. In a recent meta-analysis, the prevalence of hypopituitarism amongst subjects with severe GCS scores was 35.5% (95% CI, 27.3-44.2%), as compared with 16.8% for TBI with a mild GCS score (95% CI, 10.9%-25.0%) (Schneider, Kreitschmann-Andermahr *et al*. 2007). However, the prevalence of hypopituitarism with moderate TBI was even lower than that for mild TBI (10.9%, 95% CI 5.1-21.8%).

The same author reported data from a large German clinical database of 825 TBI patients (Schneider, Schneider *et al*. 2011). Within this cohort, TBI patients with hypopituitarism had a lower GCS (mean GCS ± SD, no hypopituitarism 12.3 ± 2.7, single deficiency 7.5 +/- 4.9, multiple deficiencies 4 +/- 1.2, *p*=0.021). However, as discussed in section 2.3.5.1, endocrine investigations were performed at the discretion of the responsible clinician, rather than according to a uniform study protocol. Therefore, it is likely that patients with severe TBI underwent more endocrine tests and were subsequently more likely to be diagnosed with hypopituitarism.

Table 2.9. Association between GCS and hypopituitarism.

Source	Prevalence of hypopituitarism	% with GCS ≤12	GCS a risk factor	Other risk factors
Agha, Rogers *et al*. 2004	28.4%	100%	No	None
Bondanelli, De Marinis *et al*. 2004	54%	68%	Yes	Old age
Aimaretti, Ambrosio *et al*. 2005	35%	53%	No	None
Tanriverdi, Senyurek *et al*. 2006	50.9%	40%	No	None
Popovic, Pekic *et al*. 2004	34%	100%	No	Old age, high BMI, male gender
Schneider, Schneider *et al*. 2006	36%	"most"	No	Diffuse axonal injury, basal skull fracture, old age.
Klose, Juul *et al*. 2007	15%	58%	Yes	Raised ICP†, duration of ventilation and admission.

† ICP = intracranial pressure

Additional clinical factors with a reported association to hypopituitarism include raised intra-cranial pressure (*p*=0.03), longer duration of intubation (*p*=0·003) and longer hospital stay (*p*=0·004) (Klose, Juul *et al*. 2007). In Klose's study, the absence of the above risk factors was strongly predictive of no hypopituitarism (87-100%), although the positive predictive value was lower (7-50%; (Klose, Juul *et*

al. 2007). In addition, Schneider reported that both diffuse axonal injury and basal skull fracture were associated with hypopituitarism (beta co-efficients 2.8 and 2.2, respectively) (Schneider, Schneider *et al*. 2006). Autopsy data and Benvenga's large case series have similarly reported an increased prevalence of pituitary damage associated these injuries (Kornblum and Fisher 1969; Crompton 1971; Benvenga, Campenni *et al*. 2000).

Although the presence of DI is often assumed to increase the risk of anterior pituitary injury, Agha found no association between anterior pituitary deficiency and either transient or permanent DI (Agha, Thornton *et al*. 2004). As discussed earlier, a small study detected an association between anti-pituitary antibodies and hypopituitarism (13/29 subjects, odds ratio 2.3; (Tanriverdi, De Bellis *et al*. 2008). However, this assessment was performed three years following TBI, and the value of antibodies as an index of risk would be dependent on how early these appear.

Most TBI studies have based structural injury descriptions on CT scans, although MRI provides a far better image of the pituitary gland. As described in 2.3.3, pituitary enlargement is common in the early period following severe TBI (Maiya, Newcombe *et al.* 2008). To date, just two TBI studies have included routine MRI scans as part of the pituitary assessment protocol, and both reported a significantly increased rate of pituitary imaging abnormalities associated with hypopituitarism (Schneider, Samann *et al*. 2007; Krahulik, Zapletalova *et al*. 2010). In one, MRI scans performed 12 months after injury demonstrated volume loss in 78% of those with major pituitary deficits, as compared with 20% in those without (p=0.016) (Krahulik, Zapletalova *et al*. 2010).

TBI is a very common problem, and identifying risk factors for hypopituitarism would allow targeted assessment. However, GCS is likely to be a relatively indirect measure of pituitary injury. It is unclear whether certain groups, such as young children, or specific injuries, such as motor vehicle accidents, place patients at greater risk. Pituitary MRI scans (to assess early swelling) and the measurement of

anti-pituitary antibodies are both potentially useful predictive tools, and more work is needed to establish their value.

2.3.9. Data from clinical practice

Although GH deficiency is commonly reported in TBI studies, TBI is a rarely identified cause of GH deficiency in clinical practice. For example, in the Pfizer International Growth (KIGS) Database, TBI accounts for just 141 of 62,000 cases of GH deficiency registered over 20 years (McDonald, Lindell *et al*. 2008). Similarly, a 2005 review of the Pfizer International Metabolic (KIMS) database of adult GH deficiency identified just 51 of 8,500 cases caused by TBI (Casanueva, Leal *et al*. 2005). This suggests that clinically significant GH deficiency caused by TBI is either rare or hugely under-recognised.

In the absence of screening, the diagnosis of hypopituitarism is dependent on clinical suspicion. However, it appears that growth receives little attention during TBI follow-up. Moon *et al.* reported that height and weight were documented in just 33% of attendances, and serial growth measurements available in just 17% of children seen in specialty clinics following severe TBI (Moon, Wilson *et al*. 2009). Furthermore, TBI patients in the KIMS database showed a significant delay in treatment as compared with patients presenting with pituitary adenomas (10.8 ± 1.5 years for TBI, compared with 6.9 ± 0.2 years for pituitary adenomas, $p<0.2$) (Casanueva, Leal *et al*. 2005). Therefore, it is conceivable that hypopituitarism is often overlooked in the care of head-injured patients.

2.3.10. Assessment guidelines

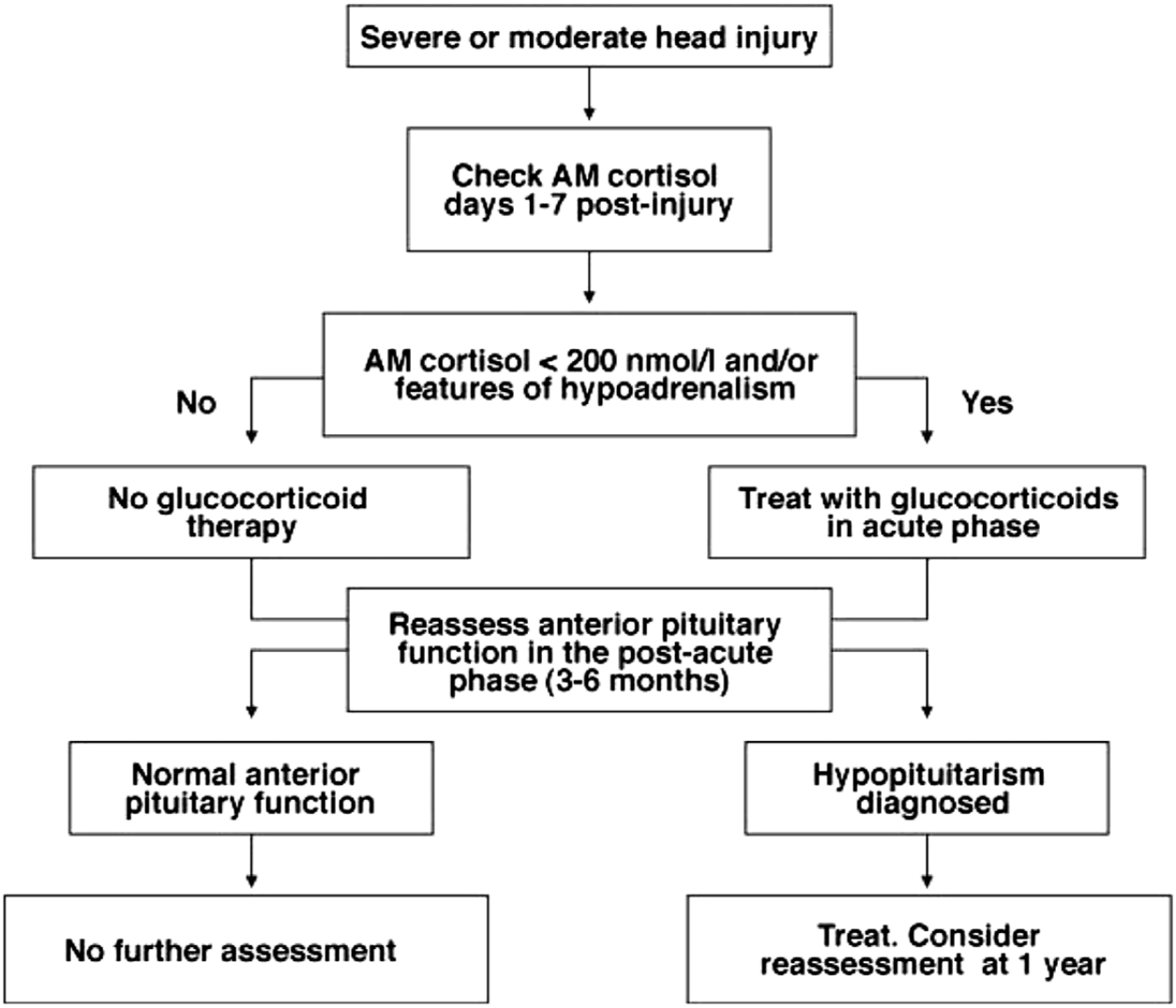
In response to the data presented, a number of expert groups now recommend routine pituitary screening following TBI (Casanueva, Ghigo *et al*. 2004; Ghigo, Masel *et al*. 2005; Schneider, Stalla *et al*. 2006). The assumption behind these recommendations is that hypopituitarism is a common, under-diagnosed problem that contributes to morbidity following TBI. However, given the current level of evidence, the value of such screening programmes is controversial. As outlined within this

literature review, major limitations include the wide variation in reported prevalence amongst systematic studies, the potential for over-diagnosis, uncertainty about the natural history of hypopituitarism, and our inability to identify high risk cases.

To date, all consensus statements have limited their recommendations to moderate to severe TBI (GCS ≤12) (Ghigo, Masel *et al*. 2005; Schneider, Stalla *et al*. 2006). This is likely to be a pragmatic consideration given the very high incidence of mild TBI; however, it is important to recognise that GCS is a weak indicator of risk. In recognition of this, Tanriverdi *et al.* suggested that assessment be considered in all TBI patients with loss of consciousness, >24 hours hospital admission, or an abnormal CT head scan (Tanriverdi, Unluhizarci *et al*. 2010). Others have proposed that all patients with posterior pituitary dysfunction be assessed (Schneider, Stalla *et al*. 2006; Corneli, Ghigo *et al*. 2007). However, none of these should be considered evidence based recommendations.

The next important question is how and when screening should be performed; a frequently-cited algorithm is shown in Figure 2.3. Most authors recommend that several basal assessments of pituitary function be performed over the first year following TBI. Although critical illness strongly limits the interpretation of early tests (Van den Berghe, de Zegher *et al*. 1998), basal serum cortisol ± thyroid function are recommended in the first week after injury (Agha and Thompson 2006; Hannon, Sherlock *et al*. ; Rose and Auble 2011). Further assessments are recommended at 3 months and 9-12 months post injury, starting with basal tests and moving to confirmatory dynamic tests for potential GH and ACTH deficiency (Casanueva, Ghigo *et al*. 2004; Ghigo, Masel *et al*. 2005; Schneider, Stalla *et al*. 2006). However, it is likely that screening programmes such as these would lead to the systematic over-diagnosis of hypopituitarism.

Figure 2.3. Suggested algorithm for pituitary assessment following moderate-severe traumatic brain injury. Reproduced with permission (Agha, Phillips *et al*. 2005).



Despite the paucity of paediatric data, screening recommendations have been extrapolated to childhood TBI (Acerini and Tasker 2007; Rose and Auble 2011). Limited data suggests a similar prevalence of hypopituitarism following childhood TBI. Furthermore, as hypopituitarism impacts growth, puberty and neuro-cognitive development, unrecognised hormone deficiency is likely to carry a greater significance during childhood. Childhood recommendations parallel those made for adult populations over the first year following TBI, with the additional proviso that growth and puberty should be monitored (Acerini and Tasker 2007; Rose and Auble 2011).

2.4. Summary and structure of this thesis

As outlined in this literature review, TBI is a very common childhood event, yet the risk of hypopituitarism is poorly defined. Unrecognised hypopituitarism during childhood would be anticipated to delay recovery from TBI, and impair normal childhood growth and development. Furthermore, given the relatively large head and weak neck of an infant, susceptibility to pituitary injury may be greater during early childhood. However, childhood TBI studies have been very small, and subject to methodological limitations. This is data should be interpreted with caution, as it is likely that the prevalence of hypopituitarism has been routinely over-estimated. Therefore, robust data based on rigorous diagnostic criteria are needed in order to define the frequency of TBI-induced hypopituitarism in childhood.

Central to this thesis is a large clinical study which aimed to assess the prevalence of permanent hypopituitarism following structural TBI in early childhood. An intended high risk sub-group was included; children who had suffered inflicted TBI. In addition, TBI was defined in structural rather than functional terms, proposed to be a more direct marker of injury severity in young children. Importantly, hypopituitarism was diagnosed using comprehensive and rigorous diagnostic criteria, with critical evaluation of potentially abnormal results. This study is the first to focus on a narrow age range, and specific insults (e.g. head shaking). Inflicted TBI was predicted to be an important unrecognised cause of acquired hypopituitarism.

This thesis is submitted with publications, and the following Results chapters are based on a series of manuscripts that have emerged from this work. These include an expert commentary, the overall results of the early childhood TBI and hypopituitarism study, an analysis of differences in “stress response” between inflicted and accidental injury groups, and of the predictive value of GCS scores in early childhood TBI.

Chapter 3. Traumatic brain injury: Is the pituitary out of harm's way?

3.1. Preface

As discussed in the previous chapter, there is increasing support for routine pituitary investigation following TBI. This chapter contains an expert commentary on the risk of hypopituitarism following childhood TBI, provides insight into the controversies and apparently contradictory results, and presents the various options available to paediatricians.

The following section contains an unaltered reproduction of the article “Traumatic brain injury: is the pituitary out of harm's way?” published in the *Journal of Paediatrics*, October 2011, volume 159(4), pages 686-690. This article has been reproduced with the permission of Elsevier, 2012. The *Journal of Pediatrics* was ranked 3rd of 107 Paediatric journals in the 2010 citation reports, and has a five year impact factor of 4.2.

Traumatic Brain Injury: Is the Pituitary Out of Harm's Way?

Natasha Heather, MBChB and Wayne Cutfield, MD, MBChB

Childhood traumatic brain injury (TBI) is a significant public health problem with potentially devastating consequences for the individual. Hypopituitarism after TBI has received increasing attention in the past decade. Once considered rare, it is now thought to be a major cause of treatable morbidity in TBI survivors. One review reported that subclinical hypopituitarism will develop in over 25% of adults who sustain TBI.[1] Limited data suggest a similar risk in childhood, which would make TBI by far the most common cause of pediatric hypopituitarism.[2,3] However, this does not match the small numbers of children with head injuries treated in endocrine clinics. The mismatch between the proposed incidence and the realities of clinical practice make this an area of uncertainty. Are we failing to identify large numbers of head-injured children with hypopituitarism or have the data been misinterpreted?

Although growth hormone (GH) is the most commonly affected hormone in TBI studies, head trauma is rarely identified as the cause of GH deficiency. TBI accounts for just 141 of the 62 000 cases registered in 20 years in the Pfizer International Growth Database.[4] This suggests that clinically significant GH deficiency caused by TBI is either rare or hugely under-recognized in childhood. Thus, awareness of the potential association between TBI and hypopituitarism raises a number of important questions, which we address in this commentary.

How Common is Pediatric TBI?

TBI is a common event in childhood, but it is under-reported in retrospective cross-sectional studies of hospital admissions. Prospective whole population studies demonstrate that the incidence of TBI is 10-fold higher than normally assumed. Although the minimum threshold of TBI is well-defined,[5] it is not easily applied to epidemiological studies.

Because most TBI cases are mild and not seen in the hospital,[6] TBI data that are based on admissions provide highly conservative estimates. The childhood incidence of hospital admission with TBI is reported as 100 to 300 per 100 000 per year,[7,8] depending on case definition and the age range considered. Additional factors such as TBI occurring outside the studied geographic region, variations in hospital coding, and lost notes may also contribute to under-reporting.

ACTH	Adrenocorticotropin
BMI	Body mass index
GCS	Glasgow Coma Scale
GH	Growth hormone
MRI	Magnetic resonance imaging
TBI	Traumatic brain injury

The Christchurch Birth Cohort Study was both prospective and population-based and offers unique insight into childhood TBI; 97% of children born within the region in 1977 were enrolled, and complete data at age 25 years were available for approximately 80% of the original cohort.[9] Minimum case definition of TBI was a blow to the head for which medical attention was sought and a diagnosis of concussion given. Events were identified through regular interviews and verified from medical records, but because the term "concussion" is loosely used by physicians and the public,[10] it is possible that such events might have been over-reported. Overall incidence was 10-fold higher than studies that have looked only at hospital admissions. By 25 years of age, a third of the population had experienced at least one TBI, and a third of these had sustained multiple events, with 10% of injuries being classified as moderate or severe.[9]

How Does TBI Grading Relate to Pituitary Function?

TBI is a heterogeneous condition, and current methods of grading are poorly predictive of possible effects on pituitary function. The Glasgow Coma Scale (GCS), for example, assesses higher cerebral function, but is likely to be a crude proxy for structural pituitary damage.

The GCS provides a functional assessment of level of consciousness after TBI and is widely used to classify TBI severity[11] despite important limitations. In particular, the increasing use of pre-hospital intubation and paralyzing or sedating agents limit the accuracy of scores.[12] The time between injury and GCS grading is highly variable, and interobserver reliability is weak.[13] Furthermore, GCS is poorly applicable to young pre-verbal children.[14] As a result of these limitations, a variety of specific pediatric scales have been proposed, but none have achieved widespread acceptance.

Alternatively, imaging studies allow structural classification of TBI and may be better predictors of possible pituitary damage. Magnetic resonance imaging (MRI) is the gold standard for pituitary imaging, but computerized tomography scans are more frequently used acutely. Trauma grading systems include the Marshall[15] and Abbreviated Injury Scores.[16] In addition, individual anatomical markers, such as the presence of intra-cranial hemorrhage, may be useful predictive tools. Ultimately, specific techniques to identify pituitary injury should be better predictors of hypopituitarism than

From the Liggins Institute, University of Auckland, Auckland, New Zealand

The authors declare no conflicts of interest.

0022-3476/$ - see front matter. Copyright © 2011 Mosby Inc.
All rights reserved. 10.1016/j.jpeds.2011.05.054

measures of cortical injury, which are reflected in current methods to assess TBI.

Is All Pediatric TBI the Same?

The rate and causes of childhood TBI vary considerably with age and population-specific features. Of particular note is the high rate of TBI in late adolescence and abusive head trauma in infancy.

Teenagers aged 15 to 20 years are at the highest risk of TBI and have double the incidence of TBI of children aged 5 to 10 years.[9] Falls, being struck by objects, and pedestrian road accidents are the most common causes of TBI in children younger than 14 years. Between 15 and 25 years of age, the most frequent causes of TBI are contact sports, motor vehicle accidents, and assaults.[9] Male individuals have higher TBI rates at all ages.[7,9]

Abusive head trauma in infancy is a particularly severe form of TBI. Infants have relatively large heads, weak necks, and thin skulls and therefore are particularly vulnerable to the effects of acceleration-deceleration and impact forces. Incidence is likely to be grossly under-reported, and it has been conservatively estimated at 15 to 25 per 100 000 per year.[17,18] Inflicted TBI occurs in young infants, with a median age of 2.2 months.[17] The frequency of abusive head trauma is greatest in low socioeconomic groups and minority populations.[18,19]

Is Hypopituitarism Common after TBI?

There is little doubt that hypopituitarism can follow TBI, which is invariably defined with the GCS; the issue is how commonly it occurs. The literature on case reports linking TBI to clinical hypopituitarism creates the impression of high incidence. Evidence for a high rate of subclinical hypopituitarism comes from cross-sectional studies[20-26] and a small number of prospective studies,[27-31] which indicate somewhat variable rates.

After early reports,[32] post-traumatic hypopituitarism received little attention until the last decade. Benvenga et al summarized the literature on post-traumatic hypopituitarism, locating a total of 367 cases reported individually or in small series.[33] Extensive delay in diagnosis was a common feature, suggesting that physicians did not anticipate pituitary disease after head injury.

Studies in the last decade report that subclinical pituitary deficiency is common after TBI.[23,25] However, individual studies report highly variable rates with very different implications. Schneider et al collated data from 10 systematic studies published from 2000 to 2007, including 809 adult subjects in the chronic phase after TBI.[1] The overall prevalence of deficiency in one or more pituitary hormone was 27.5%, but for individual studies this ranged from 15% to 50%.[27,34] Most subjects were deficient in a single axis, most commonly GH (prevalence of 6%-33%).[1] Deficiencies in gonadotropins (2%-20%), adrenocorticotropin (ACTH, 0-19%) and thyrotropin (1%-10%) were also frequently but inconsistently reported, as was hyperprolactinameia (0-10%).[1] There are very little data on posterior pituitary dysfunction, but Agha et al reported 7% diabetes insipidus (2% complete, 5% partial) in the chronic phase after TBI.[35]

A similarly high frequency has been described in the existing pediatric studies.[36-42] The overall rate is approximately 20%, but varies widely (5%-61%; Table). One study noted that despite a 25% prevalence of biochemical abnormalities, there was no definite endocrine disease.[40] Again, GH is the most commonly reported deficiency (0-42%), followed by ACTH (0-34%) and thyrotropin (0-8%).[36-42] Gonadotropin status is difficult to assess in cross-sectional pediatric studies, but precocious puberty has been reported in as

Table. Pediatric studies assessing the frequency of pituitary dysfunction after TBI

Source	Study design	Total * (%)	GHD (%)	Definition of GHD	ACTH deficient (%)	Definition of ACTH deficiency	Other axes affected (%)
Einaudi et al, 2006[39]	48 subjects, 22 cross-sectional, 26 prospective	12	6	Low HV and IGF-1, GHRH-arginine, peak GH <20 μg/L	4	Basal cortisol low, GST peak <460 nmol/L	4
Niederland, 2007[38]	26 subjects, cross-sectional	61	42	L-Dopa plus ITT, peak GH <7 μg/L	34	Low basal cortisol (level not given)	12
Poomthavorn, 2008[37]	54 subjects, cross-sectional	17	7	Low HV and IGF-1, GST peak GH <10 mU/L	11	GST or LD-SST, cortisol <450 nmol/L	9
Khadr, 2010[40]	33 subjects, cross-sectional	39	21	ITT or GST, peak GH <5 μg/L	24	ITT or GST, cortisol <470-550 nmol/L	3
Kaulfers, 2010[36]	21 subjects, prospective	29	5	Overnight spontaneous GH <2 SDS, arginine-clonidine <10 μg/L	0	LD-SST, cortisol <410 nmol/L	24
Norwood, 2010[41]	32 subjects, cross-sectional	25	16	Overnight peak GH <5 μg/L, arginine-clonidine <5-7 μg/L	19	0800 basal cortisol <130 nmol/L	6
Moon, 2010[42]	20 subjects, cross-sectional	5	0	Low IGF-1 and height or HV SDS, dynamic test when indicated	0	Low basal cortisol; <85-140 nmol/L (p.m. and a.m. limits)	5
Total	234	5%-61%	0-42%		0-34%		3%-24%

GHD, growth hormone deficiency; *IGF-1,* insulin-like growth factor 1; *HV,* height velocity; *GHRH,* growth hormone-releasing hormone; *GST,* glucagon stimulation test; *ITT,* insulin tolerance test; *LD-SST,* low-dose (1μg) synacthen test.
Cortisol levels have been converted from conventional (ng/dL) to SI units (nmol/L) using a factor of 25.6.
*Overall percentage of subjects with at least one abnormal pituitary axis, including precocious puberty.

many as 12% of cases.[36] The dramatic symptoms of diabetes insipidus are the likely explanation as to why no new such cases have been uncovered with childhood TBI studies.

The time course of post-traumatic hypopituitarism is also poorly understood. Longitudinal studies have observed subjects for 6 to 12 months after TBI[27,29,30,43] and more recently as long as 3 years.[28] Overall, early abnormalities are common, and a large proportion of the subjects will recover completely by 3 to 6 months.[44] The significance of transient deficiencies is unclear, but they could be expected to impact on recovery from TBI. New pituitary deficiencies are uncommon after 6 months.[27,29-31] Although hypopituitarism at 6 to 12 months was considered likely to persist,[31] a recent study reported recovery in approximately half of subjects with pituitary deficiencies between 1 and 3 years after TBI.[28]

What are the Mechanisms that Lead to Hypopituitarism?

The mechanism of pituitary injury has not been clearly established, although vascular and traumatic hypotheses have been proposed.[45] Large post-mortem series demonstrate that hypothalamo-pituitary damage is common after fatal TBI,[46,47] and small MRI series document pituitary changes in survivors.[48-51]

The anatomy of the pituitary gland makes it particularly vulnerable to vascular injury. The gland is suspended on a stalk within the third ventricle and potentially mobile. Long hypophyseal vessels travel down the stalk and supply the anterior pituitary via a latticework of portal vessels. These small perforating vessels are vulnerable to shearing injury from sudden acceleration-deceleration forces. The pattern of anterior pituitary infarction, seen in as many as a third of fatal head injuries, corresponds to areas supplied by portal vessels.[45,46] Pituitary enlargement (edema) is seen on MRI in the first week after TBI, providing further support for a vascular mechanism of injury,[49] as do chronic changes such as atrophy and perfusion defects.[48]

Direct mechanical trauma, either at the level of the hypothalamus or pituitary, is another potential mechanism. The pituitary is cushioned by cerebrospinal fluid and cerebral tissue and relatively protected from direct trauma. However, both pituitary and hypothalamic lesions can be associated with basal skull fractures,[50,52] which are likely to reflect greater forces at impact. Post-mortem series report a high incidence of hypothalamic lesions after TBI.[46,50]

A small study has reported that anti-pituitary antibodies are common after TBI and associated with hypopituitarism.[53] The autoimmune response is almost certainly a marker of damage, as opposed to a direct pathogenic mechanism. More work is needed to establish the value of this potentially predictive tool.

Why is the Reported Prevalence of Hypopituitarism Variable?

The rate of reported hypopituitarism varies dramatically, and it is likely that the true burden of disease has been overestimated. Information has come from small cross-sectional studies, composed of highly selected populations who have undergone non-standardized assessments. The variability in reported rates of GH and ACTH deficiencies illustrates the challenges in interpreting pituitary hormone assessments. Many subtle and borderline deficiencies have been reported without confirmatory follow-up and may not represent clinically significant disease.

Individual TBI studies are generally small, with <100 subjects. Pediatric TBI studies are particularly small, usually consisting of 20 to 50 subjects of various ages from infancy to early adulthood, although injury types and potential vulnerability may differ considerably. Subjects are recruited from highly select patient groups, including rehabilitation units, tertiary intensive care units, and neurosurgical wards. Most subjects have moderate or severe TBI according to GCS, although this may not be the most meaningful selection criteria. In addition, most studies are cross-sectional and have low recruitment rates, with subjects assessed 6 months to many years after injury.[37,40,42]

Endocrine assessment protocols are also highly variable. The diagnosis of childhood GH deficiency should be based on the assessment of growth and supplemented with laboratory tests.[54] However, some pediatric TBI studies diagnose GH deficiency solely on the basis of low stimulated GH levels and these groups of children are no shorter than those with normal GH responses.[38,40] Furthermore, in studies that restrict GH tests to children who are growing poorly (height velocity <25th percentile) or with low insulin-like growth factor 1, rates of hypopituitarism are much lower.[37,39,42]

Provocative GH tests have limited ability to differentiate between mild deficiency and normally growing children, and demonstrate low repeatability[55,56] with a high rate of false-positive results.[57,58] Arbitrary diagnostic cutoff points are used and, as expected, GH deficiency is reported as more prevalent in TBI studies that use higher GH cutoffs.[59] Many combinations of stimuli can be used and TBI studies that use weaker stimuli or only one agent report increased prevalence.[59]

Both body mass index (BMI) and pubertal status affect GH release and therefore may confound GH tests. Obesity is a common problem after TBI, and TBI subjects who fail GH tests have higher BMI than subjects who pass.[59] Few studies use BMI-adjusted reference values.[60] GH testing is difficult in early puberty, because as many as 75% of normally growing early pubertal subjects can be expected to fail unprimed tests.[57] This is likely to contribute to the high rate of GH deficiency reported by some pediatric studies.[38,40] Sex steroid priming is widely used in clinical practice to counter this effect, but has not been used in childhood TBI studies.

