The Changing Face of Hypopituitarism in Modern Endocrinology

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List of Abbreviations

ACTH	Adrenocorticotrophic Hormone
ADL	Activity of Daily Living
AST	Arginine Stimulation Test
BMI	Body Mass Index
CPET	Cardiopulmonary Exercise Testing
CT	Computed Tomography
FSH	Follicle Stimulating Hormone
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GHR	Growth Hormone Replacement
GHRH	Growth Hormone Releasing Hormone
GOS	Glasgow Outcome Scale
GST	Glucagon Stimulation Test
HADS	Hospital Anxiety and Depression Score
HPA	Hypothalamo-pituitary-adrenal
HRQOL	Health Related Quality of Life
IADL	Instrumental Activity of Daily Living
IGF-1	Insulin-like Growth Factor 1
IGHD	Isolated Growth Hormone Deficiency
ISAT	International Subarachnoid Aneurysm Trial
ISP	Intrasellar Pressure
ITT	Insulin Tolerance Test
LH	Luteinising Hormone
LHRH	Luteinising Hormone Releasing Hormone
MPHD	Multiple Pituitary Hormone Deficiency
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Scale
NFPA	Non-Functioning Pituitary Adenoma
NHP	Nottingham Health Profile
NICE	National Institute for Health and Clinical Excellence

NRES	National Research Ethics Service
PAS	Pituitary Apoplexy Score
PGWS	Psychological General Well-Being questionnaire
PIS	Patient Information Sheet
PTSD	Post Traumatic Stress Disorder
QoL-AGHDA	Quality of Life Assessment of Growth Hormone Deficiency in Adults
SAH	Subarachnoid Haemorrhage
SF-36	Short Form 36
SMR	Standardised Mortality Ratio
SRFT	Salford Royal NHS Foundation Trust
SST	Short Synacthen Test
TRH	Thryotropin Releasing Hormone
UK	United Kingdom
WHO-QoL	World Health Organisation Quality of Life Questionnaire
WHR	Waist Hip Ratio

Abstract

The Changing Face of Hypopituitarism in Modern Endocrinology

Sumithra Giritharan, For the degree of Doctor of Medicine, at the University of Manchester, September 2017.

The impact of advances in medicine, neurosurgery and critical care on clinical practice in modern endocrinology is not entirely clear. This is because reports in current literature include various confounders. Furthermore, it is becoming increasing recognised that hypopituitarism can be caused by pathologies outside the pituitary gland, such as traumatic brain injury and subarachnoid haemorrhage. The objective of this thesis is two-fold. Firstly is to examine the variables associated with pituitary dysfunction in modern clinical endocrinology. To do this, the thesis will investigate a spectrum of pituitary pathologies associated with varying degrees of hypopituitarism. This will compromise patients with pituitary apoplexy, non-functioning pituitary adenoma (NFPA) and subarachnoid haemorrhage (SAH). Secondly, given that growth hormone deficiency (GHD) is increasingly recognised as a consequence of subarachnoid haemorrhage, this thesis will investigate the impact of growth hormone replacement (GHR) on survivors of subarachnoid haemorrhage who have developed growth hormone deficiency. This is novel as there are currently no publications reporting on the use of growth hormone exclusively in this group of patients.

Data about patients with pituitary apoplexy and NFPA were collected retrospectively. Patients with SAH were prospectively screened for GHD with dynamic pituitary function testing. Patient with GHD received 36 weeks of GHR and underwent a series of quality of life, cardiorespiratory and metabolic assessment before and after treatment with GHR.

In the cohort of patients with pituitary apoplexy, rate of hypopituitarism was high regardless of management pathway (73-91%). Recovery or preservation of visual function was good. Management should be directly by visual symptoms rather than for preservation of endocrine function.

In the cohort of patients with NFPA, hypopituitarism was associated with tumour size, gender and age. After pituitary surgery, women were more likely to experience improvement in pituitary function, whereas men were more likely to experience deterioration in endocrine function. Patients with improved pituitary function had higher serum prolactin levels at presentation. It was also demonstrated that the effect of pituitary surgery of different axes is variable, with ACTH axis most likely to change.

In the cohort of patients with SAH, it was demonstrated that the rate of hypopituitarism (19%) and specifically GHD (14%) was relatively low when dynamic and confirmatory pituitary testing protocol was employed. GHR is associated with improved weight, BMI, cardiorespiratory fitness, mood and quality in patients who have developed GHD after SAH.

Declaration

No part of the work submitted in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Statement

Thesis Format

This MD thesis will be presented in the journal format (previously known as the alternative format). Most chapters are in the form of manuscripts that have been published or are suitable for publication in a peer-reviewed journal. The exception to this is the introduction chapter (Chapter 1) and the methods chapter (Chapter 3), which provide a detailed background of the hypotheses tested and study design of protocols detailed in subsequent results chapter. Each results chapter contains a chapter-specific abstract, introduction, methods, results and discussion section with a preceding preface to provide context to the overall aim of the thesis. The headings in the results chapters correspond to the titles in the title of the published/submitted article. As per submitted manuscripts, after the title there will be a list of co-authors, and a link to the relevant journal publishers' IPR policy, allowing use of any published material in this thesis. Tables and figures for the whole manuscript are embedded within the text. The references for each chapter are contained within that manuscript. This structure is in accordance with the University of Manchester presentation of thesis policy.

It was felt that the journal format was appropriate for this thesis because each results chapter contains distinct experiments which have been submitted or are suitable for submission to peer review journals as independent papers. Because each chapter is a separate manuscript but addresses a similar subject matter there will be some unavoidable repetition, in particular in the introduction, methods and references. However each chapter is an independent body of work and the thesis overall is set out as a coherent body of work.

The final chapter brings together the findings from the thesis and presents if and how these results can lead to future works. List of publications and presentations that have arisen from this thesis is listed in the appendix.

Acknowledgement

Firstly, I would like to thank my Main Supervisor, Dr Tara Kearney for introducing me to research and giving me the opportunity to carry out an academic project in Endocrinology. Her advice, direction and extensive support have been invaluable. All of this has been instrumental not only to this study, but also to my on-going development as a clinical endocrinologist. I am indebted to my Co-Supervisor, Professor Phil Kalra for taking the time to offer me guidance on how to pragmatically and systematically approach scientific research. It has been a privilege to access his immense fountain of knowledge. I am truly grateful to my PGR Advisor, Dr Annice Mukherjee for her supervision and scientific advice.

A special mention has to be given to Mr Kanna Gnanalingham, who has consistently provided expert neurosurgical input and mentorship in various aspects of this thesis production. It has been a true pleasure to have had the opportunity to work with him.

The progress that this study has achieved would not have been possible without the hard work and dedication of Mrs Joanna Cox, Endocrine Research Nurse at Salford Royal NHS Foundation Trust. Her vast experience and unshakeable enthusiasm have been instrumental in keeping the momentum going during the initial stages of this process. Following from this I am indebted to Mrs Janet Blood, Research Nurse and all of the members of the Vascular Research Network team for their support with logistical and certain administrative issues.

All of the laboratory work for this study was carried out by Mr Mark Guy, Clinical Biochemist at Salford Royal NHS Foundation Trust. I would like to thank him for his quiet but very labour intensive work behind the scenes. In spite of our overwhelming requests, he has always delivered results in a timely and professional fashion.

I am immensely grateful to all the patients involved, specifically the cohort of subarachnoid haemorrhage survivors who volunteered to participate in this study. Hopefully results generated from this study can start to impact on the long term health care of these patients.

To my parents, who have worked hard to provide me with opportunities in all aspects of life, I would like to say thank you. Last, but by no means least, I would like to extend my gratitude to my husband, Robert Davies, for his unyielding support in all my endeavours.

About the Author

I studied medicine at the University of Bristol. After graduating I trained in the South West deanery and North East deanery. During this time I developed and interest in Diabetes medicine and carried out various projects in this field. Subsequently I applied for specialist training in this area. Five years ago I moved to the North West region at started working at Salford Royal NHS Foundation Trust in the Department of Diabetes and Endocrinology. It was here that the fascinating world of endocrinology and more specifically the mesmerising scope of pituitary diseases, grabbed my attention. Certainly the exposure to the case burden of pituitary pathologies encountered at Salford Royal NHS Foundation Trust, established my interest in pituitary endocrinology.

Therefore when Dr Tara Kearney, offered me the opportunity to carry out this research project, there was no doubt that I would strive to complete this to the best of my abilities. I am grateful for this opportunity to have studied for an MD, as I have gained an array of skills in this process. I have gained a better understanding of research methodology, improved my statistical analysis skills and developed my scientific writing ability. This chance has also allowed me to present oral and poster presentations at national and international meetings. I have also participated in various pharmaceutical-sponsored clinical trials. Moreover, during this process, I have learnt to appreciate the rigorous process is involved in study design and data interpretation that forms the evidence base for our clinical practice.

I have thoroughly enjoyed this process and hope that the results from this study can contribute to the increased understanding of the pituitary gland in modern endocrinology.

Sumithra Giritharan

2017

Contribution of Author to the Research

The supervisor (Dr Tara Kearney, TK) conceived the original research idea and developed the original research protocol. Additional input about study aim and design was provided by Kanna Gnanalingham (KG). The author (Dr Sumithra Giritharan, SG), set out the hypotheses for this thesis, and refined the final study protocol. SG and Research Nurse Joanna Cox (JC), produced all patient related documents and clinical record forms for the study. Dr Sarah Cotterill provided statistical input in the initial study design and sample size estimate calculation. The aims and designs in each investigational chapter in the thesis was conceived and designed by SG, with support from TK and KG. Application for funding, ethical approval and portfolio adoption by the Clinical Research Network was carried out by TK and SG.

Patient screening and recruitment was carried out by SG and JC. Some of the logistical and administrative aspects, such as booking patient transport and approving participants monetary reimbursement were carried out by Research Nurses Janet Blood (JB), Christina Summersgill, Laura Johnston and research assistant Dace Dimza . All patients were consented by SG only.

Prescribing for testing procedures was done by SG and relevant testing materials were provided by Pharmacist, Claire Keatley and Pharmacy Technician, Jonathan Pathak. Dynamic testing of pituitary function was carried out by SG, JC and JB, and SG supervised all procedures. Processing of blood samples was carried out by Mark Guy (MG). Queries about neuroimaging results were answered by Consultant Neuroradiologist, Dr David Hughes (DH).

Exercise testing procedures were carried out by Physiotherapist Laura Smith (LS) and Kieron Bowden and all were supervised by SG. All study visits were carried out by SG with assistance from JC of JB. Staff at the Clinical Research Facility, Salford Royal NHS Foundation Trust, very kindly provided refreshments for all study participants. Patient education about administration of Growth Hormone, prescribing and monitoring was done by SG.

SG was solely responsible for data collection, interpretation and analysis. Clinical Statistician, Calvin Heal (CH), provided statistical advice on some manuscripts. All manuscripts, results and discussions were written by SG with input from TK, KG, CH, LS and DH.

Chapter 1

Introduction

1 Chapter 1 Introduction

1.1 Overview

The pituitary gland is often referred to as the 'master gland' as it modulates hormone secretion from other glands in body via pituitary hormones. Hypopituitarism is caused by deficiency of one or more pituitary hormones. In adults, this is most commonly caused by mass lesions within the pituitary region or a consequence of surgical or radiological treatment of these masses. Clinically, disruption of pituitary hormone release causes a variety of symptoms including poor energy, weight gain, cessation of menses, reduced libido and can rarely be fatal. Thyroxine, glucocorticoid and sex steroid hormone replacement is well established in the context of hypopituitarism in adults, however Growth Hormone Replacement remains controversial.

In the past 30 years various developments in clinical medicine, drug development, surgical technique and even intensive care have impacted on modern clinical endocrinology. The introduction of the endoscopic transsphenoidal method for pituitary surgery has on the whole, surpassed older techniques with its superior outcomes and lower rates of complication. Evolution of the concept of a 'dedicated pituitary surgeon' is reported to have improved rates of post-surgical hypopituitarism. Furthermore, the importance of centralising neurosurgical and endocrine management to specialised 'tertiary' centres is increasingly recognised as enhancing patient care. Development of recombinant human growth hormone and an ever expanding evidence base for its use not only in the form publications but also large international registries has increased the use of Growth Hormone Replacement in adults. More recently recognition that other pathologies beyond the pituitary can be implicated in pituitary hormone deficiency, such as traumatic brain injury and subarachnoid haemorrhage, has arisen.

This evolution will most certainly have repercussions on our understanding of hypopituitarism in modern endocrinology. To investigate factors associated with hypopituitarism in modern clinical endocrinology, this thesis will review pathologies associated with a spectrum of hypopituitarism.

At one end of the spectrum, sits patients with pituitary apoplexy, given the high rate of pituitary dysfunction associated with this event. Pituitary apoplexy is one of the few

endocrine emergencies and requires prompt resuscitation and hormonal replacement. Urgency of management is dependent on the severity of neurological and visual symptoms. As such, pituitary apoplexy allows assessment of parameters that may or may not contribute to permanent hypopituitarism when urgent intervention is required.

In the middle of the spectrum lie patients with non-functioning pituitary adenoma (NFPA), given that the reported rate of pituitary dysfunction affiliated with this pathology is not as high as pituitary apoplexy but certainly not as low as patients with brain injury. Non-functioning pituitary adenoma offers a good model to investigate the variables associated with hypopituitarism in the non-emergency setting. Surgical resection is mainly aimed at preserving/restoring visual function and therefore preservation of the gland is more likely. In addition, surgical resection can be carried out electively by a dedicated pituitary surgeon in most cases.

At the opposite end of the spectrum, are patients with subarachnoid haemorrhage. It is only in recent years that hypopituitarism has been related to this event and as such the reported rate of hypopituitarism in this group of patients has been confounded by testing methodology. Increasing evidence reveals that when rigorous testing protocols are employed, the rate of hypopituitarism in this group of patients is low. As such, hypopituitarism after subarachnoid haemorrhage provides a good platform to evaluate in detail the methods in which hypopituitarism is diagnosed in modern clinical endocrine practice.

Lastly, although growth hormone deficiency is recognised as the most common hormonal deficiency in SAH survivors, the impact of Growth Hormone Replacement in SAH survivors has not been clearly investigated. The evidence base for Growth Hormone Replacement in adults has grown over the past 20 years. This therefore provides an exciting opportunity to study if Growth Hormone Replacement has a role in the rehabilitation of SAH survivors.

1.2 Hypopituitarism after Pituitary Apoplexy

Background

Pituitary Apoplexy results from acute haemorrhage or infarction into the pituitary gland causing a sudden increase of pressure in the sella turcica with consequent compression of the surrounding neurological and vascular structures(1-3). Clinical presentation consists of a constellation of sudden onset of headache with associated vomiting, visual deficits,

ophthalmoplegia and/or alteration in level of consciousness. There is a male preponderance with a peak age of presentation between the 5th and 6th decade(4). Clinical symptoms can mimic other intracranial pathologies such as migraine, subarachnoid haemorrhage or bacterial meningitis, often leading to delayed diagnosis if not misdiagnosis(5). Even though the true incidence of this rare condition is difficult to determine, the reported incidence in current literature varies between 0.6- 17% (higher rates reported in retrospective surgical series)(1, 4, 6-8). The threat to endocrine and neuro-ophthalmic function is substantial if not catastrophic and can result in death(5, 9-11).

Predisposing factors such as bromocriptine therapy(12-14), oestrogen therapy(13), pregnancy(12), dynamic pituitary testing (15, 16), hypertension (13, 17) and anticoagulation (12, 13, 17, 18) have been described, however most cases of apoplexy occur spontaneously (12, 19).

The role of careful fluid and electrolyte management with glucocorticoid replacement in the acute phase is well established. However, other than patients with progressive visual deterioration in which urgent surgical decompression is indicated, management of all other patients with regards to the role and timing of neurosurgical intervention remains controversial. Some authors propose that surgical intervention is indicated in all patients(7, 8, 20) whereas others have proposed that in the context of mild and stable visual symptoms, a conservative approach can be adopted(17, 19, 21, 22).

Like all other rare disease, there is a lack of evidence-based guidelines and 'best practice' standards for these patients. As such, it is not uncommon to find that patient management varies from centre to centre, and is dependent not only on the endocrine and neurosurgical expertise available, but also historical clinical practice.

Guidelines For The Management of Pituitary Apoplexy

Given that a proportion of patients present with severe neurological and visual deficits necessitating urgent surgical decompression, attempting to derive evidence for best practice (emergency surgery vs elective surgery vs conservative management) via a randomised controlled trial in this patient population in impractical and unethical.

Recognising the lack of medical consensus for 'best practice' in managing patients with Pituitary Apoplexy, a subgroup of participants from the Clinicopathological Conference in Pituitary Diseases 2009, developed a set of evidenced-based guidelines for the

multidisciplinary team involved in managing patients with pituitary apoplexy with publication in May 2010(1). Other than addressing initial emergency management during the acute presentation and long term assessment, the document also discusses the available evidence base with regards to the various management options and attempts to provide guidance as to which patient should be managed surgically (Figure1.1). It is not clear however whether any particular management strategy confers superiority in terms of long term endocrine outcomes.

Pituitary Apoplexy Score (PAS)

The UK Pituitary Apoplexy Guidelines Development Group Conceived the Pituitary Apoplexy Score (PAS) as a method of assessing and monitoring clinical severity in the acute phase of pituitary apoplexy (Figure 1.2)(1). This enables the clinician to assess neurological and visual severity as part of their clinical assessment. However, the role of PAS in the clinical decision-making process has not been well described. After retrospectively applying the PAS to their population, Bujawansa et al., recommends that patients who score 4 or more be considered for surgery(22). Reddy et al., demonstrated a tendency for patients who underwent emergency decompressive surgery to have higher scores than patients operated on electively when the PAS was applied retrospectively(23).

The usefulness of the PAS in the clinical setting remains unclear given the lack of studies applying this prospectively. Its position in improving both endocrine and visual outcome (if at all) after pituitary apoplexy, needs investigating. The strengths and limitations of this scoring system will be discussed later in the thesis.

Other Scoring Systems

In their predominantly surgical series, Jho et al., describes the grading system employed in their centre (Pituitary Apoplexy Grading System), which depends on a radiological diagnosis of apoplexy and then takes into account clinical severity (24). Patients are placed into the highest grade that they meet symptom criteria. Patients with acute visual deficits or reduced GCS are scored the worst, followed by patients with ocular paresis, then patients without visual symptoms but headache, then patients with only endocrine symptoms and finally asymptomatic patients. This system also includes certain 'modifiers' that may alter the clinical decision making process. The three modifiers included are the possibility of a

prolactinoma, haemorrhage into a Rathke's cyst or presence of significant comorbidities. This is perhaps a slightly more robust method of assessment as it takes into the account the possibility that medical management may be preferable in certain pathologies (ie prolactinoma) and acknowledges that different visual symptoms perhaps reflect differing degrees of severity of the apoplectic events.

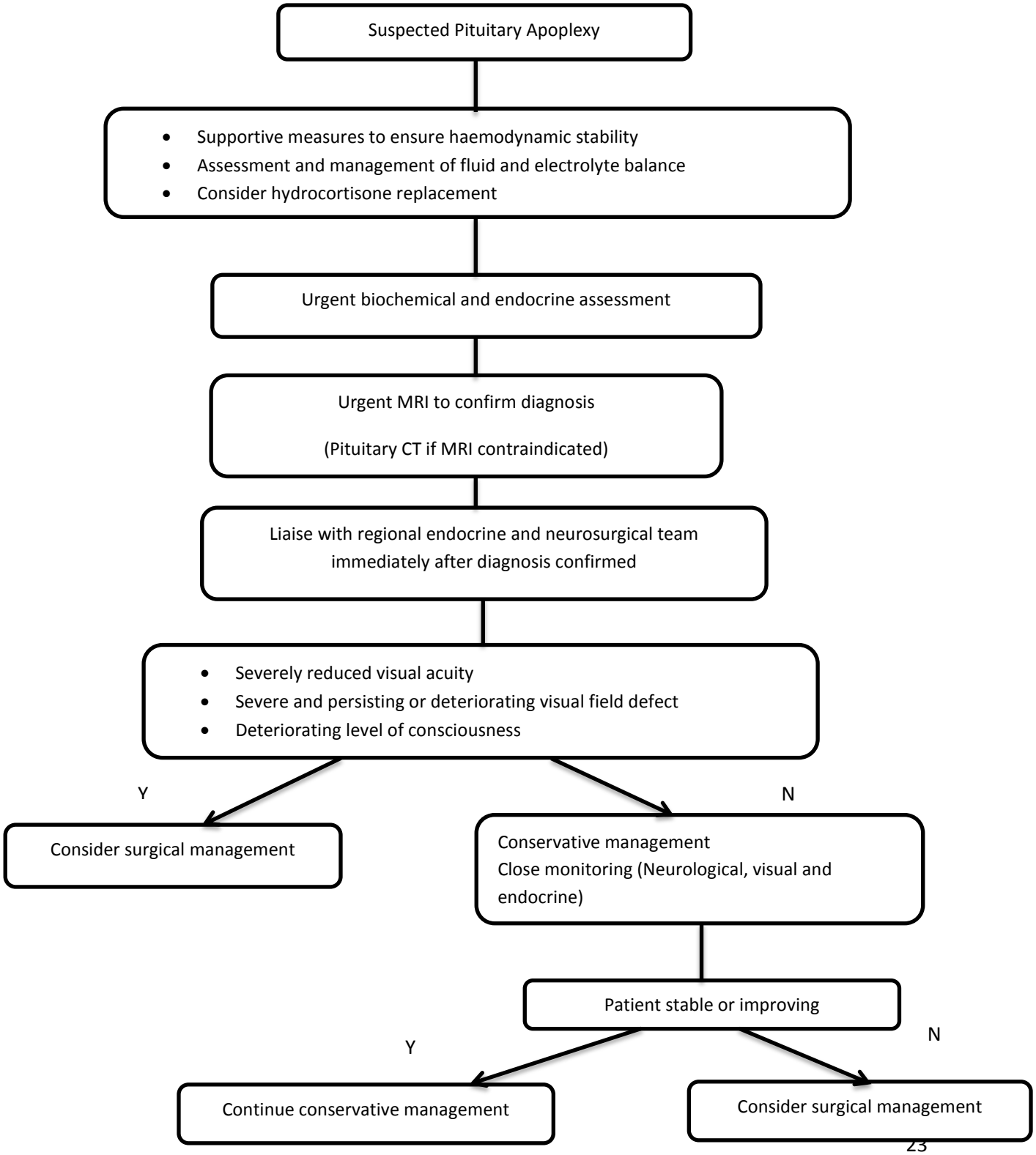

Figure 1.1 Proposed algorithm for the management of pituitary apoplexy. Adapted from Rajasekaran et al.,(1)

Variable	Points
Level of consciousness	
Glasgow coma scale 15	0
Glasgow come scale 8-14	2
Glasgow come scale <8	4
Visual acuity	
Normal* 6/6	0
Reduced- unilateral	1
Bilateral	2
Visual Field Defect	
Normal	0
Unilateral defect	1
Bilateral defect	2
Ocular paresis	
Absent	0
Present – unilateral	1
Bilateral	2

***No change from premorbid visual acuity**

Figure 1.2 Table summarising the categories and the corresponding scores that make up the Pituitary Apoplexy Scores (PAS) for the Pituitary Apoplexy patients (range 0 to 10). Adapted from Rajasekaran et al., (1)

Although it is not the main aim of this thesis to discuss visual symptoms in pituitary disease, this will be discussed briefly, later on in this thesis (Chapter 4). It is not possible to determine whether or not this grading system is well used amongst neurosurgical circles but certainly an awareness of its existence is important.

Hypopituitarism After Pituitary Apoplexy: Current Controversies

Overview

Unfortunately, advances in modern clinical endocrinology including the improvement in neuro-intensive care, adoption of the endoscopic transsphenoidal method and the development of a dedicated pituitary surgeon, have not improved endocrine outcomes after pituitary apoplexy, with up to 86% of patients requiring long term hormonal replacement (5, 6, 10, 19, 20, 22, 25, 26). The actual pathophysiology remains poorly understood and it is perhaps the different proposed mechanisms of hypopituitarism in pituitary apoplexy that have generated the lack of agreement from the endocrine and neurosurgical communities

as to how patients should be managed to preserve or improve pituitary function(if indeed possible). It has been postulated that the ischaemic necrosis to anterior pituitary cells that occurs due to the apoplectic event, leads to permanent and irreversible damage, and therefore recovery of pituitary function is limited(2). Conversely authors that demonstrate endocrine recovery post-surgically, postulate that hypopituitarism is modulated through compression of the portal vessels and/or the pituitary stalk(27). A further hypothesis is that non-haemorrhagic infarction selectively affects the pituitary tumour, as such preserving pituitary function, whereas haemorrhagic infarction limits the potential for pituitary recovery(28). The role and timing of neurosurgical intervention remains a topic of debate.

Surgical Versus Conservative Management

One of the key controversies in the management of pituitary apoplexy is whether patients with mild or moderate visual symptoms should be offered surgery or managed expectantly. It remains unclear whether superior outcomes in terms of preservation or even restoration of pituitary function is conferred by either management.

Proponents of the surgical methods quote superior endocrine and visual outcomes after surgical decompression in earlier series(20, 27). Contrary to this, modern series have demonstrated that conservative management can results in symptom resolution in patients with mild visual symptoms(19, 22).

Of course it is important to remember that regardless of the severity of presentation, there may be absolute contraindications to surgery such as medical frailty and advancing age. Furthermore it is occasionally not unreasonable to monitor the patient, as in the case of apoplexy into a suspected prolactinoma, where treatment with dopamine agonist can results in resolution of visual symptoms and satisfactory endocrine function(5).

Emergency Versus Elective Surgery

In patients where surgical decompression is clearly indicated, there is a lack of consensus as to when this should be performed. It has been reported that emergency surgical decompression (as defined in the current literature as within 8 days of presentation), results not only in significantly better visual outcomes, but also endocrine outcomes (7, 20, 29). Accurately determining pre-operative hypopituitarism can be difficult and it is often the case that patients undergoing emergency surgery do not have complete endocrine testing. Some cohorts use variable definitions of pre-operative hypopituitarism and as such

reporting 'true' recovery of pituitary function after urgent surgical decompression is not straightforward. For example in the series of Arafah et al., 1990, a proportion of patients were diagnosed with relative adrenal insufficiency (serum cortisol level inappropriate for the level of stress) pre-operatively and it unclear if this is valid diagnosis.