ACTH reserve is assessed with a variety of methods, many of which are recognized to overestimate disease. Studies that base diagnosis on a single low cortisol measurement report the highest and most variable rates of deficiency.[59] Some studies perform dynamic tests on all subjects, and other studies limit tests to subjects with low basal cortisol levels; different stimuli are used, and normal responses are defined variably.[59] Glucagon stimulation and low-dose synthetic

ACTH tests in particular, are recognized to have high false-positive rates and should be followed by confirmatory tests.[61,62]

Should Children Undergo Endocrine Evaluation after TBI?

On balance, the evidence does not support routine evaluation of pituitary function in children after TBI. Pituitary assessments are invasive and expensive. In our unit, laboratory evaluation of pituitary hormones (including provocative tests for GH and ACTH) costs approximately €340 (US $475). As discussed, pituitary tests can be difficult to interpret and will report a large proportion of false-positive results. This would lead to significant anxiety in a vulnerable group and ongoing costs of follow-up and re-testing. Thus, comprehensive endocrine assessment should be reserved for children with poor growth or other symptoms suggestive of hypopituitarism.

As GH is the most commonly reported deficiency, a reasonable alternative would be to measure growth routinely after TBI. Height, weight, and pubertal status should be assessed, and height velocity formally calculated and plotted on an appropriate growth chart. This could be done by family doctors or as part of existing hospital outpatient care. Currently, it appears that growth receives little attention during TBI follow-up. Moon et al reported that height and weight were documented in just 33% of attendances, and serial growth measurements available in just 17% of children seen in specialty clinics after severe TBI.[63]

It appears that the incidence of post-traumatic hypopituitarism is associated with TBI has been over-stated. Large prospective studies with rigorous diagnostic criteria are needed to inform clinical practice. We have yet to identify high-risk groups and strong predictive factors, but pituitary swelling on MRI or levels of anti-pituitary antibodies may provide better early assessment of risk than GCS. Transient GH deficiency may have a role in post-concussion syndrome, and this would be another interesting avenue to explore in prospective studies. ■

We thank José Derraik and Paul Hofman (University of Auckland), and Craig Jefferies (Auckland District Health Board) for valuable assistance with this manuscript.

Submitted for publication Mar 29, 2011; last revision received Apr 22, 2011; accepted May 31, 2011.

Reprint requests: Wayne Cutfield, MD, MBChB, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand. E-mail: w.cutfield@auckland.ac.nz

References

1. Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A. Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. JAMA 2007; 298:1429-38.
2. Vimpani GV, Vimpani AF, Lidgard GP, Cameron EHD, Farquhar JW. Prevalence of severe growth hormone deficiency. Br Med J 1977;2:427.
3. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M. Utah growth study: growth standards and the prevalence of growth hormone deficiency. J Pediatr 1994;125:29-35.
4. McDonald A, Lindell M, Dunger DB, Acerini CL. Traumatic brain injury is a rarely reported cause of growth hormone deficiency. J Pediatr 2008; 152:590-3.
5. Kay T, Harrington D, Adams R, Anderson T, Berrol S, Cicerone K, et al. Definition of mild traumatic brain injury. J Head Trauma Rehabil 1993; 8:86-7.
6. Corrigan JD, Selassie AW, Orman JA. The epidemiology of traumatic brain injury. J Head Trauma Rehabil 2010;25:72-80.
7. Kraus JF, Rock A, Hemyari P. Brain injuries among infants, children, adolescents, and young adults. Am J Dis Child 1990;144:684-91.
8. Hawley CA, Ward AB, Long J, Owen DW, Magnay AR. Prevalence of traumatic brain injury amongst children admitted to hospital in one health district: a population-based study. Injury 2003;34:256-60.
9. McKinlay A, Grace RC, Horwood LJ, Fergusson DM, Ridder EM, MacFarlane MR. Prevalence of traumatic brain injury among children, adolescents and young adults: prospective evidence from a birth cohort. Brain Inj 2008;22:175-81.
10. Ropper AH, Gorson KC. Concussion. N Engl J Med 2007;356:166-74.
11. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81-4.
12. Marion DW, Carlier PM. Problems with initial Glasgow Coma Scale assessment caused by prehospital treatment of patients with head injuries: results of a national survey. J Trauma 1994;36:89-95.
13. Gill MR, Reiley DG, Green SM. Interrater reliability of Glasgow Coma Scale scores in the emergency department. Ann Emerg Med 2004;43:215-23.
14. Simpson DA, Cockington RA, Hanieh A, Raftos J, Reilly PL. Head injuries in infants and young children: the value of the Paediatric Coma Scale. Review of literature and report on a study. Childs Nerv Syst 1991;7:183-90.
15. Marshall LF, Marshall SB, Klauber MR, Clark MB, Eisenberg HM, Jane JA, et al. A new classification of head injury based on computerized tomography. J Neurosurg 1991;75:S14-20.
16. Baker SP, O'Neill B, Haddon W Jr., Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974;14:187-96.
17. Barlow KM, Minns RA. Annual incidence of shaken impact syndrome in young children. Lancet 2000;356:1571-2.
18. Kelly P, Hayes I. Infantile subdural haematoma in Auckland, New Zealand: 1988-1998. N Z Med J 2004;117:U1047.
19. Harper CG, Doyle D, Adams JH, Graham DI. Analysis of abnormalities in pituitary gland in non-missile head injury: study of 100 consecutive cases. J Clin Pathol 1986;39:769-73.
20. Kelly DF, Gonzalo IT, Cohan P. Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid haemorrhage: a preliminary report. J Neurosurg 2000;93:743-52.
21. Lieberman SA, Oberoi AL, Gilkinson CR, Masel BE, Urban RJ. Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. J Clin Endocrinol Metab 2001;86:2752-6.
22. Bondanelli M, De Marinis L, Ambrosio MR, Monesi M, Valle D, Zatelli MC, et al. Occurrence of pituitary dysfunction following traumatic brain injury. J Neurotrauma 2004;21:685-96.
23. Agha A, Rogers B, Sherlock M, O'Kelly P, Tormey W, Phillips J, et al. Anterior pituitary dysfunction in survivors of traumatic brain injury. J Clin Endocrinol Metab 2004;89:4929-36.
24. Popovic V, Pekic S, Pavlovic D, Maric N, Jasovic-Gasic M, Djurovic B, et al. Hypopituitarism as a consequence of traumatic brain injury (TBI) and its possible relation with cognitive disabilities and mental distress. J Endocrinol Invest 2004;27:1048-54.
25. Leal-Cerro A, Flores JM, Rincon M, Murillo F, Pujol M, Garcia-Pesquera F, et al. Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury. Clin Endocrinol 2005;62:525-32.
26. Herrmann BL, Rehder J, Kahlke S, Wiedemayer H, Doerfler A, Ischebeck W, et al. Hypopituitarism following severe traumatic brain injury. Exp Clin Endocrinol Diabetes 2006;114:316-21.

27. Tanriverdi F, Senyurek H, Unluhizarci K, Selcuklu A, Casanueva FF, Kelestimur F. High risk of hypopituitarism after traumatic brain injury: a prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma. J Clin Endocrinol Metab 2006;91:2105-11.
28. Tanriverdi F, Ulutabanca H, Unluhizarci K, Selcuklu A, Casanueva FF, Kelestimur F. Three years prospective investigation of anterior pituitary function after traumatic brain injury: a pilot study. Clin Endocrinol 2008;68:573-9.
29. Schneider HJ, Schneider M, Saller B, Petersenn S, Uhr M, Husemann B, et al. Prevalence of anterior pituitary insufficiency 3 and 12 months after traumatic brain injury. Eur J Endocrinol 2006;154:259-65.
30. Aimaretti G, Ambrosio MR, Di Somma C, Gasperi M, Cannavo S, Scaroni C, et al. Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12-month study. J Clin Endocrinol Metab 2005;90:6085-92.
31. Agha A, Phillips J, O'Kelly P, Tormey W, Thompson CJ. The natural history of post-traumatic hypopituitarism: implications for assessment and treatment. Am J Med 2005;118:1416.
32. Cryan E. Pituitary damage due to skull base fracture. Dtsch Med Wochenschr 1918;44:1261.
33. Benvenga S, Campenni A, Ruggeri RM, Trimarchi F. Clinical review 113: hypopituitarism secondary to head trauma. J Clin Endocrinol Metab 2000;85:1353-61.
34. Klose M, Juul A, Poulsgaard L, Kosteljanetz M, Brennum J, Feldt-Rasmussen U. Prevalence and predictive factors of post-traumatic hypopituitarism. Clin Endocrinol 2007;67:193-201.
35. Agha A, Thornton E, O'Kelly P, Tormey W, Phillips J, Thompson CJ. Posterior pituitary dysfunction after traumatic brain injury. J Clin Endocrinol Metab 2004;89:5987-92.
36. Kaulfers A-MD, Backeljauw PF, Reifschneider K, Blum S, Michaud L, Weiss M, et al. Endocrine dysfunction following traumatic brain injury in children. J Pediatr 2010;157:894-9.
37. Poomthavorn P, Maixner W, Zacharin M. Pituitary function in paediatric survivors of severe traumatic brain injury. Arch Dis Child 2008;93:133-7.
38. Niederland T, Makovi H, Gal V, Andreka B, Abraham CS, Kovacs J. Abnormalities of pituitary function after traumatic brain injury in children. J Neurotrauma 2007;24:119-27.
39. Einaudi S, Matarazzo P, Peretta P, Grossetti R, Giordano F, Altare F, et al. Hypothalamo-hypophysial dysfunction after traumatic brain injury in children and adolescents: a preliminary retrospective and prospective study. J Pediatr Endocrinol Metab 2006;19:691-703.
40. Khadr SN, Crofton PM, Jones PA, Wardhaugh B, Roach J, Drake AJ, et al. Evaluation of pituitary function after traumatic brain injury in childhood. Clin Endocrinol 2010;73:637-43.
41. Norwood KW, Deboer MD, Gurka MJ, Kuperminc MN, Rogol AD, Blackman JA, et al. Traumatic brain injury in children and adolescents: surveillance for pituitary dysfunction. Clin Pediatr 2010;49:1044-9.
42. Moon RJ, Sutton T, Wilson PM, Kirkham FJ, Davies JH. Pituitary function at long-term follow-up of childhood traumatic brain injury. J Neurotrauma 2010;27:1827-35.
43. Agha A, Sherlock M, Phillips J, Tormey W, Thompson CJ. The natural history of post-traumatic neurohypophysial dysfunction. Eur J Endocrinol 2005;152:371-7.
44. Klose M, Feldt-Rasmussen U. Does the type and severity of brain injury predict hypothalamo-pituitary dysfunction? Does post-traumatic hypopituitarism predict worse outcome? Pituitary 2008;11:255-61.
45. Dusick JR, Wang C, Cohan P, Swerdloff R, Kelly DF. Chapter 1: pathophysiology of hypopituitarism in the setting of brain injury. Pituitary 2008. doi: 10.1007/s11102-008-0130-6.
46. Salehi F, Kovacs K, Scheithauer BW, Pfeifer EA, Cusimano M. Histologic study of the human pituitary gland in acute traumatic brain injury. Brain Inj 2007;21:651-6.
47. Ceballos R. Pituitary changes in head trauma (analysis of 102 consecutive cases of head injury). Ala J Med Sci 1966;3:185.
48. Schneider HJ, Samann PG, Schneider M, Croce CG, Corneli G, Sievers C, et al. Pituitary imaging abnormalities in patients with and without hypopituitarism after traumatic brain injury. J Endocrinol Invest 2007;30. RC9-12.
49. Maiya B, Newcombe V, Nortje J, Bradley P, Bernard F, Chatfield D, et al. Magnetic resonance imaging changes in the pituitary gland following acute traumatic brain injury. Intensive Care Med 2008;34:468-75.
50. Crompton MR. Hypothalamic lesions following closed head injury. Brain 1971;94:165-72.
51. Kornblum RN, Fisher RS. Pituitary lesions in craniocerebral injuries. Arch Pathol Lab Med 1969;88:242-8.
52. Schneider M, Schneider HJ, Yassouridis A, Saller B, von Rosen F, Stalla GK. Predictors of anterior pituitary insufficiency after traumatic brain injury. Clin Endocrinol 2008;68:206-12.
53. Tanriverdi F, De Bellis A, Bizzarro A, Sinisi A, Bellastella G, Pane E, et al. Antipituitary antibodies after traumatic brain injury: is head trauma induced pituitary dysfunction associated with autoimmunity? Eur J Endocrinol 2008;159:7-13.
54. GH research society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab 2000;85:3990-3.
55. Tassoni PCE, Cacciari E, Cau M, Colli C, Tosi M, Zucchini S, Cicognani A, Pirazzoli P, Salardi S, Balsamo A, et al. Variability of growth hormone response to pharmacological and sleep tests performed twice in short children. J Clin Endocrinol Metab 1990;71:230-4.
56. Hoeck HC, Vestergaard P, Jakobsen P, Laurberg P. Test of growth hormone secretion in adults; poor reproducibity of the insulin tolerance test. Eur J Endocrinol 1995;133:305-12.
57. Marin G, Domene HM, Barnes KM, Blackwell BJ, Cassorla FG, Cutler GB. The effects of estrogen priming and puberty on the growth hormone response to standardised treadmill exercise and arginine-insulin in normal girls and boys. J Clin Endocrinol Metab 1994;79:537-41.
58. Ghigo E, Bellone J, Aimaretti G, Bellone S, Loche S, Cappa M, Bartolota E, et al. Reliabilty of provocative tests to assess growth hormone secretory status. Study in 472 normally growing children. J Clin Endocrinol Metab 1996;81:3323-7.
59. Kokshoorn NE, Wassenaar MJE, Biermasz NR, Roelfsema F, Smit JWA, Romijn JA, et al. Hypopituitarism following traumatic brain injury: prevalence is affected by the use of different dynamic tests and different normal values. Eur J Endocrinol 2010;162:11-8.
60. Corneli G, Di Somma C, Baldelli R, Rovere S, Gasco V, Roce CG, et al. The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index. Eur J Endocrinol 2005;153:257-64.
61. Berg C, Meinel T, Lahner H, Yuece A, Mann K, Petersenn S. Diagnostic utility of the glucagon stimulation test in comparison to the insulin tolerance test in patients following pituitary surgery. Eur J Endocrinol 2010; 162:477-82.
62. Kazlauskaite R, Evans AT, Villabona CV, Abdu TAM, Ambrosi B, Atkinson AB, et al. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. J Clin Endocrinol Metab 2008; 93:4245-53.
63. Moon RJ, Wilson P, Kirkham FJ, Davies JH. Growth monitoring following traumatic brain injury. Arch Dis Child 2009;94:699-701.

3.3. Significance and contribution

This commentary promotes a simple, non-invasive approach to monitoring for hypopituitarism following childhood TBI. An increasing number of expert groups now recommend routine biochemical pituitary screening amongst adults, which has been extrapolated to childhood TBI. However, the prevalence and significance of hypopituitarism following TBI is not clear, and is likely to have been routinely over-estimated. Pituitary tests are invasive, and must be interpreted with caution. Therefore, in childhood, clinical surveillance of growth and development is a more balanced approach.

In writing this piece, my opinion was certainly influenced by my own emerging data. There has been no new childhood data reported in the interval between publication of this commentary and submission of my thesis. I am aware of a number of longitudinal studies of pituitary function following childhood TBI, and await these reports with interest as they will undoubtedly add an extra dimension to our understanding.

Chapter 4. Permanent hypopituitarism is rare after structural traumatic brain injury in early childhood

4.1. Preface

The aim of this study was to define the prevalence of clinically significant hypopituitarism following structural TBI in early childhood. The risk of hypopituitarism following early childhood TBI has never been systematically evaluated. In particular, children with abusive TBI (i.e. shaken baby syndrome) typically suffer from severe and repeated episodes of head injury, and may consequently be at high risk of pituitary damage. TBI was defined in structural terms, as GCS score is likely to be an unreliable index of TBI severity in early childhood, and subjects assessed at a minimum interval of twelve months following injury, in order to exclude transient hypopituitarism. Furthermore, hypopituitarism was rigorously defined, and based on comprehensive diagnostic criteria. A major strength to the data is that all cases of apparent hypopituitarism were prospectively evaluated.

The following section contains a reproduction of the article "Permanent hypopituitarism is rare after structural traumatic brain injury in early childhood," published in the *Journal of Clinical Endocrinology and Metabolism*. This is the leading international journal for research in clinical endocrinology, with a 2010 impact factor of 6.2. The article is reproduced with permission of The Endocrine Society; copyright 2012.

All of the work included in this article was carried out as part of this thesis. However, not all of the data relevant to this thesis could be included in the manuscript. As a result, the manuscript is followed by a series of additional Figures and Tables, accompanied by detailed interpretations; these include the flowchart for subject recruitment, diagnostic algorithms for GH and ACTH deficiency, and individual descriptions of subjects with apparent ACTH deficiency and with precocious puberty.

Permanent Hypopituitarism Is Rare after Structural Traumatic Brain Injury in Early Childhood

Natasha L. Heather, Craig Jefferies, Paul L. Hofman, José G. B. Derraik, Christine Brennan, Patrick Kelly, James K. M. Hamill, Rhys G. Jones, Deborah L. Rowe, and Wayne S. Cutfield

Liggins Institute (N.L.H., P.L.H., J.G.B.D., C.B., D.L.R., W.S.C.), University of Auckland; Te Kupenga Hauora Maori (R.G.J.), School of Population Health; and School of Nursing, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, 1020 Auckland, New Zealand; and Starship Children's Hospital (C.J., P.K., J.K.M.H.), Auckland District Health Board, Private Bag 92024, 1142 Auckland, New Zealand

Background: We sought to determine the incidence of permanent hypopituitarism in a potentially high-risk group: young children after structural traumatic brain injury (TBI).

Methods: We conducted a cross-sectional study with longitudinal follow-up. Dynamic tests of pituitary function (GH and ACTH) were performed in all subjects and potential abnormalities critically evaluated. Puberty was clinically staged; baseline thyroid function, prolactin, IGF-I, serum sodium, and osmolality were compared with age-matched data. Diagnosis of GH deficiency was based on an integrated assessment of stimulated GH peak (<5 μg/liter suggestive of deficiency), IGF-I, and growth pattern. ACTH deficiency was diagnosed based on a subnormal response to two serial Synacthen tests (peak cortisol <500 nmol/liter) and a metyrapone test.

Results: We studied 198 survivors of structural TBI sustained in early childhood (112 male, age at injury 1.7 $\pm$ 1.5 yr) 6.5 $\pm$ 3.2 yr after injury. Sixty-four of the injuries (33%) were inflicted and 134 (68%) accidental. Two participants had developed precocious puberty, which is within the expected background population rate. Peak stimulated GH was subnormal in 16 participants (8%), in the context of normal IGF-I and normal growth. Stimulated peak cortisol was low in 17 (8%), but all had normal ACTH function on follow-up. One participant had a transient low serum T_4. Therefore, no cases of hypopituitarism were recorded.

Conclusion: Permanent hypopituitarism is rare after both inflicted and accidental structural TBI in early childhood. Precocious puberty was the only pituitary hormone abnormality found, but the prevalence did not exceed that of the normal population. **(*J Clin Endocrinol Metab* 97: 599–604, 2012)**

Traumatic brain injury (TBI) is a common event in childhood. Incidence is best assessed by prospective population studies, such as the Christchurch Birth Cohort study, which reported that a third of the population had sustained TBI by 25 yr of age (1). The overall incidence was 1.75 per 100 per year, with 30% of injuries recurrent and 10% defined as moderate to severe (1). The New Zealand incidence of inflicted TBI (shaken baby syndrome) is conservatively estimated as 15–20 per 100,000 infants per year (2) but is likely to be greatly underreported.

The prevalence of hypopituitarism after TBI is poorly defined, particularly in childhood. A recent meta-analysis of adult TBI data reported the rate of long-term hypopituitarism as 27.5%, most commonly affecting GH or gonadotropins (3). The few childhood TBI studies have reported a highly variable rate of hypopituitarism (5–61%) (4–10). All have been small studies ($n < 50$) and used nonstandardized methods to assess and diagnose pituitary function. Routine pituitary assessment after moderate to severe TBI has been recommended for adult populations (11) and extrapolated to children as well (12).

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.
Copyright © 2012 by The Endocrine Society
doi: 10.1210/jc.2011-2284 Received August 10, 2011. Accepted October 20, 2011.
First Published Online November 16, 2011

Abbreviations: BMI, Body mass index; CV, coefficient of variation; GCS, Glasgow Coma Scale; IGFBP-3, IGF-binding protein 3; SDS, SD score; TBI, traumatic brain injury.

The mechanism of traumatic hypopituitarism is proposed to be vascular. The pituitary gland is suspended on a stalk and potentially mobile. Long hypophyseal vessels traverse the stalk and supply the anterior pituitary via a latticework of portal vessels. These small perforating vessels may be vulnerable to shearing injury from sudden acceleration-deceleration forces. The pattern of anterior pituitary infarction, seen in up to a third of fatal head injuries, corresponds to areas supplied by portal vessels (13). Inflicted injuries can be caused by shaking or impact (or a combination of both), and either mechanism can produce identical pathological changes in the brain (14). The mechanisms by which inflicted TBI is produced, and the anatomy of the infant head and neck, may make infants particularly vulnerable to pituitary injury (14).

TBI is a heterogeneous condition, and current methods of grading are poorly predictive of pituitary dysfunction. The Glasgow Coma Scale (GCS) is widely used to define severity (15), although a variety of factors such as interval to hospital presentation, prehospital interventions, and limited interobserver reliability can affect scores (16, 17). Scoring preverbal children presents further difficulty (18), and a single score may be less meaningful after the repeated injury commonly seen in inflicted TBI (19). Structural TBI is likely to be a more robust way to define significant head injury, and therefore predict pituitary damage, in young children.

There are no robust studies examining the prevalence of hypopituitarism in children after TBI. Thus, we aimed to determine the prevalence of hypopituitarism in a potentially high-risk group: young children after structural TBI.

Subjects and Methods

Starship Children's Hospital is the only hospital in New Zealand with a dedicated pediatric intensive care unit as well as being the regional neurosurgical pediatric center for the Auckland region. Admissions after accidental or inflicted TBI were identified from both the Hospital's Trauma (2000–2010) and Child Protection (1992–2010) databases. Cases were eligible if structural TBI had occurred within the first 5 yr of life and more than 12 months previously. Structural TBI was defined as the presence of skull fracture, intracranial hemorrhage (extradural, subdural, subarachnoid, or intraventricular), or cerebral injury (contusion, infarct, edema, or diffuse axonal injury) reported on computerized tomography or magnetic resonance imaging scan. Exclusion criteria were death during or after admission, residence outside of New Zealand, age under 3 yr at assessment, or pituitary dysfunction that predated TBI.

All children with inflicted TBI met the following criteria: structural TBI, injuries incompatible with the history (20), careful evaluation by the multidisciplinary child protection team, and notification to the statutory authorities. Functional TBI severity was assessed as per GCS (15), whereas structural TBI was graded according to the Abbreviated Injury Scale (21).

Assessments were performed at the Liggins Institute, University of Auckland. Height was measured to the nearest 0.1 cm using a Harpenden stadiometer. Pubertal staging was assessed as per Marshall and Tanner (22). Reported or measured parental heights were recorded. Height and height velocity SD scores (SDS) were derived from Tanner/Whitehouse reference data (22), and body mass index (BMI) SDS according to British 1990 standards (23).

Baseline fasting serum samples were taken for analysis of IGF-I, IGF-binding protein 3 (IGFBP-3), TSH, free T_4, free T_3, prolactin, sodium, and osmolality. Dynamic tests were used to evaluate GH and ACTH sufficiency. Clonidine (150 $\mu g/m^2$) was administered orally and GH samples drawn at 0, +30, +60, +90, and +120 min. Intravenous arginine (6.5 ml/kg of 10% solution) was then administered and additional samples drawn at +150 and +180 min. Low-dose Synacthen (1 μg as an iv push) was also given at baseline and cortisol measured at 0, +30, and +60 min. An additional gonadotropin stimulation test (GnRH, 100 μg) was performed in children with clinical evidence of precocious puberty, and LH and FSH measured at +30 and +60 min.

A Roche (Indianapolis, IN) E170 Modular laboratory analyzer using chemiluminescence was used for cortisol [coefficient of variation (CV) 6%], TSH (CV 5%), free T_4 (CV 7%), and free T_3 (7%). A Roche Modular ISE laboratory analyzer measured serum sodium and serum osmolality. A Siemens Immunlite 2000 (Siemens, Los Angeles, CA) using immunochemiluminescence was used for GH (CV 5%), IGF-I (CV 8%), prolactin (CV 5%), LH (CV 13%), and FSH (CV 12%). A Bioclone RIA kit (Bioclone, Marrickville, NSW, Australia) measured IGFBP-3 (CV 8%) and 11-deoxycortisol (CV 20%).

Hypopituitarism was defined as deficiency in one or more pituitary hormones. Baseline hormone values were compared with age-, sex-, and (where appropriate) pubertal stage-adjusted normal reference ranges provided by Auckland Healthcare Laboratory Services. All participants with abnormal results underwent further comprehensive review. The diagnosis of GH deficiency was based on the integrated assessment of stimulated GH peak, IGF-I, IGFBP-3, and growth parameters. Growth velocity was monitored over a minimum of 6 months among participants with peak stimulated GH below 5 μg/liter, which is New Zealand's adopted cutoff for possible childhood GH deficiency based on current assay (24). Estrogen priming was reserved for repeat GH tests in prepubertal participants (ethinyl estradiol 40 $\mu g/m^2$ orally taken for 2 d before assessment). The diagnosis of ACTH deficiency was based on consistently subnormal results. Participants with peak stimulated cortisol below 500 nmol/liter underwent a second low-dose Synacthen test, and those with a second subnormal response underwent a short metyrapone test (oral metyrapone 30 mg/kg, maximum of 2 g, taken at 2300 h). Blood samples were obtained the following morning, and a normal response was defined as the sum of cortisol plus 11-deoxycortisol higher than 450 nmol/liter and ACTH higher than 20 pmol/liter (25). Possible precocious puberty was defined in girls as Tanner stage 2 breast development at under 8 yr or onset of menstruation at under 9.5 yr and in boys as testicular volume of at 4 ml or more at under 9 yr of age. Confirmation was obtained via pubertal level of sex steroids and stimulated LH peak higher than 10 IU/liter.

Data are presented as mean ± SD. Two-tailed χ^2 tests with Yates correction were used to assess whether the frequency of precocious puberty among boys and girls who suffered TBI was greater than normal, based on reference data from the Danish national database (26).

This study was approved by the hospital (Auckland District Health Board) and regional (Northern X) ethics committees.

Written informed consent was obtained from guardians of all participants.

Results

This study identified 770 TBI admissions of children under 5 yr of age. A total of 156 children had no structural TBI, 42 were deceased, and an additional 127 were excluded due to either young age or geographical distance from the testing center. A total of 175 could not be contacted, and 270 were invited to participate. Sixty-seven declined, the most common reason being no concern about the child's health or development. Five others were excluded because secure venous access could not be obtained. As a result, 198 participants were studied, whose baseline characteristics are outlined in Table 1.

Sixty-four participants (32%) sustained inflicted and 134 (68%) accidental TBI. Computerized tomography reports were available for all but three participants and magnetic resonance imaging scans for 34%. Intracerebral hemorrhage (66%), cerebral injury (66%), and skull fractures (70%) occurred in most. Most subjects had severe to critical structural TBI, although just under half had moderate to severe injury by GCS (Table 1). Specific pituitary abnormality (posterior hemorrhage) was reported in only one case and was associated with transient diabetes insipidus. Average length of stay in hospital was 10.5 d, and 40% were admitted to intensive care (Table 1).

TABLE 1. Baseline characteristics of participants (n = 198)

Characteristic	Data
Age at injury (yr)	1.7 ± 1.5
Gender (M/F)	116/82
Cause of injury	
Fall	72 (36%)
Abuse	64 (32%)
Motor vehicle accident	43 (22%)
Other	19 (10%)
GCS at time of injury	
13–15 (mild)	109 (55%)
9–12 (moderate)	35 (18%)
3–8 (severe)	54 (27%)
Structural TBI (assessed by AIS)	
Moderate-serious (AIS 2–3)	78 (39%)
Severe-critical (AIS 4–5)	120 (61%)
Intensive care admission	77 (40%)
Acute surgical intervention[a]	47 (24%)
Duration of hospitalization (d)	10.5 ± 12.2
Time since TBI (yr)	6.5 ± 3.3
Age at assessment (yr)	8.3 ± 3.2
BMI SDS	0.9 ± 1.3
Height SDS	0.5 ± 1.3
Height SDS − MPH SDS	0.3 ± 1.4

Data are mean ± SD, n (percent), or ratio. AIS, Abbreviated Injury Scale; F, female; M, male; MPH, mean parental height.

[a] Mass evacuation or drain inserted.

Endocrine evaluation

Patients were assessed 6.5 ± 3.2 yr after injury, at an age of 8.3 ± 3.3 yr. A total of 170 participants (85%) were Tanner stage 1–2, 22 (11%) stage 3–4, and six (3%) stage 5. Chronic illness included asthma (eight participants reported taking low-dose inhaled steroids), medically treated ADHD, congenital cardiac disease, and achondroplasia (height SDS −4.8, omitted from auxological analysis). Endocrine assessment was complete in 191; four participants declined GH stimulation tests, and one additionally declined the Synacthen test. Thyroid function was not available in three cases.

GH-IGF-I axis

Peak GH response to arginine-clonidine was 14.4 ± 7.8 μg/liter. GH peak was under 10 μg/liter in 65 subjects (33%) and under 5 μg/liter in 16 (8%). Among subjects with GH under 5 μg/liter (with apparent GH deficiency), mean height SDS was 1.0 ± 1.2 and BMI SDS 2.8 ± 0.8, whereas both IGF-I and IGFBP-3 were within the normal range for all subjects (Table 2). This group was followed in growth clinics for a period of 6–36 months, and all demonstrated normal height velocity (Table 2). Repeat arginine-clonidine tests were performed in five cases. Repeat GH was more than 5 μg/liter in all but one case, likely confounded by severe obesity (BMI SDS 4.2). None of the subjects with short stature or who were short for their parents' heights had low GH or IGF-I levels. There were six subjects (3%) who had height below −2 SDS at assessment and seven (4%) with height corrected for genetic potential below −2 SDS. Only two subjects had short stature as assessed by both measures: one with achondroplasia and another with spastic quadriplegia.

ACTH axis

Basal cortisol was 270 ± 150 nmol/liter and peak 695 ± 152 nmol/liter. Suboptimal cortisol response (<500 nmol/liter) was seen in 17 (9%) participants (range 304–487 nmol/liter). None of these had hyponatremia, fasting hypoglycemia, or postural hypotension suggestive of adrenal insufficiency. Three reported regular low-dose inhaled steroids. Interim stress steroid precautions were advised in all cases. All 17 underwent repeat Synacthen tests, 13 of which achieved peak cortisol above target. Four remained low, one declined additional assessment (peak cortisol 490 nmol/liter), and three responded appropriately to metyrapone. None were considered to have significant ACTH deficiency.

TABLE 2. Hormonal and growth profile of study participants with GH peak under 5 μg/liter

Subject	Gender	Age (yr)	Tanner stage	GH peak (μ g/liter)	IGF-I (μ g/ml)	Height (cm)	Height SDS	BMI (kg/m^2)	BMI SDS	HV (cm/yr)	HV SDS	HV interval (months)
GH1	F	14	5	2.0 (6)[a]	385	167.8	1.0	30.2	2.5	ND[b]	ND[b]	ND[b]
GH2	M	8	1	2.1 (8.6)[a]	134	134	1.5	30.4	3.8	6.8	1.6	9
GH3	M	7	1	2.2 (5.6)[a]	100	122	−0.8	23.9	3.1	4.7	−0.8	31
GH4	M	12	1	2.3	144	159	1.2	34.5	3.4	8.5	2.9	6
GH5	F	9	1	2.5	123	131	2.3	30.8	3.5	7.6	2.8	6
GH6	F	6	1	3.0	143	124	1.3	25	3.3	7.2	2.1	36
GH7	M	7	1	3.1	127	128	0.5	24.4	3.1	5.9	0.6	17
GH8[c]	F	8	4	3.4 (7.6)[a]	240	124	−0.9	26	2.9	3.9	−2.1	8
GH9	F	10	1	3.8	206	139	0.1	20.8	1.3	7.1	0.5	12
GH10	M	11	1	4.6	143	163.3	2.3	26.5	2.6	4.9	−0.1	6
GH11	M	7	1	4.6	142	132	0.8	23	2.8	5.5	0.1	36
GH12	F	8	1	4.7	196	132	0.6	22.3	2.2	5.9	0.6	12
GH13	M	6	1	4.8 (4.2)[a]	151	139.5	3.6	29	4.2	5.9	0.2	6
GH14	M	6	1	4.8	231	123	1.4	19.2	2.2	6.1	0.1	7
GH15	M	10	1	4.9	221	140	0.1	22.9	2.2	5.5	0.1	18
GH16	M	12	1	4.9	180	157.3	1.2	23.8	2.2	5.5	0.8	6

F, Female; HV, height velocity; M, male.

[a] Values in *parentheses* refer to repeat arginine-clonidine GH tests, sex-steroid priming used for subjects GH2, GH3, and GH13.

[b] No data (ND) because subject GH1 had reached final adult height before the study.

[c] Subject GH8 has spastic quadriplegia with flexion contractures as well as precocious puberty and advanced bone age (+3 SDS), which collectively are growth limiting independently of GH status.

Precocious puberty

One male aged 7 yr had previously been diagnosed with precocious puberty (Tanner G3P3 with 6- to 8-ml testes, stimulated LH peak 21.4 IU/liter, testosterone 8.9 nmol/liter, and bone age +2 SDS), and was treated with regular depot injections of leuprorelin acetate. One female was diagnosed with precocious puberty at the time of assessment, with a history of breast development at 5–6 yr and menses from 7.5 yr. She had been seen by her general practitioner and reassured that her pubertal development was normal. At 8 yr, she was Tanner B4 and had stimulated LH peak 28.1 IU/liter, bone age +3 SDS advanced, and predicted final height 142 cm. Both had sustained severe TBI as assessed by GCS, structural injury, and clinical progress. The incidence of precocious puberty among boys was one in 116 and among girls was one in 82. Incidence among girls was no different ($P = 0.42$) from that of the general population (~20 in 10,000), but there was a trend for increased incidence among boys (*vs.* about four in 10,000; $P = 0.063$).

Other pituitary deficiencies

One female had possible mild central hypothyroidism on initial assessment, free T_4 of 10.6 pmol/liter (11–22 pmol/liter), free T_3 of 6.8 pmol/liter (3–10 pmol/liter), and TSH of 1.1 mU/liter (1.6 mU/liter). She was clinically well, and thyroid function normalized a month later (free T_4 of 13.3 pmol/liter and TSH of 1.4 mU/liter). No participants had hypernatremia or high serum osmolality. One female had a history of transient posttraumatic diabetes insipidus and had been off treatment and asymptomatic for 3 yr at the time of assessment. Seven subjects had mildly elevated prolactin levels (range 370–750 mIU/liter) that were not considered clinically significant. In one case, this was attributed to risperidone, and repeat prolactin was normal in all three cases where it was reassessed.

Discussion

We show that permanent hypopituitarism is rare after structural TBI in early childhood in the largest such pediatric study performed to date. There were two cases of precocious puberty, but the prevalence did not exceed that of the normal childhood population. All other apparent pituitary hormone deficiencies were shown to be erroneous, when tests were repeated or considered as part of comprehensive assessments.

Importantly, there were no cases of GH deficiency. This finding contrasts to high rates reported by many previous TBI studies, showing a prevalence of 11–31% among adults (27–30) and 16–42% in small pediatric studies (5, 7, 10). Whereas earlier studies have based the diagnosis of GH deficiency entirely on GH stimulation tests, we performed detailed assessments of GH, IGF-I, and growth pattern, with recognition of obesity.

Using provocative GH tests alone and conservative international criteria (peak GH <10 μg/liter) (31), up to 33% of our study population might have been incorrectly diagnosed with GH deficiency. All these subjects were overweight or obese but had normal height, height veloc-

ity, and IGF-I level. It is common for normally growing children to display low GH responses that may falsely suggest deficiency (32). Stimulated GH levels are inversely associated with BMI in childhood (33), and misleadingly low GH levels (suggestive of deficiency) are especially common in obese children. Nonetheless, previous childhood TBI studies have not adjusted for confounding adiposity. In addition, GH tests are poorly reproducible; individuals who undergo repeated tests have highly variable results (34). In our study, 80% of low GH responses were normal when tests were repeated, and the remainder had normal IGF-I and growth velocity. Similarly, in contrast to what is usually reported in TBI studies, we found no cases of ACTH deficiency: 5–27% for adults (27–30) and 18–34% for children (5, 7, 10). Once again, retesting of subnormal ACTH results showed that these were false positives (*i.e.* apparent ACTH deficiency in normal children).

Given the high-risk group we studied, it is surprising that we observed no cases of hypopituitarism. Young children are thought to be particularly vulnerable to the effects of acceleration-deceleration on the brain and cerebral vasculature (14). Our study population was a clearly defined homogeneous group of young children with structural TBI. It was apparent within our cohort that significant structural injury can be associated with mild GCS impairment. The relationship between TBI severity as defined by GCS and hypopituitarism has been weak and may reflect the indirect nature of GCS as an assessment tool for pituitary damage. In addition, a high-risk subgroup was included, children after inflicted TBI. Inflicted brain injuries are typically repeated and severe and affect very young infants, yet no hypopituitarism was found. Note that these findings may not be applicable to adolescents, whose physical characteristics and types of injury more closely resemble those seen in adults.

Our data on precocious puberty were within the expected prevalence for girls. There was a trend toward a significant increase for boys, although this was also within the expected range. The population prevalence of precocious puberty is not well described, and our reference data were derived from the Danish national registry (26). The authors stressed that their estimates were conservative, particularly because they relied upon referrals to pediatricians. The pathogenic mechanism of precocious puberty is loss of normal childhood hypothalamic inhibition of pituitary gonadotropins and could be anticipated to increase after TBI. However, our study shows that the rate of precocious puberty after TBI is unlikely to exceed that of the normal population. Nonetheless, not all subjects in our study had reached the normal age of pubertal onset, so that our prevalence data might also have been an underestimate. Thus, although precocious puberty appears to be rare after TBI, prevalence should ideally be assessed by longitudinal follow-up of a large population.

The major challenge for this study was recruitment, mostly due to difficulty in obtaining up-to-date case contact details. This was particularly challenging among children with inflicted injuries and as the interval from TBI increased. Overall, the rate of acceptance among those contacted was high (75%), with probable selection bias toward children with chronic disability, who would be expected to be at greater risk of hypopituitarism. Another potential limitation was the variable timing of assessments. However, because the purpose of this study was to assess the rate of permanent pituitary hormone deficiency, all assessments were performed at least 1 yr after injury (beyond which point the occurrence of new hypopituitarism is rare) (35). It is possible that some of our subjects had already recovered from transient hormone deficiency, but the significance of this would be unclear.

In conclusion, permanent hypopituitarism after TBI appears to be a very rare event. Given that all subjects with initial tests suggestive of ACTH deficiency were normal when reassessed, significant abnormality that would require treatment is likely to be rare, but further evaluation of ACTH status within a larger cohort will help to clarify this issue. In our cohort, precocious puberty was the only pituitary abnormality present. We found no cases of GH deficiency that met comprehensive assessment criteria, even though it is generally reported to be common after TBI. Because both precocious puberty and GH deficiency can be detected on clinical assessment during childhood, a pragmatic approach would be for family physicians to monitor growth and development in children after TBI. Invasive assessments should be reserved for selected cases where there is slow growth or other clinical suspicion of hypopituitarism.

Acknowledgments

We thank participants and our advisory Kaitiaki group. We also thank Rangi Dansey for his assistance with the Starship Trauma database and Andrew Law for his input in planning the study.

Address all correspondence and requests for reprints to: Wayne S. Cutfield, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand. E-mail: w.cutfield@auckland.ac.nz.

The study was supported by grants from the Health Research Council of New Zealand and the Australasian Pediatric Endocrine Group. N.L.H. was supported by the Starship Fellowship Foundation.

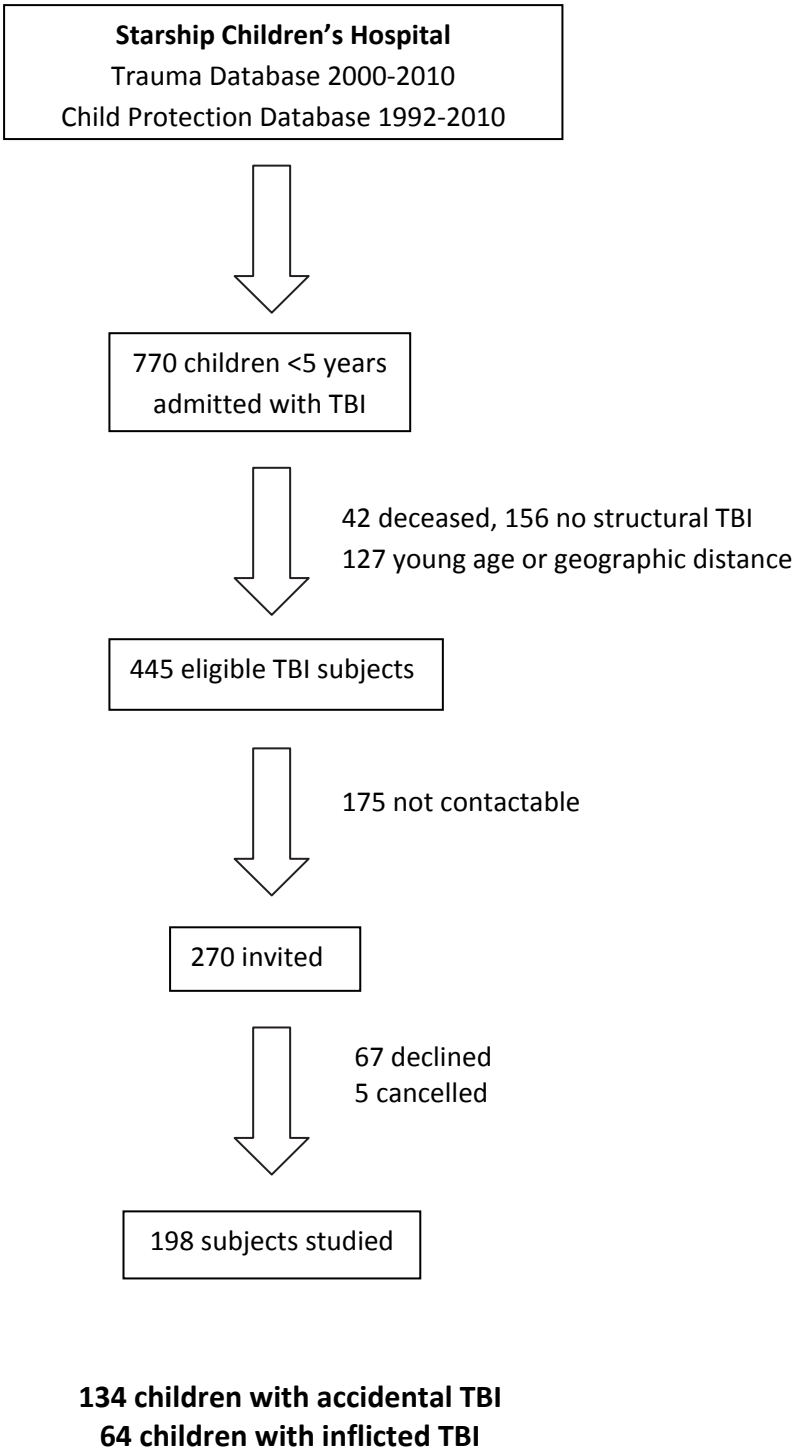
N.L.H. and W.S.C. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure Summary: All authors and respective spouses, partners, or children have no financial or non-financial interests to declare that may be relevant to this submitted work.

References

1. **McKinlay A, Grace RC, Horwood LJ, Fergusson DM, Ridder EM, MacFarlane MR** 2008 Prevalence of traumatic brain injury among children, adolescents and young adults: prospective evidence from a birth cohort. Brain Inj 22:175–181
2. **Kelly P, Farrant B** 2008 Shaken baby syndrome in New Zealand, 2000–2002. J Paediatr Child Health 44:99–107
3. **Schneider HJ, Kreitschmann-Andermahr I, Ghigo E, Stalla GK, Agha A** 2007 Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. JAMA 298:1429–1438
4. **Einaudi S, Matarazzo P, Peretta P, Grossetti R, Giordano F, Altare F, Bondone C, Andreo M, Ivani G, Genitori L, de Sanctis C** 2006 Hypothalamo-hypophysial dysfunction after traumatic brain injury in children and adolescents: a preliminary retrospective and prospective study. J Pediatr Endocrinol Metab 19:691–703
5. **Niederland T, Makovi H, Gál V, Andréka B, Abrahám CS, Kovács J** 2007 Abnormalities of pituitary function after traumatic brain injury in children. J Neurotrauma 24:119–127
6. **Poomthavorn P, Maixner W, Zacharin M** 2008 Pituitary function in paediatric survivors of severe traumatic brain injury. Arch Dis Child 93:133–137
7. **Khadr SN, Crofton PM, Jones PA, Wardhaugh B, Roach J, Drake AJ, Minns RA, Kelnar CJH** 2010 Evaluation of pituitary function after traumatic brain injury in childhood. Clin Endocrinol (Oxf) 73:637–643
8. **Kaulfers AM, Backeljauw PF, Reifschneider K, Blum S, Michaud L, Weiss M, Rose SR** 2010 Endocrine dysfunction following traumatic brain injury in children. J Pediatr 157:894–899
9. **Moon RJ, Sutton T, Wilson PM, Kirkham FJ, Davies JH** 2010 Pituitary function at long-term follow-up of childhood traumatic brain injury. J Neurotrauma 27:1827–1835
10. **Norwood KW, Deboer MD, Gurka MJ, Kuperminc MN, Rogol AD, Blackman JA, Wamstad JB, Buck ML, Patrick PD** 2010 Traumatic brain injury in children and adolescents: surveillance for pituitary dysfunction. Clin Pediatr (Phila) 49:1044–1049
11. **Ghigo E, Masel B, Aimaretti G, Léon-Carrión J, Casanueva FF, Dominguez-Morales MR, Elovic E, Perrone K, Stalla G, Thompson C, Urban R** 2005 Consensus guidelines on screening for hypopituitarism following traumatic brain injury. Brain Inj 19:711–724
12. **Acerini CL, Tasker RC** 2007 Traumatic brain injury induced hypothalamic-pituitary dysfunction: a paediatric perspective. Pituitary 10:373–380
13. **Dusick JR, Wang C, Cohan P, Swerdloff R, Kelly DF** 15 May 2008 Chapter 1: pathophysiology of hypopituitarism in the setting of brain injury. Pituitary 10.1007/s11102-008-0130-6
14. **Case ME, Graham MA, Handy TC, Jentzen JM, Monteleone JA; National Association of Medical Examiners Ad Hoc Committee on Shaken Baby Syndrome** 2001 Position paper on fatal abusive head injuries in infants and young children. Am J Forensic Med Pathol 22:112–122
15. **Teasdale G, Jennett B** 1974 Assessment of coma and impaired consciousness. A practical scale. Lancet 2:81–84
16. **Marion DW, Carlier PM** 1994 Problems with initial Glasgow Coma Scale assessment caused by prehospital treatment of patients with head injuries: results of a national survey. J Trauma 36:89–95
17. **Gill MR, Reiley DG, Green SM** 2004 Interrater reliability of Glasgow Coma Scale scores in the emergency department. Ann Emerg Med 43:215–223
18. **Simpson DA, Cockington RA, Hanieh A, Raftos J, Reilly PL** 1991 Head injuries in infants and young children: the value of the Paediatric Coma Scale. Childs Nerv Syst 7:183–190
19. **Jenny C, Hymel KP, Ritzen A, Reinert SE, Hay TC** 1999 Analysis of Missed Cases of Abusive Head Trauma. JAMA 281:621–626
20. **Bechtel K, Stoessel K, Leventhal JM, Ogle E, Teague B, Lavietes S, Banyas B, Allen K, Dziura J, Duncan C** 2004 Characteristics that distinguish accidental from abusive injury in hospitalized young children with head trauma. Pediatrics 114:165–168
21. **Association for the Advancement of Automotive Medicine** 2001 The abbreviated injury scale, 1990 revision, update 98. Barrington, IL: Association for the Advancement of Automotive Medicine
22. **Tanner JM, Whitehouse RH** 1976 Clinical longitudinal standards for height, weight, height velocity and stages of puberty. Arch Dis Child 51:170–179
23. **Cole TJ, Freeman JV, Preece MA** 1995 Body mass index reference curves for the UK, 1990. Arch Dis Child 73:25–29
24. **Barth JH, Sibley PEC** 2008 Standardization of the IMMULITE systems growth hormone assay with the recombinant IS 98/574. Ann Clin Biochem 45:598–600
25. **Berneis K, Staub JJ, Gessler A, Meier C, Girard J, Müller B** 2002 Combined stimulation of adrenocorticotropin and compound-S by single dose metyrapone test as an outpatient procedure to assess hypothalamic-pituitary-adrenal function. J Clin Endocrinol Metab 87:5470–5475
26. **Teilmann G, Pedersen CB, Jensen TK, Skakkebaek NE, Juul A** 2005 Prevalence and incidence of precocious pubertal development in Denmark: an epidemiologic study based on national registries. Pediatrics 116:1323–1328
27. **Agha A, Rogers B, Sherlock M, O'Kelly P, Tormey W, Phillips J, Thompson CJ** 2004 Anterior pituitary dysfunction in survivors of traumatic brain injury. J Clin Endocrinol Metab 89:4929–4936
28. **Aimaretti G, Ambrosio MR, Di Somma C, Fusco A, Cannavo S, Gasperi M, Scaroni C, De Marinis L, Benvenga S, degli Uberti EC, Lombardi G, Mantero F, Martino E, Giordano G, Ghigo E** 2004 Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. Clin Endocrinol (Oxf) 61:320–326
29. **Klose M, Juul A, Poulsgaard L, Kosteljanetz M, Brennum J, Feldt-Rasmussen U** 2007 Prevalence and predictive factors of post-traumatic hypopituitarism. Clin Endocrinol (Oxf) 67:193–201
30. **Schneider HJ, Schneider M, Kreitschmann-Andermahr I, Tuschy U, Wallaschofski H, Fleck S, Faust M, Renner CI, Kopczak A, Saller B, Buchfelder M, Jordan M, Stalla GK** 2011 Structured assessment of hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage in 1242 patients; the German Interdisciplinary Database. J Neurotrauma 28:1693–1698
31. **Growth Hormone Research Society** 2000 Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab 85:3990–3993
32. **Ghigo E, Bellone J, Aimaretti G, Bellone S, Loche S, Cappa M, Bartolotta E, Dammacco F, Camanni F** 1996 Reliabilty of provocative tests to assess growth hormone secretory status: study in 472 normally growing children. J Clin Endocrinol Metab 81:3323–3327
33. **Loche S, Guzzetti C, Pilia S, Ibba A, Civolani P, Porcu M, Minerba L, Casini MR** 2011 Effect of body mass index on the growth hormone response to clonidine stimulation testing in children with short stature. Clin Endocrinol (Oxf) 74:726–731
34. **Tassoni P, Cacciari E, Cau M, Colli C, Tosi M, Zucchini S, Cicognani A, Pirazzoli P, Salardi S, Balsamo A** 1990 Variability of growth hormone response to pharmacological and sleep tests performed twice in short children. J Clin Endocrinol Metab 71:230–234
35. **Tanriverdi F, Ulutabanca H, Unluhizarci K, Selcuklu A, Casanueva FF, Kelestimur F** 2008 Three years prospective investigation of anterior pituitary function after traumatic brain injury: a pilot study. Clin Endocrinol (Oxf) 68:573–579

Supplementary Figure 4.1. Flow chart of subject recruitment.

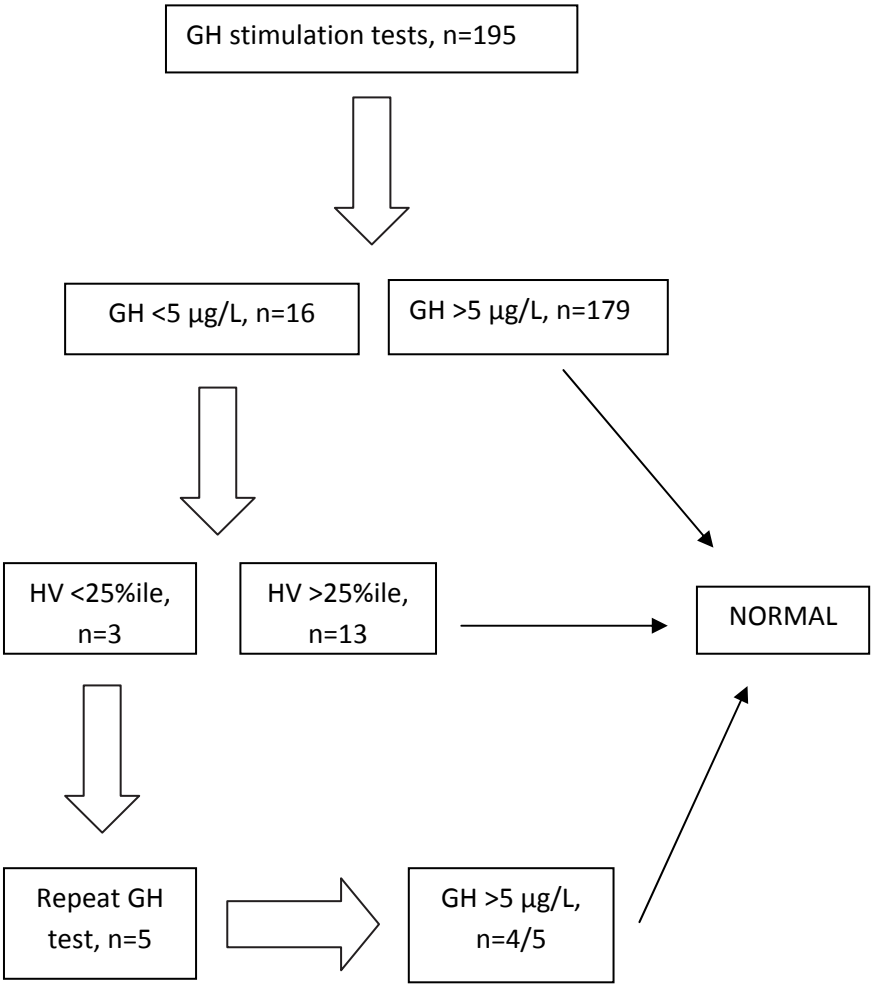


Explanation to supplementary Figure 4.1

Subjects were identified from two Starship Children's Hospital databases. The general Trauma database does not provide complete coverage of abusive injuries and was supplemented with the Child Protection database, which records all cases of definite or suspected abuse assessed within our institution. Basic inclusion criteria included admission to Starship Hospital with TBI aged <5 years, occurring at least 12 months prior to hormonal assessment. 770 traumatic brain injury (TBI) admissions were identified in children <5 years from the earliest point of each database until May 2010. Exclusion criteria included death (n=42) or no structural injury (n=127, defined as the absence of or intra-cranial injury and skull fracture on CT or head scan). For pragmatic reasons, children were only considered eligible if they were ≥3 years of age, and living within the greater Auckland region at the time of proposed assessment. A total of 445 children met these eligibility criteria, and phone contact with families and guardians was attempted, either using hospital details or through family doctors. However, this step was a major challenge, particularly amongst abusive cases and as the interval from injury increased. As a result, more than a third of those eligible (175/445) were uncontactable, and 270 subjects were consequently invited to take part. Sixty-seven (25%) declined, most citing a lack of health concerns, practical difficulties in attending, or the invasive nature of tests. A further five assessments were cancelled by the investigators as secure venous access was not easily obtained. Overall, the rate of participation was high, as 75% of those approached underwent assessments. A total of 198 pituitary assessments were performed, amongst which 64 (34%) of children were categorised as having sustained an inflicted TBI, and 134 (67%) an accidental TBI. Abusive injuries were defined using the criteria given in the manuscript; where there was uncertainty injuries were classified as accidental, therefore it is likely that the proportion of abusive cases was under-estimated.

.

Supplementary Figure 4.2. Algorithm for GH assessment.