1.3 Hypopituitarism and Non-Functioning Pituitary Adenomas

Background

The prevalence of pituitary adenoma is reported to be between 22.2 –94 cases per 100,000 persons in the general population(30, 31). The most common of these tumours are non-functioning pituitary adenomas (NFPA) which are characterised by the lack of biochemical or clinical evidence of hormone excess(32). Unlike functioning tumours that often manifest with clinical evidence of hormonal hypersecretion, NFPA's present insidiously. Patients usually present with clinical signs of mass effect on the optic apparatus, report symptoms of hypopituitarism or as is becoming increasingly common, these lesions are detected incidentally on neuroimaging done for other reasons (33-36).

Surgical intervention for NFPA is aimed at restoring or maintaining vision with reduction of tumour mass while at the same time preserving the normal gland and as such endocrine function (36-39). Advances in modern surgical technique and experience have improved surgical complications such as CFS leak, meningitis and visual deterioration (40, 41). However the role of modern surgical technique in improving pituitary function in patients with NFPA is not well established. This is complicated by the difficulty in determining the 'true' effect of pituitary surgery on deterioration or recovery of pituitary function from the current literature. This is mainly due to wide heterogeneity in the literature in certain key aspects of the available reports:

1. *Inclusion of older surgical techniques*- Transcranial surgery is associated with higher rates of not only endocrine deficiencies but other post-operative complications such as frontal lobe damage (due to excessive retraction), hypothalamic damage, optic nerve damage, increased blood loss and longer hospital stay(42)**.**

2. *Inclusion of patient with Pituitary Apoplexy*- Pituitary apoplexy is a condition with an inherently high rate of hypopituitarism at presentation and this may confound the overall reported rate of hypopituitarism(22, 43).
3. *Inclusion of patients with functioning tumours*- In certain functioning tumours, the rate of post-operative hypopituitarism is relatively low. For example, a low rate of post-operative hypopituitarism is consistently reported in patients with acromegaly. It is postulated that this is due to several reasons, including that patients with functioning tumours present earlier with symptoms of hypersecretion whereas patients with NFPA present later due to insidious symptoms(39). As such inclusion of these patients in reports may not be truly reflective of the rate of hypopituitarism in patient with NFPA.
4. *Heterogeneous method of endocrine testing and lack of uniformity in defining/reporting hypopituitarism*- Some authors have only used baseline pituitary profile to assess hypopituitarism(38), whereas others incorporate rigours dynamic testing protocols(44-46). It is also not uncommon to find hypopituitarism defined as 'requirement for new hormone replacement'(37). This is of course inaccurate given that post-menopausal women do not require oestrogen replacement in the context of new gonadotrophin deficiency, and in some men, testosterone replacement may be contraindicated (ie active prostate cancer or severe symptoms of prostatism).

Factors such as the gender(44), tumour size(47, 48), age(48, 49) and even serum prolactin level at presentation(50) have been reported to influence postoperative endocrine outcome. Furthermore it is often assumed that pituitary surgery will affect all pituitary cells in the same way, and as such the rate of normalisation or deterioration in pituitary function is often described for the gland as a whole. It is unclear if this is appropriate given that previous authors have demonstrated that that transsphenoidal surgery does not affect individual pituitary axes in the same way (44, 49, 51).

Possible Variables Associated with Pituitary Function in Patients with Non-Functioning Pituitary Adenomas

Tumour Size

Patients with larger tumours have higher rates of hypopituitarism at baseline(49, 52). Preoperative tumour size is linked with the development of hormonal deficiency post-operatively(44, 47, 48). Fatemi et al., 2008 demonstrated a correlation between increasing tumour size and increasing rate of new post-operative hypopituitarism in their cohort(46). It is possible that the tumour size affects overall endocrine outcome in two main ways. Firstly, larger tumours will have a greater mass effect on normal pituitary cells, increasing the potential for permanent damage. Secondly, it is likely that the size of the tumour is reflective of the amount of time it has been present, with larger tumours having a longer time to 'grow'. This subjects pituitary cells to higher intrasellar pressures for a greater period of time, again increasing the probability of permanent damage.

Gender

Investigating the possibility of gender difference of pituitary function pre and post-operatively in patients with NFPA, Caputo et al., elegantly demonstrated that men and women exhibited different severity of hormone deficiencies(44). Even at presentation, men are more likely to have multiple hormone deficiencies and larger tumours, as compared to women(44, 49). Caputo et al., demonstrated in their cohort that men were at significantly higher risk of post-operative multiple pituitary hormone deficiency than pre-menopausal women. The authors also demonstrated that recovery and worsening of pituitary function was different between the genders and this is discussed below (Chapter 5). It can be postulated that it is easier for menstruating females to detect disruption in hormonal function, and as such present earlier with smaller tumours.

Age of Patient

Some studies have suggested that younger age at surgery is predictive of recovery of endocrine function post-operatively(46, 49, 53). This is supported by other reports demonstrating that pre-operative hypopituitarism is more common in older patients(49) and that restoration in normal pituitary function is unlikely in the elderly population(54). Although the mechanism behind this is not entirely clear, misdiagnosis is common in the elderly, probably due to clinicians assuming that other age related visual pathologies are

responsible for patients symptoms(55). Perhaps the delay in diagnosis limits the potential for recovery of pituitary function(54).

Surgical Technique

Over the past 20 years the transspheniodal route has superseded the transcranial route, as the primary method of choice for pituitary surgery(51). Although the microscopic technique is still widely used, the fully endoscopic technique allows a wider field of visualisation, angled viewing and high magnification to allow identification and better differentiation between tumour and normal pituitary tissue. All of this allows improved tumour clearance. It is not the objective of this thesis to debate the different neurosurgical techniques however an appreciation of the advantages and disadvantages of both transcranial and transsphenoidal approach is useful. Superior endocrine outcomes are demonstrated with the less invasive transsphenoidal approach compared to the transcranial route(56).

The Congress of Neurological Surgeons recommends that surgery via the endoscopic route (microsurgery or endoscopic) is used for resection of pituitary adenoma(57). A combined surgical strategy of transsphenoidal and transcranial approach can be used in tumours with significant suprasellar, frontal or temporal extension. In terms of pituitary function there is no evidence to suggest superiority of the endoscopic technique over the microscopic technique(58, 59). At Salford Royal NHS Foundation Trust, the fully endoscopic transsphenoidal method is preferred as the primary approach.

Surgical Experience

Like all practical procedures, there is a clear relationship between volume of cases performed and outcomes, and this is no different in pituitary surgery. It is now well established that patients treated by more experienced surgeons suffer less complications, have a lower mortality rate, have shorter durations of hospital stay and even lower rates of hypopituitarism(60). Centres with low numbers of dedicated pituitary surgeons carrying out high volumes of surgical cases demonstrate superior endocrine outcomes for all pituitary tumours, when compared to low volume centres(61).

Change in Pituitary Function After Endoscopic Transsphenoidal Surgery for Non-Functioning Pituitary Adenoma

Deterioration in Endocrine Function

With use of the transsphenoidal approach post-surgical deterioration in endocrine function (or development of new endocrine deficiency), is reported to occur in between 0-33% of cases(38, 44, 51, 58). Again, axis most likely to deteriorate is variable with some authors reporting this to occur in the ACTH axis(49). Caputo et al., demonstrated that men were more likely than women to develop deficiency in the HPA axis post-operatively (33% vs 15%, p=0.033)(44). The reason for this is unclear but may imply that there is a gender difference in terms of robustness of pituitary cells.

Recovery of Endocrine Function

In the current literature the reported rate of post-surgical recovery of endocrine function varies from 0-62%(37, 38, 44, 49). However there are varying reports as to which pituitary axis is most likely to recover, with some authors detecting high rates of recovery in the TSH axis(49) and ACTH axis(44, 51). When comparing gender, Caputo et al., showed that recovery of gonadotrophin function in all women was better compared to men (41% vs 16%, p=0.04) and then overall endocrine recovery was highest in pre-menopausal women(44). Again this may be due to the fact that women present with smaller tumour, perhaps inferring that they present earlier and as such permanent damage to pituitary tissue has not occurred.

Challenges

Given that much of the data in the literature is confounded by older series and heterogeneous method of reporting, determining the true rate of hypopituitarism and variables associated with this is difficult. Teasing out which variables can be altered will generate an understanding of how current practice can be developed. Attempting to identify which individual axis is most likely to deteriorate or recovery can certainly improve patient care, and this will be discussed later on.

1.4 Hypopituitarism in Survivors of Subarachnoid Haemorrhage

Background

Subarachnoid Haemorrhage (SAH) is a rare but devastating event that occurs in about 8 to 10 per 100,000 patients per year(62). It carries a mortality of approximately 50% and about a third of survivors do not regain full independence(63). With improvements in neurointensive care and the introduction of endovascular procedures, survival rates have improved with case fatality decreasing by 17% in absolute terms in the past three decades(64). This improvement in mortality has unmasked the long term consequences of this life changing event. With increasing interest in patient reported quality of life as an outcome marker in the treatment of chronic disease, it is now clear that in spite of good physical and neurological outcome, a significant proportion of survivors report impaired quality of life(65, 66) (67, 68). Cognitive and emotional dysfunction is common among SAH survivors. Many suffer from poor memory, fatigue, anxiety and depression(69-71).

The peak incidence of this event is between the fourth and sixth decade of life, therefore most survivors are in their most economically productive years. Unlike other forms of stroke, SAH is associated with a disproportionately high impact on society given that it affects a younger population. About a third of these patients never return to full time employment(72). The costs related to SAH do not just include the direct costs of medical care, but also the indirect costs incurred from loss of productivity. The calculated economic burden of SAH in the UK is £510 million per year(64). Early detection and management of the cause of the neuropsychological consequences of SAH could potentially enhance and accelerate the rehabilitation process.

Outcomes after Subarachnoid Haemorrhage

Subarachnoid Haemorrhage, Mortality and Physical Changes

Even after successful treatment of aneurysm rupture and good neurological recovery, the mortality and morbidity rates in survivors of SAH remain higher than that of the general population. Risk of vascular events is increased in this population. Multiple large cohorts have observed the increased risk of death from cardiovascular and cerebrovascular events

in SAH survivors, with the Standardised Mortality Ratio (SMR) as high as 3.7 depending on age(73-76).

Data from the International Subarachnoid Aneurysm Trial (ISAT) also demonstrated an increased mortality rate at 1 year survival as compared to the general population, with an SMR of 1.57(77). It is not clear as to the reason for the increased vascular events in this patient group, although we can postulate that predisposing factors to SAH such as hypertension and smoking might have a contributory role. However there may be other metabolic changes that occur after SAH that increase vascular risk factors.

Fatigue is extremely common, with between 31%- 90% of survivors complaining of this(65, 68, 78, 79). Reduced energy can be debilitating but can also cause difficulties in recommencing previous activities. It is associated with impaired quality of life and poor life satisfaction(79-81). Between 30% and 46% of survivors report some form of sleep disturbance(65, 70, 82). Patients often experience insomnia and sleep fragmentation. This includes frequent awakenings, difficulty falling asleep and returning to sleep after awakening and daytime sleepiness. The frequency of sleep apnoea and severe restless leg syndrome/periodic limb movement disorder is higher than that of the general population(82).

Subarachnoid Haemorrhage and Mood

Like most other stressful life events, emotional upset after SAH is frequent. A systematic review found that about 25% of survivors screen positive for clinical levels of anxiety and/or depression(83) however the prevalence of this is thought to be higher. Depressive symptoms can occur between 33% and 47% of patients(65, 80, 84, 85). Anxiety affects between 27% and 54% of survivors(80, 83). Levels of depression and anxiety do not correlate with physical disability however are predictors of poor functional outcome(86-88).

A survey of participants in a SAH support group revealed that 77.5% had some form of psychological distress as measured by the Hospital Anxiety and Depression Scale (HADS)(89). Although the authors acknowledge that this high incidence might be influenced by the fact that patients who have on-going difficulties are more likely to attend support groups (selection bias), this survey also found that 53% of patients who reported psychological symptoms had not been assessed for this. Furthermore post-traumatic stress disorder (PTSD), which was traditionally associated with traumatic experiences from military

combat, is now well recognised as a sequelae of significant medical events including SAH and is a significant predictor of quality of life in this patient population(69, 88, 90, 91).

Subarachnoid Haemorrhage and Quality of Life

Evaluation of patient outcomes after SAH has mainly centred on recovery as measured by the Glasgow Outcome Scale (GOS) or the Modified Rankin Scale (MRS). Essentially both these scales allow an assessment of physical disability and dependence in patients after a stroke or neurological injury. They are relatively insensitive to cognitive deficits and emotional disturbances. Although physical recovery is important to regain independence, this does not necessarily translate into life satisfaction or resumption of previous duties. This has been highlighted in various studies showing that despite minimal physical disability and favourable neurological outcome as measured by GOS or MRS, quality of life outcome measures remain reduced in many survivors of SAH(65-68, 92).

Only 5-10% of SAH survivors suffer from long term physical disability(93), however up to 55% of survivors report impaired health related quality of life (HRQOL)(86). Health related quality of life measures such as the SF-36, QoL-AGHDA questionnaire, Sickness Impact Profile and Nottingham Health Profile, allow patients to report the effect of disease on their physical, mental, emotional and social circumstances. This provides a more holistic understanding of the impact of illness on their daily life. Many patients with good physical outcomes are unable to completely resume former activities without some degree of difficulty including returning to employment, social activities and maintaining relationships and this consequently affects quality of life. Between 4% and 12% of survivors experience difficulties with activities of daily living (ADLs) and between 44% and 93% have difficulties with instrumental activities of daily living (IADLs)(83). The perceived severity of impaired quality of life reported by patients does not differ significantly from that which is reported by their carers or partners(92).

Less than 50% of SAH survivors who were previously in employment are able to fully return to their former occupation after the event(62, 93). More importantly despite good physical recovery (MRS score 0), almost a third of patients are not able to return to work. Looking at the long term effect of SAH on employment, relationships and personality, Wermer et al., found that of the survivors who managed to return to work, about a third worked less hours or worked in a position of less responsibility(72). The team also found that 7% of patients

were divorced due to SAH related problems. As expected, patients who are able to return to work report better life satisfaction(93).

This therefore suggests that even after physical disability has resolved, there are other perturbations following a SAH that persist in the longer term. Traditional predictors such as age, sex, severity of bleed, clinical severity at time of admission to hospital and time of assessment have a negligible effect on patient's health related quality of life (HRQOL) as revealed in a meta-analysis(86). Clearly factors other than physical fitness play an important role in determining life satisfaction. The cause of this unique constellation of disabilities in mental health, emotional health and social interaction remains largely unexplained.

Hypopituitarism and Growth Hormone Deficiency after Subarachnoid Haemorrhage

Given the close proximity of the pituitary gland to the circle of Willis anatomically and the potential for vasospasm of the hypophyseal vasculature after SAH, it is easy to see how this injury poses a risk to the hypothalamus, pituitary gland and its stalk. In a consecutive series of autopsies on 106 patients dying after rupture of a berry aneurysm, Crompton (1963) found that 61% of specimens had hypothalamic lesions(94). In 1969, Jenkins demonstrated that pituitary insufficiencies can occur in the acute phase of SAH(95). Surprisingly, these observations have had minimal impact on clinical practice, owing to a failure to appreciate SAH induced hypopituitarism as a clinical entity. In his seminal paper Kelly et al., revived an interest in hypopituitarism after SAH(96). In this study which predominantly included patient with traumatic brain injury (TBI), isolated GHD was detected in both SAH survivors included. Subsequent studies have demonstrated that the prevalence of hypopituitarism after SAH to be between 0-57% and the prevalence of GHD to be between 0-37%(63, 97-110).

This variability is mainly due to the heterogeneous definitions and methods of assessing hypopituitarism in the literature. Studies that have only relied on basal hormone levels report higher rates of hypopituitarism(103, 106, 107), whereas studies that have employed dynamic testing protocols(99, 101, 102, 105) and further confirmatory testing(104, 109, 110) detect lower levels of hypopituitarism. Specifically with regards to assessing the somatotrophic axis, the lowest prevalence of GHD is reported in cohorts that employ dynamic testing with appropriate BMI specific cut-offs (GHRH-arginine test), accounting for the effect of BMI on GH response(104, 109, 111). Although the availability of GHRH for

testing has become an issue in recent years, an appreciation of the effect of BMI on dynamic GH testing is important when interpreting the current evidence.

Current evidence indicates that there is no correlation between clinical severity of SAH, radiological grading, location of aneurysm and the risk of developing hypopituitarism(98, 100, 101, 107, 112).

Challenges: Investigation Hypopituitarism After Subarachnoid Haemorrhage

It is important not to trivialise that SAH survivors are frequently left with neuropsychological and emotional difficulties that significantly impact on their quality of life. This is not to be overlooked as there is much to be gained from trying to support this group of patients, not only by the patient but potentially society as a whole. There are undoubtedly many similarities between symptoms suffered by SAH survivors and patients with hypopituitarism. It is not unreasonable to postulate that neuroendocrine dysfunction might contribute to this. Unfortunately assessment of neuroendocrine problem is not routinely incorporated in the management of SAH patients. As discussed above the variable rate of hypopituitarism reported in this patient group is mainly due to heterogeneous endocrine testing method. To enable endocrine testing to be routinely carried out after SAH, clear guidance regarding testing protocol is required.

1.5 Growth Hormone Deficiency after Subarachnoid Haemorrhage

Growth Hormone Deficiency, Mortality and Physical Changes

Premature mortality in hypopituitary patients with untreated growth hormone deficiency has been previously observed with a greater than two fold increase in cardiovascular deaths(113, 114). Although the exact mechanism for this remain unclear there is no doubt that adults with growth hormone deficiency develop physiological changes that favour an adverse metabolic profile, including insulin resistance, dyslipidaemia, increased intimal medial thickness and artherogenic propensity(114, 115). Undoubtedly there are physical and metabolic similarities between untreated GHD and the metabolic syndrome. More importantly treatment with GH results in improved lipid profile including reduced total cholesterol and LDL-cholesterol(115, 116).

Adults with growth hormone deficiency exhibit change in body composition with marked increase in central adiposity, increased weight, increased body fat and reduced lean body mass(114, 115) Replacement with Growth Hormone results in significant reduction in body fat (predominantly in the abdominal region), reduction in waist to hip ratio and increased lean muscle mass(116-121).

Growth hormone deficiency is also associated with reduced exercise capacity(122-124). Patients report poor energy and score poorly on vitality scores(125, 126). Replacement with growth hormone increases muscle strength, significantly improves exercise capacity, maximum power output and maximum oxygen consumption(127-134). This is associated with improved vitality, reported energy levels and physical ability(119, 135, 136).

Growth Hormone Deficiency and Mood

It has been demonstrated that adults with GHD suffer higher anxiety levels than the general population(125, 137, 138). Low mood is also common in this population with one study finding the incidence of depression in their population of adults with GHD being as high as 60% (126, 139). The role of growth hormone in the control of mood remains largely unclear however given the presence of GH and IGF receptors in the brain; one can postulate that this might be due to its direct effects on the central nervous system. Growth hormone treatment alleviates symptoms of anxiety and improvement can be seen early on upon the commencement of treatment(116, 135, 139). Improvement in cognition and body composition might account for this enhancement of mood. One study however reported significant improvement in emotional reaction scores within one month of treatment suggesting that it was too early for physical or cognitive changes to occur and that GH might itself have a role in mood regulation(126).

Growth Hormone Deficiency and Quality of Life

Prior to the introduction of growth hormone replacement in hypopituitary adults, it had been well recognised that in spite of optimal pituitary hormone replacement, these patients reported reduced well-being as compared to the normal population(137). In one of the most eminent studies of adults with GHD, McGauley et al., (1989) demonstrated these patients had significantly lower scores on quality of life assessment as measured by the Nottingham Health Profile (NHP) and Psychological General Well Being (PGWB) questionnaire as compared to healthy controls(140). Patients with GHD scored significantly

poorer in the domains of energy, emotional reaction and social isolation. The group then conducted a randomised, double blind, placebo-controlled trial with GHR and found a significant difference in quality of life scores between the groups at 6 months, with the group receiving GHR reporting improvement.

It is now well established that growth hormone deficiency is associated with impaired quality of life as compared to matched controls in the general population(113, 119, 141). This translates to poor social performance with effects on employment and even marriage (Dean et al., 1985, cited in Cuneo et al., 1998, p 115). It is associated with a higher number of disablement pensions and a tendency to early retirement. Adults with growth hormone deficiency are more likely to remain single and unemployed (Dean et al., 1985, cited in Rosen et al., 1994, p 115). Also adults with growth hormone deficiency incur increased pharmaco-economic costs(113). Marked improvement in quality of life is seen with GHR. Even though the main improvement is seen in the first 6 months, it now recognised that this is sustained in the long term. Results from the Pfizer International Metabolic Database – KIMS (which is currently the largest database of hypopituitary adults with GHD receiving GHR), demonstrated a significant improvement in quality of life as measured by QoL-AGHDA questionnaire(114). Rosilio et al., demonstrated that after 4 years of replacement, patients with GHD reported quality of life that was not significantly different from the general population(142).

Furthermore, withdrawal of GHR has detrimental psychological effects. In a double- blind study to observe the effects of growth hormone withdrawal, McMillan et al., randomised patients who had previously been on GHR to either placebo or continued treatment with GHR(143). After 3 months, the group found significant reduction in general health score (as measured by SF-36), reduced energy and greater perceived impact of hormone deficiency on physical ability in the placebo treated group as compared to those who continued treatment.

Impairment in quality of life in the context of GHD is probably due to a variety of factors including poor memory, poor concentration, lack of self-esteem, social isolation, disturbed sleep, fatigue, anxiety, change in body composition and possibly the direct effect of growth hormone on the central nervous system. The exact mechanism as to how it improves quality

of life remains unknown. It is not unreasonable to postulate that increased lean mass, energy and improved mood contribute to this.

Challenges: Growth Hormone Replacement in Patients who have developed Growth Hormone Deficiency After Subarachnoid Haemorrhage

Undeniably the resemblance in terms of physical, metabolic, emotional and psychosocial symptoms between SAH survivors and patients with GHD is striking (Figure 1.3). Given that GHD is becoming increasingly recognised as a consequence of SAH, it is possible that in SAH survivors neuroendocrine dysfunction could be responsible for the development of these symptoms. As discussed above, in adults who have acquired GHD from other aetiologies, replacement with GH results in improvement in these symptoms. Although current national guidelines allow of GHR in patients who have developed GHD after SAH, there are currently no published studies assessing the impact of GHR exclusively in this patient group. Given the potential to improve quality of life and functional outcomes in SAH survivors, further research into this area is a warranted.

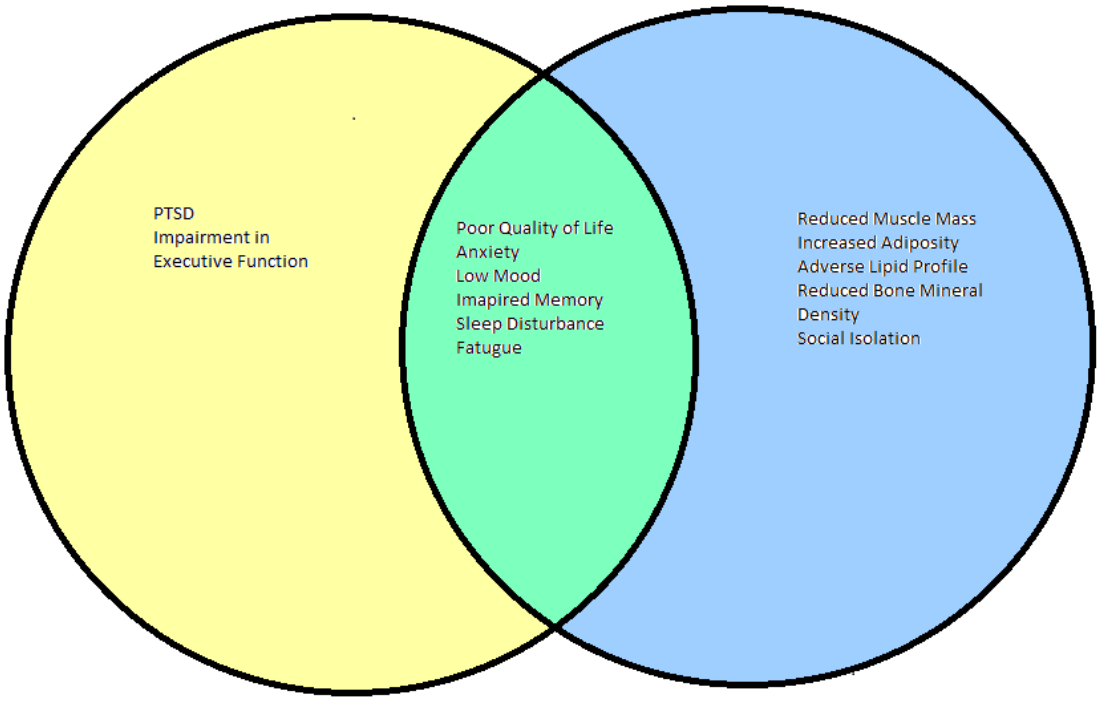

Figure 1.3 Venn diagram showing overlapping symptoms of Subarachnoid Haemorrhage (yellow circle) and Growth Hormone Deficiency (blue circle).

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Chapter 2

Hypotheses and Objectives

2 Chapter 2 Hypotheses and Objectives

2.1 Hypotheses

The hypotheses tested in this thesis are:

1. Modern approach to managing patients with pituitary apoplexy results in good endocrine and visual outcomes
2. Exclusive use of the endoscopic transsphenoidal method of pituitary surgery results in low rate of post-operative hypopituitarism in patients with Non-Functioning Pituitary Adenoma in a modern cohort
3. Prevalence of hypopituitarism in survivors of subarachnoid haemorrhage is low when dynamic and confirmatory testing protocol is employed
4. Growth Hormone Replacement can improve quality of life, mood and cardiorespiratory fitness in patients who have developed Growth Hormone Deficiency after Subarachnoid Haemorrhage

2.2 Objectives

To address these hypotheses, this thesis will:

1. Describe the study design and recruitment of patients with Pituitary Apoplexy, Non-Functioning Pituitary Adenoma and Subarachnoid Haemorrhage
2. Describe methodology of how hypopituitarism was diagnosed in the cohort with details of the type of testing protocols used
3. Describe the use of quality of life and mood questionnaires in SAH patients
4. Describe the exercise testing protocol used to assess cardiorespiratory fitness in SAH patients
5. Compare analytically baseline variables in patients presenting with pituitary apoplexy based on management (conservative management vs elective surgery vs emergency surgery)

6. Compare analytically the rate of hypopituitarism in patients with pituitary apoplexy based on management (conservative management vs elective surgery vs emergency surgery)
7. Provide analyses of patient with NFPA including reporting on rate of hypopituitarism prior to surgery, and investigating the variables associated with hypopituitarism pre-operatively
8. Investigate the rate of post-operative hypopituitarism with exclusive use of the endoscopic transsphenoidal technique by an experienced surgeon and report on the variables associated with post-operative hypopituitarism
9. Investigate rate of recovery and deterioration of function by individual pituitary axis in patients with NFPA after endoscopic transsphenoidal surgery
10. Investigate the rate of hypopituitarism in SAH survivors when dynamic endocrine testing and confirmatory testing methods of the HPA axis and somatotrophic axis is incorporated
11. Report on any variables that may predict hypopituitarism and Growth Hormone Deficiency in SAH patients
12. Investigate if Growth Hormone Replacement improves quality of life and mood in patients who have developed Growth Hormone Deficiency after Subarachnoid Haemorrhage and compare this with SAH survivors who are Growth Hormone Sufficient
13. Investigate if Growth Hormone Replacement improves cardiorespiratory fitness and metabolic parameters in patients who have developed Growth Hormone Deficiency after subarachnoid Haemorrhage

Chapter 3

Methods

3 Chapter 3 Methods

3.1 Preface

This chapter will provide a detailed description of the methodology and assessments used to address the hypothesis and aims in Chapter 2. This will lead to some degree of overlap and repetition between this and subsequent chapters.