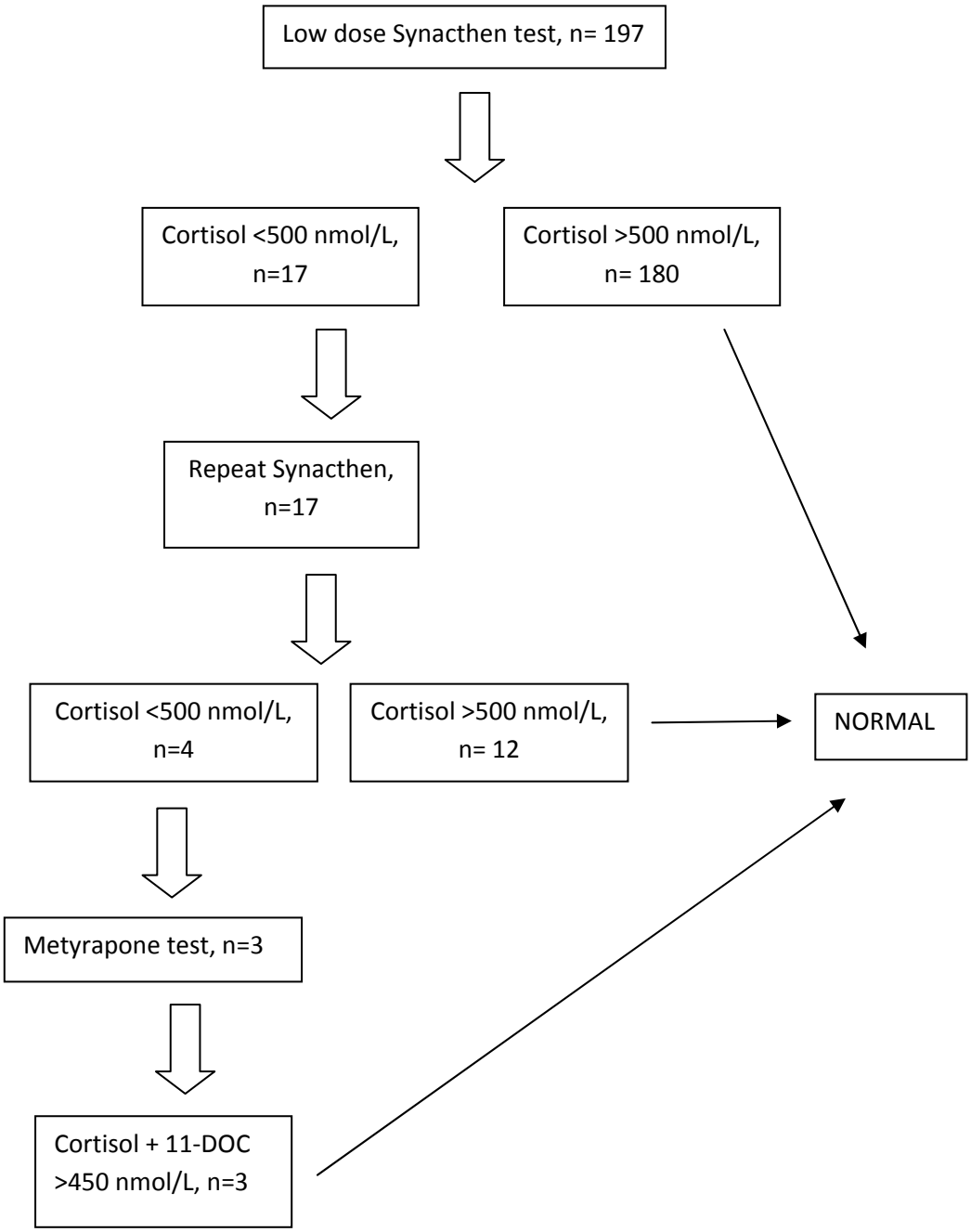


Explanation to supplementary Figure 4.2

GH = growth hormone, HV = height velocity. Sequential arginine (6.5 ml/kg 10% solution IV) and clonidine (150 µg/m^2 PO) stimulation tests were performed in 195/198 subjects. A subnormal response was defined as peak GH concentration <5 µg/L in response to both provocation tests. This reflects the current New Zealand diagnostic cut-off for child and adolescent GH deficiency, which is low by international standards (<10 µg/L in the USA and Europe) and therefore more likely to identify cases of true GH deficiency. Note that initial GH provocation tests were not sex hormone primed, in order to be comparable with previous data from childhood TBI studies. In total, 16 (8%) of subjects had a subnormal peak GH; the manuscript

includes a summary table of their individual data. This subgroup was followed prospectively over 1-3 years, and poor growth defined as that below the 25th centile for age and gender. Repeat arginine-clonidine GH tests were repeated in five subjects and sex steroid priming used in the three prepubertal subjects (ethinyl estradiol 40 μg/m^2 PO, for two days prior to assessment) to increase reliability. GH provocation tests were repeated in four subjects with poor growth during the initial period of observation (one of whom subsequently improved), and one who had already reached skeletal maturity. These were normal in all but one case, considered to be a false positive test confounded by severe obesity. The final diagnosis was comprehensive, based on the integrated assessment of GH tests, growth factors and growth pattern, with consideration given to body mass index. Although 8% of subjects initially had a subnormal GH response to provocation, indicating apparent GH deficiency, no subjects met comprehensive diagnostic criteria for GH deficiency.

Supplementary Figure 4.3. Algorithm for ACTH assessment.



Explanation to supplementary Figure 4.3

Low dose Synacthen tests (1 µg IV) were performed in 197/198 subjects. Seventeen (9%) subjects had a subnormal response, defined as peak cortisol concentration <500 nmol/L. This subgroup underwent a 2nd low dose Synacthen test, to which the majority (13/17) demonstrated a normal cortisol response (>500 nmol/L), and were subsequently re-classified as ACTH sufficient. Four subjects had a subnormal cortisol response to both Synacthen tests. One was asymptomatic, with a marginal peak cortisol concentration of 490 nmol/L, and declined further assessment. The other three underwent a short Metyrapone test (30mg/kg PO), for which a normal response was defined as the sum of cortisol and 11-deoxycortisol (11-DOC) >450 nmol/L plus ACTH >20 pmol/L, and all three met these criteria. As a result, no subjects were considered to have true, clinically significant deficiency.

Supplementary Table 4.1. Individual data for the 17 subjects with apparent ACTH deficiency.†

Subject	Basal Cortisol (nmol/L)	1st Low Dose Synacthen; peak cortisol (nmol/L)	2nd Low Dose Synacthen; peak cortisol (nmol/L)	Short Metyrapone
ACTH1	134	304	696	
ACTH2	279	377	423	Normal; 11-DOC 392 nmol/L, cortisol 60 nmol/L, ACTH 114 pmol/L
ACTH3	156	386	606	
ACTH4	155	397	774	
ACTH5	336	413	511	
ACTH6	194	428	730	
ACTH7	299	437	456	Normal; 11-DOC 284 nmol/L, cortisol 190 nmol/L, ACTH 54 pmol/L
ACTH8	204	438	497	Normal; 11-DOC 340 nmol/L, cortisol 150 nmol/L, ACTH 44 pmol/L
ACTH9	171	460	490	Declined
ACTH10	109	461	565	
ACTH11	105	462	692	
ACTH12	164	470	550	
ACTH13	105	478	867	
ACTH14	141	481	603	
ACTH15	177	486	596	
ACTH16	212	486	512	
ACTH17	203	487	639	

Explanation to supplementary Table 4.1

†Apparent ACTH deficiency defined as peak cortisol response <500 nmol/L to low dose Synacthen test (1 µg IV). This subgroup of 17/197 subjects all underwent a second low dose Synacthen test, to which four had a second subnormal response. Three subsequently underwent short Metyrapone tests (30mg/kg PO), and all demonstrated a normal response, defined as the sum of cortisol and 11-deoxycortisol (11-DOC) >450 nmol/L plus ACTH >20 pmol/L. As a result, no subjects were considered to have true, clinically significant ACTH deficiency.

Supplementary Table 4.2. Characteristics of two subjects diagnosed with precocious puberty.

Subject Demographics	Acute TBI severity scores (GCS, AIS)	Summary of acute admission	Long-term outcome	Age of pubertal onset	Bone age at diagnosis	GnRH test at diagnosis (FSH, LH in IU/L)	Treatment
4 yr Tongan male, fell from swing.	GCS 5 AIS 5	8 days ventilation, persistent seizures, raised ICP.	Severe disability; epilepsy, cognitive impairment, hemiparesis.	Tanner stage G3 (6ml testes) at 7 yrs.	Matched to 13 years at 7 years.	Basal LH 1, FSH 1 Peak LH 21, FSH 2.2 Testosterone 8.9 nmol/L	Yes.
6 mo European female, unrestrained passenger in car accident.	GCS 4 AIS 5	14 days ventilation, raised ICP.	Severe disability; bilateral hemiplegia (L>R), blind, cognitive impairment.	Breast buds and pubic hair from 6 years, menses aged 7.5 yrs.	Matched to 11 years at 8 yrs 9 months.	Basal LH 1.3, FSH 1 Peak LH 30, FSH 3	Yes.

Explanation to supplementary Table 4.2

GCS= Post-resuscitation Glasgow Coma Scale (GCS scores of 3-8 indicate a poorly responsive state and therefore severe TBI, 9-12 are classified as moderate and 13-15 mild), AIS= Abbreviated Injury Score (an anatomical injury scale from 1-6, where a score of 6 represents unsurvivable TBI, a score of 5 is considered critical, and lower scores denote progressively milder TBI), ICP= intra-cranial pressure. Both subjects with precocious puberty sustained severe brain injuries, as evidenced by low GCS and high AIS scores, the need for prolonged intensive care and severe long-term disability. For the first subject, precocious puberty was appropriately recognised by the child's General Paediatrician. The second subject was taken to see her family doctor aged six years following the development of breast buds and pubic hair; however the family were reassured that this was normal. She went on to develop early menarche aged 7.5 years, and precocious puberty was formally diagnosed by the study investigators. Both subjects had a greatly advanced bone age and a gonadotropin response to GnRH (gonadotropin releasing hormone) consistent with central puberty (LH >10 IU/L), and both received leuprorelin acetate (Lucrin) depot treatment for pubertal suppression.

4.2. Particular issues

4.2.1. TBI severity within the cohort

A potential criticism of the cohort is that many had sustained relatively mild TBI. Whilst it is true that GCS scores were relatively mild, the range and severity of structural TBI is similar to that in previous reports. In particular, 18% of our cohort had basal skull fractures, which implies significant local impact to the pituitary region. The mismatch between GCS and structural TBI in early childhood is discussed further in Chapter 6, as it is clear that the GCS scoring system does not reliably correlate with structural injury in young children.

4.2.2. Reliability of pituitary assessments

Although it is conceivable that mild pituitary abnormalities were present, I do not believe that I missed any cases of clinically significant hypopituitarism within my cohort. GH status was assessed comprehensively based on two serial stimulation tests, with consideration of BMI, IGF-I and growth rate, as conservative cut-offs mean that GH stimulation tests alone lead to the over-diagnosis of GH deficiency. Within the manuscript, Table 2 summarises individual data for the 16 subjects with apparent GH deficiency. Although BMI was very high in this subgroup, appetite was considered normal by the children's families, and therefore not suggestive of hypothalamic hyperphagia. As expected for the degree of obesity, the subgroup was taller than the overall cohort. Obesity driven growth is a possible cause of normal growth velocity in children with GH deficiency, but is accompanied by relatively low levels of IGF-I (Falorni, Galmacci *et al*. 1999; Eiholzer, Bachmann *et al*. 2000). Conversely, within my cohort, IGF-I levels were uniformly normal amongst those who failed GH tests. However, final height data, which is not yet available for the majority of subjects, would be definitive.

GH stimulation tests were performed without sex steroid priming in order to facilitate comparison with previous childhood TBI studies. However, there is no doubt that sex steroid priming would have

decreased the rate of false positive tests (Marin, Domene *et al*. 1994). Priming was used to improve the reliability of repeat assessments in pre-pubertal subjects; two out of three children subsequently had a normal GH response, with the third confounded by severe obesity.

Low dose synacthen tests are sensitive, but not highly specific, tests for ACTH deficiency (Dickstein, Shechner *et al*. 1991; Kazlauskaite, Evans *et al*. 2008). The 17 subjects with apparent ACTH deficiency (peak cortisol <500 nmol/L) are described in Supplementary Table 4.1, and none of these had true, clinically significant ACTH deficiency. In retrospect, it would have been useful to measure CBG, and calculate the free cortisol index for these subjects. There is wide population and intra-individual variability in CBG, which is a possible confounder of Synacthen tests (Dhillo, Kong *et al*. 2002). Although it is highly unlikely that we have missed clinically significant disease, we may have been able to demonstrate sufficiency based on the initial Synacthen, and obviated the need for repeated assessment.

Within the cohort, there were two clear-cut cases of precocious puberty. As described in Supplementary Table 4.2, both children sustained severe cerebral injury. Whilst 1/198 cases is not above the background population rate of precocious puberty (Teilmann, Pedersen *et al*. 2005), it is likely to be an under-estimate as it is possible that further subjects from the cohort may go on to develop precocious puberty. However, precocious puberty is detected clinically, and therefore is not an argument for routine invasive pituitary screening.

4.2.3. Timing of assessments

This study was designed to establish the prevalence of permanent hypopituitarism. The mean interval between injury and assessment was 6.3 years, and it is possible that some subjects had recovered from a period of significant transient hypopituitarism. Within our cohort, the normal height at assessment argues against prolonged GH deficiency, however, this can only be definitively addressed through longitudinal studies.

4.3. Significance and contribution

In this study I have demonstrated that permanent hypopituitarism is rare following structural TBI in early childhood. As well as being the largest paediatric study in the area, it is the first to focus on young children with abusive injuries. Contrary to my expectations, children with abusive TBI are also at low risk of hypopituitarism. The low prevalence of true hypopituitarism contrasts to that generally reported in the literature, and the high proportion with apparent hypopituitarism highlights methodological weaknesses in previous reports. As a result, this is a highly significant negative study. The article was reported in the January issue of *Endocrine News,* a publication of The Endocrine Society, which has an estimated circulation of >10,000.

Chapter 5. Cortisol response to synacthen stimulation is attenuated following abusive head trauma

5.1. Preface

My original hypothesis was that children with abusive injuries would be at increased risk of hypopituitarism. However, there were no cases of hypopituitarism in either the inflicted (TBI_I) or accidental (TBI_A) injury groups. Furthermore, when the mean hormonal concentrations for each group were compared, a reduced cortisol response amongst TBI_I was the only robust difference found (see Supplementary Table 5.1). The following manuscript explores this finding, which is likely to reflect environmental programming of the HPA axis rather than a direct injury effect.

The following section contains a reproduction of the article "Cortisol response to synacthen stimulation is attenuated following abusive head trauma," accepted for publication in *Clinical Endocrinology*, February 2012. The paper is reproduced with the permission of John Wiley and Sons. *Clinical Endocrinology* has a 2010 impact factor of 3.3. All of the work included in this article was carried out as part of this thesis.

This manuscript focuses on the HPA axis and does not include comparative data for all pituitary axes. This data is highly relevant to the thesis, and an additional table with interpretative comment follows the manuscript.

Clinical Endocrinology (2012) 77, 357–362 doi: 10.1111/j.1365-2265.2012.04376.x

ORIGINAL ARTICLE

Cortisol response to synacthen stimulation is attenuated following abusive head trauma

Natasha L. Heather*, José G. B. Derraik*, Christine Brennan*, Craig Jefferies†, Paul L. Hofman*, Patrick Kelly†, Rhys G. Jones‡, Deborah L. Rowe*,§ and Wayne S. Cutfield*

*Liggins Institute, University of Auckland, †Starship Children's Hospital, Auckland District Health Board, ‡Te Kupenga Hauora Māori, School of Population Health, University of Auckland, and §School of Nursing, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

Summary

Background Child abuse and other early-life environmental stressors are known to affect the hypothalamic–pituitary–adrenal axis. We sought to compare synacthen-stimulated cortisol responses in children who suffered inflicted or accidental traumatic brain injury (TBI).

Methods Children with a history of early-childhood TBI were recruited from the Starship Children's Hospital database (Auckland, New Zealand, 1992–2010). All underwent a low-dose $ACTH_{1–24}$ (synacthen 1 μg IV) test, and serum cortisol response was compared between inflicted (TBI_I) and accidental (TBI_A) groups.

Results We assessed 64 children with TBI_I and 134 with TBI_A. Boys were more likely than girls to suffer accidental ($P < 0{\cdot}001$), but not inflicted TBI. TBI_I children displayed a 14% reduction in peak stimulated cortisol in comparison with the TBI_A group ($P < 0{\cdot}001$), as well as reduced cortisol responses at + 30 ($P < 0{\cdot}01$) and + 60 min ($P < 0{\cdot}001$). Importantly, these differences were not associated with severity of injury. The odds ratio of TBI_I children having a mother who suffered domestic violence during pregnancy was 6·2 times that of the TBI_A group ($P < 0{\cdot}001$). However, reported domestic violence during pregnancy or placement of child in foster care did not appear to affect cortisol responses.

Conclusion Synacthen-stimulated cortisol response is attenuated following inflicted TBI in early childhood. This may reflect chronic exposure to environmental stress as opposed to pituitary injury or early-life programming.

(Received 18 November 2012; returned for revision 08 December 2012; finally revised 21 February 2012; accepted 21 February 2012)

Correspondence: Wayne S. Cutfield, Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand. Tel.: +64 9 923 5118; Fax: +64 9 373 8763; E-mail: w.cutfield@auckland.ac.nz

Introduction

Family violence (including child abuse) is pervasive, under-reported and a cause of long-term morbidity in most societies.[1] A well-recognized consequence of violence during infancy is abusive head trauma (the 'shaken baby syndrome'), which in New Zealand is conservatively estimated to affect 15–25 per 100 000 infants per year.[2] Childhood abuse is associated with a high prevalence of depression in adult life, possibly via programming of the hypothalamic–pituitary–adrenal (HPA) axis.[3]

The HPA axis function can be assessed using a variety of methods. These include assessment of unstimulated cortisol, such as baseline levels (i.e. 8 am serum measurement) and circadian cortisol rhythms (i.e. salivary levels). Other methods assess the cortisol secretory reserve, using provocative stimulation (e.g. CRH, insulin, and $ACTH_{1–24}$). The low-dose $ACTH_{1–24}$ (synacthen 1 μg IV) test is regarded as a gold standard method for the assessment of baseline and stimulated adrenal function in children and adults.[4,5] Although it has been suggested that gender differences in spontaneous cortisol levels emerge during puberty,[6,7] the data regarding the relative influence of age, gender, pubertal status, and body mass index (BMI) are conflicting.[8–10]

Nonetheless, several studies have demonstrated that childhood abuse can lead to HPA dysfunction that may persist for years. For example, adults who were abused during childhood display decreased cortisol feedback sensitivity[11] and increased pituitary sensitivity to corticotropin-releasing factor (CRF).[12] Morning salivary cortisol is decreased both amongst children in foster care[13] and those raised in neglectful institutions.[14] HPA axis challenge studies in children who have suffered abuse have been very small and report apparently contradictory results, such as a variably increased or decreased ACTH response to a CRF challenge.[15,16]

We aimed to describe the long-term impact on the HPA axis associated with inflicted traumatic brain injury (TBI), which is one objective measure of abuse in early childhood. For this purpose, we adopted a low-dose synacthen test to compare basal and stimulated serum cortisol responses between children who suffered inflicted or accidental TBI in early childhood.

© 2012 Blackwell Publishing Ltd

Methods

Study population

Starship Children's Hospital is the only hospital in New Zealand with a dedicated paediatric intensive care unit, as well as being the regional neurosurgical paediatric centre for the Auckland region. Admissions after accidental or inflicted TBI were identified from both the Hospital's Trauma (2000–2010) and Child Protection (1992–2010) databases. Cases were eligible if structural TBI had occurred within the first 5 years of life and more than 12 months previously. Structural TBI was defined as the presence of skull fracture, intracranial haemorrhage (extradural, subdural, subarachnoid or intraventricular) or cerebral injury (contusion, infarct, oedema or diffuse axonal injury) reported on computerized tomography or magnetic resonance imaging scan. Exclusion criteria were death during or after admission, residence outside of New Zealand, age under 3 years at assessment or pituitary dysfunction that predated TBI.

From the group of eligible subjects, children were recruited for a detailed follow-up assessment,[17] and were further separated into those who suffered an accidental (TBI_A) or inflicted (TBI_I) traumatic brain injury. TBI_I children had to meet the following additional criteria: injuries incompatible with the history,[18] careful evaluation by a multidisciplinary child protection team and notification to the statutory authorities.

Measured parameters

Injury data were obtained from hospital records, including age at injury, cause of injury, neuro-imaging reports and intensive care admission. Anatomical head injury severity was assessed according to the Abbreviated Injury Scale (AIS). AIS scores are based on CT or MRI scans,[19] and injuries are ranked on a 'threat to life' scale ranging from 1 to 6 (1–mild, 2–moderate, 3–serious, 4–severe, 5–critical and 6–not survivable).[19]

Ethnicity was recorded by self-report using a priority system, such that if multiple ethnicities were selected, the subject was assigned to a single ethnicity, following a hierarchical classification of Māori, Pacific Islander, Other and then European.[20] Those participants described as 'Other' were of ethnicities not otherwise stated (e.g. Indian, South-East Asian, African and Middle Eastern).

Guardianship was confirmed prior to assessment, and we recorded whether the subject was currently living with one or two biological parents, or in foster care. In addition, the accompanying guardian or birth mother was interviewed regarding domestic (interparental) violence during pregnancy, specifically, whether the mother had been physically hurt by her partner during this time.

Geo-coded deprivation scores were derived from current address using the New Zealand Index of Deprivation 2006 (NZDep2006).[21] This index is based on household census data reflecting nine aspects of material and social deprivation to divide New Zealand into tenths (scored 1–10) by residential address. Scores of 1 represent the least deprived areas and 10 the most deprived. Scores are derived from units covering a small area, each reflecting approximately 90 people.

Clinical assessments were performed at the Maurice & Agnes Paykel Clinical Research Unit, at the Liggins Institute, University of Auckland. Height was measured to the nearest 0·1 cm using a Harpender stadiometer. Height standard deviation scores (SDS) were derived from Tanner/Whitehouse reference data,[22] and weight and BMI SDS according to British 1990 standards.[23] Parental heights were whenever possible measured at the time of assessment or otherwise reported by a caregiver and used to calculate mid-parental height. Pubertal staging was assessed by a physician or a trained research nurse. Puberty was defined as Tanner stage 2 breast development in girls and testicular volume > 3 ml in boys as per Tanner and Whitehouse.[24,25]

Laboratory assessments

Low-dose (1 μg) synacthen (synthetic $ACTH_{1-24}$; Novartis, Basle, Switzerland) tests were commenced between 08:00 and 10:00 am, when an intravenous cannula was inserted into an antecubital vein using topical anaesthetic. After a 15-min period of rest, blood samples were drawn for the measurement of baseline cortisol, free thyroxine (T4), free triiodothyronine (T3) and thyroid-stimulating hormone (TSH) concentrations. A low-dose (1 μg) synacthen bolus was then given intravenously, and blood samples drawn at + 30 and + 60 min for cortisol measurement. Whole blood samples were stored in EDTA tubes at ambient temperature for up to 2 h and then centrifuged at 2400 *g* for 5 min.

Serum cortisol was measured using the Roche cortisol competitive electrochemiluminescence immunoassay (ECLIA), on a Roche E170 analyser (Indianapolis, IN, USA). Intrabatch coefficient of variation (CV) was <2·0% for values between 129 and 866 nmol/l. Interbatch CV was 5·2% at 63 nmol/l, 2·9% at 474 nmol/l and 3·0% at 852 nmol/l. Free T3 and free T4 were measured using the Roche FT4 and FT3 competitive ECLIAs on a Roche E170 analyser. Intrabatch CV for T3 was <3·5% for values between 2·8 and 22 pmol/l and for T4 < 2·0% for values between nine and 41 pmol/l. Interbatch CV for T3 was 6·2% at 4·0 pmol/l, 3·2% at 12 pmol/l and 3·3% at 22 pmol/l; for T4 were 3·4% at 13·7 pmol/l, 3·9% at 36 pmol/l and 5·7% at 89 pmol/l. TSH was measured using the Roche TSH sandwich ECLIA, on a Roche E170 analyser. Intrabatch CV was <3·0% for values between 0·04 and 9·3 IU/l, while interbatch CV was 2·2% at 0·5 IU/l, 2·6% at 6·2 IU/l and 2·7% at 36 IU/l.

Ethics

Ethics approval for this study was provided by the hospital (Auckland District Health Board) and regional (Northern X) ethics committees. Written informed consent was obtained from guardians of all participants.

Statistical analysis

Baseline demographic data were compared using one-way ANOVA. Binary logistic regressions and chi-square tests were used

© 2012 Blackwell Publishing Ltd

to compare the relative frequencies of ethnic groups between the TBI database and study cohort, as well as the incidences of admission with TBI_A and TBI_I amongst ethnic groups in relation to age-matched New Zealand Census population data. Auxological and hormonal data were analysed using linear mixed models. Where hormone data were the responses, group (TBI_I *vs* TBI_A), ethnicity and gender were included as factors, while age at assessment, BMI SDS, NZDep2006 and AIS as covariates. Note that 'time of testing' was also included as a co-variate in the models, as it was found to significantly impact most hormonal measurements. Further, the model was subsequently run also with the addition of 'violence during pregnancy' and 'placement in foster care' separately as factors. For auxology, the variable of interest was the response; group, gender, pubertal status and ethnicity were factors; while age at assessment and mid-parental height were included as covariates.

Statistical analyses were carried out in SAS v.9.2 (SAS Institute, Cary, NC, USA) and Minitab (Minitab v.15; Pennsylvania State University, PN, USA). The Johnson transformation was adopted as required to stabilize the variance. All data are expressed as mean ± standard error of the mean (SEM).

Results

This study identified 770 TBI admissions of children under 5 years of age. A total of 156 children had no structural TBI, 42 were deceased, and an additional 127 were excluded owing to either young age or geographical distance from the testing centre. A total of 175 could not be contacted, and 270 were invited to participate. Sixty-seven declined participation, and five others were excluded because secure venous access could not be obtained. As a result, 198 participants were studied: 64 TBI_I and 134 TBI_A.

Children in the follow-up cohort were slightly younger at the time of TBI than those in the database ($P = 0{\cdot}053$) and suffered comparatively more severe injuries as illustrated by longer stay in hospital ($P < 0{\cdot}001$), greater frequency of admissions to the ICU ($P = 0{\cdot}003$) as well as a greater number of subjects with severe AIS ($P < 0{\cdot}001$). The ethnic distribution within our cohort was representative of the database, as the proportion of Māori and Europeans in our cohort (33·3% and 37·4%, respectively) was nearly identical to that in the overall dataset (32·3% and 37·7%, respectively; $P = 0{\cdot}82$).

We studied more boys (116) than girls (82), reflecting a similar ratio to the overall TBI database ($P = 0{\cdot}20$), as boys were more likely than girls to suffer accidental ($P < 0{\cdot}001$) but not inflicted TBI (Table 1). Primary causes of accidental TBI were falls ($n = 71$), road traffic accidents ($n = 41$) and other events ($n = 22$). There was no difference in socio-economic status between the TBI_I and TBI_A groups.

Based on the age-matched New Zealand Census population data, Māori children in the Auckland region were over-represented in the TBI database and were 2·7 times more likely to suffer TBI than Europeans (95% CI: 1·3–5·7; $P < 0{\cdot}001$). Further, the odds ratio of a Māori child suffering inflicted TBI or having a parent who reported domestic violence during pregnancy was 5·7× (95% CI: 3·1–10·5; $P < 0{\cdot}001$) and 3·5× (95% CI: 1·3–9·6; $P = 0{\cdot}015$) those of Europeans, respectively. Although Māori children were significantly more socio-economically disadvantaged than Europeans (NZDep2006 6·7 ± 0·4 *vs* 5·3 ± 0·4, $P < 0{\cdot}006$), differences in the incidence of violence remained even after SES was controlled for in the analyses.

Although both TBI_I and TBI_A groups were assessed at similar ages, children who suffered TBI_I were younger at the time of injury ($P < 0{\cdot}001$; Table 1). The likelihood of intensive care admission was similar in both groups (Table 1). Structural head injuries (AIS) were more severe amongst TBI_I children ($P < 0{\cdot}001$), whose odds ratio of suffering subdural haemorrhage was over 10 times that of TBI_A children (95% CI: 4·9–21·1; $P < 0{\cdot}001$) (Table 1). Importantly, the majority of TBI_I cases had radiological evidence of recurrent subdural haemorrhage

Table 1. Demographics and auxology of children who suffered inflicted and accidental traumatic brain injury (TBI)

	Inflicted TBI	Accidental TBI	*P*-value
Demographics			
n	64	134	
Gender	34 M, 30 F	82 M, 52 F	0·29†
Ethnicity			
European	17 (27%)	59 (44%)	0·020
Māori	29 (45%)	37 (28%)	0·016
Pacific Islander	14 (22%)	27 (20%)	0·85
Other	4 (6%)	11 (8%)	0·78
NZDep 2006	6·94 ± 0·39	6·28 ± 0·28	0·15
Interparental violence during pregnancy*	40%	10%	<0·001
Living in foster care	52%	0%	<0·001
Auxology			
Age at assessment (years)	8·7 ± 0·5	8·1 ± 0·2	0·52
Pubertal status			
Tanner 1	65%	81%	0·030
Tanner 2–3	16%	16%	0·99
Tanner 4–5	19%	3%	<0·001
Height SDS	0·72 ± 0·15	0·87 ± 0·12	0·24
Weight SDS	0·82 ± 0·17	0·87 ± 0·12	0·016
BMI SDS	0·78 ± 0·16	0·97 ± 0·11	0·006
TBI parameters			
Age at injury (years)	0·9 ± 0·1	2·1 ± 0·1	<0·001
AIS severe–critical (AIS 4–5)	52 (81%)	70 (52%)	<0·001
Subdural haemorrhage	52 (81%)	40 (30%)	<0·001
Intensive care unit admission	27 (42%)	51 (38%)	0·64
Evidence of recurrent subdural haemorrhage	34 (53%)	0	<0·001

Where applicable, data are mean ± SEM. AIS, Abbreviated Injury Scale, ranging 1 (mild) to 6 (not survivable); BMI, body mass index; NZDep2006, socio-economic index scored 1–10, where 1 indicates the least and 10 the greatest deprivation; SDS, standard deviation scores; TBI, traumatic brain injury.