3.2 Study Design

This was a single centre study consisting of a retrospective and prospective arm. The retrospective arm of the study, was designed to investigate hypopituitarism in patients who had received treatment for Pituitary Apoplexy and Non-Functioning Pituitary Adenoma at Salford Royal NHS Foundation Trust between 2005 and 2015. To avoid inter-surgeon variability, surgical data from only one pituitary surgeon was analysed (KG). It is noteworthy that during this time period, most pituitary surgery was performed by KG. Patients who did not have endocrine follow up at this centre were excluded.

The prospective arm of the study was designed to investigate the prevalence of hypopituitarism in SAH patients and the impact of growth hormone replacement in SAH patients who have developed growth hormone deficiency after SAH. Patients who had received treatment for SAH at Salford Royal NHS Foundation Trust between 2006 and 2014 were invited to participate. Given that screening for pituitary insufficiency is not routine in SAH patients, eligible participants were required to give written consent prior to screening for hypopituitarism. Patients with GHD who met NICE criteria for GHR(Appendix 2)(1), were required to undergo a series of quality of life, metabolic and cardiorespiratory assessments before and after 36 weeks of GHR. At the end of the 36 weeks, participants who qualified to continue with GHR based on national guidelines, were referred to Department of Endocrinology at Salford Royal NHS Foundation Trust.

3.3 Participants and Eligibility Criteria

All participants were required to be aged 18 years or above at the time of treatment. Patients were included if they had received treatment for the primary condition (ie pituitary surgery, neurovascular coiling or neurosurgical clipping, SAH monitoring) at Salford Royal

NHS Foundation Trust. Additional criteria for each type of pathology are provided below. Further justification of the eligibility criteria is presented in the individual results section.

Pituitary Apoplexy

Inclusion Criteria

- 'Classical' Pituitary Apoplexy as defined by the UK Guidelines For The Management of Pituitary Apoplexy (2010)(2). This is defined as acute onset headache and/or acute visual disturbance and radiological evidence of haemorrhage and/or infarction into the pituitary gland.
- Received treatment at Salford Royal NHS Foundation Trust between 2005 and 2014.
- Endocrine follow up at Salford Royal NHS Foundation Trust

Exclusion Criteria

- Subclinical Pituitary Apoplexy

Non-Functioning Pituitary Adenoma

Inclusion Criteria

- Non-functioning pituitary adenoma was defined as pituitary adenoma without clinical or biochemical evidence of excess hormonal production
- Underwent surgical treatment at Salford Royal NHS Foundation Trust between 2005 and 2015.
- Underwent post-operative assessment of pituitary function as Salford Royal NHS Foundation Trust

Exclusion Criteria

- Functioning pituitary adenoma (ie biochemical evidence of GH excess, cortisol excess, prolactin excess)

- Non-adenomatous pituitary lesions
- Classical Pituitary Apoplexy
- Patients who received pituitary radiotherapy prior to surgical intervention
- History of other cranial irradiation
- Patients who underwent surgery via the transcranial route as primary surgical method

Subarachnoid Haemorrhage

Inclusion Criteria

- Diagnosis of SAH more than 12 months ago and less than 10 years ago, at time of recruitment

Exclusion criteria

- Critically ill patients
- Clinical contraindication to glucagon stimulation testing (Appendix 3)
- History of cranial irradiation
- Other untreated or on-going brain pathology that could affect cognitive function and thus affect interpretation of results
- Hypothalamic/pituitary disease that was diagnosed prior to SAH
- History of dementia or cognitive impairment unrelated to SAH
- Significant medical or psychiatric condition, which, in the opinion of the investigator, may interfere with participation in the study
- Have taken another investigational drug within 30 days of recruitment
- Pre-existing diagnosed hormonal deficit other than GHD without evidence of stable treatment for at least 3 months prior to recruitment.
- Participants unable to communicate in English, as translation of questionnaires will affect their content.
- Contraindication to Growth Hormone Replacement therapy (Appendix 4)

3.4 Ethical Considerations

The study involving participants with Subarachnoid Haemorrhage was approved by NRES Committee North West – Greater Manchester West (Reference 14/NW/0191). All study procedures complied with the principles of the Declaration of Helsinki (2013). All participants were required to provide written informed consent prior to study enrolment.

3.5 Funding Details

The Subarachnoid Haemorrhage arm of this study was funded by Investigator-Initiated Research (IIR) award from Pfizer Ltd (UK) (Reference WI184597), which was awarded to Dr Tara Kearney.

3.6 Patient Identification and Data Collection

Potential participants were identified from the Trust electronic records, Subarachnoid Haemorrhage audit log and surgeon specific database. Patient identification, screening and recruitment pathway is detailed in the results section.

Baseline demographics, co-morbidities, medication records, details of pituitary function, radiological findings, details of interventional procedures, complications related to interventional procedures, complications during admission, histology reports and information regarding multidisciplinary team (MDT) discussions, were obtained from electronic patient records. In addition, Clinical Record Form with the above details was completed and confirmed with all SAH patients prior to dynamic pituitary testing to absolutely ensure no contraindications to testing. Patient receiving GHR in the SAH arm of the study were issued with a study diary to document any side-effects, new diagnosis or new medication during the study period.

Data regarding pituitary function for all participants was obtained from biochemical results available on electronic patient records and not clinical letters. On occasion in the pituitary apoplexy and NFPA cohort, insufficient biochemical results prior to treatment were not available electronically, mainly due to these patients being referred urgently from other centres. In these cases, every effort to obtain these results from the referring centre was

made. If this data was still not available, this is made clear in the individual results section. Queries about pituitary hormone status was discussed and confirmed with TK.

Given the prospective nature of the SAH arm of the study, potential participants were sent the relevant Patient Information Sheet (PIS) and letter of invitation into the study. Potential participants were given a maximum of 3 weeks to contact the study. If no reply was obtained after this time, potential participants were contacted by phone.

3.7 Initial Sample Size Estimation

The German KIMS database (largest database of patients with GHD) of 418 adults with GH deficiency who received long-term growth hormone (GH) replacement therapy(3) found that after one year on growth hormone, the mean change in QoL-AGHDA score was -2.1 in men (95% CI -3.0 to -1.3) and -2.4 in women (95% CI -3.3 to -1.4). Based on this, a study looking at the effectiveness of GHR would require 153 participants in a 'treatment' group and 153 participants in a 'control' group to detect a difference in score of 2.25 ± SD7.0* on QoL-AGHDA questionnaire to achieve 80% statistical power. Previous unpublished data from our center, "The incidence of hypopituitarism in Post Interventional Subarachnoid Haemorrhage" (abstract submission to BES 2014 meeting), revealed that the incidence of severe growth hormone deficiency post SAH was 22.5%. Based on this estimated incidence, to be able to obtain the required 306 participants with GHD as above, would require screening of 1360 survivors of SAH.

As previously mentioned, the incidence of SAH is relatively low, occurring between 8 to 10 per 100,000 patient years(4). Salford Royal NHS Foundation Trust (SRFT) is a tertiary neurosurgical centre covering the Greater Manchester area and sees approximately 100 patients with SAH annually. Therefore it is clear that the recruitment of such a large number of subjects would require multi-centre participation or a prolonged study period and neither is practical nor possible in the required time frame. As such, the sample size set out for this study is based on the number of patients seen at SRFT and feasibility of screening and completing all study procedures within 24 months. It was estimated that it would be possible to screen 100 SAH survivors with dynamic pituitary function testing with the time and resources available. Based on previous research done at our centre, we initially

estimated that GHD would be detected in 20 of these patients and all of these patients would be willing have treatment with GHR.

No specific sample size was set for the Pituitary Apoplexy and NFPA arms of this study, given retrospective observational nature of the study. However, all patients with Pituitary Apoplexy or NFPA who received treatment at Salford Royal NHS Foundation Trust from 2005 to 2015 and met inclusion and exclusion criteria were included in data analysis.

* The confidence intervals from the German KIMS publication(3) have been converted to estimated standard errors: Men mean -2.1 ± SD 6.8 Women mean -2.4 ± SD 7.2. We are not seeking to detect any difference in men and women, so we have used the mid-point of the values in our calculations, i.e. Mean -2.25 ± SD 7.0.

3.8 Statistical Analyses

Data analysis was carried out using IBM SPSS Statistics 22 (IBM SPSS Statistics for Windows, Version 20 NY, USA; 2011) and STATA 14 (StataCorp 2015. *Stata Statistical Software: Release 14.* College Station, TX). Descriptive statistics is used to present baseline demographics. Where not specified baseline characteristics for categorical data are expressed as n(%) and continuous data as mean ± standard deviation. Categorical data were analysed with either the Chi-squared test or the Fisher exact test as appropriate. Non-categorical data were analysed using the Independent t-test or Mann-Whitney U test depending whether data followed normal distribution. Where three groups were compared, analysis of variance was used. To compare pre and post-treatment data, the paired t-test was used. To compare outcomes from treatment group and control group, ANCOVA analysis with Bonferroni correction was used. Variables that were significant ($p<0.05$) on univariate analysis were included in multivariate model. Linear regression was used to assess correlation between peak GH levels achieved on GST with pre-treatment weight, BMI, relative $VO_{2\ peak}$, QoL-AGHDA score, WHO-QoL-Bref scores and HADS scores in SAH patients. Logistic regression was used to determine the association between the age, gender, tumour size, incidental finding and hypopituitarism pre- and post-operatively in patients with NFPA. A two-tailed p-value of <0.05 was considered statistically significant.

3.9 Dynamic Testing of Endocrine Function

At this point, it is worth discussing the reasoning behind the type of dynamic tests employed in this study protocol. Hoffman et al., 1994 demonstrated a clear difference in peak stimulation GH levels during the Insulin Tolerance Test (ITT) between patients with extensive organic pituitary disease and age, sex and BMI-matched controls(5). Peak growth hormone achieved by hypopituitary patients (range <0.2 – 3.1mcg/L) was clearly lower than controls (5.3 - 42.5mcg/L). As such consensus guidance recommends that the diagnosis of adult GHD be established in patients with an appropriate clinical history by demonstrating a peak GH concentration of less than 3mcg/L following insulin-induced hypoglycaemia(6). Although the Insulin Tolerance Test (ITT) is considered diagnostically the 'gold standard' in assessing GH and ACTH axis, it is cumbersome and requires close medical supervision as a nadir blood glucose level of less than 2.2mmol/L must be achieved. Furthermore it is not without significant potential side effects such as development of severe neuroglycopaenic symptoms, loss of consciousness, rarely seizures and precipitating an adrenal crisis in patients with no adrenal reserve. It is contraindicated in the elderly, in cardiac disease, cerebrovascular disease and seizures. As such the Glucagon Stimulation Test (GST) was deemed a safer, more convenient alternative. GST allows assessment of both the somatotrophic and adrenocorticotrophic axis simultaneously. No specific level of hypoglycaemia is required for it to be considered a valid test. It is relatively easy to undertake, with few contraindications (insulinoma and phaeochromocytoma) and has minimal side-effects. Its assessment of the GH axis is comparable to the ITT. Berg et al., showed that when a peak GH cut-off value of 2.5ng/mL is used, the GST revealed a sensitivity of 95% and specificity of 79% in diagnosing severe GHD(7). This high sensitivity and specificity has also been shown by Conceicao et al., with a sensitivity of 97% and specificity of 88%(8).

The Growth Hormone Releasing Hormone (GHRH)-Arginine test allows interrogation of the somatotrophic axis alone which is as reliable as the ITT(9, 10). It has previously been shown that in healthy subjects, peak GH response is BMI dependent, in that a higher BMI is associated with a poorer GH response. BMI specific cut-offs for GH peaks are established for the GHRH-Arginine Stimulation test, with severe GHD defined as a GH of less than 11µg/L with a BMI <25kg/m^{2,}, a peak GH value of less than 8µg/L with a BMI 25-30kg/m^2, or

a peak GH value of less than 4.2µg/L with a BMI> 30kg/m^2. These BMI specific cut-off values have not been established for other stimulatory tests. However in recent years there has been difficulty in obtaining GHRH. As such the Arginine Stimulation Test has become a common alternative as a confirmatory test of the somatotrophic axis. However it has a lower sensitivity and specificity as compared to the GHRH-Arginine test, with one study showing that if a peak GH cut-off value of 3µg/L was used, 59% of healthy controls would be misdiagnosed as having GHD(10). It is relatively easy to carry out, with good patient tolerability and few side effects. Therefore it is commonly used as a second confirmatory test.

For purposes of diagnosing GHD in this thesis, the validated cut-off of 3mcg/L is used and it is beyond the scope of this thesis to discuss the relative merits and drawbacks of this. However it is important to highlight the difficulties in diagnosing adult GHD when population specific cut-offs are not available.

For reasons discussed above, in all patients the primary method of assessing pituitary function is by measurement of baseline pituitary function test (Appendix 5) in combination with glucagon stimulation tests to assess cortisol and GH dynamic response. Isolated GHD is confirmed with an arginine stimulation test in all patients. On occasion where patient demonstrated a suboptimal cortisol response during GST, this is confirmed with a short synacthen test

3.10 Protocols for Dynamic Endocrine Tests

Short Synacthen Test (SST)

- An indwelling peripheral venous cannula is inserted and allowed to rest for 30 minutes
- Baseline blood sample for cortisol measurement is drawn
- Intramuscular injection of 250µg of Synacthen (Tetracosactide, Questcor Operations, UK) is administered
- Blood samples for cortisol are drawn at 30 and 60 minutes.

Glucagon Stimulation Test (GST)

- After an overnight fast an intravenous cannula is inserted and allowed to rest for 30mins

- Baseline sample for of GH, IGF-1, testosterone/estradiol, LH, FSH, cortisol, ACTH, fT4, TSH and prolactin is drawn.
- Glucagon (GlucaGen, Novonordisk Ltd) is administered subcutaneously at a dose of 1mg (1.5mg for patients >100kgs).
- Blood samples for GH and cortisol are taken at 90, 120, 150, 180, 210 and 240minutes.

Arginine Stimulation Test (AST)

- After an overnight fast as above, intravenous cannulae are inserted into both forearms and are allowed to rest for 30 minutes
- A baseline blood sample is taken at 0mins for GH
- 30g arginine is infused over 30minutes (150mls of 20% L-arginine hydrochloride (Stockport Pharmaceuticals, UK))
- Blood samples for GH are taken at 30, 60, 90 and 120 minutes.

3.11 Diagnostic Criteria for Hypopituitarism

Hypogonadotrophic hypogonadism in men was diagnosed if a low serum testosterone (morning sample) was associated with low or inappropriately normal gonadotrophin levels. In premenopausal women, hypogonadotrophic hypogonadism was defined as low serum estradiol and inappropriately low gonadotrophins associated with amenorrhoea or oligomenorrhoea. In post-menopausal women, this was defined as inappropriately low gonadotrophins for age. Secondary hypothyroidism was defined as a low serum free T4 associated with low or inappropriately normal serum TSH.

Prior to the 26th January 2015, HPA axis deficiency was diagnosed as a failure to reach a peak cortisol value of 550nmol/L on the GST and SST. After this time deficiency of the HPA axis was diagnosed as failure to reach a peak cortisol value of 450nmol/L on GST and SST. This change in cut-off value is due to change in the assay used for serum cortisol measurement. Prior to 26th January 2015 serum cortisol was analysed using Electrochemical Luminescent Immunoassay (Roche Cobas 8000). After this time, serum cortisol measurements was analysed using competitive Chemiluminescent Immunoassay (Siemens

Advia Centaur). Severe GHD was diagnosed as a failure to reach a peak GH value of 3µg/L (9mU/L) on GST or AST.

3.12 Definitions

The following definitions were used for data collection:

Baseline Pituitary Profile was defined as baseline serum ACTH, LH, FSH, TSH, prolactin, cortisol, testosterone/estradiol, fT4 and IGF-1 levels measured in the morning.

Pituitary Apoplexy was defined as haemorrhage, infarction or haemorrhagic infarction into the pituitary gland. The 'classical' form of pituitary apoplexy was defined as acute onset headache and/or acute visual disturbance and radiological evidence of haemorrhage and/or infarction into the pituitary gland.

Non-Functioning Pituitary Adenoma was defined as pituitary adenoma in the absence of clinical or biochemical evidence of hormonal hypersecretion. In all patients, hormonal hypersecretion was confirmed biochemically. Adenomatous tissue was confirmed on histological diagnosis.

Aneurysmal Subarachnoid Haemorrhage was defined extravasation of blood into the subarachnoid space due to rupture of cerebral aneurysm or arteriovenous malformation. This was confirmed by the presence of blood on computed tomographic (CT) imaging of the brain or on cerebrospinal fluid (CSF) analysis obtained by lumbar puncture.

Diabetes Mellitus was defined as a documented history a diabetes mellitus diagnosed by the primary care physician, use of anti-diabetic medication, a fasting venous plasma glucose ≥7.0nmol/L or a random venous plasma glucose of ≥11.1nmo/L.

Hypertension was defined as a documented history of hypertension as diagnosed by the primary care physician, use of anti-hypertensive medication, or a blood pressure over 140/90mmHg on two separate occasions.

Ischaemic Heart Disease was defined as a documented history of myocardial infarction, angina, coronary artery bypass grafting or percutaneous coronary intervention.

3.13 Assessments

Quality of Life Assessment Format

Quality of Life in Adults with Growth Hormone Deficiency Assessment (QoL-AGHDA) Questionnaire

The QoL-AGHDA Questionnaire is a disease specific questionnaire that is used to assess the impact of growth hormone deficiency on quality of life in adults. There are 25 'yes' and 'no' questions in this self-administered questionnaire, with a higher score indicating a worse perception of quality of life. Its validity in adults with GHD is well established(11-14). Current NICE guidance allows for GHR in adults with severe GHD (peak GH level of less than 3mcg/L on a validated dynamic test of the somatotrophic axis) with a QoL-AGHDA score of greater than 11(1). These guidelines also stipulate that GHR should be discontinued in patients who do not demonstrate an improvement in QoL-AGHDA score by at least 7 points after 9 months (36 weeks) of GHR. Therefore to comply with national guidelines, QoL-AGHDA questionnaire was administered to all patients receiving GHR.

WHO-QoL Bref Questionnaire

The WHO-QoL Bref was derived from the WHO-QOL 100, which is a well establish tool used to gain information about patients perception of their own quality of life. Both the WHO-QoL 100 and the WHO-QoL Bref were developed by the World Health Organisation (WHO) with the support of 15 centres worldwide as a method of estimating patients perception of their quality of life in relation to their health(15). The WHO-QoL 100 contains 100 items incorporating the domains of physical health, psychological health, level of independence, social relations, environment and spirituality/religion/personal beliefs(16). The WHO-QoL Bref contains 26 questions; one item from the 24 facets of the WHO0QoL 100 is included and a further 2 items about overall quality of life and general health is included(17, 18).This self-administered questionnaire allows assessment of quality that encompasses the domains of physical health, psychological health, social relationships and environmental effects. The WHO-QoL Bref is frequently used in settings were the WHO-QoL 100 may be inappropriate or difficult use, given the length of the questionnaire. Given the memory and concentration difficulties in the SAH patient population, it was therefore deemed that this abbreviated questionnaire would be more appropriate. The WHO-QoL questionnaire has been demonstrated to be a reliable method of assessing quality of life in SAH patients(19).

Psychological Assessment

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a validated and practical tool designed to provide clinicians with a reliable tool for identifying and quantifying symptoms of anxiety and depression in patients(20, 21). This self-administered questionnaire contains 14 items; 7 pertaining to anxiety and 7 pertaining to depression. Each item is score between 0-3 and therefore a patient can score between 0-21 for either anxiety or depression. The HADS score has been used to assess mood symptoms in the SAH population(22).

Assessment of Cardiorespiratory Fitness

Cardiorespiratory fitness was assessed by measurement of peak oxygen consumption ($VO_{2\ peak}$) during cardiopulmonary exercise testing (CPET) via treadmill walking. There are currently no validated CPET treadmill protocols for the SAH population. However the Modified Balke protocol has been used in patient recovering from TBI and has been shown to be reliable in this population(23, 24).

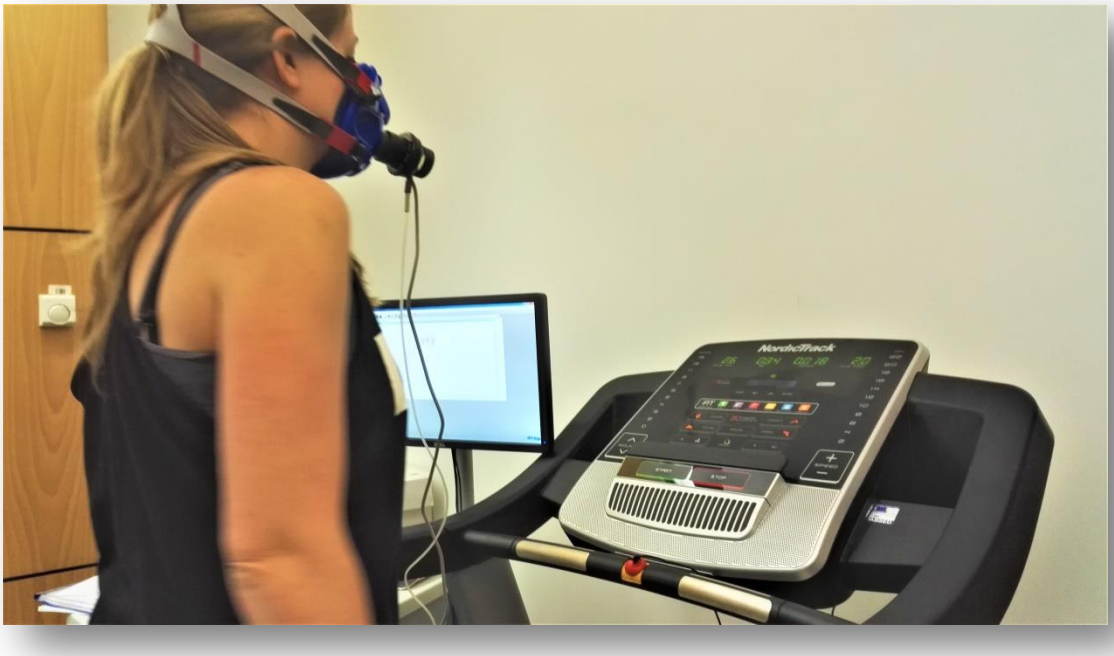
The Modified Balke protocol is a graded protocol that allows for treadmill walking speed to be determined by the individual participant. As such it was deemed that this protocol would be both safe and suitable for this patient population, given that SAH patients often have walking and balance impediments, in spite of good overall outcomes. Participants are subject to a 2 minute warm up at 1% incline, during which the treadmill speed is slowly increased to a comfortable walking pace for the subject. During the test, the velocity is kept constant while the incline is increased by 2% every minute to increase workload. During this time oxygen consumption (VO_2) is measured. Participants are exercised to volitional exhaustion and termination of test occurs at patient request or if the study doctor deemed it unsafe to continue. It is assumed that if the subject is exercised to exhaustion, VO_2 will plateau and as such maximal oxygen uptake can be calculated ($VO_{2\ peak}$). Treadmill (Norditrack) used enabled a maximum incline of 15%. If participants did not achieve volitional exhaustion at maximum possible incline, the treadmill speed was gradually increased every 1 minute.

Prior to each test, the flow sensor was calibrated according to manufacturer instructions. The bi-directional digital turbine system was calibrated using a 3-litre calibration syringe and

the system was calibrated using certified gases of known concentrations (Oxygen: 5%, Carbon Dioxide:16%). Expired gas was measured continuously over the exercise period and averaged over 15seconds (Quark CPET metabolic cart, Cosmed, Rome, Italy). The highest value was used recorded as VO_2 peak and relative VO_2 peak per kg body weight was obtained. Heart rate was monitored by a heart rate belt fitted around the thorax. It is assumed that if patients are exercised to exhaustion, VO2 will plateau and as such peak oxygen uptake (VO_2 peak) can be calculated. Data regarding walking speed, maximum incline achieved and total ambulatory time (TAT) was also gathered.

CPET procedures were conducted at the Human Performance Laboratory at the Wellcome Trust Clinical Research Facility, Manchester (WTCRF). All patients were requested not to be fasted on the day of testing. Upon attendance of the WTCRF, SG confirmed again that there were no clinical contraindications to exercise testing. Given multiple medical comorbidities of the SAH participants, all CPET testing procedures were supervised by SG.