*$n = 55$ for children with inflicted and 72 with accidental TBI.

†*P*-values for the assessment of a sex ratio different from 1:1 were $P = 0{\cdot}62$ amongst Inflicted and $P < 0{\cdot}001$ amongst Accidental TBI groups.

© 2012 Blackwell Publishing Ltd

and thus repeated episodes of injury, which was not observed in any TBI_A subject (Table 1).

Following adjustment for all confounding factors, baseline (0 min) cortisol concentrations were not different amongst groups ($P = 0{\cdot}27$), but TBI_I children had reduced cortisol concentrations at +30 ($P = 0{\cdot}005$) and +60 ($P < 0{\cdot}001$) min (Fig. 1). Further, TBI_I children also displayed a 14% reduction in peak stimulated cortisol ($P < 0{\cdot}001$; Fig. 1). Importantly, these differences were not associated with injury severity graded as per AIS. In addition, there were no differences amongst the TBI_I group in baseline or peak cortisol concentrations between those with evidence of pre-existing subdural haemorrhage (presumed to have suffered from previous episodes of TBI) *vs* those without it. There were no observed differences between TBI_I and TBI_A in the thyroid hormones assessed: free T3 (6·44 ± 0·10 *vs* 6·64 ± 0·07 pmol/l; $P = 0{\cdot}49$), free T4 (17·44 ± 0·24 *vs* 17·05 ± 0·19 pmol/l; $P = 0{\cdot}29$) and TSH (2·00 ± 0·09 *vs* 2·14 ± 0·09 mU/l; $P = 0{\cdot}76$), respectively.

In addition, even when all other factors and covariates were accounted for, stimulated (but not baseline) cortisol concentrations were also shown to be affected by age at assessment, gender and BMI SDS. Interestingly, it was not pubertal status but age and gender that affected cortisol levels. Girls had basal cortisol concentrations that were 9·5–16·7% greater than boys at + 30 min (693 ± 15 *vs* 633 ± 10; $P < 0{\cdot}001$), +60 min (665 ± 23 *vs* 569 ± 18; $P < 0{\cdot}001$) and peak (739 ± 18 *vs* 663 ± 13; $P < 0{\cdot}0001$). Age was negatively associated with peak cortisol ($P < 0{\cdot}0001$), as well as concentrations at +30 ($P < 0{\cdot}001$) and +60 ($P = 0{\cdot}002$) min. BMI SDS was also negatively associated with cortisol response at +60 min ($P = 0{\cdot}030$), and it tended to negatively affect baseline response as well ($P = 0{\cdot}087$).

Overall, there were 17 subjects with mildly abnormal peak cortisol concentrations (<500 nmol/l), whose mean response was 435 ± 12 nmol/l. Ten of these cases occurred in the TBI_I group, so that the prevalence of an abnormal response was much greater amongst TBI_I (16%) than TBI_A (5%) children

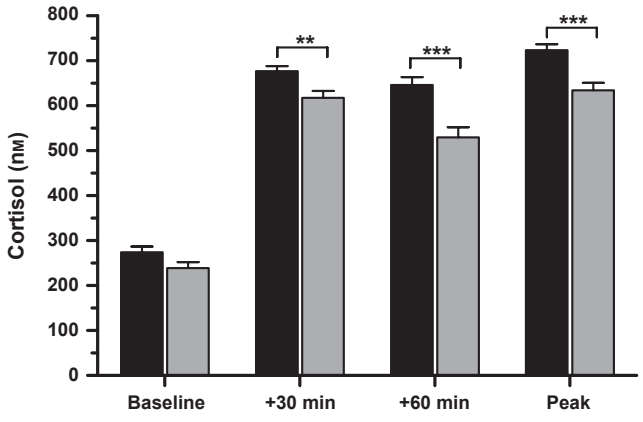


Fig. 1 Timed cortisol response following a low-dose synacthen test. Black bars represent children who suffered accidental traumatic brain injury (TBI), and grey bars those who suffered inflicted TBI. $^{**}P < 0{\cdot}01$, $^{***}P < 0{\cdot}001$ for accidental *vs* inflicted TBI.

($P = 0{\cdot}027$). All children with low stimulated cortisol levels were reviewed by endocrinologists at Starship Children's Hospital, and none required cortisol replacement.

At the time of assessment, 48% of the TBI_I group were living with at least one biological parent and 52% were in foster care. However, neither these living arrangements nor their socio-economic status (NZDep2006) had an observed effect on cortisol concentrations, either at baseline or following synacthen stimulation. 127 subjects (55 TBI_I and 72 TBI_A) provided information on interparental violence during pregnancy, which was reported to have occurred in 10% of the TBI_A and 40% of TBI_I group. The odds ratio of a TBI_I child having a mother who was a victim of domestic violence during pregnancy was 6·2 times that of the TBI_A group (95% CI: 2·4–16·0; $P < 0{\cdot}001$; Table 1). However, as observed for living arrangements, there were no effects on cortisol concentrations associated with interparental violence during gestation.

Discussion

Our study shows that the cortisol response to synacthen stimulation was 14% lower amongst children who suffered inflicted TBI. Notably, the observed differences between groups are likely to be underestimated, as children in the inflicted group were slimmer and had a proportionally greater ratio of girls than the accidental group, both of which were shown to be associated with increased stimulated cortisol concentrations.

There are a number of potential explanations for the lower stimulated cortisol levels observed in TBI_I children. Firstly, inflicted TBI may lead to greater incidence of traumatic ACTH deficiency, which may in turn lead to the observed cortisol differences between groups. Inflicted TBI is typically severe and is likely to involve repeated events, so that abused children may be a group particularly at risk of pituitary damage. However, although hypopituitarism has a reported prevalence of 10–60% after childhood brain injury, we recently showed that this is likely to have been greatly overestimated.[17] In addition, we show in this study that the observed differences in cortisol responses between TBI_I and TBI_A children were not associated with injury severity. Further, we did not observe any differences between groups in the thyroid axis. Thus, the blunted cortisol responses in TBI_I children were most likely associated with other environmental stressors, rather than a direct result of the head injury itself.

Another possible explanation is HPA programming, as inflicted TBI is a marker of abuse in early childhood. The strongest evidence for environmental programming of the HPA axis comes from rodent studies, where maternal separation in the early postnatal period led to an increased cortisol response to subsequent stressors.[26] This occurs in part through methylation of glucocorticoid receptors and a subsequent decrease in negative feedback.[27–29] In humans, maternal depression and anxiety during the third trimester have both been associated with increased basal salivary cortisol levels in offspring.[30,31] Within our TBI_I cohort, violence during pregnancy was reported in over half of the cases. Although we found no cortisol differences associated with this history, synacthen tests do not provide a

© 2012 Blackwell Publishing Ltd

sensitive assessment of cortisol negative feedback. Therefore, although domestic violence would likely lead to perinatal programming of the HPA axis, its impact within out cohort is unclear.

It is also possible that attenuation of stimulated cortisol reflects a greater level of day-to-day environmental stressors amongst TBI_I subjects. Although stress is classically associated with increased cortisol production, low levels are increasingly recognized in conditions of chronic stress.[32] For example, cortisol levels are low in association with post-traumatic stress disorder despite increased CRH, and there is exaggerated feedback sensitivity.[33] Similarly, low basal levels of salivary cortisol have been observed in young children exposed to institutional neglect[14] or raised by depressed mothers in extreme poverty.[34] Although we found no differences in either basal or stimulated cortisol when subjects were grouped according to their current living situation (i.e. foster placement), it may be that living arrangements are not a good predictor of a stable environment. Further, although the majority of subjects lived in the most deprived quintile, deprivation scores did not affect cortisol levels in this study. It is nonetheless conceivable that ongoing environmental adversity might have influenced the HPA axis and be responsible for the observed differences.

We acknowledge that there are possible limitations associated with our study. We conducted a cross-sectional rather than a prospective study, which ideally should have commenced from early pregnancy and included mothers with and without risk factors for physical abuse. A limitation inherent to any study of this kind is the difficulty in obtaining accurate and complete information about domestic violence and details regarding ongoing child abuse. A major challenge for this study was recruitment, mostly owing to difficulty in obtaining up-to-date case contact details. This was particularly challenging amongst children with inflicted injuries and as the interval from TBI increased. Although we managed to achieve a high rate of acceptance amongst those contacted (73%), in practice, we could only achieve a 44% rate of recruitment amongst the eligible TBI subjects. Finally, there are a range of different techniques to assess aspects of HPA axis function, but we have chosen a single gold standard technique for this study.

It should be noted that our data corroborate previous evidence showing a high concurrence between child abuse and interparental violence, which often escalates during pregnancy.[35,36] In our study, children who suffered inflicted TBI were over sixfold more likely to have a mother who suffered domestic violence. Thus, one intervention to prevent abusive TBI in children might be through measures to prevent interparental violence.

In conclusion, our study provides new evidence on HPA axis alterations in children who have been abused in childhood. We observed that children who suffered abusive TBI in early childhood had a blunted cortisol response to synacthen stimulation, possibly as a result of ongoing chronic stress during childhood. This study is part of a growing body of work documenting that child abuse is associated with long-term alterations to the HPA axis. However, in the absence of longitudinal data, the significance of our findings is unclear, and robust longitudinal studies are warranted.

Acknowledgements

We thank participants and our advisory Kaitiaki group. We also thank Rangi Dansey (Auckland City Hospital) for his assistance with the Starship Trauma database. The study was supported by grants from the Health Research Council of New Zealand and the Australasian Paediatric Endocrine Group. Natasha Heather was supported by the Starship Fellowship Foundation. The authors have no financial or nonfinancial interests to declare that may be relevant to this submitted work. We acknowledge the Paykel Trust for long-term funding of the Maurice & Agnes Paykel Clinical Research Unit at the Liggins Institute.

Disclosure statement

The authors have nothing to disclose.

References

1 Kelly, P. (2011) Corporal punishment and child maltreatment in New Zealand. *Acta Paediatrica*, **100**, 14–20.

2 Kelly, P. & Farrant, B. (2008) Shaken baby syndrome in New Zealand, 2000–2002. *Journal of Paediatrics and Child Health*, **44**, 99–107.

3 Heim, C., Newport, D.J., Mletzko, T. *et al.* (2008) The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology*, **33**, 693–710.

4 Dickstein, G., Shechner, C., Nicholson, W.E. *et al.* (1991) Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test. *Journal of Clinical Endocrinology and Metabolism*, **72**, 773–778.

5 Kazlauskaite, R., Evans, A.T., Villabona, C.V. *et al.* (2008) Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. *Journal of Clinical Endocrinology and Metabolism*, **93**, 4245–4253.

6 Oskis, A., Loveday, C., Hucklebridge, F. *et al.* (2009) Diurnal patterns of salivary cortisol across the adolescent period in healthy females. *Psychoneuroendocrinology*, **34**, 307–316.

7 Stroud, L.R., Papandonatos, G.D., Williamson, D.E. *et al.* (2011) Sex differences in cortisol response to corticotropin releasing hormone challenge over puberty: pittsburgh pediatric neurobehavioral studies. *Psychoneuroendocrinology*, **36**, 1226–1238.

8 Rosmalen, J.G.M., Oldehinkel, A.J., Ormel, J. *et al.* (2005) Determinants of salivary cortisol levels in 10–12 year old children; a population-based study of individual differences. *Psychoneuroendocrinology*, **30**, 483–495.

9 Koupil, I., Mann, V., Leon, D.A. *et al.* (2005) Morning cortisol does not mediate the association of size at birth with blood pressure in children born from full-term pregnancies. *Clinical Endocrinology*, **62**, 661–666.

10 Tornage, C.J. & Alfven, G. (2006) Diurnal salivary cortisol concentration in school-aged children: increased morning cortisol concentration and total cortisol concentration negatively correlated with body mass index in children with recurrent abdominal

© 2012 Blackwell Publishing Ltd

pain of psychosomatic origin. *Journal of Pediatric Endocrinology and Metabolism*, **19**, 843–854.

11 Heim, C., Mletzko, T., Purselle, D. *et al.* (2008) The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biological Psychiatry*, **63**, 398–405.

12 Heim, C., Newport, D.J., Bonsall, R. *et al.* (2001) Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *American Journal of Psychiatry*, **1**, 282–289.

13 Bruce, J., Fisher, P.A., Pears, K.C. *et al.* (2009) Morning cortisol levels in preschool-aged foster children: differential effects of maltreatment type. *Developmental Psychobiology*, **51**, 14–23.

14 Carlson, M. & Earls, F. (1997) Psychological and neuroendocrinological sequelae of early social deprivation in institutionalized children in Romania. *Annals of the New York Academy of Sciences*, **807**, 419–428.

15 Kaufman, J., Birmaher, B., Perel, J. *et al.* (1997) The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. *Biological Psychiatry*, **42**, 669–679.

16 De Bellis, M.D., Chrousos, G.P., Dorn, L.D. *et al.* (1994) Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *Journal of Clinical Endocrinology and Metabolism*, **78**, 249–255.

17 Heather, N.L., Jefferies, C., Hofman, P.L. *et al.* (2012) Hypopituitarism is rare following structural traumatic brain injury in early childhood. *Journal of Clinical Endocrinology and Metabolism*, **97**, 599–604.

18 Bechtel, K., Stoessel, K., Leventhal, J.M. *et al.* (2004) Characteristics that distinguish accidental from abusive injury in hospitalized young children with head trauma. *Pediatrics*, **114**, 165–168.

19 Association for the Advancement of Automotive Medicine. (1998) The Abbreviated Injury Scale 1990 Revision. Association for the Advancement of Automotive Medicine, Des Plaines, IL, USA.

20 Douglas, N.M. & Dockerty, J.D. (2007) Survival by ethnicity for children diagnosed with cancer in New Zealand during 1990–1993. *Journal of Paediatrics and Child Health*, **43**, 173–177.

21 Salmond, C., Crampton, P. & Atkinson, J. (2007) NZDep2006 index of deprivation user's manual. Wellington School of Medicine and Health Sciences, University of Otago, Wellington.

22 Tanner, J.M. & Whitehouse, R.H. (1976) Clinical longitudinal standards for height, weight, height velocity and stages of puberty. *Archives of Disease in Childhood*, **51**, 170–179.

23 Cole, T.J., Freeman, J.V. & Preece, M.A. (1995) Body Mass Index reference curves for the UK, 1990. *Archives of Disease in Childhood*, **73**, 25–29.

24 Marshall, W. & Tanner, J.M. (1969) Variations in pattern of pubertal changes in girls. *Archives of Disease in Childhood*, **44**, 291–303.

25 Marshall, W.A. & Tanner, J.M. (1970) Variations in the pattern of pubertal changes in boys. *Archives of Disease in Childhood*, **45**, 13–23.

26 Plotsky, P.M. & Meaney, M.J. (1993) Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Molecular Brain Research*, **18**, 195–200.

27 Weaver, I.C.G., Cervoni, N., Champagne, F.A. *et al.* (2004) Epigenetic programming by maternal behavior. *Nature Neuroscience*, **7**, 847–854.

28 Liu, D., Diorio, J., Tannenbaum, B. *et al.* (1997) Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science*, **277**, 1659–1662.

29 Meaney, M.J. & Szyf, M. (2005) Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues in Clinical Neuroscience*, **7**, 103–123.

30 O'Connor, T.G., Ben-Shlomo, Y., Heron, J. *et al.* (2005) Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biological Psychiatry*, **58**, 211–217.

31 Oberlander, T.F., Weinberg, J., Papsdorf, M. *et al.* (2008) Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics*, **3**, 97–106.

32 Heim, C., Ehlert, U. & Hellhammer, D.H. (2000) The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology*, **25**, 1–35.

33 Yehuda, R. (2002) Post-traumatic stress disorder. *New England Journal of Medicine*, **346**, 108–114.

34 Fernald, L.C.H., Burke, H.M. & Gunnar, M.R. (2008) Salivary cortisol levels in children of low-income women with high depressive symptomatology. *Development and Psychopathology*, **20**, 423–436.

35 Edleson, J.L. (1999) The overlap between child maltreatment and woman battering. *Violence Against Women*, **5**, 134–154.

36 McFarlane, J., Parker, B. & Soeken, K. (1996) Abuse during pregnancy: associations with maternal health and infant birth weight. *Nursing Research*, **45**, 37–42.

© 2012 Blackwell Publishing Ltd

Supplementary Table 5.1 Hormone profiles of the accidental and inflicted TBI groups.

Pituitary axes		TBI_A	TBI_I
GH	**GH peak (µg/l)**	13.6 ± 0.7*	16.1 ± 0.9
	IGF-I (µg/l)	181 ± 11	233 ± 20
	IGFBP-3 (µg/l)	2.23 ± 0.05	2.31 ± 0.09
	Height SDS	0.68 ± 0.13	0.42 ± 0.18
ACTH	**Baseline cortisol (nmol/l)**	284 ± 15	239 ± 13
	Peak cortisol (nmol/l)	723 ± 13***	637 ± 17
TSH	**T3 (pmol/l)**	6.64 ± 0.07	6.44 ± 0.10
	T4 (pmol/l)	17.1 ± 0.2	17.4 ± 0.2
	TSH (mU/l)	2.14 ± 0.09	2.27 ± 0.28
Prolactin (mIU/l)		142 ± 10	154 ± 16
Serum sodium (mmol/l)		139.3 ± 0.3	139.3 ± 0.2

Explanation to supplementary Table 5.1

TBI_A = accidental TBI group (*n*=134), TBI_I = inflicted TBI group (*n*=64). GH = growth hormone, IGF-I = insulin-like growth factor 1, IGFBP-3 = IGF binding protein 3, SDS = standard deviation score, ACTH = adrenocorticotropin, T3 = triiodothyronine, T4 = thyroxine, TSH = thyroid stimulating hormone. Data are mean ± standard error of the mean, **p* <0.05, **p <0.01, ****p* <0.001. Note that peak cortisol concentration was decreased amongst the TBI_I group as compared with TBI_A (*p* <0.001), and there was a similar non-significant trend for decreased basal cortisol concentrations amongst TBI_I. In contrast to this, GH peaks appeared greater amongst TBI_I (*p* <0.05), although no corresponding group difference was observed for IGF-I, IGF-BP3 or height SDS. On face value, this could indicate a degree of GH resistance amongst children with inflicted injuries. A number of factors can induce physiological GH resistance, including malnutrition and chronic illness, although these factors were not identified on basic anthropometry or clinical review. There is also large biological variability inherent to GH stimulation tests, so that the difference may reflect a type I error. Ultimately, the only way to prove this would be to perform repeated assessments, or test a larger group - neither of which was practical in the context of this study. There was no significant group difference in the serum concentration of thyroid hormones, prolactin or sodium. Gonadotropin status could not be compared as subjects were predominantly prepubertal. Overall, this data does not support an increase in subclinical hypopituitarism (which would indicate a greater degree of pituitary injury) within the TBI_I group.

5.2. Particular issues

5.2.1. Assessment of the HPA axis

A variety of differential tests can be used to assess the HPA axis. In this study, we employed a physiological dose of $ACTH_{1-24}$ (i.e. the low dose Synacthen test), which is widely used in clinical practice. However, it would have been preferable to undertake a more comprehensive HPA assessment in order to characterise the injury groups, including a salivary cortisol profile to define background cortisol production and a CRH-dexamethasone suppression test to assess negative feedback. Furthermore, serum cortisol is predominantly bound CBG, the levels of which vary between individuals and over time (Brien 1981; Dhillo, Kong *et al*. 2002). Although the biologically active free cortisol index can be calculated from total serum cortisol and CBG, this is not standard practice, and was not available for our cohort.

5.3. Significance and contribution

HPA programming is proposed to underlie the greatly increased lifetime risk of depression (Heim, Newport *et al*. 2008). However, previous studies examining the HPA axis following childhood abuse have been very small, and do not account for possible biological confounders to HPA assessments such as age, gender and pubertal stage. This is a valuable addition to the literature as it describes the response to a biological dose of Synacthen in a large, well described cohort of children exposed to physical abuse during infancy.

Chapter 6. Glasgow Coma Scale and outcomes after structural traumatic head injury in early childhood

6.1. Preface

The Glasgow Coma Score (GCS) is commonly used to define TBI severity; however GCS scores may not be a reliable index of injury severity in early childhood. As a result, a structural TBI definition was adopted for the early childhood hypopituitarism study. This contrasts with previous studies in adults, which have defined TBI according to GCS category.

The following study sought to investigate the reliability of GCS scores in early childhood. I examined the relationship between GCS score, radiological markers of head injury and various measures of short and long-term outcome. The analysis is based on 10 years of head injury admission data from the Starship Children's Hospital, as well as outcome data from the cohort of children followed in the hypopituitarism study. Note that I have used the more inclusive term "head injury" rather than TBI throughout the manuscript, in acknowledgement of the proportion of children in whom there was no functional or structural evidence of brain injury. In addition, the number of subjects in the follow-up subgroup (n=164) is less than the cohort for the original hypopituitarism study, as it only includes cases that were identified from the Trauma database.

The following section contains the manuscript "Glasgow Coma Scale and outcomes after structural traumatic head injury in early childhood." This manuscript has been submitted for peer review.
All of the work included in this article was carried out as part of this thesis.

Glasgow Coma Scale and outcomes after structural traumatic head injury in early childhood

Natasha Louise Heather[1], José Guilherme Behrensdorf Derraik[1], John Beca[3], Paul Leslie Hofman[1,2], Rangi Dansey[4], James Hamill[4], Wayne Stephen Cutfield[1,2,*]

[1] Liggins Institute, University of Auckland, New Zealand

[2] National Research Centre for Growth and Development, University of Auckland, Auckland, New Zealand

[3] Paediatric Intensive Care Unit, Starship Children's Hospital, Auckland District Health Board, Auckland, New Zealand

[4] Trauma Service, Starship Children's Hospital, Auckland District Health Board, Auckland, New Zealand

* Author for correspondence: Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand; Ph: +64.9. 923.5118; Fax: +64.9.373.8763; Email: w.cutfield@auckland.ac.nz

Running title: GCS & traumatic head injury in childhood

Keywords: Abbreviated Injury Scale, Glasgow Coma Scale, children, head injury

Word count: 2,900

Abbreviations: AIS, Abbreviated Injury Scale; GCS, Glasgow Coma Scale; KOSCHI, King's Outcome Score for Childhood Head Injury; ICU, intensive care unit; THI, traumatic head injury.

NLH and WSC conceived and designed the study, with input from PLH, JGBD and JB. Clinical studies performed by NLH. Data were compiled by NLH, RD, and JH. Data were analysed by JGBD. NLH, WSC, and JGBD wrote the initial drafts of the manuscript. NLH, WSC, and JGBD revised the manuscript with input from JB, PLH, RD, JH. NLH and WSC are the guarantors.

All authors have no financial or non-financial interests to declare that may be relevant to this submitted work.

Abstract

Context: Traumatic head injury (THI) is a very common event in childhood, and the Glasgow Coma Scale (GCS) a simple tool used to assess level of consciousness following head injuries. Thus, it is important to determine whether post-resuscitation GCS scores have predictive value for short- and long-term outcomes following THI in young children.

Objective: To assess the association of GCS with radiological evidence of injury (the Abbreviated Injury Scale, AIS) in young children hospitalized with THI, and the predictive value of GCS and AIS scores for long-term impairment.

Methods: Our study involved a 10-year retrospective review of a database encompassing all patients admitted to Starship Children's Hospital (Auckland, New Zealand, 2000-2010) with THI. Follow-up long-term data were available for outcomes from a smaller subset.

Results: We studied 658 children aged <5 years at the time of THI, with long-term outcome data available for 161 subjects. Both GCS and AIS scores were predictive of length of intensive care (ICU) and hospital stay (all $p<0.0001$). GCS was correlated with AIS ($\rho=-0.46$; $p<0.001$), although a mild GCS commonly under-estimated the severity of radiological injury: 42% of children with mild GCS scores had serious–critical head injury (AIS 3–5). Increasingly severe GCS or AIS scores were both associated with a greater likelihood of long-term impairment (neurological disability, residual problems, and educational support). However, long-term impairment was also relatively common in children with mild GCS scores who had structural head injury more severe than a simple linear skull fracture.

Conclusion: Severe GCS scores will identify most cases of severe radiological injury in early childhood, and are good predictors of poor long-term outcome. However, young children admitted to hospital with structural head injury and mild GCS scores have an appreciable risk of long-term disability, and also warrant long-term follow-up.

Introduction

Traumatic head injury (THI, injury to the scalp, skull or brain) is a very common childhood event (McKinlay, Grace *et al*. 2008), and brain injuries the most frequent cause of trauma fatality during childhood (Hiu Lam and Mackersie 1999). The Glasgow Coma Scale (GCS) is a simple tool used to assess level of consciousness following head injuries, with lower scores denoting greater impairment and more severe THI (Teasdale and Jennett 1974). However, GCS scores are subject to a number of limitations, including inter-observer reliability (Rowley and Fielding 1991; Gill, Reiley *et al*. 2004; Holdgate, Ching *et al*. 2006), time elapsed since injury, as well as the confounding effects of seizures, early sedation or intubation, and physiological shock (Marion and Carlier 1994). Furthermore, the GCS is designed for an adult level of cognition and may be less reliable in young pre-verbal children (Simpson, Cockington *et al*. 1991).

Given their inherent limitations, it is not surprising that GCS scores show a weak and inconsistent association with survival, functional outcome, and radiological severity scores within adult THI populations (Gennarrelli, Spielman *et al*. 1982; Demetriades, Kuncir *et al*. 2004; Udekwu, Kromhout-Schiro *et al*. 2004; Foreman, Caesar *et al*. 2007; Timmons, Bee *et al*. 2011). Similarly, although low GCS scores during childhood are associated with greater mortality, these are not sufficiently reliable to justify limitation of treatment (Chung, Chen *et al*. 2006; Ducrocq, Meyer *et al*. 2006; Fortune and Shann 2010). In addition, there is a weak relationship between injury severity according to initial GCS score and long-term cognitive and behavioural outcomes following early childhood THI (Anderson, Godfrey *et al*. 2012; Crowe, Catroppa *et al*. 2012).

THI can also be graded in terms of radiological markers of injury, which may provide a more reliable index of severity than GCS scores in early childhood. The Abbreviated Injury Scale (AIS) is an anatomical scoring system, where injuries are ranked on a “threat to life” scale of 1 to 6 (1 – mild, 2 – moderate, 3 – serious, 4 – severe, 5 – critical, and 6 – not survivable) (Association for the Advancement of Automotive Medicine, 1998). For example, a head injury where the only anatomical

injury is a scalp contusion would be scored as AIS 1, and a head injury with a skull vault fracture as 2–3, depending on whether it is a simple linear or comminuted/depressed fracture (Association for the Advancement of Automotive Medicine, 1998). Brain contusions are scored between 3–5 depending on their size, location and multiplicity, while subdural haemorrhages are scored as 4–5, also depending on magnitude (Association for the Advancement of Automotive Medicine, 1998). Head region AIS scores are predominantly based on computerised tomography (CT) findings, and correlate with both mortality and functional outcome in adult populations (Demetriades, Kuncir *et al*. 2004; Foreman, Caesar *et al*. 2007; Timmons, Bee *et al*. 2011). Recent versions of the AIS include consensus-derived adaptations for childhood, although these have not been extensively validated (Association for the Advancement of Automotive Medicine, 1998).

The purpose of this study was to assess the predictive value of post-resuscitation GCS within a large cohort of young children who were admitted to a tertiary paediatric hospital with THI. We hypothesised that the post-resuscitation GCS would be a poor indicator of THI severity in early childhood. Therefore, we aimed to examine the association between post-resuscitation GCS, head region AIS, and the length of stay after early childhood THI. In addition, we aimed to assess the association between GCS and AIS scores with disability within a subset of patients for whom follow-up data were available.

Methods

Starship Children's Hospital is the only paediatric neurosurgical centre in the greater Auckland area (New Zealand), receiving all children admitted with THI in the region (population approximately 1.5 million). Subjects admitted with THI at an age <5 years were identified from the Starship Children's Hospital Trauma database (which includes information on all childhood THI admissions) over a 10-year period from 2000-2010. Children whose primary injury was extra-cranial (e.g. major abdominal trauma or limb fracture) paired with relatively mild THI were excluded, as their inclusion could distort ward and ICU admission data.