Figure 3.1 – Laura Smith demonstrating set up and procedure for cardiopulmonary exercise testing procedure. Clockwise from top left: Participants were fitted with a silicone face mask according to face size with head cap. Flowmeter with sampling lead was then connected to face mask. Participants began the exercise testing procedure after warm up period. During the testing procedure pulse rate and breath-by-breath gas exchange analysis was monitored. Treadmill gradient and incline was altered manually during the testing procedure. Courtesy of Laura Smith



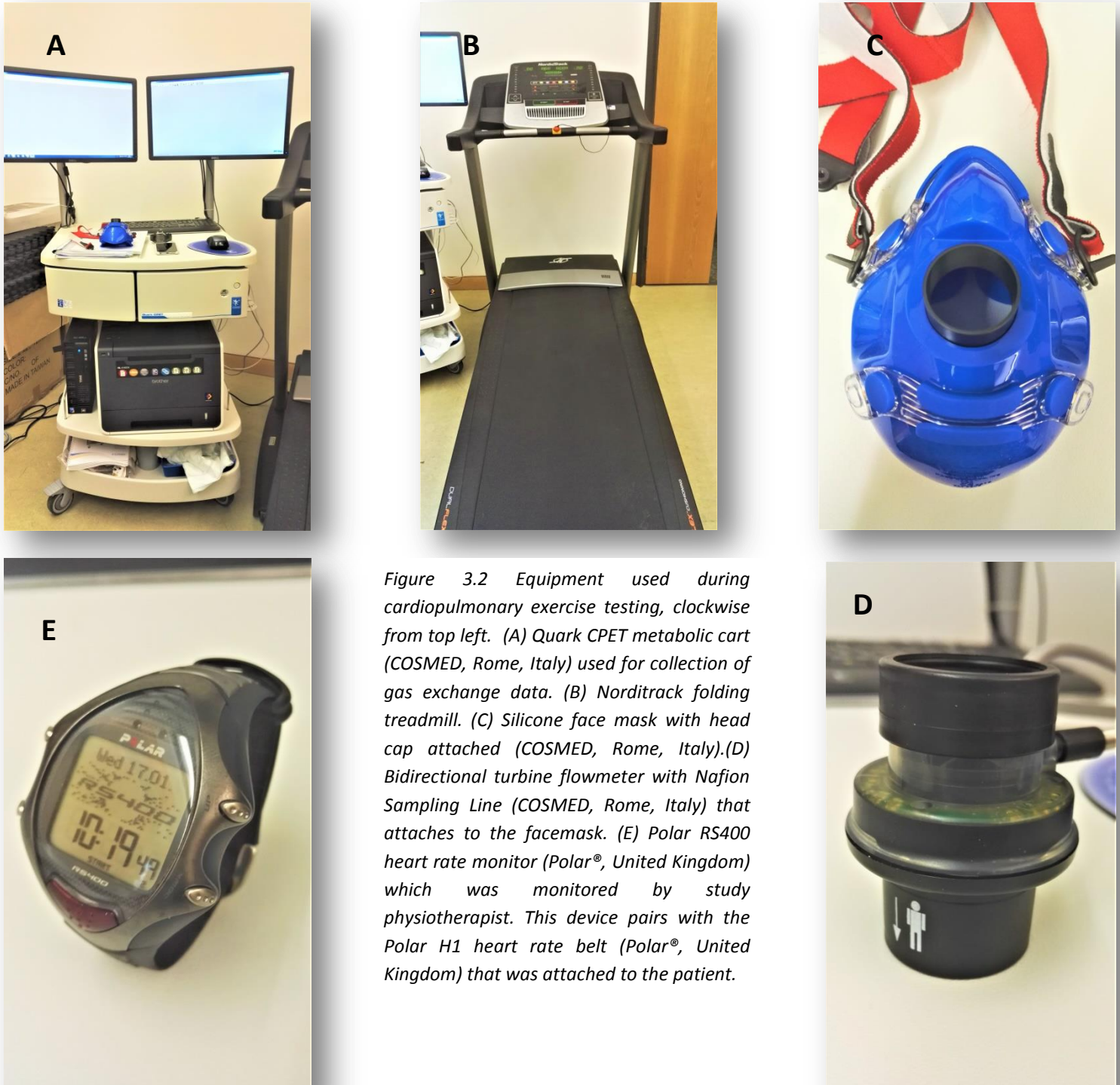


Figure 3.2 Equipment used during cardiopulmonary exercise testing, clockwise from top left. (A) Quark CPET metabolic cart (COSMED, Rome, Italy) used for collection of gas exchange data. (B) Norditrack folding treadmill. (C) Silicone face mask with head cap attached (COSMED, Rome, Italy).(D) Bidirectional turbine flowmeter with Nafion Sampling Line (COSMED, Rome, Italy) that attaches to the facemask. (E) Polar RS400 heart rate monitor (Polar®, United Kingdom) which was monitored by study physiotherapist. This device pairs with the Polar H1 heart rate belt (Polar®, United Kingdom) that was attached to the patient.

Assessment of Cardiovascular Parameters

Body weight (measured to the nearest 0.1kg using a Marsden weighing scale) and height (measured to the closest 0.5cm) were used to calculate the body mass index (BMI). Patients were required to dress in light clothing for this. Waist and hip circumference were measured to the closest 0.5cm and the waist to hip ratio (WHR) was then calculated. Blood pressure was measured using Welch Allyn automated sphygmomanometer.
Fasting blood samples were taken for fasting lipid profile, fasting blood glucose and HbA1c.

Radiological Assessment

Almost all patients underwent magnetic resonance imaging (MRI) to enable radiological assessment of the pituitary gland, if there were no contraindications to this. Standard MR pituitary protocol at our centre involves T1 and T2 sequences with coronal and sagittal views. Contrast (with gadolinium) is not routinely administered during initial MR imaging of the pituitary gland in our centre but may be used if deemed necessary by the radiology team.

3.14 Assay Details

Prior to the 26th January 2015, plasma cortisol, fT4, TSH, prolactin, LH, FSH, testosterone and estradiol were analysed using Electrochemical Luminescent Immunoassay (Roche Cobas 8000). After this time, these measurements were analysed using competitive Chemiluminescent Immunoassay (Siemens Advia Centaur). ACTH and GH were analysed using Siemens Immulite 2000 Two Site Enzymatic Chemiluminescent Immunoassay. IGF-1 levels were analysed using Siemens Immulite 2000 Enzymatic Chemiluminescent Immunoassay.

3.15 Prescribing and Monitoring of Growth Hormone Replacement

Participants were allowed to choose Growth Hormone delivery device. Method of delivery of GH via respective device and subcutaneous injection technique was demonstrated by SG. All participants were given 'Growth Hormone Training Kit' and were given a minimum of 48 hours to become familiar and competent with their chosen injection device, storage requirements and disposal procedures. Participants were only issued GHR after being able to demonstrated satisfactory devise usage and injection technique to SG.

GH was commenced at a dose of 0.2mg/per day subcutaneously in men and a dose of 0.3mg/per day in women. Dose of GH was titrated with the aim of keeping the serum IGF-1 in the upper third of the age and gender specific reference range, if tolerated by the patient. All GH dose changes were done by SG.

Patients were given a study diary to record any new medical diagnoses or medication, but also to document any potential side effects from GHR. Participants were also required to record doses of GH administered to provide a measure of compliance. If a dose was not administered or administered at a different time, it was required that participants provided a reason for this. SAH patients receiving GHR were reviewed at week 4, 8, 12, 24 and 36 and at each visit were assessed by SG for any potential side effects of GHR.

3.16 Strengths and Limitations of the Study

For each cohort, strengths and limitations of each study design will be presented in the respective results section. An overview will be discussed in this section. There are a few limitations to the study. Firstly in retrospective arms of this study, data collection was dependent on accuracy and precision of clinical documentation. Where data was not available, every effort was made to contact the referring centre to provide this. Furthermore, given the observational nature of the retrospective arm, causality cannot be assumed between the observed variables and end points. Secondly, in the SAH arm of the study, a degree of selection bias is likely to have been encountered, given that patients who felt more unsatisfied with their health, were more likely to participate in this study. No 'control' group was allocated in the interventional phase of this study and the reasons for this will be discussed in the results section. However, the lack of a control group, makes it difficult to exclude the possibility of the 'placebo-effect' accounting for results observed.

The major strength of this study is the use of validated dynamic tests of pituitary function with clear definitions of endocrine deficiency. Information regarding hormonal status was obtained from actual biochemical results even in the retrospective arm of the study. Secondly, hypopituitarism has been analysed separately in patients with pituitary apoplexy, NFPA and SAH rather than as a whole. This minimises confounding, but also makes the results more accurate when translated to the individual patient group. Thirdly, the large number of patients in the NFPA and SAH cohorts, strengthens the validity of the results. Finally, there are currently no publications reviewing the impact of GHR exclusively in SAH survivors with GHD, and it is hoped that publication arising from this thesis will be the first to address this.

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Chapter 4

Pituitary Apoplexy- Bespoke Patient Management Allows Good Clinical Outcome

4 Chapter 4 Pituitary Apoplexy- Bespoke Patient Management Allows Good Clinical Outcome

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4.1 Preface

In this chapter, the management of pituitary apoplexy based on clinical presentation will be analysed. This is reflective of how patients with pituitary apoplexy are managed in a tertiary endocrine and neurosurgical centre with access to modern monitoring and interventional techniques. The main aim of this chapter is to evaluate the endocrine and visual outcomes based on management in these patients and thereby establishing superiority of a particular management option (if any). For the purposes of this thesis, a flow diagram detailing how patients were identified is provided at the end of this chapter (not included in journal publication).

4.2 Abstract

Objective

To describe the clinical presentation, management and outcomes of pituitary apoplexy from a single-centre and retrospectively apply the Pituitary Apoplexy Score (PAS).

Design

Retrospective review of patients presenting with classical pituitary apoplexy to a single neurosurgical centre in the Greater Manchester region.

Results

A total of 31 cases with classical pituitary apoplexy were identified between 2005 and 2014.

The mean age at presentation was 55 years and there were 19 males. In only one patient was there prior knowledge of a pituitary adenoma. Eleven (35%) patients were managed conservatively and 20 (65%) patients managed surgically. Emergency surgery was carried out in 11 patients.

At presentation, visual symptoms were present in a higher proportion of patients in the surgical (90%) group compared to the conservatively (64%) managed group. At final follow-up visual recovery was apparent in most patients in both the surgical (100%) and conservatively (86%) managed groups. The proportion of patients with hypopituitarism was high in both the surgical (86%) and conservative (73%) groups at presentation and this failed to improve at final follow-up (90% versus 73% respectively). The median PAS scores were higher in the surgical (PAS 2), compared to conservatively (PAS 0) managed group

Conclusion

In pituitary apoplexy patients managed conservatively or surgically, there is good recovery of visual symptoms but not endocrine function. Patients should be managed on a case-by-case basis based on the severity of symptoms at presentation, progression of disease and surgical expertise available. Further prospective studies using the PAS are required to determine its usefulness in clinical practice.

4.3 Introduction

Pituitary apoplexy is a rare medical and neurosurgical emergency. This is caused by haemorrhage or infarction of the pituitary gland, which results in a sudden increase of pressure in the sella turcica and compression of the surrounding structures (1). This places patients at significant and permanent risk of endocrine and neuro-ophthalmic deficits.

Classical pituitary apoplexy is defined as a clinical syndrome that consists of sudden onset of headache associated with vomiting, visual impairment and/or decreased consciousness. It is imperative to emphasise that pituitary apoplexy is a clinical diagnosis (2), rather than a diagnosis based on purely radiological or histological findings and that classical pituitary apoplexy evolves within hours or days. Difficulty in making this diagnosis was recognised early on by Brougham et al (3) who described five cases of pathological findings of necrosis or extensive haemorrhage of the pituitary gland.

Although predisposing factors such as bromocriptine therapy (4-6), oestrogen therapy (6), pregnancy (4), dynamic pituitary testing (7, 8), hypertension (6, 9) and anticoagulation (4, 6, 9, 10) have been described, most cases of apoplexy occur spontaneously (4, 11). The reported incidence of apoplexy in pituitary adenomas is typically between 2-7%, although in some surgical series, the reported rates vary greatly between 0.6% and 17% (12-15).

In spite of advances in neurointensive care and neurosurgical techniques, there is still a lack of consensus as to how this condition is best managed. Unfortunately the rarity and emergency nature of this condition limits the evidence base for management to mostly uncontrolled, retrospective case-series. As such, best practice with regards to surgical versus conservative management, especially in patients with moderate symptomology, still remains controversial. Neurosurgical proponents consider decompression the treatment of choice to improve visual outcomes (5, 13, 14). Some authors advocate urgent surgical decompression in all patients regardless of the severity of visual symptoms (5). Urgent surgical decompression has been deemed superior by certain authors, not only in terms of improving vision but also endocrine recovery (16, 17). Conversely, others have noted that favourable visual and endocrine outcomes can be achieved with expectant management, in the context of non-progressive visual symptoms (9, 11, 18-20).

We describe the modern day management of pituitary apoplexy at a single tertiary neurosurgical centre. Our objectives were to (i) describe the clinical presentation of pituitary apoplexy, (ii) to present the endocrine and visual outcomes of our cohort and (iii) to retrospectively apply the Pituitary Apoplexy Score (PAS) tool to our cohort and discuss its use in the clinical setting.

4.4 Patient and Methods

Salford Royal NHS Foundation Trust is a tertiary endocrine and neurosurgical centre that serves the Greater Manchester region of approximately 4 million adults. About 100 pituitary surgeries are carried out each year. This is a retrospective analysis of all patients referred to our centre with a diagnosis of classical pituitary apoplexy between 2005 and 2014. Electronic patient records were reviewed to collect data.

This series only included review of patients presenting with ‘classical’ pituitary apoplexy, defined according to the UK Guidelines for the Management of Pituitary Apoplexy (2010)

(21). Therefore patients were included if they presented with acute onset of headache and/or acute visual disturbance and radiological evidence of haemorrhage and/or infarction into the pituitary gland.

We acknowledge sub-clinical pituitary apoplexy as an entity in itself given that there exists a subgroup of patients who experience a lesser degree of haemorrhage/infarction (2). These patients do not experience classical clinical signs making the diagnosis difficult, which is often made retrospectively. Undoubtedly, these patients are also at risk of visual and endocrine compromise, and in some cases even more so than patients with the classical apoplexy, given that subclinical pituitary apoplexy can present insidiously. Inherently however it presents with a different clinical picture and course, which affects its management, and is best addressed separately from 'classical' pituitary apoplexy. We have therefore not included patients with a diagnosis of subclinical pituitary apoplexy in this review.

Data regarding initial presentation, investigations, management and follow-up was obtained. The visual symptoms and endocrine results recorded at presentation and at follow-up allowed us to determine if any changes to the visual symptoms and endocrine function had occurred at follow-up. Given the emergency nature of the condition, complete endocrine profile was not always available at presentation, especially in patients undergoing emergency surgery. Missing data were noted.

The Pituitary Apoplexy Score (PAS) was calculated retrospectively based on documentation of clinical assessment at presentation to our centre (Table 4.1). Resolution of visual symptoms was defined as return of vision to premorbid status as described by the patient and on formal assessment. Histopathological examination with immunohistochemical staining for pituitary hormones was carried out on surgical specimens available from patients who underwent surgery.

Statistical analysis

Data analysis was carried out using IBM SPSS Statistics 22 (IBM SPSS Statistics for Windows, Version 20 NY, USA; 2011). Categorical data was analysed with either the Chi-squared test or the Fisher exact test as suitable. Non-categorical data was analysed using the Kruskall-Wallis or ANOVA depending whether data followed normal distribution. A two-tailed p-value of <0.05 was considered statistically significant.

Table 4.1.
Table summarising the categories and the corresponding scores that make up the Pituitary Apoplexy Scores (PAS) (range 0 to 10). (1)

Variable	Points
Level of consciousness	
Glasgow coma scale 15	0
Glasgow come scale 8-14	2
Glasgow come scale <8	4
Visual acuity	
Normal* 6/6	0
Reduced- unilateral	1
Bilateral	2
Visual Field Defect	
Normal	0
Unilateral defect	1
Bilateral defect	2
Ocular paresis	
Absent	0
Present – unilateral	1
Bilateral	2

***No change from premorbid visual acuity**

4.5 Results

Demographics and Presenting Symptoms

A total of 31 patients met the above diagnostic criteria (19 men, 61%) with a mean age at presentation of 55 years (range 22 – 88 years). The median time to follow up was 59 months (range 22 – 129).

All 31 patients experienced headaches at presentation and other common symptoms included visual disturbance (81%) and nausea or vomiting (55%; Table 4.2). The most common visual symptom was visual field deficit (58%), followed by ophthalmoplegia (39%) and impairment in visual acuity (23%) (Table 4.2). Seven patients presented directly to our

centre and the remaining were referred from other hospitals.

In only 1 patient (3%) was there prior knowledge of a pre-existing adenoma. Overall, in 11 (35%) patients there was an identifiable precipitating factor which included pre-existing history of hypertension, pregnancy, recent haemodialysis (with use of heparin) and use of oral anticoagulant (dabigatran) (Table 4.2).

Table 4.2
Table summarising the presenting symptoms and risk factors for the patients with pituitary apoplexy

Symptoms	**Number (% total)**
Headache	31 (100%)
Nausea or Vomiting	17 (55%)
Visual Symptoms	25 (81%)
Visual Field Defect	18 (58%)
Reduced Visual Acuity	7 (23%)
Ocular Paresis - **CNIII** - **CNVI**	12 (39%) 8 (26%) 6 (19%)
Predisposing factors - **Hypertension** - **Oral anticoagulation** - **Heparinisation** - **Pregnancy** - **Previously known adenoma**	11 (35%) 5 (16%) 3 (10%) 1 (3%) 1 (3%) 1 (3%)
MR findings - **Microadenoma (<1cm)** - **Macroadenoma (1-2.5cm)** - **Giant adenoma (>2.5cm)** - **Median maximum tumour diameter (mm)** - **Radiological Evidence of Haemorrhage/Infarction**	 0 (0%) 21 (68%) 10 (32%) 20.4 (11- 45) 29 (94%)

Initial assessment confirmed that 28 (90%) cases of apoplexy occurred in patients with biochemically non-functioning adenomas, 2 (7%) cases were growth hormone secreting adenomas and 1 (3%) case of a prolactinoma. At presentation 22 (71%) of patients had some evidence of hypopituitarism and 5 (16%) patients were eupituitary. In 4 patients, evidence of hypopituitarism at presentation could not be accurately determined, as they promptly proceeded to surgery.

Management

In our cohort, 11 (35%) patients were managed conservatively and 20 (65%) patients were managed surgically. Eleven (35%) patients underwent emergency surgery (defined as surgery within seven days of presentation in keeping with current literature) and 9 (29%) patients underwent elective surgery (ie surgery after 7 days). The mean time to emergency surgery from presentation to our centre was 3 days (range 1 to 5 days). The mean time to elective surgery was 55 days (range 9 to 173 days). All patients in our surgical cohort underwent endoscopic transsphenoidal surgery.

Conservative management consisted of instigation of necessary supportive measures, appropriate hormonal replacement and monitoring of visual symptoms. There were no deaths related to pituitary apoplexy in our cohort.

Table 4.3 summarises the endocrine function and visual symptoms in the three patient groups at presentation. Biochemical evidence of hypopituitarism was similar between the elective, emergency surgical and the conservative groups (p= 0.22; Table 4.3). The proportion of patients with visual symptoms, notably ophthalmoplegia and reduced visual acuity was slightly greater in the surgical groups as compared to the conservative group (p= 0.08; Table 4.3).

The patient with highest PAS (PAS 6) in our cohort was managed conservatively, as he was not medically fit for surgery due to age and comorbidities. One other patient presented with an acute 3rd cranial nerve palsy and was discovered to have a serum prolactin level of almost 8000U/L at presentation. He was commenced on dopamine agonist therapy and within days his symptoms started to improve, with complete resolution of visual symptoms at follow up 4 weeks later. The patient was monitored in hospital until improvements in vision were observed.

Table 4.3

Table summarising the clinical signs, presence of hypopituitarism and radiological findings at presentation in our cohort when categorised with respect to management type as described in methods.
* Complete endocrine status at presentation could not be assessed in four patients, who presented acutely.
a Chi-square test; bOne way ANOVA; cKruskall-Wallis tests

	Conservative (N=11)	Elective Surgery (N=9)	Emergency Surgery (N=11)	P-value
Male : Female	7:4	4:5	8:3	0.43[a]
Mean age (years)	53 ± 22 (range 22-88)	57 ± 12 (range 34-76)	55 ± 12 (range 35-73)	0.83[b]
Visual signs (all)	7 (64%)	8 (89%)	10 (91%)	0.21[a]
- Visual field deficit	6 (55%)	6 (67%)	6 (55%)	0.83
- Ophthalmoplegia	2 (18%)	3 (33%)	7 (64%)	0.08
- Reduced visual acuity	1 (9%)	1 (11%)	5 (46%)	0.08
Biochemical evidence of hypopituitarism at presentation	8/11 (73%)	5/7 (71%)*	9/9 (100%)*	0.22[a]
Median PAS score	0 (range 0-6)	2.0 (range 0-4)	3.0 (range 0-5)	0.01[c]
MR findings - Median maximum diameter (mm)	17.9 (11 - 31)	21.5 (17- 45)	21.3 (15 – 31)	0.13[c]

Endocrine outcomes

Listed in Table 4.4 is the endocrine outcomes based on management. For patients managed conservatively, endocrine status at the most recent clinic visit was documented. One patient in the conservatively managed cohort went on to have transsphenoidal surgery 4 years later for ongoing biochemically active acromegaly. In this patient, endocrine status just before surgical intervention is documented. For surgical patients, the most recent post-operative endocrine results are presented before any further interventions such as radiotherapy or repeat surgery that might have confounded the final pituitary status.

Overall, 26 (84%) of patients developed one or more anterior pituitary hormone deficiency. Twenty three (74%) patients were diagnosed with severe growth hormone deficiency and 21 (68%) patients required long term steroid replacement. Long term thyroxine replacement was required in 20 (65%) patients and 20 (65%) patients were gonadotrophin deficient. No patients had long term diabetes insipidus.

Overall, the rates of hypopituitarism at follow-up was similar between the emergency surgical (91%), elective surgical (89%) and the conservative (73%) treatment groups (p=0.58; Table 4.4).

Visual outcomes

Table 5 shows the visual outcomes for those patients initially presenting with visual symptoms (N=25). Overall 18 (72%) of these patients noted that their vision returned to premorbid status and a further 6 (24%) noted a partial improvement in visual symptoms. Only 1 patient in our cohort experienced deterioration in visual symptoms. This was the patient with the highest PAS score, in whom we were unable to proceed with surgery due to medical frailty and advanced age. Visual recovery was not significantly different between the three groups (p =0.841, Table 4.5).

Radiology and histopathology

One patient in our cohort only underwent a computed tomography (CT) imaging of the pituitary gland due to the presence of a magnetic resonance (MR) incompatible pacemaker. All other patients had MR imaging. There were macroadenomas in 21 (68%; ie 1-2.5cm maximum diameter) and giant adenomas in 10 (32%; ie >2.5cm in maximum diameter). There was radiological evidence of haemorrhage/infarction in 29 (94%) of patients. The median time to follow-up imaging in the conservative cohort (N=11) was 4.7 months which all showed either stable or reduction in tumour size.

In the surgical cohort (N=20) evidence of haemorrhage, necrosis or both was reported in 16 (76%) of histological samples. In 12 (60%) no histological subtyping was possible as only necrotic tissue was seen. In the rest, immunohistochemistry identified 5 (25%) gonadotroph adenomas, 2 (10%) corticotroph adenomas and 1 (5%) somatotroph adenoma. Figure 4.1 illustrates the MR changes in a typical example of conservatively and surgically managed patient with classical apoplexy from our cohort.

Table 4.4
Table summarising the extent of hypopituitarism at final follow-up in the Pituitary apoplexy patients, when categorised with respect to management type as described in methods.
P value given for Fisher's exact test.
[a]GH status at follow up could not be determined in 2 patients.
[b]One patient had on-going biochemically active acromegaly

Endocrine deficiency at final follow-up	**Conservative, (N=11)**	**Elective Surgery (N=9)**	**Emergency Surgery (N=11)**	**P value**
Growth Hormone	6/9 (67%)[a]	8/9 (89%)	9/11 (82%)[b]	0.30
Gonadotrophin	5/11 (45%)	7/9 (78%)	8/11 (73%)	0.33
ACTH	6/11 (55%)	6/9 (67%)	9/11 (82%)	0.40
TSH	6/11 (55%)	7/9 (78%)	7/11 (64%)	0.58
ADH	0/11 (0%)	0/9 (0%)	0/11 (0%)	NA
Total	**8/11 (73%)**	**8/9 (89%)**	**10/11 (91%)**	**0.58**

Further procedures

Of the patients managed conservatively one patient required surgery, 4 years after the original episode of apoplexy. The indication for surgery was on-going biochemically active acromegaly that was unresponsive to medical treatment. This patient was left in the conservative group with respect to data analysis.

One patient in the conservative group had a further apoplectic event 13 months after the first episode, which coincided with restarting oral anticoagulation therapy. On both occasions there was no evidence of visual compromise and therefore the patient was managed conservatively.

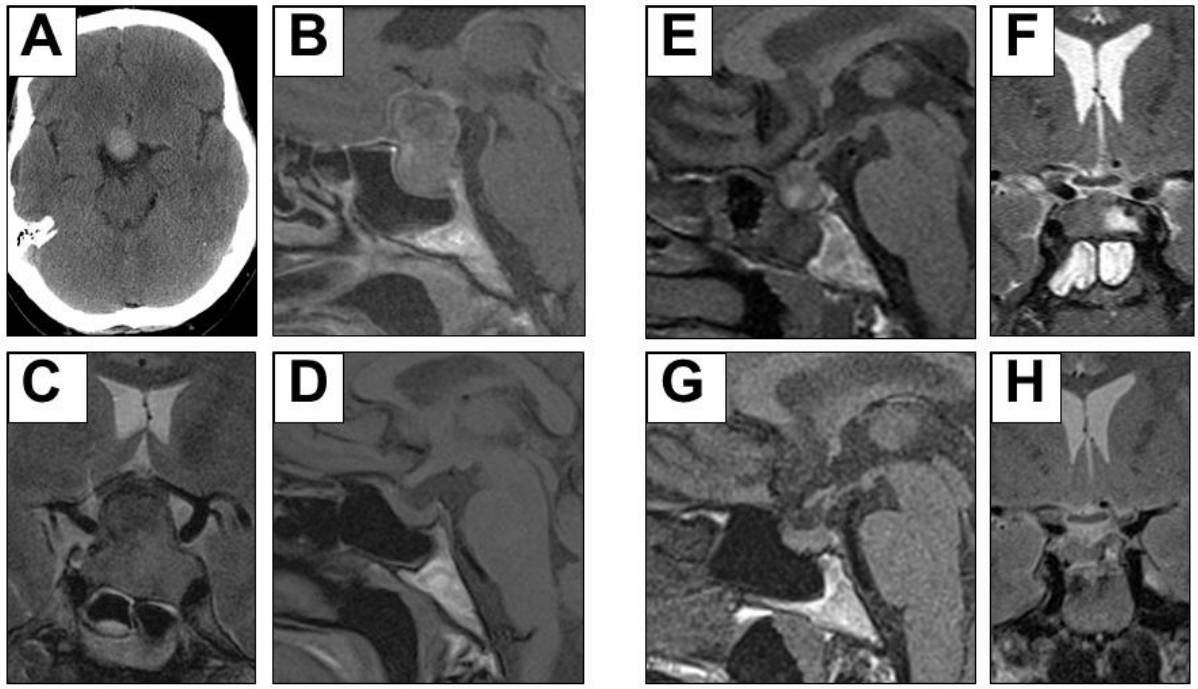
Table 4.5

Table summarising the recovery in visual symptoms at final follow-up in the pituitary apoplexy patients, when categorised with respect to management type as described in methods. Only those patients with visual symptoms are included, as indicated by the denominator for each management group. There was no significant difference across groups (p =0.841 Fisher's exact test).