Demographic data included age at injury, gender, survival to discharge, and duration of admission to both ICU and hospital. Initial hospital post-resuscitation GCS was recorded, and classified as mild (GCS 13–15), moderate (9–12), or severe (3–8) (Rimel, Giordani *et al*. 1982). In addition, the head region AIS (1990 version) was scored based on the initial computerised tomography (CT) scan (Association for the Advancement of Automotive Medicine, 1998). As a result, AIS scores were only available in children who had undergone an acute CT head scan.

Within our institution, the absolute indications for performing an acute CT head scan include GCS score ≤13, neurological deterioration, focal neurological signs, penetrating injury, or a depressed skull fracture. Relative indications include high risk injury mechanism, ≥4 episodes of vomiting, loss of consciousness >1 minute, prolonged lethargy or irritability, or infants with a scalp haematoma. Children with structural head injury evident on CT scan (excluding simple linear skull fracture) are routinely admitted to hospital, as are children with delayed seizures, disabling symptoms, poor access to medical care, and cases of suspected child abuse.

Long-term outcome data were available for a subgroup of patients who had previously been recruited for follow-up as part of another THI study (Heather, Jefferies *et al*. 2012). Children in this subgroup were also recruited from the Trauma database, and further selection criteria included structural THI with head region AIS ≥2 (essentially a skull fracture, intracranial haemorrhage, or cerebral injury) and a minimum interval of 12 months between THI and assessment.

All follow-up clinical assessments were carried out at the Maurice & Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland). Assessments included neurological examination and enquiry about visual or hearing impairment. Neurological disability was defined as motor or sensory deficit sufficient to impair function. In addition, parents were asked about epilepsy, behavioural difficulties, as well as special education needs and input. The child's overall functional status was assessed according to the King's Outcome Scale for Childhood Head Injury (KOSCHI) (Crouchman, Rossiter *et al*. 2001), a paediatric adaptation of the original Glasgow Outcome Scale. The KOSCHI

scale incorporates social and behavioural problems following THI (Crouchman, Rossiter *et al*. 2001), and so has greater sensitivity for functional disability. THI outcomes were classified as either good (score of 5, no sequelae that impact on well-being or function) or including residual problems (4 – moderate disability, 3 – severe disability, 2 – vegetative state) (Crouchman, Rossiter *et al*. 2001).

For this follow-up cohort, data on ethnicity and socio-economic status were also recorded. Ethnicity was identified by self-report using a prioritised system, such that if multiple ethnicities were selected, the subject was assigned to a single ethnicity, following a hierarchical classification (Douglas and Dockerty 2007). Socio-economic status was determined using geo-coded deprivation scores derived from current address, using the New Zealand Index of Deprivation 2006 (NZDep2006) (Salmond, Crampton *et al.* 2007).

Statistical analyses

Non-parametric Spearman's rank correlations were used to examine the association between GCS and AIS scores, as well as to compare the association between each scale with length of hospitalization and ICU stay. For multivariate models, GCS scores were grouped as previously described (mild, moderate, and severe), while AIS scores were grouped as mild–moderate (AIS 1–2), serious–severe (AIS 3–4), and critical (AIS 5). Binary logistic regressions were used to assess those parameters affecting the likelihood of children staying in hospital ≥48 hours and being admitted to ICU. Models included ethnicity, sex, and either GCS or AIS as factors, and age at injury as a covariate.

Baseline data for the follow-up subset were compared to the large cohort using one-way ANOVA or the non-parametric Kruskal-Wallis test. For the follow-up data, binary logistic regressions were adopted to determine the parameters associated with sub-normal KOSCHI outcomes, long-term neurological disability, and allocation of a teacher aide at school. Models included ethnicity, sex, and either GCS or AIS as factors, while age at injury, time interval from injury to assessment, and NZDep2006 scores were included as covariates.

Statistical analyses were carried out in SAS v.9.2 (SAS Institute, Cary, NC, USA) and Minitab v.16 (Pennsylvania State University, USA). The Johnson transformation was adopted as required to stabilize the variance.

Ethics

Ethics approval for this study was provided by the Northern X Regional Ethics Committee and the Auckland District Health Board Research Review Committee. For subjects in the follow-up subset, written informed consent was obtained from guardians of all participants.

Results

Over the 10-year study period, 725 children with THI who were less than five years of age were admitted to Starship Children's Hospital. A total of 29 cases were subsequently excluded: 24 due to incomplete data, and 5 others whose primary injury was extra-cranial. During the admission, 38 children died (5%), all of whom had severe GCS and severe–critical AIS scores. These subjects were excluded from the subsequent analysis, so that 658 THI cases were studied, of whom 171 (26%) required admission to ICU. Their baseline characteristics are shown in Table 6.1.

GCS versus AIS

At the time of hospital admission, 594 children were allocated both GCS and AIS scores. Among these subjects, GCS and AIS scores were correlated (ρ=-0.46; $p<0.0001$), and the relationship between the two scales is illustrated in Figure 6.1. Within our cohort of children admitted to hospital with THI, severe GCS was a good predictor of severe radiological injury, however mild GCS scores were less predictive of mild radiological injury (Figure 6.1). Thus, 39% of children with mild GCS had serious–severe radiological injury (AIS 3 or 4), and a further 3% had critical head injuries (AIS 5; Figure 6.1). Importantly, the child's age at THI appeared to have little effect on this association, as the relationship between GCS and AIS scores was very similar among children <2 and 2–5 years of age (data not shown).

Stay in hospital and ICU

Both GCS and AIS scores were highly predictive of hospitalization for ≥48 hours and ICU admission (Table 6.2). Overall, GCS scores were stronger predictors of the length of ICU admission (ρ=-0.70; $p<0.0001$) than AIS (ρ=0.50; $p<0.0001$). However, the association between GCS and AIS with duration of hospital admission was virtually identical (GCS ρ=-0.59, $p<0.0001$; AIS ρ=0.59; $p<0.0001$). Neither sex nor age at injury was associated with length of admission to hospital or ICU, when AIS or GCS scores were accounted for. Note that separate analyses of the data for children <2 and 2–5 years yielded similar results (data not shown).

Long-term outcomes

Follow-up data were available for 161 children who suffered comparatively more severe injuries than the larger cohort from the database. These children stayed longer in hospital ($p<0.001$), had a greater frequency of admission to ICU ($p<0.01$), and encompassed more subjects with severe GCS ($p<0.001$), and severe ($p<0.01$) and critical AIS ($p<0.01$) compared to those in the larger cohort (Table 6.1).

At follow-up, 98 (61%) of children had made a complete recovery (KOSCHI 5), whilst 56 had residual problems that were graded as moderate (38%, KOSCHI 4), and 7 as severe (4%, KOSCHI 3). Motor or sensory neurological deficits were found in 39 children (24%). There were 18 subjects with impaired vision (cortical blindness, visual field defect, or paralytic strabismus), six with sensorineural hearing loss, and 30 with motor weakness (predominantly hemiplegia). Seven children (4%) were educated in a special needs class, while a further 36 (22%) were allocated time with an individual teacher aide. In addition, nine subjects were diagnosed with epilepsy, and six with attention deficit hyperactivity disorder.

Both GCS (ρ=0.44; $p<0.0001$) and AIS (ρ=0.36; $p<0.0001$) were correlated with KOSCHI scores. As a result, multivariate analyses showed that children with a severe GCS score or a critical AIS injury were considerably more likely to have residual problems (as per KOSCHI scores) at follow-up (Table

6.3). GCS and AIS scores were also good predictors of physical neurological disability, whose odds were much greater among children with severe GCS scores or a critical radiological injury (Table 6.3). Further, among school-aged children (>5 years; n=131), GCS and AIS scores were also predictive of the need for educational support in school (Table 6.3). Notably, long-term outcome measures were largely unaffected by sex, ethnicity, socio-economic status (NZDep2006), age at injury, or interval between injury and assessment.

Injury severity

There were 23 children diagnosed with radiological head injuries consisting solely of simple linear skull fractures (i.e. AIS score of 2). Of these, 20 subjects were ascribed a mild GCS score and the remaining three a moderate score. None of these children were left with motor or sensory neurological deficits or were allocated a teacher aide. Only two children were graded as having residual problems (KOSCHI 4), with parents reporting poor concentration and specific learning difficulties in both cases. Both children had suffered short distance falls (<1.5 m) at around 18 months of age.

Among the children who suffered head injuries more serious than a simple linear skull fracture, mild GCS scores were poor predictors of long-term outcome (Table 6.4). In this group of children, 9% of subjects had a motor or sensory neurological deficit, 18% were allocated an individual teacher aide, and 34% reported residual problems (KOSCHI 3-4, predominantly behavioural and learning difficulties). Of note, the rate of adverse long-term outcomes in this group of children was similar among those ascribed mild and moderate GCS scores (Table 6.4).

Discussion

Among young children admitted to hospital with head injury, mild GCS scores commonly under-estimated the degree of structural head injury. Further, follow-up of those with mild GCS scores and structural head injury revealed an appreciable risk of long-term disability, particularly learning and

behavioural problems. However, we did find that low GCS scores were good predictors of both short- and long-term outcome following early childhood THI.

The literature reports a very low prevalence of cognitive deficits, and educational or behavioural problems, among children admitted to hospital with mild traumatic brain injury (Carroll, Cassidy *et al*. 2004). However, we showed that a third of young children admitted to hospital with mild GCS scores and structural THI reported ongoing problems. Our follow-up cohort was made up of children who suffered relatively severe head injuries, all of whom underwent an acute CT scan and were found to have either a skull fracture or intra-cranial injury. In this group, the prevalence of educational support and residual problems was similar in children ascribed mild or moderate GCS scores. In contrast, it is reassuring to note that the smaller sub-group of children whose worst structural diagnosis was a simple linear skull fracture did well. Such fractures are relatively common in young children with head injuries, and do not carry the same risk of long-term sequelae as more severe structural injuries.

Despite concerns that the GCS may be less reliable in infancy, we found that age at injury did not affect the relationship between GCS and AIS scores. Nonetheless, mild GCS scores provided an unreliable estimate of structural head injury severity, as a third of young children admitted to our institution with mild GCS scores had severe radiological markers of THI (i.e. severe–critical AIS, indicating significant intracranial injury, such as intracerebral haemorrhage, or extensive cerebral contusion). No previous studies have compared AIS and GCS scores in young children, and, as our study encompassed over 600 subjects with THI and represented the 10-year experience of a tertiary paediatric hospital, the results are likely to be applicable to other populations. However, it is important to note that our analyses were based on hospital admissions with THI. Thus, our findings are not representative of the larger group of young children who present to an emergency department or family doctor with head injury and mild GCS scores, and have a much lower likelihood of structural THI. Clearly, it would be inappropriate to perform CT scans in all young children with

mild THI, and validated clinical prediction rules outline the indications for imaging in infants and children (Kuppermann, Holmes *et al*. 2009).

The limitations of this study include the use of retrospective data, which were taken from the trauma database of a tertiary children's hospital. However, AIS scores were assigned in a uniform manner, and were allocated by a single trained user throughout the 10-year period. Post-resuscitation GCS scores were taken from the medical notes, but likewise, this was done in a consistent manner. Follow-up assessments were cross-sectional and occurred at varied intervals following THI, but this interval was included in our multivariate models. Further, we acknowledge that KOSCHI outcome scores may over-estimate the impact of THI, particularly where there is little available information about pre-injury behavioural characteristics and learning.

Overall, our data indicate that severe GCS scores in early childhood will identify most cases of THI with severe radiological injury and requiring urgent initial management, and these scores are also good predictors of poor long-term outcome. However, it is important to recognise the limitations of GCS scores in early childhood. Among young children admitted to hospital with structural head injury, mild GCS scores did not reliably indicate a mild structural injury, and these children also carried an appreciable risk of long-term disability. Thus, children admitted to hospital with structural head injury should receive long-term follow-up irrespective of GCS score.

Acknowledgements

We thank participants and our advisory Kaitiaki group (in particular Deb Rowe and Rhys Jones). We also thank Andrew Law for his input in planning the parent study examining traumatic brain injury, and Alistair Gunn for constructive feedback on this manuscript. This study was supported by grants from the Health Research Council of New Zealand and the Australasian Paediatric Endocrine Group. Natasha Heather was supported by the Starship Fellowship Foundation. We acknowledge the Paykel

Trust for long-term funding of the Maurice & Agnes Paykel Clinical Research Unit at the Liggins Institute.

Table 6.1. Demographics of the studied population.
Where applicable, data are mean ± SD. *p<0.05, **p<0.01, ***p<0.001 for traumatic head injury (THI) database vs. follow-up subgroup**.**

	THI database	Follow-up subgroup
n	658	161
Age at injury (years)	1.9 ± 1.5	2.0 ± 1.6
Males	64%	60%
Age at follow-up assessment (years)	-	7.7 ± 2.6
Time elapsed from injury to follow-up (years)	-	5.7 ± 2.3
Glasgow Coma Scale		
mean score	13.0 ± 3.3	11.5 ± 3.9***
mild (13–15)	73%	53%***
moderate (9–12)	12%	21%*
severe (3–8)	15%	26%***
Abbreviated Injury Scale		
mean score	2.9 ± 1.2	3.6 ± 0.9***
mild (1)	10%	nil***
moderate (2)	36%	16%***
serious (3)	15%	27%**
severe (4)	31%	43%**
critical (5)	8%	15%**
Time spent in hospital (days)	5.9 ± 9.1	10.6 ± 12.3***
Intensive care unit admission	26%	41%**
Time spent in ICU (days)	4.3 ± 4.6	5.2 ± 5.7

Table 6.2 Hospitalization and ICU admission among children admitted to hospital with traumatic head injury (n=658). Data are odds ratios and 95% confidence intervals according to Abbreviated Injury Scale (AIS) and Glasgow Coma Scale (GCS) scores. ****p<0.0001 for the association of AIS or GCS with the outcome measure.

	Hospitalization ≥48 hr	**ICU admission**
n	312	206
AIS		
Mild–moderate (1-2)	1.0 (reference)****	1.0 (reference)****
Serious–severe (3-4)	6.7 (4.5–10.0)	6.1 (3.8–9.9)
Critical (5)	143 (8.6–1000)	84.9 (31.7–227)
GCS		
Mild (13-15)	1.0 (reference)****	1.0 (reference)****
Moderate (9-12)	5.9 (3.1–11.2)	11.5 (6.7–19.7)
Severe (3-8)	66.7 (13.1–339)	127 (56.2–286)

Table 6.3. Adverse long-term outcomes among children admitted to hospital with traumatic head injury. Data are odds ratios and 95% confidence intervals according to Abbreviated Injury Scale (AIS) and Glasgow Coma Scale (GCS) scores. *p<0.05, **p<0.01, ***p<0.001, and ****p<0.0001 for the association of AIS or GCS with the outcome measure.

	Neurological disability	**Residual problems**	**Educational support**
n	161	161	131
AIS			
Mild–moderate (1-2)	1.0 (reference)***	1.0 (reference)**	1.0 (reference)*
Serious–severe (3-4)	6.4 (0.4–97.0)	3.1 (0.8–11.7)	5.5 (1.0–30.8)
Critical (5)	41.6 (2.4–715)	18.7 (3.6–98.6)	13.8 (1.9–101)
GCS			
Mild (13-15)	1.0 (reference)****	1.0 (reference)***	1.0 (reference)**
Moderate (9-12)	3.6 (0.6–20.5)	1.0 (0.4–2.8)	2.5 (0.4–14.6)
Severe (3-8)	46.3 (8.3–258)	6.7 (2.4–19.0)	20.8 (3.8–114)

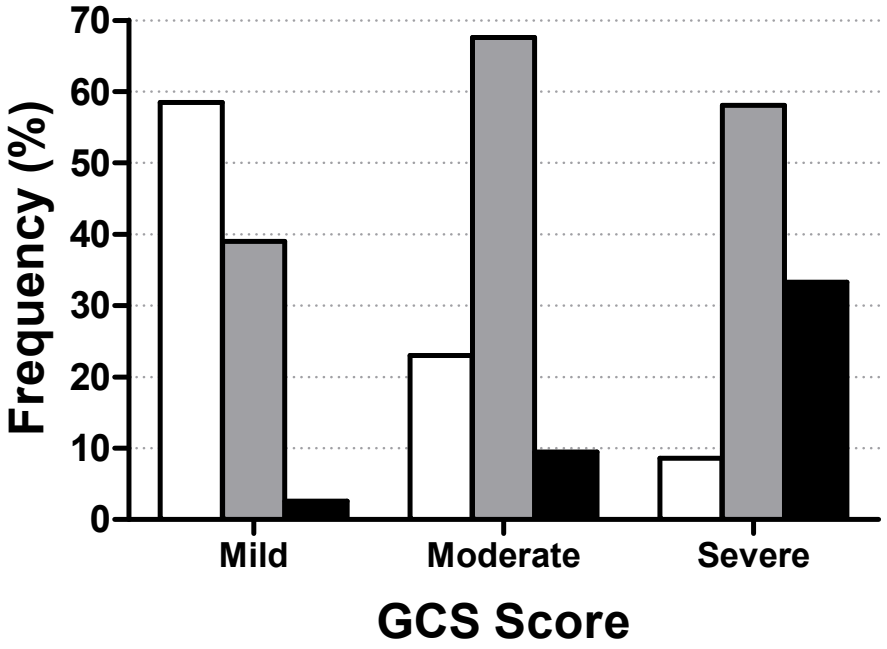
Neurological disability - sensory or motor deficit; residual problems - score of <5 as per the King's outcome scale for childhood head injury (KOSCHI); educational support - allocation of an individual teacher aide or placement in a special needs class.

Table 6.4. GCS scores and the prevalence of long-term disability among children admitted to hospital with traumatic head injury, with a radiological diagnosis more severe than a simple linear skull fracture (n=138). Educational support refers solely to school-aged children (>5 years, n=114).

GCS Score	Neurological disability	Residual problems	Educational support
Mild (13-15)	9% (6/65)	34% (22/65)	18% (10/56)
Moderate (9-12)	23% (7/31)	35% (11/31)	22% (5/23)
Severe (3-8)	62% (26/42)	76% (32/42)	60% (21/35)
Total cohort	28% (39/138)	47% (65/138)	32% (36/114)

GCS - Glasgow Coma Scale; Neurological disability - sensory or motor deficit; Residual problems - score of <5 as per the King's outcome scale for childhood head injury (KOSCHI); Educational support - allocation of an individual teacher aide or placement in a special needs class.

Figure 6.1. The association between GCS and AIS scores among children who suffered early childhood traumatic head injury.
Bars represent AIS scores. The darker the bar the more serious the radiological injury: from mild–moderate (white), serious–severe (gray), and critical (black) (n = 594).



6.2. Particular issues

6.2.1. Inflicted head injury

Although not discussed in the manuscript, GCS scoring may be a poorer index of head injury severity amongst children with inflicted injuries. This is because scores are intended to describe the acute response to a single injury, whereas abusive injuries typically involve a series of repeated events, compounded by delayed medical presentation. The Trauma database did not contain sufficient information to identify cases of suspected/definite abuse, and cannot be used to answer this question. However, the relationship between GCS and radiological head injury grade was analysed separately amongst children <2 years and 2-5 years, and no difference found. As inflicted head injury is far more common amongst children <2 years, this suggests little overall impact from this factor.

6.3. Significance and contribution

Level of consciousness is an integral part of clinical assessment following head injury, and is almost universally defined using the GCS. However, there is surprisingly little data to support the validity and reliability of this scale during early childhood. My analysis of the predictive value of GCS scores in early childhood head injury is based on a large, comprehensive database, and multiple short and long-term outcome measures. In addition, it is the first study to compare GCS scores to a grading scale for structural head injury in early childhood. Importantly, over a quarter of young children admitted to hospital with mild GCS scores had radiological markers of severe brain injury, which was associated with an appreciable risk of long-term cognitive, behavioural and educational problems. The clinical message is that young children who are admitted to hospital with structural head injury should receive long-term follow-up irrespective of GCS score.

Chapter 7. Summary and future directions

7.1. Summary

7.1.1. TBI and hypopituitarism

TBI is very a common problem in all populations. It can have a devastating impact on individuals, and creates a large burden of disability across communities. Hypopituitarism is proposed to be a greatly under-recognised complication of TBI, affecting an astounding 25% of adults who sustain a moderate-severe TBI (Schneider, Kreitschmann-Andermahr *et al*. 2007). As a result, a number of expert groups have issued recommendations for routine pituitary screening following TBI (Casanueva, Ghigo *et al*. 2004; Ghigo, Masel *et al*. 2005; Schneider, Stalla *et al*. 2006). However, as outlined in Chapter 2 and Chapter 3, it is highly likely that the prevalence of hypopituitarism has been routinely over-estimated.

The central aim of this thesis was to consider the paediatric application of this emerging paradigm. Chapter 3 is based on an expert commentary of this topical issue, and provides insight into the controversies and apparently contradictory results within the literature (Heather and Cutfield 2011). The few paediatric studies have been small, and report a highly variable rate (5-61%) of hypopituitarism (Niederland, Makovi *et al*. 2007; Moon, Sutton *et al*. 2010). In New Zealand, it is estimated that a third of the population will have suffered an episode of TBI by 25 years of age (McKinlay, Grace *et al*. 2008). Thus, even at the lower end of the reported risk, hypopituitarism should be an extremely prevalent condition. However, this does not reflect what is seen in clinical practice, as very few children with head injuries are treated in endocrine clinics.

The mismatch between the proposed incidence and realities of clinical practice make this a controversial subject; either we are missing large numbers of affected children, or the data has been misinterpreted. Pituitary evaluations are invasive and expensive, and generate a high proportion of false positive results. Therefore, as outlined in this thesis, the current level of evidence does not justify routine invasive pituitary assessments following childhood TBI. Conversely, significant hypopituitarism during childhood could also be detected by simple observation of growth and development, and this is a better approach to population screening (Heather and Cutfield 2011).

7.1.2. Early childhood TBI

The core of this thesis is a clinical study which aimed to assess the risk of permanent hypopituitarism following early childhood TBI (Heather, Jefferies *et al*. 2012). This cohort of 198 children is the largest to date, and their inclusion doubles the total number reported in the literature. My intention was to assess the prevalence of true, clinically significant, hypopituitarism. Therefore, I used stringent and comprehensive diagnostic criteria, with careful evaluation of potentially abnormal results. Earlier studies have based the diagnosis of GH deficiency entirely on GH stimulation tests, whereas I performed a detailed assessment of GH, IGF-I and growth pattern, with consideration given to pubertal stage and obesity. Although up to 33% of the study population might have been labelled with GH deficiency based on GH stimulation tests alone, no subjects had true deficiency supported by comprehensive assessment criteria. No other studies have used comprehensive criteria to verify their results, and the high false positive rate intrinsic to GH tests (results that falsely suggest disease in normal subjects) will have undoubtedly lead to the routine over-reporting of GH deficiency following TBI.

Furthermore, this is the first study to focus on young children, and includes a potentially high risk sub-group of infants with inflicted TBI. Abusive head trauma occurs in the very young, and typically

involves multiple episodes of TBI (Barlow and Minns 2000). Furthermore, the injury mechanism (violent shaking ± impact) may place victims at high risk of shear injury to pituitary vessels, analogous to the retinal haemorrhages which act as markers for abusive head trauma (Bechtel, Stoessel *et al*. 2004). In retrospect, it is surprising that this group has received such little attention, as the consequences of undiagnosed hypopituitarism in early childhood are highly significant, and abused children a vulnerable group who suffer considerable long-term neurological morbidity (Jayawant, Rawlinson *et al*. 1998).

As a result of this work, I have demonstrated that permanent hypopituitarism is rare following structural TBI in early childhood. Although the age of the cohort differed to that previously studied, structural injuries were comparable, and it is likely that the results can be extrapolated to older populations. The rate of apparent hypopituitarism was also comparable to previous studies; however, I was able to demonstrate that these were all false positive results in normal subjects. Therefore, comprehensive assessment and prospective surveillance revealed the limitations of the "one-off" pituitary assessments that previous studies have used to diagnose hypopituitarism. For these reasons, this is a significant negative study which challenges current thinking.

7.1.3. Inflicted TBI

My original hypothesis was that hypopituitarism would be more common after TBI that was inflicted as opposed to accidental. However, the only significant hormonal difference between injury groups was that the cortisol response to Synacthen was lower amongst TBI_I. Although the decrease in stimulated cortisol was appreciable (14%), no subjects required treatment for adrenal insufficiency. As outlined in Chapter 5, the data were analysed using mixed linear models, controlling for appropriate confounding factors, in particular age and gender. Furthermore, there was no relationship between cortisol concentration and the severity of structural TBI. Therefore, although

injury severity was greater in the inflicted group, the cortisol difference is unlikely to be explained by a greater prevalence of pituitary injury (and isolated partial ACTH deficiency) within this group.

My results are in accordance with a number of previous studies reporting HPA dysfunction following childhood abuse (De Bellis, Chrousos *et al*. 1994; Carlson and Earls 1997; Heim, Newport *et al*. 2001; Carpenter, Tyrka *et al*. 2009). These changes have been demonstrated to occur following various forms of child abuse (including sexual abuse and neglect), and so are likely to reflect a common response to environmental adversity. This is a valuable addition to the literature as it describes a large cohort with well defined physical characteristics (age, gender, pubertal stage) who were exposed to severe physical abuse during infancy. Furthermore, the assessment was made using a gold standard test of pituitary and adrenal function, with a control group composed of similar aged children who had suffered accidental TBI.

Given the high concurrence of child abuse and interparental violence, which often escalates during pregnancy (Edleson 1999), it is conceivable that HPA programming in abused children begins prenatally. There are no published data on the human offspring effect of violence during pregnancy, although animal studies provide strong evidence that maternal stress during pregnancy can have a lifelong impact on offspring HPA function (Plotsky and Meaney 1993). Although I was unable to demonstrate an association between violence and cortisol concentrations within my cohort, limitations included small numbers within subgroups, and the likely under-reporting of violence. Therefore, although domestic violence during pregnancy could be anticipated to programme the HPA axis, its influence within my cohort is unclear.

The link between childhood abuse and an attenuated “stress” cortisol response raises a number of important questions. In particular, the natural history and the mental and metabolic health significance of the observed difference are unknown.

7.1.4. GCS and head injury severity

Unlike previous authors, I adopted a structural (AIS) rather than functional (GCS) definition of head injury in the early childhood hypopituitarism study. The association between GCS and hypopituitarism is weak; possible explanations include the limited reliability of GCS scores, that GCS is a rather indirect proxy for pituitary damage, or the over-diagnosis of hypopituitarism. Furthermore, GCS may be less reliable in pre-verbal children, and therefore a less valuable index of injury severity during early childhood. However, as there were no cases of true hypopituitarism within my cohort, I was unable to validate my approach by comparing the likelihood of hypopituitarism at different AIS and GCS scores.

Instead, I sought to evaluate the reliability of GCS scores as an index of injury severity in young children admitted to hospital with head injuries. My data is based on the analysis of a large and comprehensive database of early childhood trauma admissions to a tertiary paediatric hospital over 10 years. Within this large cohort of >600 children, increasingly severe GCS scores were associated with more severe structural injuries, greater length of stay, and a greater likelihood of poor long-term outcome. Of concern, mild GCS scores were commonly ascribed to children with severe structural head injury, an appreciable proportion of whom also demonstrated long-term disability.

Few TBI studies have looked at the prognostic value of childhood GCS scores, and these have included children of all ages and focused predominantly on those with severe scores (Lieh-Lai, Theodorou *et al*. 1992; Ducrocq, Meyer *et al*. 2006). My data has provided insight into outcomes for young children who are hospitalised with apparent mild TBI, and highlights the risk of long-term disability within this group.

7.2. Future directions

7.2.1. TBI and hypopituitarism

Ideally, the prevalence and significance of hypopituitarism following childhood TBI would be evaluated through an auxology-based multi-centre study. Childhood TBI encompasses a range of age groups and injury mechanisms, so that a definitive cohort would need to be very large. However, it is difficult to justify such a large-scale investigation given the low risk of hypopituitarism, and it is unlikely that this data will be obtained.

To date, the risk of hypopituitarism following adolescent TBI has been largely overlooked. The incidence of TBI is particularly high during this period, and often sustained during competitive sports. There are concerning case reports of hypopituitarism following repeated episodes of sports-related concussion (Kelestimur, Tanriverdi *et al*. 2004; Ives, Alderman *et al*. 2007). Given the large numbers of adolescents who play contact sports, it would be important to investigate whether sports-related concussion carries an appreciable risk of pituitary injury, either transient or permanent.

Furthermore, prolonged concussive symptoms are common following TBI, and associated with considerable morbidity. It is possible that the so-called post concussion syndrome is actually caused by mild, transient hormone deficiency (particularly GH). Large cohorts report a general trend towards recovery of pituitary function in the first year after TBI (Agha, Phillips *et al*. 2005; Klose, Juul *et al*. 2007), although the significance of this and the relationship to cognitive symptoms is uncertain. At this stage, there are no data describing the effects of short-term hormone replacement during recovery from TBI, and the treatment threshold for early biochemical deficiency remains unclear.