Visual Outcome	**Conservative (N=7)**	**Elective surgery (N=8)**	**Emergency surgery (N=10)**
Return to premorbid vision	5/7 (71.4%)	6/8 (75.0%)	7/10 (70.0%)
Improved vision (but not back to premorbid level)	1/7 (14.3%)	2/8 (25.0%)	3/10 (30.0%)
No change in vision	0/7 (0%)	0/8 (0%)	0/10 (0%)
Deterioration in vision	1/7 (14.3%)	0/8 (0%)	0/10 (0%)

In the surgical cohort, 2 patients required post-surgical radiotherapy for tumour residuum. A further 2 patients required re-do surgery at a later date. In one patient, re-do transsphenoidal surgery was carried out 10 months after the original surgery for a sizeable tumour residuum that was abutting the chiasm and histological findings revealing a Ki67 labelling index of greater than 4% (gonadotroph adenoma). This was then followed by radiotherapy. The second patient had re-do endoscopic transsphenoidal surgery 65 months after the original operation for a gradually increasing residuum. The original histology revealed a Ki67 labelling index of between 6-8% (gonadotroph adenoma). Post-op radiotherapy was also administered.

Figure 4.1 Examples of pituitary apoplexy patients who were treated by surgery (A-D) or conservatively (E-F). The surgically managed patient (A-D) was a 43 year old male with a 2 day history of acute onset headaches and severe bitemporal visual deterioration. Axial CT (A), sagittal T1 (B) and coronal T2 (C) weighted MR scans show a large pituitary adenoma with chiasmal compression and evidence of bleed. Visual symptoms progressive resolved post-transsphenoidal surgery and sagittal T1 MR scan at 5 months (D) confirm satisfactory decompression of chiasm. The medically managed patient (E-F) was a 43 year old female who presented with acute headaches and a left sided partial third nerve palsy, that had started to improve at the time of hospital admission and fully resolved 3 months later. Sagittal T1 (E) and coronal T2 (F) weighted images reveal likely left sided bleed into a pituitary adenoma, with involution of lesion on MR 3 months later (G & H).



PAS score

PAS scores were applied retrospectively based on documentation of clinical signs and symptoms at presentation. Overall, there was a tendency for patients with lower PAS scores to be managed conservatively, and patients with a higher PAS score to be managed surgically (Supplementary Figure 4(a)). This difference in PAS score between the emergency, elective surgical and conservative groups was statistically significant ($p<0.05$, Table 4.3).

4.6 Discussion

We present a modern cohort of patients with classical pituitary apoplexy managed in a

single centre and analysed the endocrine and visual outcomes, based on treatment modality. Despite the retrospective nature of data collection, we present a relatively modern case series and therefore the outcomes in our surgical cohort are not confounded by older surgical techniques. Unlike some of the previous studies, patients with sub clinical apoplexy were excluded.

Endocrine changes

From our cohort it is apparent that the presentation of pituitary apoplexy can range in clinical severity. In most cases there was no prior knowledge of a pre-existing pituitary adenoma and the apoplectic event was spontaneous with no identifiable precipitating factor.

A high proportion of patients (71%) had evidence of hypopituitarism at presentation and this is consistent with other publications (11, 13, 18, 22, 23). In our cohort, no patients experienced improvement in pituitary function and at follow up 84% of our patients had evidence of hypopituitarism. A slightly higher proportion of patients in the surgical groups had evidence of hypopituitarism at final follow up, although this may reflect selection bias (Supplementary Figure 4(b)).

Other authors have made varying conclusions about the superiority of surgical intervention in preserving or restoring pituitary function (17, 24). Arafah et al demonstrated relatively low incidence of hypopituitarism in their cohort, all of whom had urgent decompressive surgery, and the authors postulated that compression of the portal vessels and/or the pituitary stalk as the mechanism of hypopituitarism (24). More recently however, Zayour et al not only demonstrated extremely elevated intrasellar pressure (ISP) in pituitary apoplexy, but that ISP in tumour apoplexy was higher than reported ISP in pituitary tumours cases without apoplexy (25). Using serum prolactin levels as a marker of anterior pituitary cell viability, the authors demonstrated an inverse relationship between ISP and serum prolactin levels, inferring that ischaemic necrosis of anterior pituitary cells was a major mechanism responsible for hypopituitarism in apoplexy. The authors therefore postulated that due to this, there was limited potential for recovery of pituitary function after apoplexy. Our results would be consistent with this and other authors who have shown that endocrine recovery from this event is rare, regardless of the management (9, 22). We would therefore agree

with Bujawansa et al, that the presence or absence of endocrine deficiency at presentation, should not solely influence decision making with regards to management (18).

Visual symptoms

In our cohort, the majority of patients with visual symptoms at presentation were noted to have a partial (24%) or complete (72%) recovery of vision back to premorbid status. Patients with visual impairments at presentation, notably reduced visual acuity or ophthalmoplegia were more likely to be managed surgically. Improvement in vision was noted in the majority (85%) of conservatively managed patients except for deterioration in vision in one patient, for who transsphenoidal surgery could not be undertaken due to co-morbidity and the increased surgical risks.

Whether conservative or surgical management results in superior visual outcomes in pituitary apoplexy is somewhat controversial. Surgical advocates have demonstrated better outcomes when decompression is performed urgently, and warn that delayed intervention could impair the potential for recovery (5, 13, 26-28). However, not all case series have revealed similar results (9, 22). Spontaneous resolution of visual and neurological symptoms with expectant management has also been described (19, 20, 29). This disparity in results is likely due to several factors. Firstly, part of the effect observed is likely to be due to selection bias (9, 18, 22, 30). Evidence showing better visual outcomes with urgent decompression is derived mainly from surgical case series that usually include a high proportion of patients with impairments in vision. Likewise apoplexy patients with less severe visual symptoms are more likely to be managed expectantly. The relative merits of each treatment modality cannot be accurately determined due to such selection bias. Furthermore the availability of a dedicated pituitary surgical service and the experience of the surgeon will no doubt influence surgical outcomes.

While we concur that immediate surgical decompression may not be necessary when visual signs and symptoms progress in a favourable direction, a degree of caution should be exercised if a 'watch and wait' approach is taken, with regular monitoring of symptoms. Any deterioration in vision should prompt a review of treatment options.

Moreover, it is unclear if it is appropriate to place equal weight on different types of visual symptoms such as visual field deficits, ophthalmoplegia, or impairment in visual acuity.

These reflect different aspects of visual pathway with different potentials for recovery. Jho et al proposed that when assessing patients suffering from pituitary apoplexy, patients with impairment in visual acuity were graded as having more severe symptoms than patients with ophthalmoplegia (30). Indeed Rovit et al (12) noted in his case series that ophthalmoplegia was compatible with an alert state, and that defects in visual acuity were often associated with altered consciousness. It has been previously demonstrated that ophthalmoplegia is more likely to recover as compared to complete blindness (2, 4, 13, 19). The current literature also suggests that the presence of ophthalmoplegia in isolation can be managed conservatively given that it frequently recovers spontaneously (20, 23, 31, 32).

With regards to loss of visual acuity, some authors have demonstrated better prognosis when surgery is performed urgently (13, 27). In a review of the literature of patients with pituitary apoplexy presenting with blindness, Turgut et al (33) concluded that delayed surgery might negatively impact on visual recovery, although the authors did find that the duration of symptoms prior to presentation was probably more important. Patients with impairment in visual acuity were more likely to undergo urgent neurosurgical decompression in our series, with resulting good visual recovery at follow-up. Although there are reports of improvement in spite of severe damage to visual acuity with expectant management alone (9), this is not our experience in the present cohort.

Scoring systems in apoplexy

In an attempt to provide a standardised tool for assessing clinical severity, the Pituitary Apoplexy Guidelines Development Group conceived the Pituitary Apoplexy Score (PAS) (Figure 1) (1). This system has yet to be trialled prospectively. In the present study we observed that the PAS score did relate to the preferred treatment option. Patients with a lower PAS score were generally managed conservatively and patients with a higher score were managed surgically, but there were exceptions. We would caution against the use of the PAS scoring system solely in the decision making process, as there are other elements that should also be considered, when deciding on a treatment modality.

Firstly, the PAS scoring system does not incorporate the possibility that the apoplectic event could have arisen from a functioning adenoma such as a prolactinoma, which may be amenable to medical management. We and others have demonstrated good clinical

response in such cases to dopamine agonist therapy, with the patient in our cohort experiencing complete resolution of visual symptoms (6, 17). Secondly the PAS in its current version does not accurately capture the severity of visual symptoms nor the duration of visual symptoms that may influence visual outcome (9, 33). For example impairment in acuity ranges from a spectrum of mild reduction in reading vision to complete blindness. The PAS however, quantifies the impairment in visual acuity simply based on whether it is monocular or binocular. As such, a patient with a reduced reading vision of 6/12 in one eye, will score the same number of points as a patient with monocular blindness. It is intuitive that a patient presenting with acute complete visual loss over a few hours will be dealt with greater urgency than a patient with mild reduction in visual acuity developing over days. Thirdly as evident from the present cohort, patient co-morbidity and thus the anaesthetic risks would be an important factor when deciding on intervening surgically.

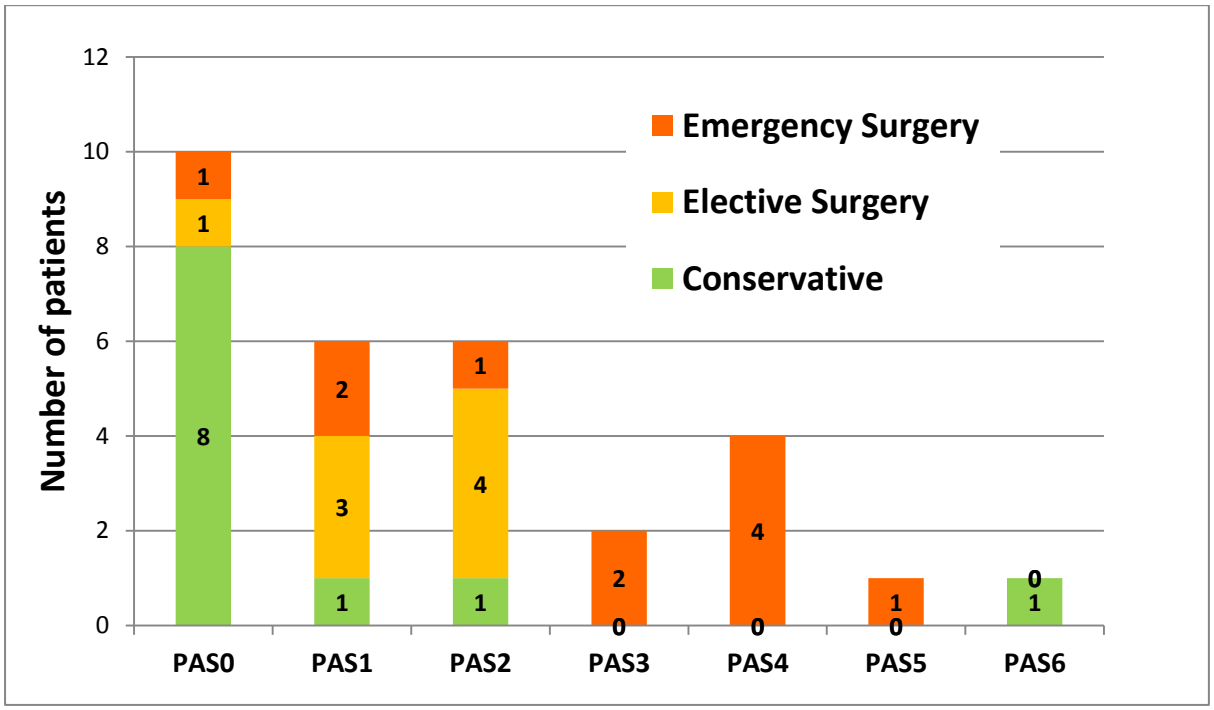
Despite some of these limitations, PAS is likely to prove a useful tool for clinicians to objectively grade and monitor the severity of pituitary apoplexy and potentially assist in selecting appropriate treatments. It may also be valuable to track patients' clinical progress.

4.7 Conclusion

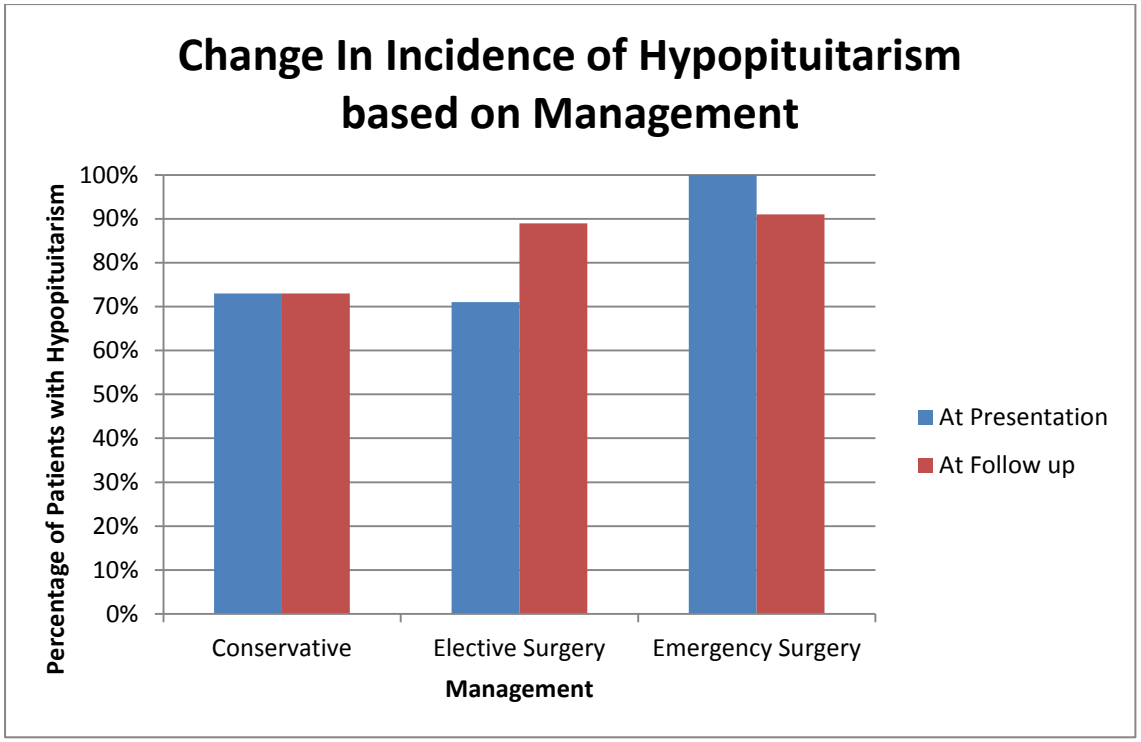
The presentation of pituitary apoplexy ranges in clinical severity. It is evident that the clinical severity at presentation, evidence of progression and expertise available, should guide management of patients presenting with pituitary apoplexy. Evaluation of each patient on a case-by-case basis with close liaison between the endocrine and neurosurgical team is imperative. In general patients with mild or improving visual symptoms may be managed conservatively, while in the hands of an experienced pituitary surgeon, urgent surgical intervention for patients with more severe visual symptoms can be associated with good visual outcome.

Pituitary apoplexy is associated with a high rate of anterior hypopituitarism that does not typically recover unlike the visual symptoms. Given the rarity of the condition, designing a randomised study to investigate the superiority of treatment modality may prove difficult. However, further prospective studies will be useful to determine the role of scoring systems in the clinical management of pituitary apoplexy.

4.8 Supplementary Figures

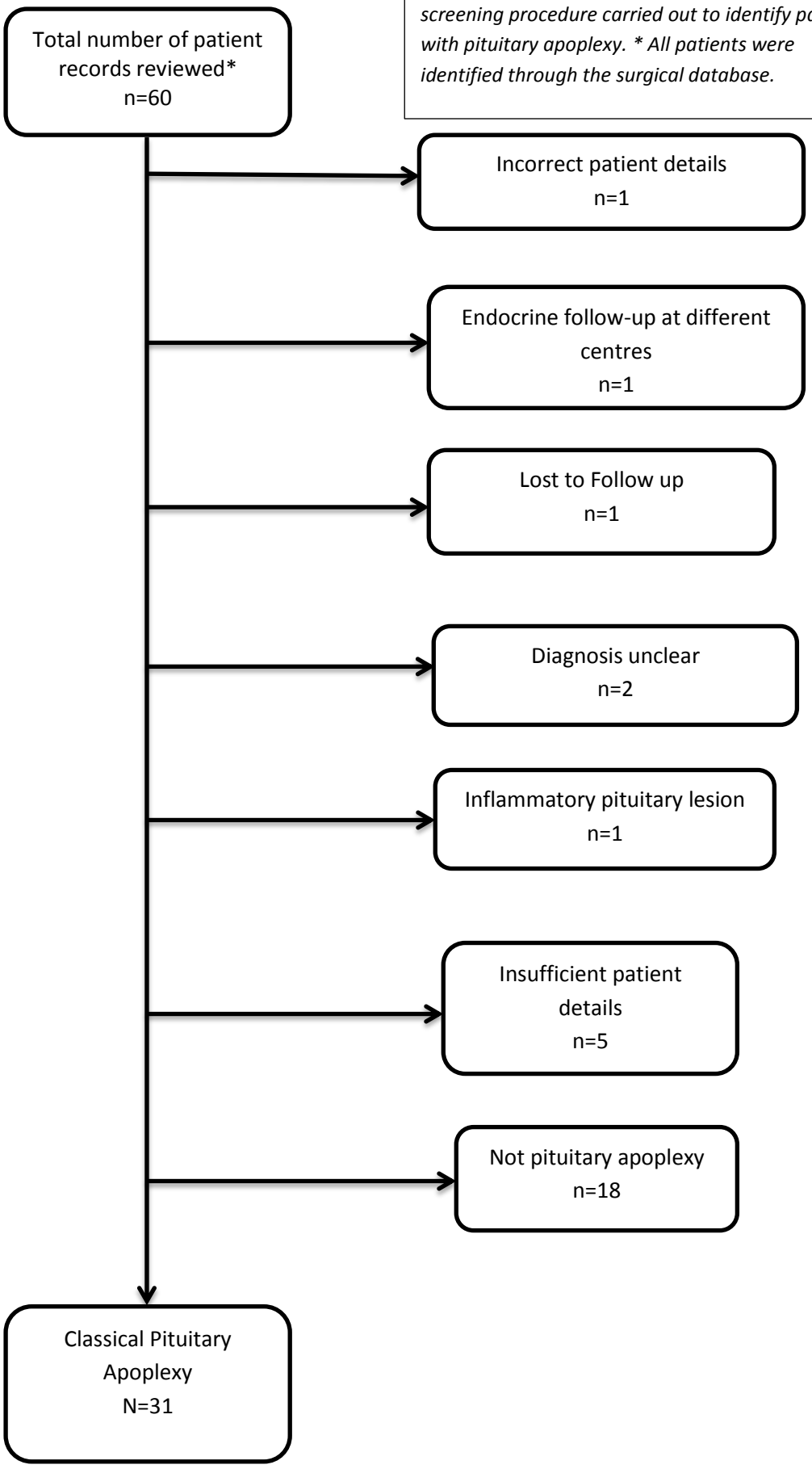


Supplementary Figure 4(a). Bar chart demonstrating the management type (ie conservative, elective and emergency surgery as described in methods) when categorised with respect to the Pituitary Apoplexy Scores (PAS) for the Pituitary apoplexy patients.



Supplementary Figure 4(b). Bar charts demonstrating the overall extent of hypopituitarism at presentation and at follow-up in the Pituitary apoplexy patients, when categorised with respect to management type as described in methods.

*Supplementary Figure 4(c). Flow diagram showing screening procedure carried out to identify patients with pituitary apoplexy. * All patients were identified through the surgical database.*



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Chapter 5 Variables Associated with Hypopituitarism in Non-Functioning Pituitary Adenoma- A Large Single-Surgeon Series

5 Chapter 5 Variables Associated with Hypopituitarism in Non-Functioning Pituitary Adenoma- A Large Single-Surgeon Series

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5.1 Preface

This chapter will analyse the variables associated with hypopituitarism exclusively in patients with non-functioning pituitary adenoma (NFPA), both at presentation and after surgical intervention. With the relatively contemporary cohort of patients and use of only the endoscopic transsphenoidal approach, the results in this chapter provide a good representation of the endocrine outcomes in patients with NFPA in modern clinical practice. This allows better identification of factors related to hypopituitarism and more importantly how they can influence change in pituitary function after surgery. For completion, a flow diagram detailing how patients with NFPA were identified is provided at the end of the chapter.

5.2 Abstract

Objective

To identify variables associated with pre- and post-operative hypopituitarism in patients with non-functioning pituitary adenoma (NFPA). To report on variables associated with change in pituitary function and to report on change in pituitary function by individual axis.

Methods

Retrospective review of 150 patients with NFPA who underwent endoscopic transsphenoidal surgery and endocrine follow up at our centre.

Results

On multivariate analysis, intact pituitary function was associated with female gender (OR 3.1, p=0.008) and smaller tumour size (giant adenoma OR 0.15, p<0.001). Post-operative hypopituitarism was associated with gender (female = OR 0.12, p < 0.001), increasing age (OR 1.05 per year, p =0.004) and having a giant adenoma (OR 6.53, p<0.001). Improvement in pituitary function after surgery was more likely in women (p=0.043) and in patients with

higher serum prolactin level at baseline (p=0.023). Men were more likely to experience worsening in pituitary function post-operatively (p=0.031). Change in endocrine function was different for different pituitary axis.

5.3 Introduction

The prevalence of pituitary adenomas is reported to be between 22 –94 cases per 100,000 persons in the general population(1, 2). The most common of these tumours are non-functioning pituitary adenomas (NFPA) which are characterised by the lack of biochemical or clinical evidence of hormone excess(3). Unlike functioning tumours that often manifest with clinical evidence of hormonal hypersecretion, NFPA's present insidiously. Patients usually present with clinical signs of mass effect on the optic apparatus, report symptoms of hypopituitarism or as is becoming increasingly common, these lesions are detected incidentally on neuroimaging done for other reasons(4-7).

Surgical intervention for NFPA is aimed at restoring or maintaining vision with reduction of tumour mass while at the same time preserving the normal gland and as such endocrine function(7-10). Hypopituitarism is reported as a common sequalae of pituitary surgery(11), and although much importance has been placed on surgical technique and experience, factors such as the gender(12), tumour size(13, 14), age(14, 15) and even serum prolactin level at presentation(16) have been reported to influence postoperative endocrine outcome. Determining the potential impact of these variables on improvement or deterioration in pituitary function after modern pituitary surgery from the current literature is not straight forward. This is due to several factors including studies that report on older surgical techniques, inclusion of cases of pituitary apoplexy, multi-surgeon case-series, heterogeneous method of testing for endocrine deficiency and lack of uniformity in how this is reported (Supplementary Table 5(a)). Furthermore it is often assumed that pituitary surgery will affect all pituitary cells in the same way, and as such the rate of normalisation or deterioration in pituitary function is often described for the gland as a whole. It is unclear if this is appropriate given that previous authors have demonstrated that that transsphenoidal surgery does not affect individual pituitary axes in the same way(12, 15, 17).

We present the results of a single-surgeon case series of non-functioning pituitary adenomas, managed at our centre. There are three main objectives of our report. Firstly is to report on the variables associated with hypopituitarism pre- and post-operatively.

Secondly is to identify variables associated with change in pituitary function after pituitary surgery. Lastly we will report on the improvement and deterioration in endocrine function by individual axis in this cohort.

5.4 Methods

This is a retrospective follow up study. Patients who received surgical treatment at our centre for non-functioning pituitary adenoma from July 2005 to February 2015 were identified through a surgical database. Salford Royal NHS Foundation Trust is a tertiary neurosurgical centre receiving referrals from hospitals in the Greater Manchester region. To simplify data collection, only patients who underwent post-operative pituitary testing and follow-up at our centre were included in this analysis. Patients were excluded if there was a clinical diagnosis of classical pituitary apoplexy or if they had received radiotherapy prior to surgical intervention, due to the inherent risk of hypopituitarism associated with these (11, 18, 19). In keeping with current neuroradiological guidance, magnetic resonance imaging of the sellar with pituitary protocol was carried out during pre-operative assessment in all patients, unless this was contraindicated(20).

Non-functioning pituitary adenoma was defined as pituitary adenoma without clinical or biochemical evidence of excess hormonal production(21). All patients underwent surgery via the transsphenoidal route as the initial approach by a single surgeon. Endocrine function was assessed by measurement of baseline pituitary function test (BPFT) and a glucagon stimulation test (GST). ACTH deficiency was diagnosed as a failure to reach a peak cortisol value of 450nmol/L (550nmol/L prior to January 2015) on GST. Growth Hormone (GH) deficiency was defined as a failure to reach a peak serum GH value of 3µg/L (9mU/L) on GST. If patients went on to have post-operative radiotherapy or re-do surgery, pituitary function prior to these further interventions was assessed and included in analysis. Hypogonadotrophic hypogonadism in men was diagnosed if a low serum testosterone (morning sample) was associated with low or inappropriately normal gonadotrophin level. In premenopausal women, hypogonadotrophic hypogonadism was defined as low serum estradiol and inappropriately low gonadotrophins associated with amenorrhoea or oligomenorrhoea. In post-menopausal women, this was defined as inappropriately low

gonadotrophins for age. Secondary hypothyroidism was defined as a low serum free T4 associated with low or inappropriately normal serum TSH.

Given that the majority of patients did not have dynamic testing of the somatotrophic axis pre-surgically, this was excluded in the analysis of pre-operative endocrine status. Post-operatively, isolated GHD was excluded from analysis given that a proportion of patients did not undergo confirmatory testing of this axis.

Statistical Analyses

Patient demographics and characteristics are presented in descriptive statistics. Data analysis was carried out using IBM SPSS Statistics 22 (IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY, USA: 2013) and STATA 14 (StataCorp 2015. *Stata Statistical Software: Release 14.* College Station, TX). Categorical data were analysed with either the Chi-squared test or the Fisher exact test where appropriate. Non-categorical data were analysed using the Independent t-test or the Mann-Whitney U test where appropriate. When three or more categories were investigated, analysis of variance was used. A two tailed p-value<0.05 was considered statistically significant. Variables that were statistically significant on univariable analysis were then included in multivariable analysis. Logistic regression was used to determine the association between variables and the outcomes (pre and post-operative hypopituitarism).

5.5 Results

Demographics

One hundred and fifty (150) patients were included in this analysis. Eighty-seven patients (58%) were male. Mean age at presentation was 61 years (range 23 to 87 years). During this follow up period, there were eleven deaths in our cohort but none were directly related to the surgical procedure. Three patients were lost to follow up after post-operative testing and one patient moved to another region after 12 months follow-up in our centre.