Again, there is very little longitudinal paediatric data, although I am aware of several prospective studies currently underway. In particular, it would be important to assess the impact of transient low

hormone levels on growth, learning and development. The ability to return to school is an important clinical outcome, which could justify short-term hormone replacement within childhood TBI populations.

One of the major difficulties in this area is that TBI is a highly heterogeneous condition. Increasingly sophisticated models, integrating demographics, injury details and clinical course are now used to predict TBI outcome (Lingsma, Roozenbeek *et al*.). Over time, it may be possible to predict the risk of hypopituitarism based on a similar combination of factors. However, at this stage, the search for early markers has been disappointing.

In particular, both early MRI and anti-pituitary antibody levels may have a useful role in quantifying the risk of hypopituitarism The frequency of gross structural pituitary abnormalities is high amongst case reports (Benvenga 2005), but low within systematic series. Subtle changes, such as early pituitary oedema, may be important, although larger datasets are needed to confirm this (Maiya, Newcombe *et al*. 2008). Similarly, the level of anti-pituitary antibodies is likely to reflect the degree of pituitary damage, so that high levels may also predict hypopituitarism. However, the only group to look at this association reported antibody levels at three years after TBI (Tanriverdi, De Bellis *et al*. 2008), so that the value of early measurements is not clear.

Furthermore, the proposed mechanism of injury has never been demonstrated in animal models. Instead, a vascular mechanism is suggested based on the anatomy, historical autopsy data, and small MRI series. In particular, there is no data linking hormone levels to histological injury, although this could easily be achieved in an animal model. A further advantage to animal work is the ability to define injury exposure. Had hypopituitarism been as common as expected within my cohort, it would have been important to follow this up with a model to evaluate the vulnerability of pituitary vessels to shaking injuries in early life. Similar models could be used to explore the threshold of

pituitary or hypothalamic injury to different injury types, such as falls, motor vehicle accidents or repetitive trauma, or to physiological insults such as hypotension, asphyxia or raised ICP.

7.2.2. Abuse and HPA dysfunction

In addition, the link between abuse and an attenuated stress response raises important questions. There is an urgent need for studies to assess the longitudinal course and significance of HPA dysfunction following abuse of mothers and children. Such studies would ideally commence in early pregnancy, including mothers with and without risk factors for abuse, and following offspring throughout their childhood. As with the early childhood TBI study, recruitment would be logistically difficult; families would need to be approached sensitively, and a high drop-out rate anticipated. Key outcomes would be to document HPA function over time amongst children with and without exposure to family violence, as well as the mental health and metabolic status within these groups.

7.3. Summary

In this thesis, I have presented a body of work that arose from the hypothesis that hypopituitarism is common amongst infants with the shaken baby syndrome. In a highly significant negative study, I have demonstrated that permanent hypopituitarism is rare following either accidental or abusive TBI in early childhood. Furthermore, in the absence of comprehensive diagnostic criteria, a third of subjects within my cohort could have been mislabelled with GH deficiency.

Pituitary tests are costly, invasive, and potentially harmful and should not form a part of “routine” care following childhood TBI. Instead, simple surveillance of growth and development, either by family doctors or as part of existing hospital outpatient care, could similarly identify the very small number of head-injured children who develop hypopituitarism. This data will undoubtedly impact clinical practice and the future management of large numbers of head injured children.

Chapter 8. Appendices

8.1. Awards and abstracts

Awards and presentations

- Heather N. Traumatic brain injury and hypopituitarism - a battered myth? Australasian Paediatric Endocrine Group (APEG) annual scientific meeting, Perth 2011.

  Winner of the APEG young investigator award, 2011.

- Heather N. Hypopituitarism is rare following traumatic brain injury in early childhood. Auckland Hospital research celebration, 2011.

  Winner of the Auckland Hospital young investigator award and best poster, 2011.

Submitted abstracts

- Heather N, Cutfield W. Cortisol response to synacthen stimulation is attenuated following abusive head trauma. Endocrinology, Houston, June 2012.

8.2. Letter to prospective study participants

2-6 Park Avenue, Grafton
Private Bag 92019
Auckland, New Zealand
Telephone: 64 9 373 7599 ext. 84476
Facsimile: 64 9 373 7497
Email: w.cutfield@auckland.co.nz
Web: www.liggins.auckland.ac.nz

INFORMATION SHEET

Study title: **Assessment of Pituitary function in children who sustained Traumatic Brain Injury in infancy**

Principle investigator: **Dr Wayne Cutfield**
Director of Paediatric Endocrinology
Starship Hospital
Professor of Paediatrics
University of Auckland
Phone 373 7599 ext 84476

You are invited to participate in a research study looking at the risk of pituitary damage in children who suffered a serious head injury in infancy. Please take time to consider this invitation carefully. Taking part is entirely voluntary, and your refusal will in no way affect you or your child's continuing health care.

Study background:

The brain's pituitary gland produces hormones that are essential for growth and well-being. Studies in adults have shown that many victims of serious head injury have low levels of at least one of these hormones. It is not routine to check the function of the pituitary gland after serious head injury. This has meant that some adults have had low pituitary hormone levels that were not detected or treated.

Children with low pituitary hormone levels may suffer from health problems. These include poor growth and pubertal development, muscle weakness, weight gain, extreme tiredness, poor school performance and an inability to cope with illness. Fortunately, all of these symptoms can be successfully treated with hormones.

We plan to do a thorough follow-up study to assess the pituitary function in children who suffered serious head injury in infancy. We expect to find some children with low pituitary hormone levels and they will receive appropriate treatment that will improve their health and well-being.

Our study will also look at the risk factors for pituitary damage after serious head injury. In the future this knowledge will help doctors to identify children at risk of low pituitary hormone levels and mean that they can be diagnosed and given effective treatment as early as possible.

Who is being selected?

The study is recruiting children aged 2-18 years who are patients of Starship Children's Health and suffered from traumatic brain injury in the first five years of life. The injury will have been graded in hospital as moderate or severe, with bleeding in the head or a fracture seen on X-ray or head scan. We hope to study a total of 200 children.

Please tell the researcher if your child suffers from any medical illness or takes medication as some conditions, particularly endocrine disorders that were known about before the injury and high doses of oral steroids, may prevent your child being eligible for this study. If your teenager is pregnant they will not be able to take part in the study.

What does the study involve?

There is a single assessment which will take approximately 4 hours. We make appointments for first thing in the morning as children need to have had nothing to eat or drink overnight. A doctor or nurse will perform all testing.

The assessment will be performed at the Clinical Research Unit on the ground floor of the Liggins Institute Building, which is located close to the Medical School. Parking will be available and free to you at the Liggins Institute.

Overall, we will do the following:

1. A brief medical history and examination will be undertaken. We will ask for both parents' height then measure your child's height and weight and assess puberty.

2. At the start of the study the children will be given 3 or 4 medicines that stimulate hormone production. These are arginine (a protein), clonidine (a blood pressure lowering medicine), synacthen and possibly GnRH (both synthetic hormones.)

3. An intravenous cannula (a drip) will be put into an arm vein using anaesthetic cream to numb the area of skin. Blood samples will be taken from the drip every 30 minutes - this is painless and very well tolerated by children. The total volume of blood taken is small (approximately 2-3 teaspoons).

The test will take around 3 hours and during this time the child can watch a video of his or her choice. At the end of the test, breakfast/ brunch will be provided.

Please note that teenagers will not be able to drive themselves home as they may be drowsy.

What are the potential benefits and risks?

We have been performing these tests at Starship to assess pituitary function in children for over 20 years and have a lot of experience in doing them. There is a small risk of bruising or distress while the drips are placed, but this is rare, and any distress is minimised by using anaesthetic cream.

We do not know whether it is safe to take the assessment drugs during pregnancy. Clonidine sometimes makes children drowsy for a few hours and can occasionally cause nightmares and disturbed sleep. Allergic reaction to the assessment drugs is very rare.

The main benefit of the study is that we expect to identify some children with undiagnosed low pituitary hormone levels. These children will then be given appropriate treatment which will improve their health.

Will I be able to see the results?

Any abnormal findings discovered during this study will be discussed with the child's parents as soon as they are found and appropriate treatment arranged. Most parents will be told of their child's individual results after the all of the results have been analysed (this may take some months). You will also be told of the results of the group as a whole if you request this on your consent form.

Do I have to participate?

Participation in this study is entirely voluntary (your choice). If you choose not to take part in this study it will not affect any future care or treatment. If you do agree to take part you are

free to withdraw at any time, without having to give any reason. Participation in this study will be stopped if the doctor feels that continuing is not in the best interests of the child or family. We would always discuss this with you first.

Confidentiality

No material, which could personally identify you or your child, will be used in any reports on this study. A unique study number will be used to identify each participant's specimens and recorded details. This unique number will ensure the confidentiality of any records we keep. All blood samples will be destroyed at the end of the study.

Compensation issues:

As for any medical study, we have to address the unlikely event of physical injury as a result of participation in this study. You or your child may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case would need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act.

If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

Who should I contact if I have further questions?

If you would like further information or have any questions regarding the study, please feel free to contact:

Dr Natasha Heather (Study Coordinator), xxx

Christine Brennan (Research Nurse), xxx

Dr Craig Jefferies - xxx

Dr Paul Hofman - xxx

Dr Wayne Cutfield - xxx

For Maori Health Support please contact:

Auckland District Health Board: Mata Forbes, RGON, Coordinator/Advisor, Maori Health Services Auckland Hospital, mobile xxx, telephone xxx.

If you have any queries or concerns regarding your rights as a participant in this research study, you may contact an independent Health and Disability Advocate. This is a free service provided under the Health and Disability Commissioner Act:

Telephone (NZ wide):	0800 555 050
Free Fax (NZ wide):	0800 2787 7678 (0800 2 SUPPORT)
Email:	advocacy@hdc.org.nz

If you agree to participate you will be asked to sign a consent form.

This study has received ethical approval from the Northern X Regional Ethics Committee.

8.3. Copyright permissions

Dear Dr. Natasha Heather,

Thank you for placing your order through Copyright Clearance Center's RightsLink service. Elsevier has partnered with RightsLink to license its content. This notice is a confirmation that your order was successful.

Order Details
Licensee: Natasha Heather
License Date: Mar 10, 2012
License Number: 2865550985946
Publication: Endocrinology and Metabolism Clinics of North America
Title: NEUROENDOCRINE AGING IN MEN: Andropause and Somatopause
Type Of Use: reuse in a thesis/dissertation
Total: 0.00 USD

Order Details
Licensee: Natasha Heather
License Date: Mar 10, 2012
License Number: 2865550985946
Publication: Endocrinology and Metabolism Clinics of North America
Title: NEUROENDOCRINE AGING IN MEN: Andropause and Somatopause
Type Of Use: reuse in a thesis/dissertation
Total: 0.00 USD

This is a License Agreement between Natasha Heather ("You") and Elsevier ("Elsevier"). The license consists of your order details, the terms and conditions provided by Elsevier, and the payment terms and conditions.

Get the printable license.

License Number	2843361131333
License date	Feb 06, 2012
Licensed content publisher	Elsevier
Licensed content publication	The American Journal of Medicine
Licensed content title	The natural history of post-traumatic hypopituitarism:

	Implications for assessment and treatment
Licensed content author	Amar Agha,Jack Phillips,Patrick O'Kelly,William Tormey,Christopher J. Thompson
Licensed content date	December 2005
Licensed content volume number	118
Licensed content issue number	12
Number of pages	7
Type of Use	reuse in a thesis/dissertation
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1
Format	both print and electronic
Are you the author of this Elsevier article?	No
Will you be translating?	No
Order reference number	
Title of your thesis/dissertation	Permanent hypopituitarism is rare following early childhood traumatic brain injury
Expected completion date	Apr 2012
Estimated size (number of pages)	100
Elsevier VAT number	GB 494 6272 12
Permissions price	0.00 USD
VAT/Local Sales Tax	0.0 USD / 0.0 GBP

ELSEVIER LICENSE
TERMS AND CONDITIONS

Mar 04, 2012

This is a License Agreement between Natasha Heather ("You") and Elsevier ("Elsevier") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Elsevier, and the payment terms and conditions.

Supplier	Elsevier Limited The Boulevard,Langford Lane Kidlington,Oxford,OX5 1GB,UK
Registered Company Number	1982084
Customer name	Natasha Heather
Customer address	25 Wairiki Rd

	Auckland, New Zealand 1024
License number	2856751318578
License date	Feb 26, 2012
Licensed content publisher	Elsevier
Licensed content publication	The Journal of Pediatrics
Licensed content title	Traumatic Brain Injury: Is the Pituitary Out of Harm's Way?
Licensed content author	Natasha Heather,Wayne Cutfield
Licensed content date	October 2011
Licensed content volume number	159
Licensed content issue number	4
Number of pages	5
Start Page	686
End Page	690
Type of Use	reuse in a thesis/dissertation
Intended publisher of new work	other
Portion	full article
Format	both print and electronic
Are you the author of this Elsevier article?	Yes
Will you be translating?	No
Title of your thesis/dissertation	Traumatic brain injury in early childhood – what is the risk of hypopituitarism?
Expected completion date	Apr 2012

The Endocrine Society
8401 Connecticut Avenue, Suite 900
Chevy Chase, MD 20815-5817
Telephone: 301-941-0200
Fax: 301-941-0259
www.endo-society.org
TIN Number: 73-0531256

Form was submitted by: n.heather@auckland.ac.nz

Original author to publish in a Dissertation.

Date: March 4, 2012
Reference Number:

Name: Natasha Heather
Organization: Liggins Institute
Department:
Address: University of Auckland
Private bag 92019
City, State and Postal Code: Auckland, 1142
Country: New Zealand
Phone: +64 9 923 6691
Fax:
Email: n.heather@auckland.ac.nz

Journal: The Journal of Clinical Endocrinology & Metabolism
Author Name: N Heather
Title: Permanent hypopituitarism is rare after structural traumatic brain injury in early childhood
Year: 2012
Volume: 97
Page Range: 599-604
Figure Reproduction:
Figure Number(s): Table 1, Table 2
Where will the figures appear:
- Dissertation
- Title: Traumatic brain injury in early childhood - what is the risk of hypopituitarism?
- Publisher: University of Auckland

Title: Journal Publications Coordinator
Date: March 4, 2012

JOHN WILEY AND SONS LICENSE
TERMS AND CONDITIONS

Mar 04, 2012

This is a License Agreement between Natasha Heather ("You") and John Wiley and Sons ("John Wiley and Sons") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by John Wiley and Sons, and the payment terms and conditions.

License Number	2862170047185
License date	Mar 04, 2012
Licensed content publisher	John Wiley and Sons
Licensed content publication	Clinical Endocrinology
Licensed content title	Cortisol response to synacthen stimulation is attenuated following abusive head trauma
Licensed content author	Natasha L Heather,José G B Derraik,Christine Brennan,Craig Jefferies,Paul L Hofman,Patrick Kelly,Rhys G Jones,Deborah L Rowe,Wayne S Cutfield
Licensed content date	Feb 1, 2012
Start page	n/a
End page	n/a
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic
Portion	Full article
Will you be translating?	No
Order reference number	
Total	0.00 USD

References

Acerini, C. L. and R. C. Tasker (2007). "Traumatic brain injury induced hypothalamic-pituitary dysfunction: a paediatric perspective." Pituitary **10**(4): 373-380.

Acerini, C. L., R. C. Tasker, *et al*. (2006). "Hypopituitarism in childhood and adolescence following traumatic brain injury: the case for prospective endocrine investigation." European Journal of Endocrinology **155**(5): 663-669.

Adamo, M. A., D. Drazin, *et al*. (2009). "Comparison of accidental and nonaccidental traumatic brain injuries in infants and toddlers: demographics, neurosurgical interventions, and outcomes." Journal of Neurosurgery: Pediatrics **4**(5): 414-419.

Agha, A., J. Phillips, *et al*. (2005). "The natural history of post-traumatic hypopituitarism: implications for assessment and treatment." American Journal of Medicine **118**(12): 1416.

Agha, A., B. Rogers, *et al*. (2004). "Anterior pituitary dysfunction in survivors of traumatic brain injury." Journal of Clinical Endocrinology and Metabolism **89**(10): 4929-4936.

Agha, A., J. Ryan, *et al*. (2005). "Spontaneous recovery from posttraumatic hypopituitarism." American Journal of Physical Medicine & Rehabilitation **84**(5): 381-385.

Agha, A., M. Sherlock, *et al*. (2005). "The natural history of post-traumatic neurohypophysial dysfunction." European Journal of Endocrinology **152**(3): 371-377.

Agha, A. and C. J. Thompson (2006). "Anterior pituitary dysfunction following traumatic brain injury (TBI)." Clinical Endocrinology **64**(5): 481-488.

Agha, A., E. Thornton, *et al*. (2004). "Posterior pituitary dysfunction after traumatic brain injury." Journal of Clinical Endocrinology & Metabolism **89**(12): 5987-5992.

Aimaretti, G., M. R. Ambrosio, *et al*. (2004). "Hypopituitarism and growth hormone deficiency (GHD) after traumatic brain injury (TBI)." Growth Hormone & IGF Research **14 Suppl A**: S114-117.

Aimaretti, G., M. R. Ambrosio, *et al*. (2004). "Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury." Clinical Endocrinology **61**(3): 320-326.

Aimaretti, G., M. R. Ambrosio, *et al*. (2005). "Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12-month study." Journal of Clinical Endocrinology & Metabolism **90**(11): 6085-6092.

Al-Salamah, M. A., I. McDowell, *et al*. (2004). "Initial emergency department trauma scores from the OPALS study: the case for the motor score in blunt trauma." Academic Emergency Medicine **11**(8): 834-842.

Amed, S., E. Delvin, *et al*. (2008). "Variation in growth hormone immunoassays in clinical practice in Canada." Hormone Research in Paediatrics **69**(5): 290-294.

Anawalt, B. D. and G. R. Merriam (2001). "Neuroendocrine aging in man: andropause and somatopause." Endocrinology and Metabolism Clinics of North America **30**(3): 647-669.

Anderson, V., C. Godfrey, *et al*. (2012). "Predictors of cognitive function and recovery 10 years after traumatic brain injury in young children." Pediatrics **129**(2): e254-e261.

Arlt, W. and B. Allolio (2003). "Adrenal insufficiency." Lancet **361**: 1881-1993.

Barbeau, C., B. Jouret, *et al*. (1998). "Pituitary stalk transection syndrome." Archives of Paediatrics **5**(3): 274-279.

Barlow, K. M. and R. A. Minns (2000). "Annual incidence of shaken impact syndrome in young children." Lancet **356**(9241): 1571-1572.

Barlow, K. M., E. Thomson, *et al*. (2005). "Late neurologic and cognitive sequelae of inflicted traumatic brain injury in infancy." Pediatrics **116**(2): e174-e185.

Barzilay, Z. and E. Somekh (1988). "Diabetes insipidus in severely brain damaged children." Journal of Medicine **19**(1): 47-64.

Baxter, R. A. C., A. S. Brown, *et al*. (1982). "Radioimmunoassay for somatomedin-C: comparison with radioreceptor assay in patients with growth disorders, hypothyroidism and renal failure." Clinical Chemistry **28**: 488-495.

Bechtel, K., K. Stoessel, *et al*. (2004). "Characteristics that distinguish accidental from abusive injury in hospitalized young children with head trauma." Pediatrics **114**(1): 165-168.

Benvenga, S. (2005). "Brain injury and hypopituitarism: the historical background." Pituitary **8**(3-4): 193-195.

Benvenga, S., A. Campenni, *et al*. (2000). " Hypopituitarism secondary to head trauma." Journal of Clinical Endocrinology & Metabolism **85**(4): 1353-1361.

Benvenga, S., T. Vigo, *et al*. (2004). "Severe head trauma in patients with unexplained central hypothyroidism." American Journal of Medicine **116**(11): 767-771.

Berg, C., T. Meinel, *et al*. (2010). "Diagnostic utility of the glucagon stimulation test in comparison to the insulin tolerance test in patients following pituitary surgery." European Journal of Endocrinology **162**(3): 477-482.

Berg, C., A. Oeffner, *et al*. (2010). "Prevalence of anterior pituitary dysfunction in patients following traumatic brain injury in a German multi-centre screening program." Experimental and Clinical Endocrinology and Diabetes **118**(2): 139-144.

Bidlingmaier, M. and P. U. Freda (2010). "Measurement of human growth hormone by immunoassays: current status, unsolved problems and clinical consequences." Growth Hormone and IGF Research **20**(1): 19-25.

Billmire, M. E. and P. A. Myers (1985). "Serious head injury in infants: accident or abuse?" Pediatrics **75**(2): 340-342.

Bondanelli, M., L. De Marinis, *et al*. (2004). "Occurrence of pituitary dysfunction following traumatic brain injury." Journal of Neurotrauma **21**(6): 685-696.

Bottner, A., J. Kratzsch, *et al*. (2005). "Comparison of adrenal function tests in children - the glucagon stimulation test allows the simultaneous assessment of adrenal function and growth hormone response in children." Journal of Pediatric Endocrinology and Metabolism **18**(5): 433-442.

Brien, T. G. (1981). "Human corticosteroid binding globulin " Clinical Endocrinology **14**(2): 193-212.

Browne, G. J., A. J. Cocks, *et al*. (2001). "Current trends in the management of major paediatric trauma." Emerg Med **13**: 418-425.

Bushnik, T., J. Englander, *et al*. (2007). "Fatigue after TBI: Association with neuroendocrine abnormalities." Brain Injury **21**(6): 559-566.

Caffey, J. (1972). "On the theory and practice of shaking infants: its potential residual effects of permanent brain damage and mental retardation." American Journal of Diseases of Children **124**(2): 161-169.

Caffey, J. (1974). "The whiplash shaken infant syndrome: manual shaking by the extremities with whiplash-induced intracranial and intraocular bleedings, linked with residual permanent brain damage and mental retardation." Pediatrics **54**(4): 396-403.

Carlson, M. and F. Earls (1997). "Psychological and neuroendocrinological sequelae of early social deprivation in institutionalized children in romania." Annals of the New York Academy of Sciences **807**(1): 419-428.

Carpenter, L. L., A. R. Tyrka, *et al*. (2009). "Effect of childhood emotional abuse and age on cortisol responsivity in adulthood." Biological Psychiatry **66**(1): 69-75.

Carroll, L. J., J. D. Cassidy, *et al*. (2004). "Prognosis for mild traumatic brain injury: results of the WHO collaborating centre task force on mild traumatic brain injury." J Rehabil Med **S43**: 84-105.

Casanueva, F., A. Leal, *et al*. (2005). "Traumatic brain injury as a relevant cause of growth hormone deficiency in adults: A KIMS-based study." Archives of Physical Medicine and Rehabilitation **86**(3): 463-468.

Casanueva, F. F., E. Ghigo, *et al*. (2004). "Hypopituitarism following traumatic brain injury (TBI): a guideline decalogue." Journal of Endocrinological Investigation **27**(8): 793-795.

Case, M. E. (2008). "Accidental Traumatic Head Injury in Infants and Young Children." Brain Pathology **18**(4): 583-589.

Case, M. E. (2008). "Forensic Pathology of Child Brain Trauma." Brain Pathology **18**(4): 562-564.

Case, M. E., M. A. Graham, *et al*. (2001). "Position paper on fatal abusive head injuries in infants and young children." The American Journal of Forensic Medicine and Pathology **22**(2): 112-122.

Ceballos, R. (1966). "Pituitary changes in head trauma (analysis of 102 consecutive cases of head injury)." Alabama Journal of Medical Sciences **3**(2): 185.

Chung, C.-Y., C.-L. Chen, *et al*. (2006). "Critical score of glasgow coma scale for pediatric traumatic brain injury." Pediatric Neurology **34**(5): 379-387.

Clemmons, D. R. (2007). "IGF-I assays: current assay methodologies and their limitations." Pituitary **10**(2): 121-128.

Cohan, P., C. Wang, *et al*. (2005). "Acute secondary adrenal insufficiency after traumatic brain injury: A prospective study." Critical Care Medicine **33**(10): 2358-2366 2310.1097/2301.CCM.0000181735.0000151183.A0000181737.

Corneli, G., C. Di Somma, *et al*. (2005). "The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index." European Journal of Endocrinology **153**: 257-264.

Corneli, G., C. Di Somma, *et al*. (2007). "Cut-off limits of the GH response to GHRH plus arginine test and IGF-I levels for the diagnosis of GH deficiency in late adolescents and young adults." European Journal of Endocrinology **157**(6): 701-708.

Corneli, G., E. Ghigo, *et al*. (2007). "Managing patients with hypopituitarism after traumatic brain injury." Current opinion in endocrinology, diabetes and obesity **14**(4): 301-305.

Corrigan, J. D., A. W. Selassie, *et al*. (2010). "The epidemiology of traumatic brain injury." Journal of Head Trauma Rehabilitation **25**(2): 72-80.

Crompton, M. R. (1971). "Hypothalamic lesions following closed head injury." Brain **94**(1): 165-172.

Crouchman, M., L. Rossiter, *et al*. (2001). "A practical outcome scale for paediatric head injury." Archives of Disease in Childhood **84**(2): 120-124.

Crowe, L. M., C. Catroppa, *et al*. (2012). "Intellectual, behavioral, and social outcomes of accidental traumatic brain injury in early childhood." Pediatrics **129**(2): e262-e268.

Cyran, E. (1918). "Hypophysenschadigung durch schadelbasisfraktur." Dtsch Med Wochenschr **44**: 1261.

Daniel, P. M., M. M. Prichard, *et al*. (1959). "Traumatic infarction of the anterior lobe of the pituitary gland." Lancet **28**(7109): 927-931.

Davidson, J. S., M. J. Bolland, *et al*. (2006). "A case of low cortisol-binding globulin: use of plasma free cortisol in interpretation of hypothalamic-pituitary-adrenal axis tests." Annals of Clinical Biochemistry **43**(3): 237-239.

De Bellis, M. D., G. P. Chrousos, *et al*. (1994). "Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls." Journal of Clinical Endocrinology and Metabolism **78**(2): 249-255.

Demetriades, D., E. Kuncir, *et al*. (2004). "Mortality prediction of head Aabbreviated Injury Score and Glasgow Coma Scale: analysis of 7,764 head injuries." Journal of the American College of Surgeons **199**(2): 216-222.

Dhillo, W. S., W. M. Kong, *et al*. (2002). "Cortisol-binding globulin is important in the interpretation of dynamic tests of the hypothalamic-pituitary-adrenal axis." European Journal of Endocrinology **146**(2): 231-235.

Dickstein, G., C. Shechner, *et al*. (1991). "Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test." Journal of Clinical Endocrinology & Metabolism **72**: 773-778.

Douglas, N. M. and J. D. Dockerty (2007). "Survival by ethnicity for children diagnosed with cancer in New Zealand during 1990–1993." Journal of Paediatrics and Child Health **43**(3): 173-177.

Ducrocq, S. C., P. G. Meyer, *et al*. (2006). "Epidemiology and early predictive factors of mortality and outcome in children with traumatic severe brain injury: experience of a French pediatric trauma center." Pediatric Critical Care Medicine **7**(5): 461-467.

Duhaime, A.-C., C. W. Christian, *et al*. (1998). "Nonaccidental head injury in infants - ”the shaken-baby syndrome"." New England Journal of Medicine **338**(25): 1822-1829.

Duhaime, A. C., A. J. Alario, *et al*. (1992). "Head injury in very young children: mechanisms, injury types, and ophthalmologic findings in 100 hospitalized patients younger than 2 years of age." Pediatrics **90**(2): 179-185.

Dusick, J. R., C. Wang, *et al*. (2008). "Pathophysiology of hypopituitarism in the setting of brain injury." Pituitary.

Edleson, J. L. (1999). "The overlap between child maltreatment and woman battering." Violence Against Women **5**(2): 134-154.

Eiholzer, U., S. Bachmann, *et al*. (2000). "Is there growth hormone deficiency in prader-willi syndrome?" Hormone Research in Paediatrics **53**(Suppl. 3): 44-52.

Eiholzer, U., M. Zachmann, *et al*. (1986). "Recovery from post-traumatic anterior pituitary insufficiency." European Journal of Pediatrics **145**(1-2): 128-130.

Einaudi, S. and C. Bondone (2007). "The effects of head trauma on hypothalamic-pituitary function in children and adolescents." Current Opinion in Pediatrics **19**(4): 465-470.

Einaudi, S., P. Matarazzo, *et al*. (2006). "Hypothalamo-hypophysial dysfunction after traumatic brain injury in children and adolescents: a preliminary retrospective and prospective study." Journal of Pediatric Endocrinology and Metabolism **19**(5): 691-703.

Escamilla, R. F. and H. Lisser (1942). "Simmonds disease." Journal of Clinical Endocrinology and Metabolism **2**: 65-96.

Falk, A. C., C. Cederfjäll, *et al*. (2005). "Management and classification of children with head injury." Child's Nervous System **21**(6): 430-436.

Falorni, A., G. Galmacci, *et al*. (1999). "Using obese-specific charts of height and height velocity for assessment of growth in obese children and adolescents during weight excess reduction." European Journal of Clinical Nutrition **53**(3): 181-188.

Feldman, K. W., R. Bethel, *et al*. (2001). "The cause of infant and toddler subdural hemorrhage: a prospective study." Pediatrics **108**(3): 636-646.

Fiad, T M, K. J. M., Cunningham S K, McKenna J (1994). "The overnight single-dose metyrapone test is a simple and reliable index of the hypothalamic-pituitary-adrenal axis " Clinical Endocrinology **40**: 603-609.

Foreman, B. P., R. R. Caesar, *et al*. (2007). "Usefulness of the abbreviated injury score and the injury severity score in comparison to the glasgow coma score in predicting outcome after traumatic brain injury." Journal of Trauma **62**(4): 946-950.

Fortune, P. and F. Shann (2010). "The motor response to stimulation predicts outcome as well as the full Glasgow Coma Scale in children with severe head injury " Pediatric Critical Care Medicine **11**(3): 339-342 310.1097/PCC.1090b1013e3181c1014ab.

Gandrud, L. M. and D. M. Wilson (2004). "Is growth hormone stimulation testing in children still appropriate?" Growth Hormone & IGF Research **14**: 185-194.

Gean, A. D. (1994). Imaging of head trauma. New York, Raven press.

Gennarrelli, T. A., G. M. Spielman, *et al*. (1982). "Influence of the type of intracranial lesion on outcome from head injury." Journal of Neurosurgery **56**: 26-32.

GH research society (2000). "Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH research society." Journal of Clinical Endocrinology & Metabolism **85**(11): 3990-3993.

Ghigo, E., J. Bellone, *et al*. (1996). "Reliability of provocative tests to assess growth hormone secretory status. Study in 472 normally growing children." Journal of Clinical Endocrinology & Metabolism **81**(9): 3323-3327.

Ghigo, E., B. Masel, *et al*. (2005). "Consensus guidelines on screening for hypopituitarism following traumatic brain injury." Brain Injury **19**(9): 711-724.

Gill, M. R., D. G. Reiley, *et al*. (2004). "Interrater reliability of Glasgow Coma Scale scores in the emergency department." Annals of Emergency Medicine **43**(2): 215-223.

Gold, P. W., F. K. Goodwin, *et al*. (1988). "Clinical and biochemical manifestations of depression." New England Journal of Medicine **319**(7): 413-420.

Greer, M. A. (1951). "Evidence of hypothalamic control of the pituitary release of thyrotropin." Proceedings of the Society for Experimental Biology and Medicine **77**: 603-608.

Guillemin, R. (2011). "Neuroendocrinology: a short historical review." Annals of the New York Academy of Sciences **1220**(1): 1-5.

Hamrahian, A. H., T. S. Oseni, *et al*. (2004). "Measurements of serum free cortisol in critically ill patients." New England Journal of Medicine **350**(16): 1629-1638.

Hannon, M. J., M. Sherlock, *et al*. (2011). "Pituitary dysfunction following traumatic brain injury or subarachnoid haemorrhage." Best Practice & Research Clinical Endocrinology & Metabolism **25**(5): 783-798.

Harris, G. W. (1948). "Neural control of the pituitary gland." Physiological Reviews **28**(2): 139-179.

Hawley, C. A., A. B. Ward, *et al*. (2003). "Prevalence of traumatic brain injury amongst children admitted to hospital in one health district: a population-based study." Injury **34**(4): 256-260.

Healey, C., T. M. Osler, *et al*. (2003). "Improving the Glasgow Coma Scale score: motor score alone is a better predictor." The Journal of Trauma **54**(4): 671-680.

Heather, N. and W. Cutfield (2011). "Traumatic brain injury: is the pituitary out of harm's way?" The Journal of pediatrics **159**(4): 686-690.

Heather, N. L., C. Jefferies, *et al*. (2012). "Permanent hypopituitarism is rare after structural traumatic brain injury in early childhood." Journal of Clinical Endocrinology and Metabolism.

Heim, C., T. Mletzko, *et al*. (2008). "The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma." Biological Psychiatry **63**(4): 398-405.

Heim, C., D. J. Newport, *et al*. (2001). "Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse." American Journal of Psychiatry **1**(3): 282-289.

Heim, C., D. J. Newport, *et al*. (2008). "The link between childhood trauma and depression: insights from HPA axis studies in humans." Psychoneuroendocrinology **33**(6): 693-710.

Herrmann, B. L., J. Rehder, *et al*. (2006). "Hypopituitarism following severe traumatic brain injury." Experimental and Clinical Endocrinology and Diabetes **114**(06): 316,321.

Hettler, J. and D. S. Greenes (2003). "Can the initial history predict whether a child with a head injury has been abused?" Pediatrics **111**(3): 602-607.

Hindmarsh, P. C., C. E. Brain, *et al*. (1991). "The interaction of growth hormone releasing hormone and somatostatin in the generation of a GH pulse in man." Clinical Endocrinology **35**: 353-360.

Hiu Lam, W. and A. Mackersie (1999). "Paediatric head injury: incidence, aetiology and management." Pediatric Anesthesia **9**(5): 377-385.

Ho, K. K. Y. (2007). "Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia." European Journal of Endocrinology **157**: 695-700.

Holdgate, A., N. Ching, *et al*. (2006). "Variability in agreement between physicians and nurses when measuring the Glasgow Coma Scale in the emergency department limits its clinical usefulness." Emergency Medicine Australasia **18**(4): 379-384.

Holmes, J. F., M. J. Palchak, *et al*. (2005). "Performance of the pediatric Glasgow Coma Scale in children with blunt head trauma." Academic Emergency Medicine **12**(9): 814-819.

Ives, J. C., M. Alderman, *et al*. (2007). "Hypopituitarism after multiple concussions: a retrospective case study in an adolescent male." Journal of Athletic Training **42**(3): 431-439.

Jayawant, S., A. Rawlinson, *et al*. (1998). "Subdural haemorrhages in infants: population based study." BMJ (Clinical Research Ed.) **317**(7172): 1558-1561.

Jenny, C., K. P. Hymel, *et al*. (1999). "Analysis of missed cases of abusive head trauma." JAMA: The Journal of the American Medical Association **281**(7): 621-626.

Juul, A., K. Holm, *et al*. (1997). "Free insulin-like growth factor I serum levels in 1430 healthy children and adults, and Its diagnostic value in patients suspected of growth hormone deficiency." Journal of Clinical Endocrinology and Metabolism **82**(8): 2497-2502.

Kaufman, J., B. Birmaher, *et al*. (1997). "The Corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children." Biological Psychiatry **42**(8): 669-679.

Kaulfers, A.-M. D., P. F. Backeljauw, *et al*. (2010). "Endocrine dysfunction following traumatic brain injury in children." Journal of Pediatrics **157**(6): 894-899.

Kazlauskaite, R., A. T. Evans, *et al*. (2008). "Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis." Journal of Clinical Endocrinology and Metabolism **93**(11): 4245-4253.

Keenan, H. T., D. K. Runyan, *et al*. (2003). "A population-based study of inflicted traumatic brain injury in young children." JAMA: The Journal of the American Medical Association **290**(5): 621-626.

Kelestimur, F. (2005). "Chronic trauma in sports as a cause of hypopituitarism." Pituitary **8**(3): 259-262.

Kelestimur, F., F. Tanriverdi, *et al*. (2004). "Boxing as a sport activity associated with isolated GH deficiency." Journal of Endocrinological Investigation **27**(11): RC28-32.

Kelly, D. F., I. T. Gonzalo, *et al*. (2000). "Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid haemorrhage: a preliminary report." Journal of Neurosurgery **93**(5): 743-752.

Kelly, P. and B. Farrant (2008). "Shaken baby syndrome in New Zealand, 2000–2002." Journal of Paediatrics and Child Health **44**(3): 99-107.

Kelly, P., J. MacCormick, *et al*. (2009). "Non-accidental head injury in New Zealand: The outcome of referral to statutory authorities." Child Abuse and Neglect **33**(6): 393-401.

Khadr, S. N., P. M. Crofton, *et al*. (2010). "Evaluation of pituitary function after traumatic brain injury in childhood." Clinical Endocrinology **73**(5): 637-643.

Klose, M., A. Juul, *et al*. (2007). "Prevalence and predictive factors of post-traumatic hypopituitarism." Clinical Endocrinology **67**(2): 193-201.

Klose, M., A. Juul, *et al*. (2007). "Acute and long-term pituitary insufficiency in traumatic brain injury: a prospective single-centre study." Clinical Endocrinology **67**(4): 598-606.

Kojima, M., H. Hosoda, *et al*. (1999). "Ghrelin is a growth hormone-releasing peptide from the stomach." Nature **402**: 656-660.

Kokshoorn, N. E., J. W. A. Smit, *et al*. (2011). "Low prevalence of hypopituitarism after traumatic brain injury: a multicenter study." European Journal of Endocrinology **165**(2): 225-231.

Kokshoorn, N. E., M. J. E. Wassenaar, *et al*. (2010). "Hypopituitarism following traumatic brain injury: prevalence is affected by the use of different dynamic tests and different normal values." European Journal of Endocrinology **162**(1): 11-18.

Kornblum, R. N. and R. S. Fisher (1969). "Pituitary lesions in craniocerebral injuries." Archives of Pathology & Laboratory Medicine **88**(3): 242-248.

Krahulik, D., J. Zapletalova, *et al*. (2010). "Dysfunction of hypothalamic-hypophysial axis after traumatic brain injury in adults." Journal of Neurosurgery **113**(3): 581-584.

Kraus, J. F., A. Rock, *et al*. (1990). "Brain injuries among infants, children, adolescents, and young adults." American Journal of Diseases of Children **144**: 684-691.

Kuppermann, N., J. F. Holmes, *et al*. (2009). "Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study." Lancet **374**(9696): 1160-1170.

Leal-Cerro, A., J. M. Flores, *et al*. (2005). "Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury." Clinical Endocrinology **62**(5): 525-532.

LeRoith, D. and A. Buler (2001). "What is the role of circulating IGF-1?" Trends in Endocrinology and Metabolism **12**: 48-52.

Liddle, G. W., H. L. Estep, *et al*. (1959). "Clinical application of a new test of pituitary reserve." Journal of Clinical Endocrinology and Metabolism **19**(8): 875-894.

Lieberman, S. A., A. L. Oberoi, *et al*. (2001). "Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury." Journal of Clinical Endocrinology and Metabolism **86**(6): 2752-2756.

Lieh-Lai, M. W., A. A. Theodorou, *et al*. (1992). "Limitations of the Glasgow Coma Scale in predicting outcome in children with traumatic brain injury." The Journal of Pediatrics **120**(2, Part 1): 195-199.

Lindsay, R., M. Feldkamp, *et al*. (1994). "Utah growth study: growth standards and the prevalence of growth hormone deficiency." Journal of Pediatrics **125**: 29-35.

Lingsma, H. F., B. Roozenbeek, *et al*. (2010). "Early prognosis in traumatic brain injury: from prophecies to predictions." The Lancet Neurology **9**(5): 543-554.

Loche, S., C. Guzzetti, *et al*. (2011). "Effect of body mass index on the growth hormone response to clonidine stimulation testing in children with short stature." Clinical Endocrinology **74**(6): 726-731.

Maas, A. I. R., C. W. P. M. Hukkelhoven, *et al*. (2005). "Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors." Neurosurgery **57**(6): 1173-1182.

Maas, A. I. R., E. W. Steyerberg, *et al*. (2007). "Prognostic value of computerized tomography scan characteristics in traumatic brain injury: results from the IMPACT study." Journal of Neurotrauma **24**(2): 303-314.

Maghnie, M., D. Larizza, *et al*. (1991). "Hypopituitarism and stalk agenesis: a congenital syndrome worsened by breech delivery?" Hormone Research in Paediatrics **35**(3-4): 104-108.

Maghnie, M., C. Strigazzi, *et al*. (1999). "Growth Hormone (GH) deficiency (GHD) of childhood onset: reassessment of GH status and evaluation of the predictive criteria for permanent GHD in young adults." Journal of Clinical Endocrinology and Metabolism **84**(4): 1324-1328.

Maiya, B., V. Newcombe, *et al*. (2008). "Magnetic resonance imaging changes in the pituitary gland following acute traumatic brain injury." Intensive Care Medicine **34**(3): 468-475.

Marie, P. (1886). "Due deux cas d'acromegalie." Rev de Med **6**: 197-333.

Marin, G., H. M. Domene, *et al*. (1994). "The effects of estrogen priming and puberty on the growth hormone response to standardised treadmill exercise and arginine-insulin in normal girls and boys." Journal of Clinical Endocrinology & Metabolism **79**(2): 537-541.

Marion, D. W. and P. M. Carlier (1994). "Problems with initial Glasgow Coma Scale assessment caused by prehospital treatment of patients with head injuries: results of a national survey." Journal of Trauma **36**(1): 89-95.

Marmarou, A., J. Lu, *et al*. (2007). "Prognostic value of the glasgow coma scale and pupil reactivity in traumatic brain injury assessed pre-hospital and on enrollment: an IMPACT analysis." Journal of Neurotrauma **24**(2): 270-280.

Marshall, L. F., S. B. Marshall, *et al*. (1991). "A new classification of head injury based on computerized tomography." Journal of Neurosurgery **75**(1S): S14-S20.

MartÍnez A.S, D. H. M., Ropelato G, Jasper H.G, Pennisi P.A, Escobar M.E (2000). "Estrogen priming effect on growth hormone (GH) provocative test: a useful tool for the diagnosis of GH deficiency." Journal of Clinical Endocrinology & Metabolism **85**: 4168-4172.

May, M. T. (1968). Galen on the usefulness of the parts of the body. New York, Cornell University Press.

McDonald, A., M. Lindell, *et al*. (2008). "Traumatic brain injury is a rarely reported cause of growth hormone deficiency." Journal of Pediatrics **152**(4): 590-593.

McGowan, P. O., A. Sasaki, *et al*. (2009). "Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse." Nature Neuroscience **12**(3): 342-348.

McKinlay, A., R. C. Grace, *et al*. (2008). "Prevalence of traumatic brain injury among children, adolescents and young adults: prospective evidence from a birth cohort." Brain Injury **22**(2): 175-181.

Association for the Advancement of Automotive Medicine (1998). The Abbreviated Injury Scale 1990 Revision. Barrington, Illionois.

Menegazzi, J. J., E. A. Davis, *et al*. (1993). "Reliability of the Glasgow Coma Scale when used by emergency physicians and paramedics." The Journal of Trauma **34**(1): 46-48.

Meredith, W., R. Rutledge, *et al*. (1995). "Field triage of trauma patients based upon the ability to follow commands: a study in 29,573 injured patients." The Journal of Trauma **38**(1): 129-135.

Miller, W. L., S. L. Kaplan, *et al*. (1980). "Child abuse as a cause of post-traumatic hypopituitarism." New England Journal of Medicine **302**(13): 724-728.

Mills, J. L., L. B. Schonberger, *et al*. (2004). "Long-term mortality in the United States cohort of pituitary-derived growth hormone recipients." Journal of Pediatrics **144**: 430-436.

Moon, R. J., T. Sutton, *et al*. (2010). "Pituitary function at long-term follow-up of childhood traumatic brain injury." Journal of Neurotrauma **27**(10): 1827-1835.

Moon, R. J., P. Wilson, *et al*. (2009). "Growth monitoring following traumatic brain injury." Archives of Disease in Childhood **94**(9): 699-701.

Morsky, P., U. Tiikkainen, *et al*. (2005). "Problematic determination of serum growth hormone: experience from external quality assurance surveys 1998-2003." Scandinavian Journal of Clinical and Laboratory Investigation **65**(5): 377-386.

Murphy, H., J. Livesey, *et al*. (1998). "The low dose ACTH test—a further word of caution." Journal of Clinical Endocrinology & Metabolism **83**: 712-713.

Niederland, T., H. Makovi, *et al*. (2007). "Abnormalities of pituitary function after traumatic brain injury in children." Journal of Neurotrauma **24**(1): 119-127.

Norwood, K. W., M. D. Deboer, *et al*. (2010). "Traumatic brain injury in children and adolescents: surveillance for pituitary dysfunction." Clinical Pediatrics **49**(11): 1044-1049.

Outwater, K. M. and M. A. Rockoff (1984). "Diabetes insipidus accompanying brain death in children." Neurology **34**(9): 1243.

Parslow, R. C., K. P. Morris, *et al*. (2005). "Epidemiology of traumatic brain injury in children receiving intensive care in the UK." Archives of Disease in Childhood **90**(11): 1182-1187.

Plotsky, P. M. and M. J. Meaney (1993). "Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats." Molecular Brain Research **18**(3): 195-200.

Poomthavorn, P., W. Maixner, *et al*. (2008). "Pituitary function in paediatric survivors of severe traumatic brain injury." Archives of Disease in Childhood **93**(2): 133-137.

Popovic, V., S. Pekic, *et al*. (2004). "Hypopituitarism as a consequence of traumatic brain injury (TBI) and its possible relation with cognitive disabilities and mental distress." Journal of Endocrinological Investigation **27**(11): 1048-1054.

Powell, G. F., J. A. Brasel, *et al*. (1967). "Emotional deprivation and growth retardation stimulating idiopathic hypopituitarism. Clinical evaluation of the syndrome." New England Journal of Medicine **276**: 1271-1278.

Powell, G. F., J. A. Brasel, *et al*. (1967). "Emotional deprivation and growth retardation simulating idiopathic hypopituitarism. Endocrine evaluiation of the syndrome." New England Journal of Medicine **276**(23): 1279-1283.

Ranke, M. B., A. Lindberg, *et al*. (2007). "Age at growth hormone therapy start and first-year responsiveness to growth hormone are major determinants of height outcome in idiopathic short stature." Hormone Research **68**(2): 53-62.

Ranke, M. B., R. Schweizer, *et al*. (2004). "Insulin-like growth factors as diagnostic tools in growth hormone deficiency during childhood and adolescence: the KIGS experience." Horm Res **62**(suppl 1): 17-25.

Reece, R. M. and R. Sege (2000). "Childhood head injuries: accidental or inflicted?" Archives of Pediatrics and Adolescent Medicine **154**(1): 11-15.

Regal, M., C. Páramo, *et al*. (2001). "Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain." Clinical Endocrinology **55**(6): 735-740.

Rimel, R. W., B. Giordani, *et al*. (1982). "Moderate head injury: completing the cinical spectrum of brain trauma." Neurosurgery **11**(3): 344-351.

Rose, S. R. and B. A. Auble (2011). "Endocrine changes after pediatric traumatic brain injury." Pituitary **ePub**.

Rosenfeld, S., K. Albertsson-Wikland, *et al*. (1995). "Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited." Journal of Clinical Endocrinology and Metabolism **80**(5): 1532-1540.

Ross, S. E., C. Leipold, *et al*. (1998). "Efficacy of the motor component of the Glasgow Coma Scale in trauma triage." The Journal of Trauma **45**(1): 42-44.

Rowley, G. and K. Fielding (1991). "Reliability and accuracy of the Glasgow Coma Scale with experienced and inexperienced users." The Lancet **337**(8740): 535-538.

Runyan, D. K. (2008). "The challenges of assessing the incidence of inflicted traumatic brain injury: a world perspective." American Journal of Preventive Medicine **34**(4, Supplement 1): S112-S115.

Salehi, F., K. Kovacs, *et al*. (2007). "Histologic study of the human pituitary gland in acute traumatic brain injury." Brain Injury **21**(6): 651-656.

Salmond, C, C. P., Atkinson J. (2007). NZDep2006 index of deprivation user's manual. . Wellington., Department of Public Health, Wellington School of Medicine and Health Sciences.

Sapolsky, R. M., L. M. Romero, *et al*. (2000). "How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative Actions." Endocrine Reviews **21**(1): 55-89.

Scacchi, M., A. I. Pincelli, *et al*. (1999). "Growth hormone in obesity." International Journal of Obesity and Related Metabolic Disorders **23**.

Scheepens, A., E. S. Sirimanne, *et al*. (2001). "Growth hormone as a neuronal rescue factor during recovery from CNS injury." Neuroscience **104**(3): 677-687.

Schneider, H. J., G. Aimaretti, *et al*. (2007). "Hypopituitarism." Lancet **369**(9571): 1461-1470.

Schneider, H. J., I. Kreitschmann-Andermahr, *et al*. (2007). "Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review." JAMA **298**(12): 1429-1438.

Schneider, H. J., P. G. Samann, *et al*. (2007). "Pituitary imaging abnormalities in patients with and without hypopituitarism after traumatic brain injury." Journal of Endocrinological Investigation **30**(4): RC9-RC12.

Schneider, H. J., M. Schneider, *et al*. (2011). "Structured assessment of hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage in 1242 patients: the German Interdisciplinary Database." Journal of Neurotrauma **28**(9): 1693-1698.

Schneider, H. J., M. Schneider, *et al*. (2006). "Prevalence of anterior pituitary insufficiency 3 and 12 months after traumatic brain injury." European Journal of Endocrinology **154**(2): 259-265.

Schneider, H. J., G. K. Stalla, *et al*. (2006). "Expert meeting: hypopituitarism after traumatic brain injury and subarachnoid haemorrhage." Acta Neurochirurgica **148**(4): 449-456.

Selye, H. (1936). "A syndrome produced by diverse noxious agents." Nature **138**: 32-36.

Shah, A., R. Stanhope, *et al*. (1992). "Hazards of pharmacological tests of GH secretion in childhood." British Medical Journal **304**: 173-174.

Sherlock, M., J. Ayuk, *et al*. (2010). "Mortality in patients with pituitary disease." Endocrine Reviews **31**(3): 301-342.

Simmonds (1914). "Uber hypophysisschwund mit todlichem ausgang." Dtsch Med Wschr **40**(7): 322.

Simpson, D. A., R. A. Cockington, *et al*. (1991). "Head injuries in infants and young children: the value of the Paediatric Coma Scale." Child's Nervous System **7**(4): 183-190.

Skuse, D., A. Albanese, *et al*. (1996). "A new stress-related syndrome of growth failure and hyperphagia in children, associated with reversibility of growth-hormone insufficiency." The Lancet **348**(9024): 353-358.

Soliman, A. T., A. E. Hassan, *et al*. (1986). "Serum insulin-like growth factors I and II concentrations and growth hormone and insulin responses to arginine infusion in children with protein-energy malnutrition before and after nutritional rehabilitation." Pediatric Research **20**: 1122-1130.

Stanley, T. L., L. L. Levitsky, *et al*. (2009). "Effect of body mass index on peak growth hormone response to provocative testing in children with short stature." Journal of Clinical Endocrinology and Metabolism **94**(12): 4875-4881.

States, J. D. (1971). "Rating the Severity of Tissue Damage." JAMA: The Journal of the American Medical Association **215**(2): 277-280.

Staub J J, N. J., Girard J B, Bauman S, Ratcliffe J G (1979). "The short metapyrone test: comparison of the plasma ACTH response to metyrapone and insulin induced hypoglycaemia." Clinical Endocrinology **10**: 595-601.

Staworn, D., L. Lewison, *et al*. (1994). "Brain death in pediatric intensive care unit patients: Incidence, primary diagnosis, and the clinical occurrence of Turner's triad." Critical Care Medicine **22**(8): 1301-1305.

Stocchetti, N., F. Pagan, *et al*. (2004). "Inaccurate early assessment of neurological severity in head injury." Journal of Neurotrauma **21**(9): 1131-1140.

Tamborlane, W. V., R. I. Hintz, *et al*. (1981). "Insulin infusion pump treatment of diabetes: influence of improved metabolic control on plasma somatomedin levels." New England Journal of Medicine **305**: 303-307.

Tanriverdi, F., A. De Bellis, *et al*. (2008). "Antipituitary antibodies after traumatic brain injury: Is head trauma induced pituitary dysfunction associated with autoimmunity?" European Journal of Endocrinology.

Tanriverdi, F., H. Senyurek, *et al*. (2006). "High risk of hypopituitarism after traumatic brain injury: a prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma." Journal of Clinical Endocrinology and Metabolism **91**(6): 2105-2111.

Tanriverdi, F., H. Ulutabanca, *et al*. (2008). "Three years prospective investigation of anterior pituitary function after traumatic brain injury: a pilot study." Clinical Endocrinology **68**(4): 573-579.

Tanriverdi, F., K. Unluhizarci, *et al*. (2010). "Pituitary function in subjects with mild traumatic brain injury: a review of literature and proposal of a screening strategy." Pituitary **13**(2): 146-153.

Tauber, M. t., P. Moulin, *et al*. (1997). "Growth hormone (GH) retesting and auxological data in 131 GH-deficient patients after completion of treatment." Journal of Clinical Endocrinology and Metabolism **82**(2): 352-356.

Teasdale, G. and B. Jennett (1974). "Assessment of coma and impaired consciousness. A practical scale." Lancet **2**(7872): 81-84.

Teasdale, G., R. Knill-Jones, *et al*. (1978). "Observer variability in assessing impaired consciousness and coma." Journal of Neurology, Neurosurgery and Psychiatry **41**(7): 603-610.

Teilmann, G., C. B. Pedersen, *et al*. (2005). "Prevalence and incidence of precocious pubertal development in denmark: an epidemiologic study based on national registries." Pediatrics **116**(6): 1323-1328.

Thorner, M. O., M. L. Vance, *et al*. (1992). The anterior pituitary. William Textbook of Endocrinology. W. J.D. and D. W. Foster. Philadelphia, W.B. Saunders.

Timmons, S. D., T. Bee, *et al*. (2011). "Using the abbreviated injury severity and glasgow coma scale scores to predict 2-week mortality after traumatic brain injury." Journal of Trauma-Injury Infection & Critical Care **71**(5): 1172-1178.

Toni, R. (2000). "Ancient views on the hypothalamic-pituitary-thyroid axis: an historical and epistemological perspective." Pituitary **3**(2): 83-95.

Udekwu, P., S. Kromhout-Schiro, *et al*. (2004). "Glasgow coma scale score, mortality, and functional outcome in head-injured patients." The Journal of Trauma and Acute Care Surgery **56**(5): 1084-1089.

van Aken, M. and S. Lamberts (2005). "Diagnosis and treatment of hypopituitarism: an update." Pituitary **8**(3): 183-191.

van Baalen, B., E. Odding, *et al*. (2003). "Traumatic brain injury: classification of initial severity and determination of functional outcome." Disability & Rehabilitation **25**(1): 9-18.

Van den Berghe, G., F. de Zegher, *et al*. (1998). "Acute and prolonged critical illness as different neuroendocrine paradigms." Journal of Clinical Endocrinology and Metabolism **83**(6): 1827-1834.

Van der Eerden, A. W., M. T. Twickler, *et al*. (2010). "Should anterior pituitary function be tested during follow-up of all patients presenting at the emergency department because of traumatic brain injury?" European Journal of Endocrinology **162**(1): 19-28.

Vimpani, G. V., A. F. Vimpani, *et al*. (1977). "Prevalence of severe growth hormone deficiency." British Medical Journal **2**: 427.

Wachter, D., K. Gündling, *et al*. (2009). "Pituitary insufficiency after traumatic brain injury." Journal of Clinical Neuroscience **16**(2): 202-208.

Weintrob N, S. E., Josefberg Z, WEininger C, Aubach-Klipper Y, Lazard D, Karp M, Pertzelan A (1998). "Standard and low dose short adrenocorticotropin test compared insulin induced hypoglycaemia for assessment of the hypothalamo-pituitary-adrenal axis in children with idiopathic multiple pituitary hormone deficiencies." Journal of Clinical Endocrinology & Metabolism **83**(1): 88-92.

Williams, D. H., H. S. Levin, *et al*. (1990). "Mild head injury classification." Neurosurgery **27**(3): 422-428.

Wyatt, D. T., D. Mark, *et al*. (1995). "Survery of growth hormone treatment ptactices by 251 pediatric endocrinologists." Journal of Clinical Endocrinology & Metabolism **80**: 989-1004.

Yager, J. Y., B. Johnston, *et al*. (1990). "Coma scales in pediatric practice." American Journal of Diseases of Children **144**(10): 1088-1091.

Yamanaka, C., T. Momoi, *et al*. (1993). "Acquired growth hormone deficiency due to pituitary stalk transection after head trauma in childhood." European Journal of Pediatrics **152**(2): 99-101.

Ye, P. and A. J. De Ercole (1999). "Insulin-like growth factor I protects oligodendrocytes from tumor necrosis factor induced injury." Endocrinology **140**(7): 3063-3072.

Yuan, X. Q. and C. E. Wade (1991). "Neuroendocrine abnormalities in patients with traumatic brain injury." Frontiers in Neuroendocrinology **12**(3): 209-230.