Pre-operative characteristic

Presenting symptoms, baseline vision and endocrine function is presented in Table 5.1. Complete pre-operative endocrine data was available in 138 patients. Most patients (67.4%) had evidence of hypopituitarism at presentation. The most common hormone deficiency

was gonadotrophin deficiency in 86 (62.3%) patients, followed by TSH deficiency in 56 (40.6%) patients and ACTH deficiency in 27 (19.5%) patients. No patients had evidence of diabetes insipidus pre-operatively. Primary hypothyroidism was present in 10 patients.

On univariate analysis, pre-operative hypopituitarism was significantly higher in men (men vs women, 76.3% vs 55.2%, p=0.011), patients with larger tumours (giant adenoma vs macroadenoma, 85.9% vs 51.4%, p<0.001) and patients reporting endocrine symptoms (symptoms vs no symptoms, 83.3% vs 63.0%, p=0.047). Where tumours were detected incidentally, these patients were more likely to be eupituitary at presentation (p=0.020)(Table 5.2).

After controlling for gender, age, tumour size and incidental detection of tumour, on multivariate analysis intact pituitary function (eupituitary) was significantly associated with female gender (OR 3.1, p=0.008) and smaller tumour size (giant adenoma OR 0.15, p<0.001).

Table 5.1

Table presenting baseline demographics in the NFPA cohort

	Number (percentage)
Male/Female	87/63 (58/42%)
Mean age (years)	61 (23 – 87)
Presenting symptoms (n=150)	
Headache	27 (18.0%)
Reported Visual symptoms	61 (40.7%)
Endocrine deficiency	31 (20.7%)
Incidental finding	48 (32.0%)
Median duration of admission (days) (IQR)	4 (3 – 5)
Size	
Macroadenoma (10mm)	80 (53.3%)
Giant Adenoma (>25mm)	70 (46.7%)
Pre-operative vision	
Normal	62 (41.3%)
Unilateral deficit	27 (18.0%)
Bilateral deficit	60 (40.0%)
Unavailable	1 (0.7%)
Endocrine Status Pre-operatively (n=138)	
Eupituitary	45 (32.6%)
Hypopituitary	93 (67.4%)
Number of pituitary axes lost (n=138)	
0	45 (32.6%)
1	36 (26.1%)
2	34 (24.6%)
3	23 (16.7%)
4	0 (0%)

Table 5.2
Pre-operative characteristics of patients with intact pituitary function and hypopituitarism

	Eupituitary Preoperatively (n=45)	**Hypopituitary Preoperatively (n=93)**	**P-value**
Gender			**P=0.011**
Male	19 (23.8%)	61 (76.3%)	
Female	26 (44.8%)	32 (55.2%)	
Size			**P<0.001**
Macroadenoma	36 (48.6%)	38 (51.4%)	
Giant	9 (14.1%)	55 (85.9%)	
Baseline serum prolactin level (U/L)	426 ± SD 426	594 ± SD 659	P=0.112
Mean Age (years ± SD)	60.5 ± 13.3	62.2 ± 13.5	P=0.477
Presenting symptoms			
Headache	7 (28.0%)	18 (72.0%)	P=0.645
Visual Symptoms	15 (27.3%)	40 (72.7%)	P=0.354
Endocrine Symptoms	5 (16.7%)	25 (83.3%)	
No endocrine symptoms	40 (37.0%)	68 (63.0%)	**P=0.047**
Incidental finding	21 (46.7%)	24 (53.3%)	
Not incidental finding	24 (25.8%)	69 (74.2%)	**P=0.020**

Post-Operative Endocrine Outcomes

Post-operatively endocrine data was available in all 150 patients. Hypopituitarism was present in 70.0% of patients. The most common deficiency was Growth Hormone deficiency (69.3%), followed by gonadotrophin deficiency (62.7%), TSH deficiency (41.3%), ACTH deficiency (24.0%), partial ACTH deficiency (11.3%) and ADH deficiency in 1.3% of the cohort

(Figure 5.1). Isolated gonadotrophin deficiency was detected in 3.3% and isolated ACTH deficiency in 2.0% of patients. During the immediate post-operative period 7.3% of patients experienced SIADH and 17.3% experienced transient diabetes insipidus.

Post-operative hypopituitarism was significantly higher in men (men vs women, 85.1% vs 49.2%, p<0.001) and patients with larger tumours (giant adenoma vs macroadenoma, 84.3% vs 57.5%, p<0.001)(Table 5.3). In our cohort patients with post-operative hypopituitarism were older (p=0.011). Patients who underwent surgery between 2005-2010 were more likely to have hypopituitarism post-operatively than patient who underwent surgery between 2011-2015 (p=0.033).

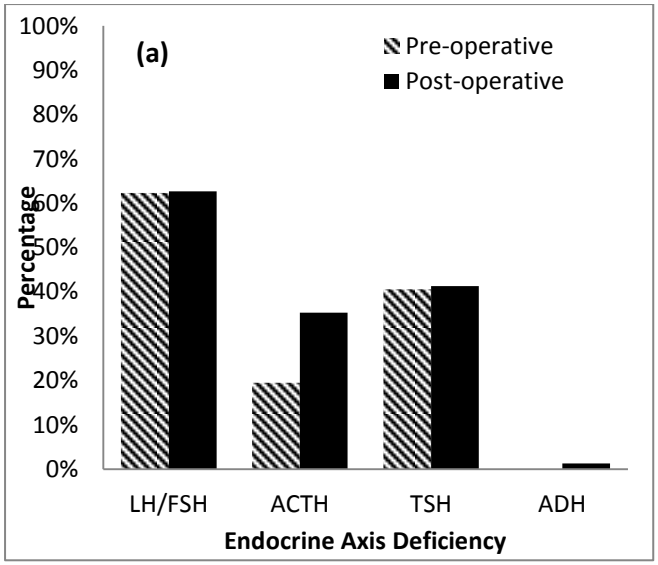
On multivariate analysis, after controlling for gender, age, and tumour size, post-operative hypopituitarism was significantly associated with gender (female = OR 0.12, p < 0.001), age (OR 1.05 per year, p =0.004) and having a giant adenoma (OR 6.53, p<0.001).

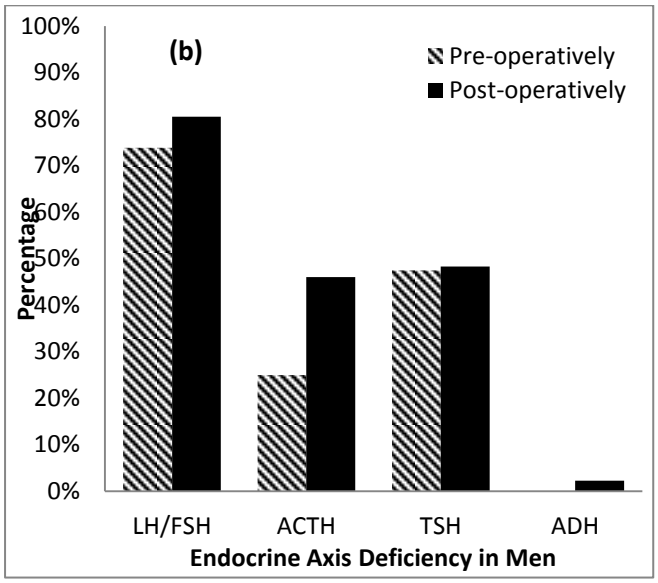
New Endocrine Deficiency

Complete paired pre- and post-operatively endocrine data was available in 138 patients. Of the patients who were eupituitary pre-operatively, 8 (17.8%) patients developed new endocrine deficiency (Figure 5.2). On univariate analysis, these patients were more likely to be men (p=0.031), but otherwise so significant difference was observed in terms of tumour size (p=1.00), age (p=0.085), serum prolactin level at presentation (p=0.156) or year of surgery category (p=0.399)†. In patients with evidence of hypopituitarism pre-operatively, further deterioration in pituitary function was not associated with the variables of gender (p=0.121), age (0.386), tumour size (p=0.245) and year of surgery category (p=0.293)†, when compared to patients with static or improved pituitary function.

When reviewed by individual axis, new endocrine deficiency developed in 1.4-25.2% of cases (Table 5.4). There was a significant difference in terms of gender, with men more likely to experience deterioration in gonadotrophin axis (men vs women, 33.3% vs 0%, P<0.001) and ACTH axis (men vs women, 33.3% vs 15.7%, P=0.048).

†Patients operated on between 2005-2010 compared to 2011-2015 cohort





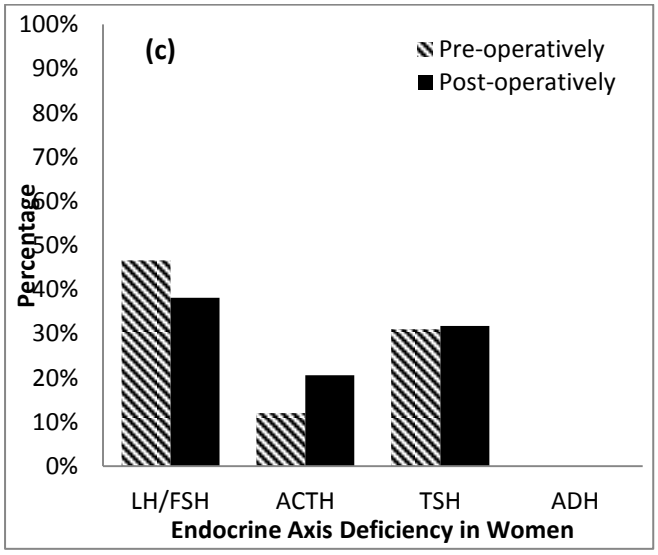


Figure 5.1 (a) Pre-operative and post-operative hormone deficiency for the whole cohort. Pre-operatively: Gonadotrophin deficiency 86/138 (62.3%), ACTH deficiency 27/138 (19.5%) and TSH deficiency 56/138 (40.2%).Post-operatively: Gonadotrophin deficiency 94/150 (62.7%), full and partial ACTH deficiency 53/150 (35.3%), TSH deficiency 62/150 (41.3%) and permanent ADH deficiency 2/150 (1.3%). (b) Pre and post-operative hormone deficiency for men only. Pre-operatively: Gonadotrophin deficiency 59/80 (73.8%), ACTH deficiency 20/80 (25.0%) and TSH deficiency 38/80 (47.5%).Post-operatively: Gonadotrophin deficiency 70/87 (80.5%), ACTH deficiency 40/87 (46.0%), TSH deficiency 42/87 (48.3%) and ADH deficiency 2/87 (2.3%). (c) Pre and post-operative hormone deficiency for women only. Pre-operatively: Gonadotrophin deficiency 27/58 (46.6%), ACTH deficiency 7/58 (12.0%) and TSH deficiency 18/58 (31.0%). Post-operatively: Gonadotrophin deficiency 24/63 (38.1%), ACTH deficiency 13/63 (20.6%) and TSH deficiency 20/63 (31.7%). There was no ADH deficiency in women.

Table 5.3
Differences between patients with intact pituitary function and hypopituitarism post-operatively

	Eupituitary Post-operatively	Hypopituitary Post-operatively	P-value
Gender			
Male	13 (14.9%)	74 (85.1%)	
Female	32 (50.8%)	31 (49.2%)	**P<0.001**
Size			
Macroadenoma	34 (42.5%)	46 (57.5%)	
Giant Adenoma	11 (15.7%)	59 (84.3%)	**P<0.001**
Baseline Serum Prolactin Level (U/L)	667 ± SD 762	485 ± SD 480	P=0.504
Mean Age (years)	57.1 ± 13.5	63.2 ± 13.2	**P=0.011**
Duration of admission (days)	5 ± 3	6 ± 5	P=0.663
BMI at latest follow up (kg/m2)	25.3 ± 9.3	28.1 ± 8.9	P=0.09
Year of surgery			
2005-2010	14 (20.9%)	53 (79.1%)	
2011-2015	31 (37.3%)	52 (62.7%)	**P=0.033**

Post-operative Endocrine Recovery

After surgery, 11.8% of patients who had evidence of hypopituitarism pre-operatively, experienced recovery of one or more pituitary hormone axis (Figure 5.2). Only 4.3% of patients with hypopituitarism prior to surgery, became eupituitary post-operatively. Patients who experienced improvement in pituitary function after surgery, had higher baseline serum prolactin level as compared to patients whose pituitary function remained static or deteriorated ($H(2)=7.545$, $p=0.023$), with mean rank of 66 for patients with improved function, 44 for patients with unchanged function and 43 for patients with deterioration in function (Kruskall-Wallis H test). Improved function was more likely in

females (percentage females improved vs others, 63.6% vs 30.5%, p=0.043) (data not presented).

When reviewed by individual axis endocrine recovery occurred in 3.6-26.9% of cases, depending on axis. Women were more likely to experience endocrine recovery in all axes and a statistically significant difference was observed in the gonadotrophin axis (women vs men, 18.5% vs 1.7%, P=0.011) (Table5.5).

Table 5.4

Development of new endocrine deficiency by axis post-operatively. Numerator represents number of patients diagnosed with new hormonal deficiency post-operatively. Denominator represents number of patients with intact function pre-operatively

	Males	**Females**	**Total**	**p-value**
LH/FSH axis	7/21 (33.3%)	0/31	7/52 (13.5%)	**P<0.001**
ACTH axis	20/60 (33.3%)	8/51 (15.7%)	28/111 (25.2%)	**P= 0.048**
TSH axis	3/38 (7.9%)	1/34 (2.9%)	4/72 (5.6%)	P=0.617
ADH axis	2/80 (2.5%)	0/58	2/138 (1.4%)	P=0.509

Table 5.5

Improvement in endocrine function by axis post-operatively. Denominator represents number of patients with hormone deficiency post-operatively. Numerator represents number of patients who experienced recovery of this function.

	Males	**Females**	**Total**	**P-value**
LH/FSH axis	1//59 (1.7%)	5/27 (18.5%)	6/86 (7.0%)	**P=0.011**
ACTH axis	4/20 (20.0%)	3/6 (50%)	7/26 (26.9%)	P=0.293
TSH axis	1/38 (2.6%)	1/18 (5.6%)	2/56 (3.6%)	P=0.544

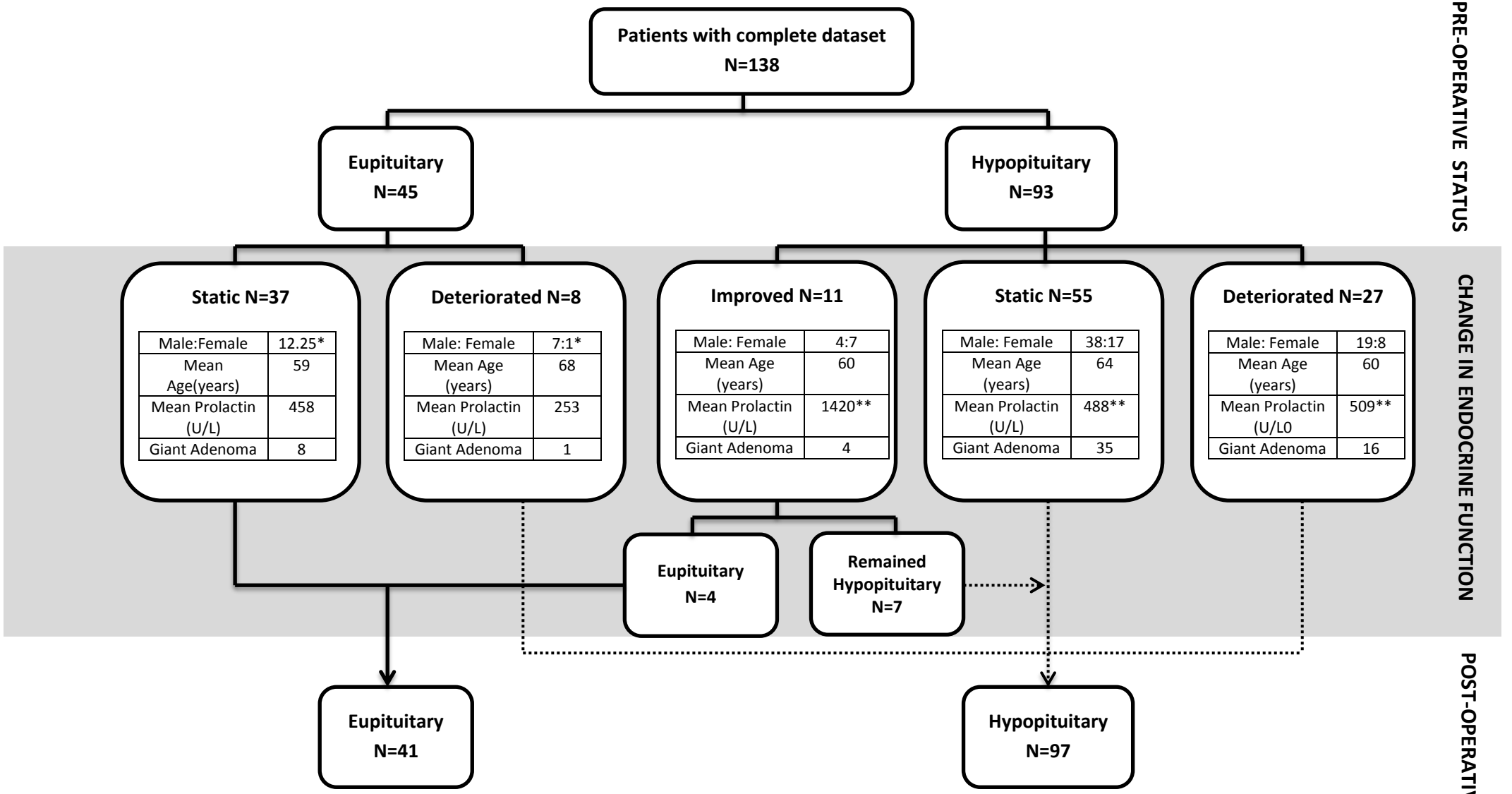


Figure 5.2 Flow diagram demonstrating change in pituitary function after transsphenoidal surgery. Improvement in pituitary function was defined as recovery of function in at least one axis. Deterioration in function was defined as loss of function in at least one axis.

**Men who were eupituitary at baseline were more likely to experience deterioration in endocrine function (p=0.031) as compared to women.*

***Patients who experienced improvement in pituitary function had higher baseline serum prolactin levels than patients in which pituitary function remained the same or deteriorated (p=0.019).*

5.6 Discussion

To our knowledge, this is one of the largest single-surgeon series reporting on endocrine outcomes exclusively in patients with NFPA. The prevalence of hypopituitarism at baseline in our cohort is within the range quoted in the current literature(9, 12, 21, 22). In our cohort, tumour size at presentation was associated with hypopituitarism both pre-and post-operatively. This is consistent with other cohorts(12-15, 23). Presumably the size of tumour at presentation is reflective of the amount of time it has been present, with a larger tumour being present for a longer duration. As such normal pituitary cells are subject to the mass effect of the tumour a longer period of time, impairing the potential for return of function in spite of surgical resection. Additionally, it is not unreasonable to postulate that larger tumours exert higher pressures in the sellar, thereby causing more damage to normal pituitary tissue.

Although we did not demonstrate any significant age difference between patients with and without pituitary hormone deficiency at baseline, this has been detected in previous studies(15). Younger age is a predictor of post-operative endocrine recovery(24). Patients with hypopituitarism after surgery were significantly older than those who were eupituitary in our cohort. Del Monte et al., demonstrated in their elderly population, that surgery was unlikely to restore normal pituitary function and suggested that due to these patients age, there were delays in diagnosis of NFPA. When reviewing the management of pituitary adenoma in patients above the age of 65 years, Hong et al., noted that a third of their cohort was initially misdiagnosed(25).The majority of patients in this cohort presented with visual symptoms and the authors postulated that it may not be easy to distinguish between pituitary pathology and age related visual conditions in this population. As such, a delay in diagnosis may very well contribute to the limited potential for endocrine recovery postoperatively. Also, it is tempting to entertain the notion, that like all other cells in the body, the robustness of pituitary cells decreases with advancing age.

We observed that gender seemed to be an important variable, not only because the gender distribution was significantly different in the presence or absence of hypopituitarism, but also in terms of change in pituitary function. In our cohort, the rate of hypopituitarism both pre and post-operatively was significantly higher in men. Moreover, when investigating change in pituitary function, more men than women experienced deterioration in pituitary

function (p=0.031), whereas more women than men experienced improvement in pituitary function (p=0.043). It is noteworthy that previous studies have shown that men are more likely to have multiple hormone deficiencies at presentation than women (12, 15). Reporting on gender differences in NFPA patients, Caputo et al., demonstrated that men tended to have larger tumours when compared to premenopausal women and this almost reached statistical significance (p=0.056)(12).We did not demonstrated any statistically significant difference at baseline in terms of tumour size or presenting symptoms between genders in our cohort (data not presented), however we did not analyse pre and post-menopausal women separately. Caputo et al., then went on to very eloquently demonstrate how pituitary surgery affected men and women differently, with the most recovery occurring in premenopausal females in their cohort. The authors then went on to postulate that women in their cohort presented with smaller tumours and as such possibly a shorter disease duration that would cause less damage to the normal pituitary cells which increased chances of function recovery. Certainly it is easier for pre-menopausal women to detect hormonal disruption with change or cessation in menstrual pattern and as such it may be that younger women are able to present earlier.

In our cohort, patients who experienced improvement in pituitary function, had a higher mean serum prolactin level at baseline as compared to others (p=0.023). When Arafah et al., made a similar observation, the authors postulated that this was due to the compression of the pituitary stalk and portal vessels and therefore hypopituitarism was caused by the interruption of hypothalamic hormones(16). It has been shown that intrasellar pressure correlates inversely with serum prolactin levels and not tumour size(26). As such, the recovery of pituitary function observed in patients with higher prolactin levels may reflect the effect of surgery decompressive effect of surgery on the stalk and portal vessels.

As demonstrated in this cohort, the rate of improvement or deterioration in function after surgery varies with individual axis. Post-operatively, new loss of ACTH function was noted in 25.2% of patients but new loss of TSH function was only noted in 5.6% of patients. New loss of gonadotrophin function was noted in 33.3% of males and none detected in women. Recovery of ACTH function occurred in 26.9% of affected patients, whereas recovery of TSH axis only occurred in 3.6% of patients. Recovery of gonadotrophin axis was significantly higher in female than males (18.5% vs 1.7%). Caputo et al., demonstrated similar rates of in terms of deterioration in the ACTH axis and male gonadotrophin axis, however rates of

recovery was higher in all axes as compared to our cohort(12). We note however that the mean age for that cohort was younger than ours and this may have affected the potential for pituitary hormone recovery. Conversely, Jahangiri et al., demonstrated that gonadotrophin recovery in their cohort was higher in men as compared to women(15).Rate of recovery of TSH axis was again higher than our cohort, but recovery of ACTH axis was only 3%. However pre-operative rate of hypopituitarism was lower than our cohort. Furthermore, the use of SST to assess HPA axis might underestimate ACTH deficiency in this group of patients. In the group of patient who exclusively underwent endoscopic surgery for the first time in the report by Zaidi et al., new hormonal loss was most likely in the ACTH axis in 20.8% of patients, followed by the gonadotrophin axis in 18.9% of patients and TSH deficiency in 13.2%(17). Type of dynamic endocrine testing however is not clarified. The only large meta-analyses reviewing surgical outcome in NFPA, reported that pituitary function improved in 30% of patients (95% CI 12-57%) and new anterior pituitary hormone deficiency occurred in 9% of patients (95% CI 3-23%). The analysis revealed that the gonadotrophin axis was most likely to change (improve or deteriorate) after surgery. Whether or not these results imply that the durability of pituitary cells is variable is unclear. Regardless, our results provide further evidence that pituitary surgery affects the pituitary cells in different ways. Recognition that the effect of pituitary surgery on pituitary hormones may be variable is important especially when counselling patients. For example, retaining gonadotrophin function might be more important in younger patients in whom preservation of fertility is paramount. Equally for an elderly patient with memory impairment, loss of ACTH function and the requirement of lifelong steroid replacement may be undesirable.

One of the strengths of this report is the use of validated dynamic tests of pituitary function in all patients postoperatively with clear definitions of endocrine deficiency. As highlighted in a previous meta-analysis, one of the difficulties when trying derive the 'true' rate of hypopituitarism post-surgically in the NFPA group from the literature is not just the heterogeneous methods of endocrine testing but also the variability in the definition of hypopituitarism(27). Whereas in some studies no dynamic testing methods are employed(9) or not undergone by all patients(28) , in other cohorts, new endocrine deficiency is defined as requirement for new hormonal replacement(10, 29). In some reports the type of endocrine test used is unclear (8, 30, 31). Therefore the use of the glucagon stimulation test

with its validation cut-offs in this cohort, allows us to report on hypopituitarism post-surgically more accurately.

Another difficulty encountered when discussing hypopituitarism in this patient group, is the fact that on occasion in the literature, outcomes of patient with NFPAs are reported together with patients with other pituitary pathologies (28, 29, 32, 33). Inclusion of patients with other pituitary pathologies in other reviews will confound the overall results, and should be interpreted with caution as they cannot be directly be applied to NFPA patients. Exclusive inclusion of patients with NFPA in our review is one of the strengths of this review as it makes our results better representative of this specific patient group.

Over the last 20 years, pituitary surgery via the endoscopic transsphenoidal approach has gained increasing popularity(30) the safety and utility of this method is now well established(29). The exclusive use of the endoscopic transsphenoidal approach in this modern case-series therefore limits the confounding effects of older surgical techniques, including surgery via the cranial approach, on the final endocrine outcome. Furthermore all patients were operated on by the same surgeon, controlling for variation is surgical technique between different surgeons in terms of post-operatively outcome.

We have not only reported on variables associated with hypopituitarism but have also attempted to identify significant variables associated with both improvement and deterioration in pituitary function. Lastly the size of this cohort, strengthens the validity of our results.

Given the retrospective method of this study, data collection was dependent on accuracy of documentation. As such we were unable to obtain full pre-operatively endocrine data on all the patients in the series. Also, we are aware that we have not reported on all potential confounders of post-operative endocrine outcome, including time to surgery, the amount of tumour resected, pericavernous invasion and tumour residuum.

Regardless, we have methodologically investigated and reported on the main variables associated with pituitary function on our cohort of patients with NFPA.

5.7 Conclusion

From this large cohort of patients with NFPA, it was demonstrated that pre-operative hypopituitarism was associated with tumour size, whereas post-operative hypopituitarism

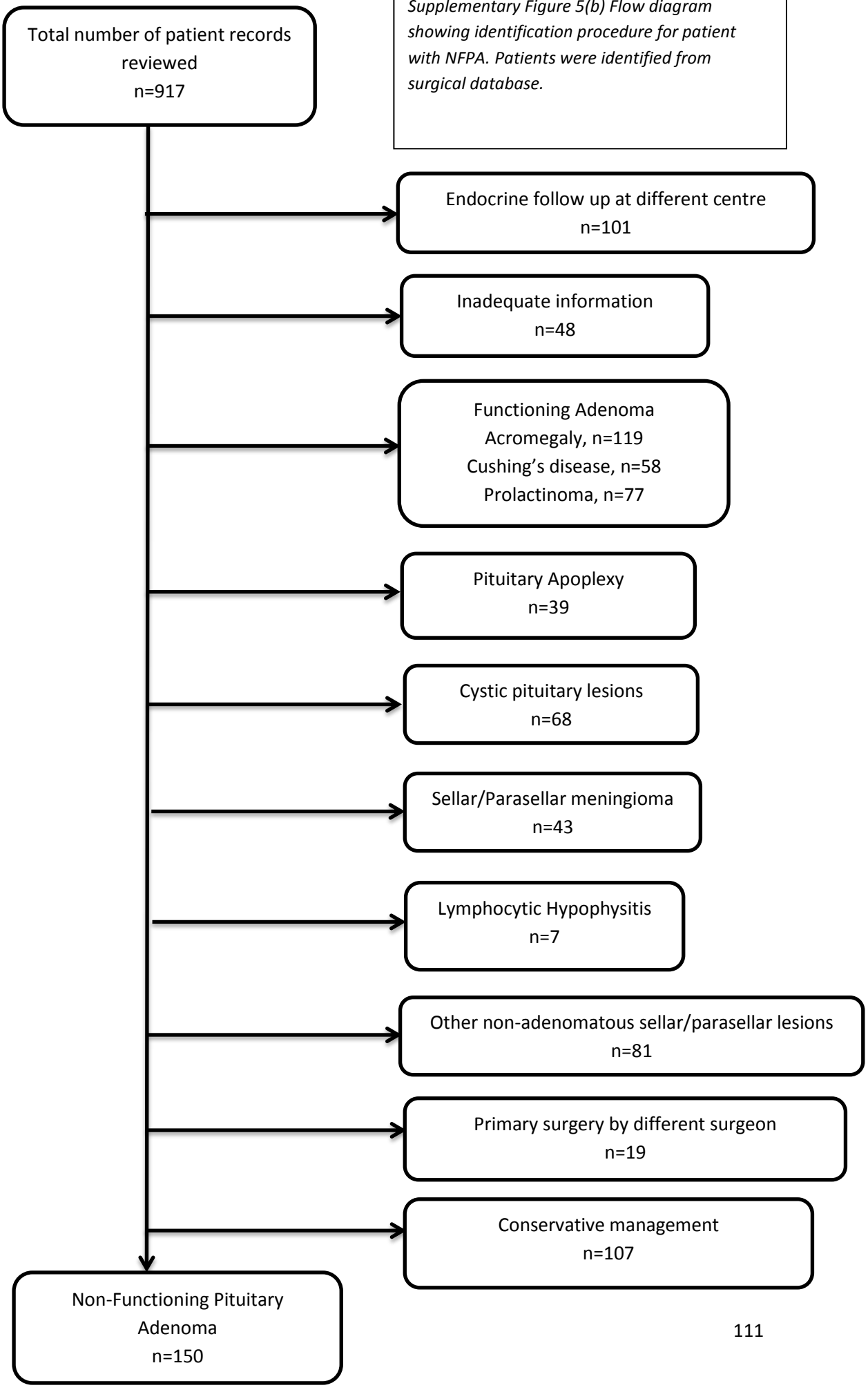
was associated with age and tumour size. Gender was associated with pre and post-operative pituitary function, with more females experiencing improvement and more males experiencing deterioration in function. Patients who experienced improvement in pituitary function after surgery, had higher mean serum prolactin levels at baseline. Transsphenoidal surgery affects pituitary axes differently. We would encourage further reports on factors associated with hypopituitarism in patients with NFPA.

5.8 Supplementary Tables and Figures

Study	No. of participants	Hypopituitarism Pre-operatively	Type of Surgery	Single Surgeon Case Series	Method of Endocrine Testing (Postoperatively)	New Endocrine Deficiency	Hormonal Recovery
Jahangiri et al., 2016	305 (number of surgeries)	50%	Microscopic and Endoscopic transsphenoidal	**N**	Baseline pituitary profile, SST	14%	3-49% (data is presented for individual axis)
Laws et al., 2016	55	Not presented for subgroup	Endoscopic transsphenoidal	**N**	New hormone replacement requirement	10.9%**	0%**
O-Reilly et al., 2016	470₸ (multicentre)	Not presented	Transsphenoidal and Transcranial	**N**	Baseline pituitary profile, SST, GST, ITT	23.3%	5.5%
Zaidi et al., 2016	55 80	Not presented	Endoscopic Transsphenoidal Microscopic	**Y** **Y**	New hormone replacement requirement or 'diagnosis of hypopituitarism' at follow up	0-20.8% (data for individual axis) 2.5-18.8% (as above)	Not presented
Karppinen et al., 2015	144 41	59% 56%	Microscopic Endoscopic transsphenoidal	**N**	Baseline pituitary profile, GHRH-arginine stimulation test	13% 9%	7% 9%
Caputo et al., 2013	93*	LH/FSH 67% TSH 39% ACTH 24%	TSS	N	Baseline pituitary profile, early morning cortisol level, SST, ITT GH axis not included	17-31% (data for individual axis)	26-62%
Fatemi et al., 2008	231	59%	Endoscopic transsphenoidal	**Y**	Baseline pituitary profile, cosyntropin test, metyrapone test, GHRH-arginine test, ITT‡	7%	48%
Giritharan et al., 2018	150	67.4%	Endoscopic transsphenoidal	**Y**	Baseline pituitary profile, glucagon stimulation test	1.4-25.2% (data for individual axis)	3.6- 26.9% (data for individual axis)

Supplementary Table 5(a) Summary of recent studies reporting of hypopituitarism in patients with NFPA. *Number of participants with paired pre and post op data available. **Calculated from data provided. ₸ Total number of patient who were managed surgically. This included 183 patients who underwent radiotherapy. ‡Not all patients underwent dynamic testing of HPA axis.

Supplementary Figure 5(b) Flow diagram showing identification procedure for patient with NFPA. Patients were identified from surgical database.



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Chapter 6

The Prevalence of Growth Hormone Deficiency in Survivors of Subarachnoid Haemorrhage – Results from a Large Single Centre Study

6 Chapter 6 The Prevalence of Growth Hormone Deficiency in Survivors of Subarachnoid Haemorrhage – Results from a Large Single Centre Study

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6.1 Preface

Growth Hormone Deficiency is increasingly recognised as a consequence of subarachnoid haemorrhage, however the 'true' prevalence of this is difficult to determine due to the heterogeneous testing and reporting methods in the literature. This chapter will examine the rate of hypopituitarism and specifically growth hormone deficiency after subarachnoid haemorrhage when dynamic endocrine testing and confirmatory testing protocol is employed. Included at the end of this chapter is a flow diagram detailing patient recruitment (not included in journal publication version). Details of the dynamic testing protocols used have already been discussed in Chapter 3.

6.2 Abstract

Objective

The variation in reported prevalence of Growth Hormone Deficiency (GHD) post subarachnoid haemorrhage (SAH) is mainly due to methodological heterogeneity. We report on the prevalence of GHD in a large cohort of patients following SAH, when dynamic and confirmatory pituitary hormone testing methods are systematically employed.

Design

In this cross-sectional study, pituitary function was assessed in 100 patients following SAH. Baseline pituitary hormonal profile measurement and Glucagon Stimulation Testing (GST) was carried out in all patients. Isolated GHD was confirmed with an Arginine Stimulation Test (AST) and ACTH deficiency was confirmed with a Short Synacthen Test (SST).

Results

The prevalence of hypopituitarism in our cohort was 19% and the prevalence of GHD was 14%. There was no association between GHD and the clinical or radiological severity of SAH at presentation, treatment modality, age, or occurrence of vasospasm. There were statistically significant differences in terms of Glasgow Outcome Scale (GOS; p=0.03) between patients diagnosed with GHD and those without. Significant inverse correlations between GH peak on GST with body mass index (BMI) and waist hip ratio (WHR) was also noted ($p<0.0001$ and $p<0.0001$ respectively).

Conclusion

Using the current testing protocol, the prevalence of GHD detected in our cohort was 14%. It is unclear if the BMI and WHR difference observed is truly due to GHD or confounded by the endocrine tests used in this protocol. There is possibly an association between the development of GHD and worse GOS score and QoL-AGHDA score. Routine endocrine screening of all SAH survivors with dynamic tests is time consuming and may subject many patients to unnecessary side-effects. Furthermore the degree of clinical benefit derived from Growth Hormone Replacement (GHR) in this patient group, remains unclear. Increased understanding of the most appropriate testing methodology in this patient group and more importantly which SAH survivors would derive most benefit from GHD screening is required.

6.3 Introduction

Subarachnoid Haemorrhage (SAH) is a rare but devastating event that occurs in about 8 to 10 per 100,000 patients per year (1). In the past mortality was approximately 50% and about a third of survivors did not regain full independence (2). Improvements in neurointensive care and the introduction of endovascular procedures have improved survival rates, with case fatality decreasing by 17% in absolute terms in the past three decades (3). However, this improvement in mortality has unmasked the long term consequences of this life changing event. With increasing interest in patient reported quality of life as an outcome marker in the treatment of chronic diseases it is now clear that in spite of good physical and

neurological outcome, a significant proportion of survivors report impaired quality of life (4-7).

Chronic sequelae of SAH include poor memory, fatigue, anxiety, depression and impaired quality of life (4, 8-11). Undoubtedly some of the cognitive, emotional and psychosocial consequences seen in survivors of SAH resemble that of patients with untreated hypopituitarism (2), specifically Growth Hormone Deficiency (GHD). Pituitary dysfunction developing post SAH was first documented in the seminal publication of Kelly et al (12). Early studies have reported the prevalence of hypopituitarism in SAH survivors to be as high as 55% (2, 13-16). However, more recent studies report a much lower prevalence of pituitary dysfunction in this patient group (17-22) (Table 6.1). A recent meta-analysis has demonstrated that the pooled frequency of long term GHD is 19%, however the range reported in the literature is wide, between 0% and 37% (23).

We present the results from the screening phase of a study to assess the impact of GH replacement in survivors of SAH with GHD. The prevalence of GHD detected in this cohort using the testing protocol employed is reported.

6.4 Subject and Methods

Patient recruitment

This was a single centre cross sectional study of patients with SAH presenting to the regional neurosurgical centre. Patients who had received treatment for SAH between 2006 and 2014 were invited to participate 1 year or more after ictus. Study posters were also placed in a local head injury centre.

SAH was confirmed by the presence of blood on computed tomographic (CT) imaging of the brain or on cerebrospinal fluid (CSF) analysis obtained by lumbar puncture. Exclusion criteria were clinical contraindication to dynamic pituitary testing, history of cranial radiotherapy, hypothalamic/pituitary disease that was diagnosed prior to SAH and recent use of oral corticosteroids. Participants with prior history of hormonal deficiency were required to have been on stable replacement (where appropriate) for at least 3 months preceding recruitment. This study was approved by NRES Committee North West – Greater Manchester West (Reference 14/NW/0191). All participants were required to provide written informed consent prior to study enrolment.

Measures of severity of SAH

The World Federation of Neurosurgical Societies (WFNS) grading system (24) was used to assess clinical severity of patients at presentation based on clinical information from medical records. Fisher grading system (25) was used to grade the radiological severity of SAH. If this information was not clear from the medical notes, the admission neuroimaging was reviewed by a single neuroradiologist. The location of the aneurysm, presence of hydrocephalus, insertion of extraventricular drain (EVD), presence of vasospasm and type of intervention (neurosurgical clipping or endovascular coiling) were recorded. Glasgow Outcome Scale (GOS) (26) was assessed at time of hormonal screening and graded in severity as grade 1 (death), grade 2 (persistent vegetative state), grade 3 (severe disability – conscious but disabled), grade 4 (disabled but independent as far as daily life) and grade 5 (good recovery and there may be minor deficits).

Anthropometric and Quality of Life Measures

Body weight (measured to the nearest 0.1kg using a Marsden weighing scale) and height (measured to the closest 0.5cm) were used to calculate the body mass index (BMI). Waist and hip circumference were measured to the closest 0.5cm and the waist to hip ratio (WHR) was then calculated. All participants completed the Quality of Life in Adults with Growth Hormone Deficiency (QoL-AGHDA) questionnaire (27) at the screening visit.

Clinical Protocol

All patients agreeing to take part were screened by measurement of baseline pituitary hormones (IGF-1, testosterone/estradiol, LH, FSH, cortisol, ACTH, fT4, TSH and prolactin) and a Glucagon Stimulation Test (GST). Given the tendency of the GST to overestimate ACTH insufficiency, all patients with a suboptimal cortisol response on GST were required to undergo a confirmatory Short Synacthen Test (SST).

All patients with Isolated Growth Hormone Deficiency (IGHD) were required to undergo a second confirmatory test; the Arginine Stimulation Test (AST). Given that this was primarily a study to assess the impact of GH replacement on survivors of SAH with GHD, participants who did not demonstrate impaired quality of life on the QoL-AGHDA questionnaire (and

therefore did not meet the National Institute for Health and Care Excellence criteria for GH Replacement (28)), were allowed to decline confirmatory testing of GH axis.

Assay and diagnostic criteria

Prior to the 26th January 2015, plasma cortisol, fT4, TSH, prolactin, LH, FSH, testosterone and estradiol were analysed using Electrochemical Luminescent Immunoassay (Roche Cobas 8000). After this time, these measurements were analysed using competitive Chemiluminescent Immunoassay (Siemens Advia Centaur). ACTH and GH were analysed using Siemens Immulite 2000 Two Site Enzymatic Chemiluminescent Immunoassay. IGF-1 levels were analysed using Siemens Immulite 2000 Enzymatic Chemiluminescent Immunoassay.

ACTH deficiency was diagnosed as a failure to reach a peak cortisol value of 450nmol/L on both the GST and SST. Severe GHD was diagnosed as a failure to reach a peak GH value of 3µg/L on dynamic testing. Hypogonadotrophic hypogonadism in men was diagnosed if a low serum testosterone (morning sample) was associated with low or inappropriately normal gonadotrophin level. In premenopausal women, hypogonadotrophic hypogonadism was defined as low serum estradiol and inappropriately low gonadotrophins associated with amenorrhoea or oligomenorrhoea. In post-menopausal women, this was defined as inappropriately low gonadotrophins for age. Secondary hypothyroidism was defined as a low serum free T4 associated with low or inappropriately normal serum TSH.

Statistical Analyses

Data analysis was carried out using IBM SPSS Statistics 22 (IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY, USA: 2013). The prevalence of GHD was reported with descriptive statistics. Categorical data was analysed with either the Chi-squared test or the Fisher exact test where appropriate. Non-categorical data was analysed using the t-test or the Mann-Whitney U test where appropriate. A two tailed p-value<0.05 was considered statistically significant.

Study	Biochemical Test	Number of patients	Time of assessment	Prevalence of hypopituitarism	Prevalence of GHD
Kreitschmann-Andermahr et al., 2004	Basal hormone values, ITT, TRH-LHRH-arginine test	40	27.3 months (mean)	55%	20%
Aimaretti et al.,2004	Basal hormone values, GHRH-arginine test, morning serum cortisol, 24 urinary cortisol	40	3 months	37.5%	25%
Aimaretti et al.,2005	Basal hormone values, GHRH-arginine test, morning serum cortisol, 24 urinary cortisol	32	12 months	37.5%	21.8%
Dimopoulou et al., 2005	Basal hormone values, IGF-1 level, low dose ACTH test	30	12-24months	47%	37%
Tanriverdi et al., 2007	Basal Hormone values (within 24 hours)	22	Within 24 hours	63.6%	22.7%
	GST, GHRH-arginine (12 months)		12 months	45%	36.4%
Javanovic et al., 2010	Basal hormone values, IGF-1	93	1.8 years (mean)	49.5%	29%
Klose et al.,2010	ITT, SST, GHRH-arginine test, clomiphene test	62	14 months	0%	0%
Parenti et al., 2011	Basal hormone values, IGF-1 levels	60	Within 72 hours	56.9%	22%
Lammert et al., 2012	Basal hormone values, SST, ITT*	20	12 months	15%	15%
Dutta et al., 2012 ₸	Basal hormone values, IGF-1 level	60	At or after 6 months	31.6%	15%
Karaca et al., 2013	Basal hormone values, GST	20	3 years	20%	20%*
Gardner et al., 2013	GST, SST, GHRH-arginine	64	3 months	45%	20%
		50	12 months	12%	10%
Hannon et al., 2014	ITT, GST, SST	41	15 months	14.6%	13.3% (4/30)
Khajeh et al, 2014 (HIPS)	Basal Hormone Values, Ghrelin test (Baseline) +/- metyrapone stimulation test	84 (baseline)	32 days (mean)	44%	31%
	Baseline hormone values and GHRH-arginine (6 months)	72	6 months	31%	11%
	Basal hormone values and GHRH-arginine test (14 months)	68	14 months	9%	7%
Kronvall et al., 2014	Basal hormone values, GHRH-arginine test	45	3 – 6 months	27%	7%
	Basal hormone values, GHRH-arginine test, ITT, SST	44	12-24 months	43%	25%

Table 6.1

Summary of studies investigating hypopituitarism after subarachnoid haemorrhage. To calculate the frequency of pituitary dysfunction at each time point, the actual number of patients at each follow-up time point is used as the denominator, rather than the number of patients at baseline. Studies providing pooled Traumatic Brain Injury (TBI) and SAH data are not included *ITT only performed in patients with suspected GHD and ACTH deficiency. 3 and 6 months data from this cohort not presented. ₸ Retrospective and prospective cohort

6.5 Results

Patient Demographics and Clinical Features of Subarachnoid Haemorrhage

One hundred patients (32 males and 68 females) were screened, with a mean age at screening of 57±10 years (range 32-83 years). The mean age at time of SAH was 53±10 years (range 24-78 years) and the median interval from ictus to pituitary hormone testing was 35 months (range 14-117 months). The mean body weight was 74.6±15.1 kg, with a BMI of 27.3±4.6 and mean WHR of 0.89±0.08. Majority of patients presented with WFNS grades 1 or 2 (n=82) and the commonest Fisher grade was 4 (n=39; Table 6.2)

On angiographic studies, anterior circulation aneurysms (n=72) and notably anterior communicating artery aneurysms, (n=27) were the commonest (Table 6.2). Presence of other incidental aneurysms (not source of acute bleeding) was noted in 21 (21%) patients. Insertion of EVD was required in 16 (16%) patients due to the development of hydrocephalus. Twenty three patients had radiological evidence of vasospasm during the acute admission. In one patient, details regarding the acute in patient admission were not available as she was managed at different centre.

Interventional procedures were carried out in 86 (86%) patients and this was either endovascular coiling or surgical clipping. Perimesencephalic type SAH was diagnosed in 14 (14%) patients as no aneurysms were detected on neuroimaging and therefore these patients did not require endovascular or neurosurgical treatment. In 4 patients, multiple aneurysms were coiled during the acute episode (Table 6.2).

Baseline pituitary profile and Glucagon Stimulation Tests

After screening GST, 37 (37%) patients were diagnosed with some degree of hypopituitarism (Figure 6.1). The most common deficiency was severe GHD which was diagnosed in 27 of patients, followed by ACTH deficiency in 18 patients and lastly gonadotrophin deficiency in 4 patients. No cases of female hypogonadism were detected. No cases of TSH deficiency or hyperprolactinaemia were detected. In patients with GHD, 16 patients had isolated GHD, 10 patients had GHD in association with ACTH deficiency and 1 patient had GHD in association with hypogonadism.

Table 6.2

Clinical characteristics of SAH survivors included in our cohort.

** Patients presenting with perimesencephalic pattern SAH were not given Fisher score.*

***In these patients copies of admission imaging were not available electronically*.

	Number (n=100)
Male/Female	32/68
Mean age at screening (months)	57 ± 10
Mean age at time of SAH (months)	53 ± 10
Median time from SAH to pituitary hormone testing (months)	35 (IQR 22-73)
Mean weight (kg)	74.6 ±15.1
Mean BMI	27.3 ±4.6
Mean WHR	0.89 ±0.08
Procedure	
Endovascular coiling	67
Neurosurgical clipping	15
Multiple coiling procedures during acute admission	4
None	14
Location of aneurysm	
Anterior Circulation	
Anterior communicating artery	27
Middle cerebral artery	19
Posterior communicating artery	18
Internal carotid artery	7
Pericallosal artery	1
Posterior Circulation	
Basilar artery	6
Posterior inferior cerebellar artery	3
Vertebral artery	1
Perimesencephalic	14
Multiple Aneurysms (unable to determine site of bleeding)	4
WFNS	
1	69
2	13
3	4
4	3
5	6
Unavailable	4
Fisher grade*	
1	13
2	15
3	11
4	39
Too late	2
Not available**	6
GOS	
4	15
5	85
QoL-AGHDA ≥ 11	69

Short Synacthen Test

Results of all patients with peak cortisol values less than 450nmol/L on GST were reviewed. One patient had baseline cortisol of 328nmol/L with a peak cortisol was 425nmol/L on GST and this patient did not report any symptoms of cortisol deficiency. Another 4 patients had baseline cortisol results above 400nmol/L and none of these patients had any symptoms of glucocorticoid insufficiency. As such these patients were thought overall to be ACTH sufficient. 11 patients completed the confirmatory SST, and all achieved a peak cortisol response of greater than 450nmol/L. Two patients did not attend their follow up SST (Figure 6.1)

Arginine Stimulation Test

Following the initial GST and confirmatory testing of the ACTH axis, 26 patients were diagnosed with isolated GHD and therefore were required to undergo confirmatory testing of the somatotrophic axis. Six of these patients had QoL-AGHDA score of less than 11 and thus did not meet NICE guidelines for GH replacement(28). Five of these patients declined the confirmatory AST. Therefore, 21 patients underwent the AST and this confirmed isolated GHD in 13 patients (Figure 6.1).

After confirmatory testing, the total number of patients with GHD in our cohort was 14 (13 patients with isolated GHD and 1 patient with GHD combined with hypogonadism). Isolated gonadotrophin deficiency was noted in 3 further patients. Assuming that the 2 patients who did not attend follow up SST were ACTH deficient (given that we were not able to confirm this), the prevalence of hypopituitarism in our cohort is 19%.

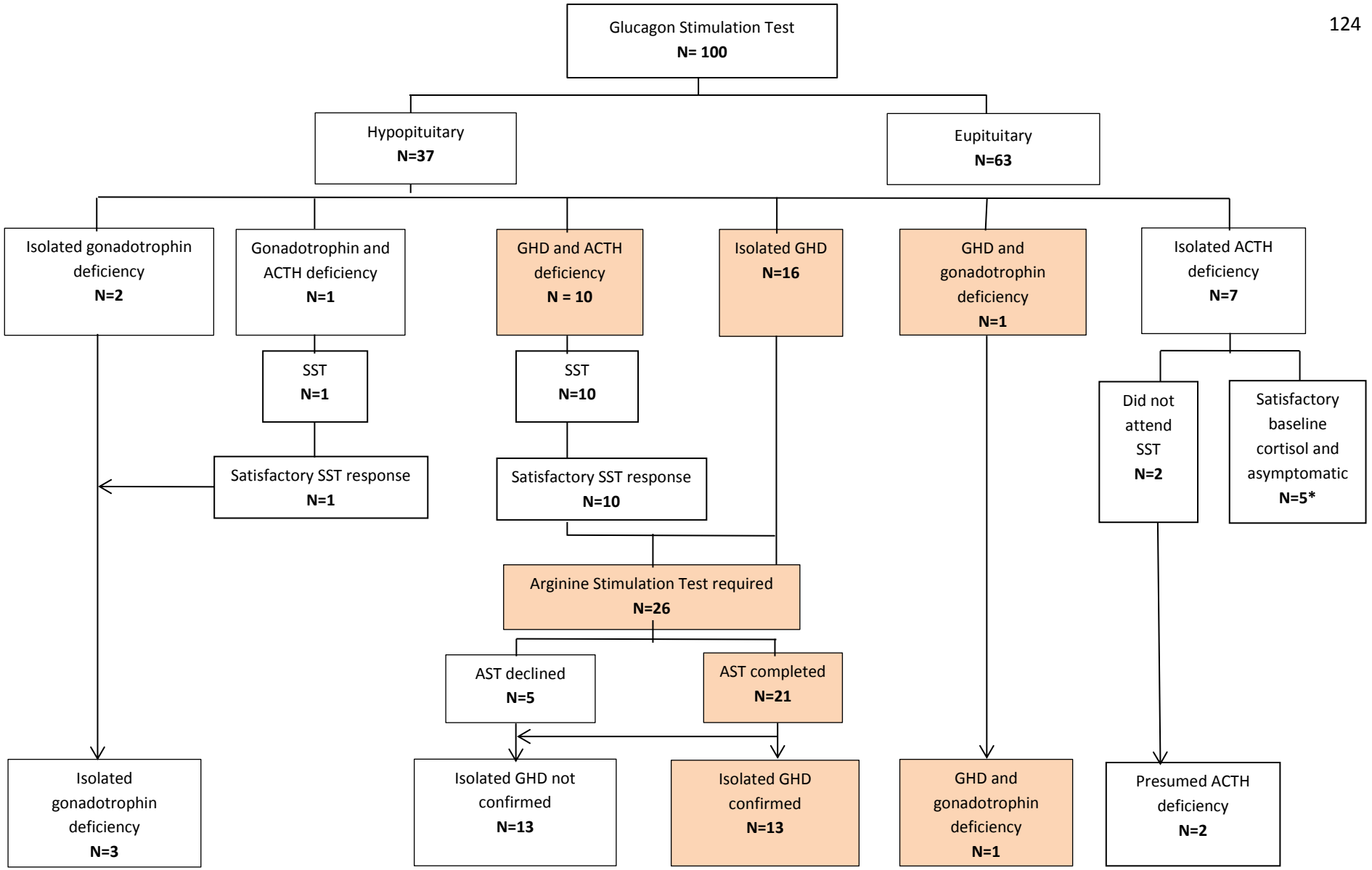


Figure 6.1 Flowchart demonstrating progression of patients through the study protocol. Only male hypogonadism was detected in this cohort.
**Five patients diagnosed with ACTH deficiency on GST, were deemed to be sufficient after results were re-reviewed (see results section).*

Factors related to GHD

On univariate analysis, the differences in body weight, BMI and WHR between patients with GHD compared to patients without GHD were significant (Table 6.3). There was a negative correlation between peak GH level on GST and the patient's BMI (R=-0.52; p<0.0001) and the WHR in our cohort (R=-0.43; p<0.0001; Figure 6.2)

On univariate analysis there was no significant difference between the patients with GHD and those without GHD, with respect to the mean age of onset of SAH (p=0.73), the age (p=0.66) and time to screening post SAH (p=0.25), the GCS at presentation (p=0.52), WFNS grade (p=0.58), site of aneurysm (p=0.61), Fisher grade of SAH (p=0.57), EVD insertion (p=0.26), occurrence of vasospasm (p=0.33) and treatment modality (p=0.11; Table 6.3). Patients with GHD had worse GOS scores at screening than those without GHD (p=0.03; Table 6.3).

Logistic regression was carried out to assess how the covariates of BMI, WHR, ADGHA score, gender, age at screening and hydrocephalus were associated with GHD. After running our models, all of which included BMI, gender, WHR, age, QoL-AGHDA score and GOS as covariates, we found the following to be positively associated with GHD: BMI (OR 1.527, 95%CI 1.17- 1.994), AGHDA score (OR 1.38, 95%CI 1.102 – 1.737) and hydrocephalus (OR 7.671, 95%CI 1.139 -51.68). In spite of the small number of patients with GHD this model remained resilient. However the interpretation of these results should be done cautiously. For example the unfeasibly high upper confidence interval of hydrocephalus suggests an odds ratio of 51.68, and is unlikely to reflect the truth.

Figure 6.2 Correlation between peak GH on GST with BMI and waist hip ration (WHR)

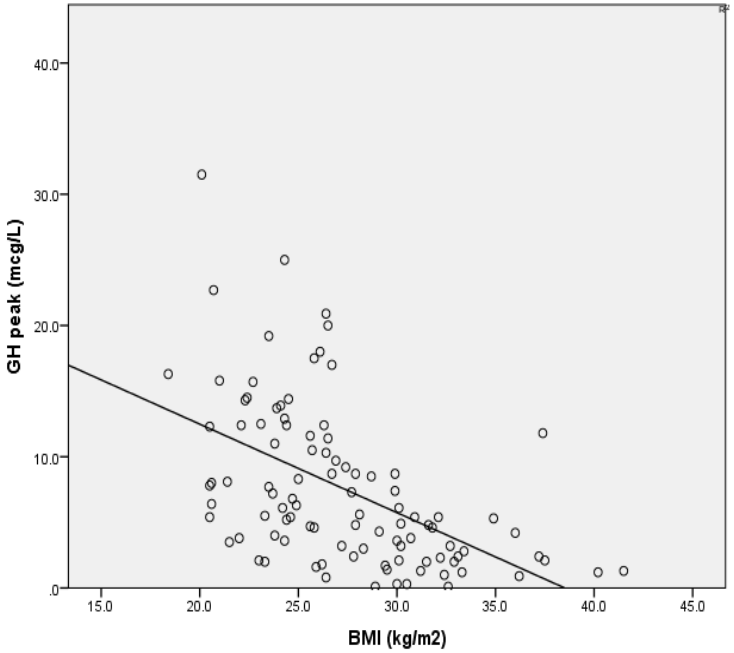


Figure 6.2A Peak GH response on GST vs BMI in all patients in our cohort , R=-0.519 (p<0.001).

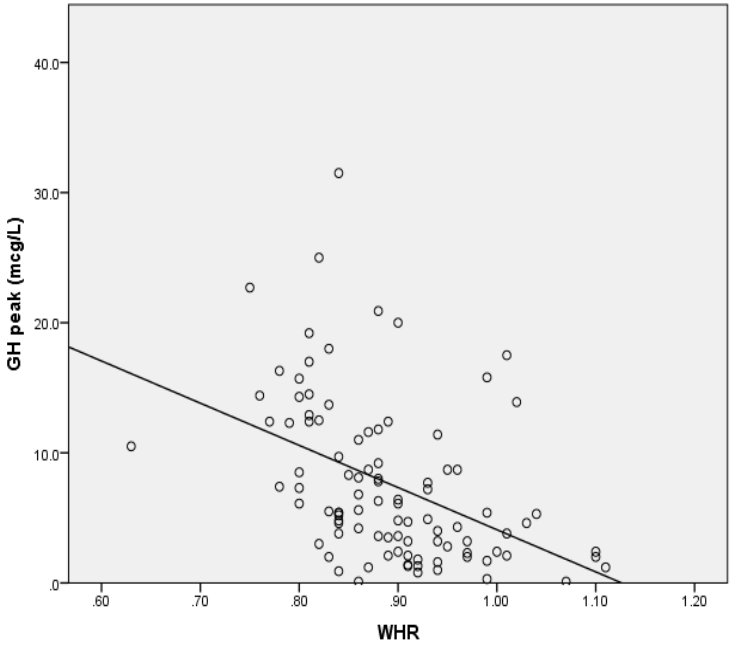


Figure 6.2B Peak GH response on GST vs waist to hip ratio (WHR), R=-0.434 (p<0.001).

Table 6.3

Comparison between patients with confirmed GHD and those without GHD. Fisher grading on admission was not available for eight patients. WFNS grading on admission was not available for four patients.
[a]Chi-square test; [b]t-test; [c]Mann-Whitney U test; [d]Fisher exact test

	GHD (n=14)	Not GHD (n=86)	p-value
M/F	7/7	24/61	0.13[a]
Mean Weight (kg)	88.3 ± 13.3	72.4 ± 14.2	**<0.0001[b]**
Mean BMI (kg/m2)	31.9 ± 3.9	26.6 ± 4.5	**<0.0001[b]**
Mean WHR	0.94 ± 0.07	0.88 ± 0.08	**0.008[b]**
Mean age at presentation (years)	52 ± 10	53 ± 10	0.73[b]
Mean time to screening (months)	34 ± 18	48 ± 32	0.25[c]
Mean age at screening (years)	55 ± 10	57 ± 10	0.66[b]
Procedure			0.11[d]
None	3	11	
Endovascular coiling	7	60	
Clipping	2	13	
Multiple Endovascular coiling	2	2	
Site of aneurysm			0.61[d]
Anterior Circulation			
Anterior communicating artery	3	24	
Middle Cerebral Artery	2	17	
Posterior communicating artery	3	15	
Internal Carotid Artery	0	7	
Pericallosal Artery	0	1	
Posterior Circulation			
Basilar Artery	1	5	
Posterior Inferior Cerebellar Artery	0	3	
Vertebral Artery	0	1	
Perimesencephalic	3	11	
Multiple Aneurysms	2	2	
WFNS			0.58[d]
1	10	59	
2	3	10	
3	0	4	
4	1	2	
5	0	6	
Fisher			0.57[d]
1	3	10	
2	2	13	
3	1	10	
4	4	35	
GOS			0.03[a]
4	5	10	
5	9	76	

6.6 Discussion

This is a large study assessing endocrine function in SAH patients with dynamic testing of pituitary function. After the initial GST, GHD was detected in 27% of patients which is consistent with other studies employing this test (19, 29). Additional testing with the arginine stimulation test, reduced prevalence of GHD detected in our cohort to 14% and the prevalence of hypopituitarism to 19%. This is consistent with more recent studies that incorporated confirmatory testing (18-20). This study also confirms that isolated GHD is the most common pituitary hormone deficiency post subarachnoid haemorrhage.

The retrospective method of recruitment in this study is likely to favour patients with better clinical outcomes and less severe SAH. This is reflected by the high proportion of survivors with good WFNS grade and GOS score at screening in our cohort and may not truly reflect the risk of hypopituitarism after severe SAH. However, this preponderance of patients with mild-moderate clinical severity and high proportion of treatment via the endovascular route is similar to other modern cohorts (19-21). It is noted however, that the radiological severity as measured by the Fisher grade in our cohort is less severe than other studies and this might confound our results. Perimesencephalic-type SAH is associated with good clinical outcome (30) and the inclusion of these patients (14%) in our analysis may additionally contribute to the low prevalence of GHD in our cohort.

As it was not compulsory for participants to undergo confirmatory testing of the somatotrophic axis if the QoL-AGHDA score was <11, it is possible that the prevalence of isolated GHD is slightly underestimated in our cohort. It is understandable that some participants who did not meet NICE criteria for GHR were reluctant to re-attend our centre for a second dynamic test, as they were not eligible for GHR. Additional factors such as poor mental and physical health were contributory factors for the poor compliance in this regard. However this does highlight one of the difficulties in conducting a 'real life' clinical study in this patient population and should be considered when planning further studies involving this patient group.

The variation in reported prevalence of hypopituitarism and GHD in the literature is most likely reflective of the heterogeneous endocrine tests used to diagnose hormonal deficiency, different time points of endocrine assessment and varying thresholds for defining GHD (23, 31, 32). Indeed, several of previous studies relied solely on low serum IGF-1 concentrations to diagnose GHD (13, 15, 33, 34), in spite of its limited diagnostic accuracy (35-37).

Additionally, even though isolated GHD is consistently reported as the most common deficiency post SAH, few studies confirm this with a second dynamic test (19-21). The potential to misdiagnose isolated GHD on a single dynamic test is well established (38) and as such it is likely that studies that have only relied on a single test may over-estimate the prevalence of GHD (14, 39). Studies that have employed dynamic pituitary tests and subsequent confirmatory testing report a lower prevalence of GHD of between 0 and 13.3% (19-21). Therefore the size of our study and the use of two different dynamic tests to confirm GHD strengthens the validity of our results.

The difference in terms of weight, BMI and WHR between patients with confirmed GHD and those with adequate GH response in our cohort, was statistically significant. Although it has been demonstrated that GHD in adults is associated with increased weight, body fat and central adiposity (40, 41), it is unclear if our findings are truly reflective of this and therefore causality cannot be assumed. The GST has been shown to overestimate GHD in overweight adults with no known pituitary disease (42). We have demonstrated an inverse correlation between the peak GH on GST and both BMI and WHR. Obesity is recognised as a confounder of GH response (42-44). The mechanism by which glucagon stimulates GH release is unclear, however it is not unreasonable to postulate that it may be affected by the metabolic consequences associated with weight gain and central adiposity.

Even other stimulatory tests, such as the Insulin Tolerance Test (ITT) and Growth Hormone Releasing Hormone (GHRH)-arginine stimulation test, show that GH response is BMI dependent (44, 45). It has even been suggested that waist circumference corrected cut-offs for GH peaks should be established (37) given that serum GH levels correlate inversely with WHR and abdominal fat in adults with no pituitary disease (46). Diagnosing GHD in the presence of obesity can therefore be very challenging, and an appreciation of this is vital to ensure that results are interpreted with caution.

Interestingly, no difference in BMI between patients who were hypopituitary and those with normal pituitary function was demonstrated by Gardner et al, who employed GHRH-arginine stimulation test with BMI-specific cut-offs in their cohort (19). It is noteworthy that studies that incorporate the GHRH-arginine stimulation test with its validated BMI-specific cut-offs report the prevalence of GHD to be only be as high as 10% (18, 19, 21). Kronvall et al 2014, using the GHRH-arginine test reported a 7% prevalence of GHD at 3-6 months and 25% at 12-24 months testing (47). However it is noted that at 12-24 months, patients were tested

with either the ITT or GHRH-arginine and this may account for the higher prevalence of GHD detected at that time point. There are studies that have reported higher frequency of GHD even when GHRH-arginine stimulation test was used, however these studies did not incorporate current validated BMI specific cut-offs when diagnosing GHD (16, 39). Therefore it is possible that GHD is also overestimated in our cohort, due to the limitations mentioned above. Further assessment of this cohort with a GHRH-arginine stimulation tests is recommended.

Like other studies, there was no association between development of GHD and clinical or radiological severity of SAH, GCS at presentation, age at presentation, treatment modality or the presence of vasospasm (2, 15, 16, 33) in this cohort.

Given the lack of clinical predictors of GHD in this patient population consensus guidelines recommend endocrine screening in all SAH survivors in whom there is an intention to treat (48, 49). However such a recommendation may have a significant impact on clinical practice. Routine screening for endocrine dysfunction in all SAH survivors with dynamic pituitary testing incurs a significant financial, logistic and work force requirement. Furthermore, such a screening process will subject a large number of patients to the unpleasant and on occasion detrimental side-effects associated with dynamic pituitary testing. Importantly, the value of detecting GHD in this patient population remains unclear, given that data regarding the impact or benefit of Growth Hormone Replacement in SAH survivors is scant. Lastly, uncertainty exists as to whether development of pituitary dysfunction after SAH is permanent. Several authors including a recent meta-analysis, have demonstrated that the prevalence of pituitary dysfunction including that of the somatotrophic axis, can change with time (14, 19, 22, 23, 29, 39, 47, 50). As such it remains unclear whether pituitary function should be continually re-assessed in SAH patients, and if so, at what time points.

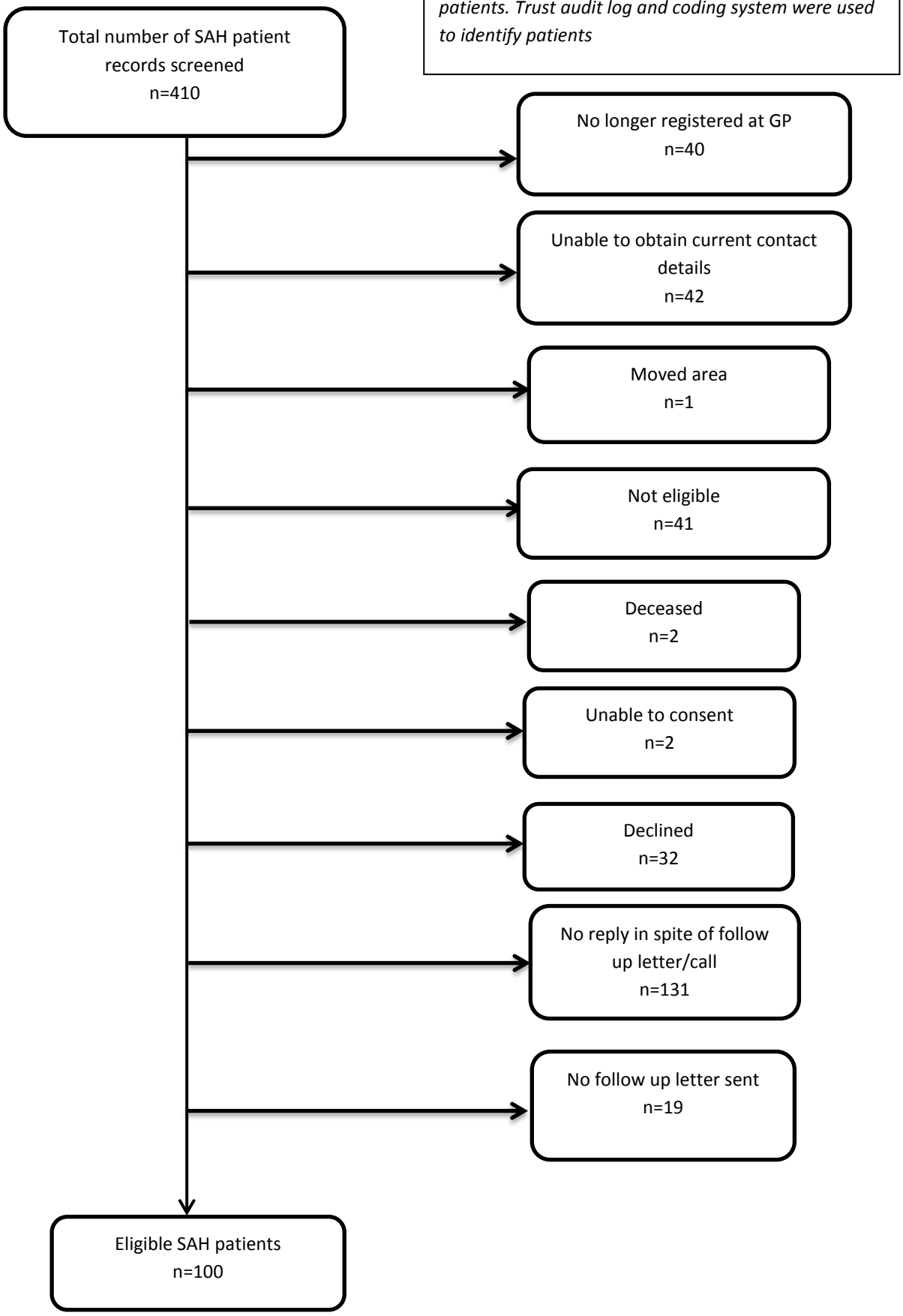
6.7 Conclusion

The prevalence of GHD in our cohort was 14%, when dynamic pituitary testing and confirmatory testing was employed. The varied prevalence reported in the literature is likely due to heterogeneous testing methods. Even though there was a significant difference in terms of BMI and WHR in patients with and without GHD, this may be due to the testing methodology employed. Further testing with protocols that incorporate BMI-specific cut-

offs are planned. Even though GHD is associated with worse quality of life as measured by the QoL-AGHDA score, there are no good clinical predictors of GHD. Although it is recommended that all SAH survivors be screened for endocrine dysfunction, this may not be always be feasible and has a substantial impact on resources. Further guidance is required as to which patients to assess, type of endocrine tests to use, timing of patient assessment and importantly which patients would derive clinical benefit from growth hormone testing and subsequently hormonal replacement.

6.8 Supplementary Figures

Supplementary Figure 6(a) Flow diagram showing identification and recruitment procedure for SAH patients. Trust audit log and coding system were used to identify patients



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Chapter 7

The Impact of Growth Hormone Replacement on Cardiorespiratory Fitness and Metabolic Parameters in Patients with Growth Hormone Deficiency Following Subarachnoid Haemorrhage

7 Chapter 7 The Impact of Growth Hormone Replacement on Cardiorespiratory Fitness and Metabolic Parameters in Patients with Growth Hormone Deficiency Following Subarachnoid Haemorrhage

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7.1 Preface

Some of the energy symptoms and metabolic changes seen in survivors of subarachnoid haemorrhage resemble that of adults with untreated growth hormone deficiency. Growth hormone replacement improves these changes in adults who have acquired growth hormone deficiency from other aetiologies. This chapter is a novel investigation into whether growth hormone replacement in patients who have developed growth hormone deficiency after subarachnoid haemorrhage experience an improvement in cardiorespiratory fitness and metabolic profile.

7.2 Abstract

Objective

To investigate if Growth Hormone Replacement (GHR) can improve cardiorespiratory fitness and metabolic parameters in patients who have developed Growth Hormone Deficiency (GHD) following Subarachnoid Haemorrhage (SAH).

Methods

Thirteen patients who had developed GHD after SAH were treated with GHR for 36 weeks. Weight, BMI, blood pressure, lipid profile, HbA1c and peak oxygen uptake was assessed before and after treatment.

Results

Prior to treatment, a correlation between the peak GH level achieved during screening GST and relative VO_2 peak achieved during cardiopulmonary testing was observed (r=0.558,

p=0.047). After 36 weeks of GHR, a significant reduction in weight (mean change -2.9 ± SD 3.5kg, p=0.012) and BMI (mean change -0.8 ± SD 1.2, p=0.015) was observed. During cardiopulmonary exercise testing, participants demonstrated a significant improvement in maximum speed achieved (mean change 0.28 ± SD 0.36km/hr, p=0.044), however improvement in relative VO_2 peak (mean change 2.23 ± SD 3.36ml/min/kg, p=0.053), total ambulatory time (mean change 1.40 ± SD 1.52min, p=0.108) and maximum gradient achieved (mean change 0.4 ± SD 2.6%, p=0.642) was not significant. No significant improvement in waist hip ratio or lipid profile was observed.

Conclusion

After 36 weeks of GHR, reduction in weight and BMI with improvement in some markers of cardiorespiratory fitness was observed. Larger studies involving this particular patient group are required to examine if these results are reproducible and whether GHR can be associated with long term health benefits in SAH patients who have GHD.

7.3 Introduction

Improved mortality in the immediate period after subarachnoid haemorrhage(SAH) due to developments in modern neurosurgical, neurovascular and intensive care techniques, has unmasked the long term consequences of this life changing event (1). Long term fatigue is reported in up to 90% of SAH survivors(2-5). It has been previously postulated that one of the contributors to fatigue post SAH is physical deconditioning due to reduced cardiorespiratory fitness(4). Recent data from the Hypopituitarism in Patients with Subarachnoid Haemorrhage (HIPS)-Rehab study has shown that cardiorespiratory fitness, including maximum oxygen uptake, is significantly reduced in SAH survivors as compared to controls, and that this was worse in patients who reported higher levels of fatigue(6).

Furthermore survivors of SAH remain at risk of further vascular events. The risk of both fatal and non-fatal vascular diseases in SAH survivors is increased with Standardised Mortality Ratio (SMR) for death from vascular events in young patients as high as 3.7 in spite of good functional recovery(7, 8) (9). It has been reported that SMR, on condition of survival at one year, is increased in SAH survivors as compared to the general population (1·57, 95% CI 1·32–1·82; p<0·0001)(10). This is mainly due to cerebrovascular and cardiovascular disease(11). Although this increased risk is often attributed to underlying predisposing

factors to SAH such as hypertension and smoking, it is possible that there are other metabolic alterations that might contribute to this.

Hypopituitarism and specifically growth hormone deficiency (GHD) is recognised as one of the sequalae of SAH with a reported prevalence of between 0-31%(12-15). It is established that adults with growth hormone deficiency from other causes exhibit an adverse metabolic profile including insulin resistance, dyslipidaemia and change in body composition including increased weight, central adiposity, increased fat, reduced lean body mass and reduced maximum oxygen consumption(16-18). Replacement with GH has a significant positive effect on overall exercise capacity, maximum power and maximum oxygen consumption in adults(19-25). Also growth hormone replacement (GHR) in these patients results in improved lipid profile, reduction in body fat (predominantly in the abdominal region) and increased lean body mass(16-18, 26-29).

It is therefore possible that growth hormone replacement (GHR) may ameliorate some of these symptoms and have a role in the rehabilitation process of SAH survivors who have GHD. Current consensus guidance, allows for GHR in SAH survivors who have developed GHD(30). However, data regarding the positive effects of GHR is derived primarily from patients who have developed GHD from tumours in the pituitary region or more recently from patients who have sustained traumatic brain injury(17, 18, 26, 31-35). As far as we are aware, there are no published studies evaluating the impact of GHR exclusively in SAH patients. Therefore it remains unclear if GHR can have a similar beneficial effect in patients who have developed GHD after SAH.

We therefore propose to investigate the effect of GHR on cardiorespiratory fitness and metabolic parameters in patients with Growth Hormone Deficiency following subarachnoid haemorrhage.

7.4 Patient and Methods

Patient Recruitment

This was a single-centre, prospective study. Patients who received treatment for SAH at our centre between 2006 and 2014 were invited to participate. A total of 100 patients were screened for growth hormone deficiency (GHD) based on clinical protocol previously published using glucagon stimulation testing (GST) and arginine stimulation testing

(AST)(36). In accordance with national guidance, patients qualified for growth hormone replacement (GHR) if they had biochemical evidence of severe GHD in association with impaired quality of life as measured by the QoL-AGHDA score (score≥11)(37). Given the requirement for cardiopulmonary exercise testing (CPET), it was required that all patients were able to mobilise independently. This study was approved by NRES Committee North West – Greater Manchester West (Reference 14/NW/0191). All participants were required to provide written informed consent prior to study enrolment.

Study Protocol

Prior to treatment with GHR, all patients were required to undergo a series of baseline investigations including weight, height, waist circumference, hip circumference and blood pressure measurement. Blood samples were taken for assessment of metabolic profile. All patients were required to undergo cardiopulmonary exercise testing (CPET) in the form of a graded treadmill test. Patients were commenced on GHR and reviewed at weeks 4, 8, 12, 24 and 36 for monitoring and dose titration. At each visit weight and blood pressure were monitored and serum IGF-1 level was measured. Patients received GHR for 36 weeks. At the end of this period all baseline investigations were repeated. During the study period patients were given a diary to document any side-effects, medication changes by other healthcare providers or new diagnosis.

Metabolic Parameters

Fasting blood samples were taken for lipid profile, glucose and HbA1c. Body weight was measured to the nearest 0.1kg using a Marsden weighing scale. Height was measured to the closest 0.5cm. Body mass index (BMI) was then calculated. Waist and hip circumference were measured to the closest 0.5cm and the waist to hip ratio was then calculated.

Cardiorespiratory Fitness and Cardiopulmonary Exercise Testing

The protocol used for the treadmill test was the Modified Balke protocol. Currently, there is no exercise testing protocol that is validated in the SAH population. The Modified Balke protocol has been used in patients recovering from traumatic brain injury (TBI) and has been shown to be reliable in the TBI population(38). Given the varying degree of mobility and balance impediments in SAH patients, this protocol, that enabled speed to be determined on an individual basis, was deemed safe and suitable for our patient group.

Using this protocol, patients started with a 2 minute warm up at 1% incline, during which the treadmill speed was slowly increased to a comfortable walking speed for the patient. Once the test started, the treadmill speed was kept at a constant while workload was increased by increasing the treadmill incline by 2% every minute. Patients were exercised to volitional exhaustion and termination of the test only occurred if the patient requested to stop due to exhaustion or study doctor deemed it unsafe to continue. The maximum incline possible on the treadmill was 15%, therefore if patients did not achieve exhaustion at the maximum incline, the speed was then increased.

Prior to each test, the flow sensor was calibrated according to manufacturer instructions. The bi-directional digital turbine system was calibrated using a 3-litre calibration syringe and the system was calibrated using certified gases of known concentrations (Oxygen: 5%, Carbon Dioxide:16%). Expired gas was measured continuously over the exercise period and averaged over 15 seconds (Quark CPET, Cosmed, Rome, Italy). The highest value was used recorded as VO_2 peak and relative VO_2 peak per kg body weight was obtained. Heart rate was monitored by a heart rate belt (Polar heart rate monitor) fitted around the thorax. It is assumed that if patients are exercised to exhaustion, VO_2 will plateau and as such peak oxygen uptake (VO_2 peak) can be calculated. Data regarding walking speed, maximum incline achieved and total ambulatory time (TAT) was also gathered.

At the post-treatment visit, patients were required to start the test at the same speed they had set during baseline testing. All testing procedures were carried out in the presence of the study physician and study physiotherapist.

Growth Hormone Replacement and Monitoring

Growth Hormone Replacement was commenced in accordance with current clinical guidelines(37). Men were started at a dose of 0.2mg daily and women were started at a dose of 0.3mg daily. Dose was titrated to achieve serum IGF-1 levels in the upper third of the age and gender specific reference range. At each study visit, patients were monitored for any side-effects of GHR.

Statistical Analyses

Data analysis was carried out using IBM SPSS Statistics 22 (IBM SPSS Statistics for Windows, Version 20 NY, USA; 2011). Descriptive statistics is used to present baseline demographics. Continuous data were analysed using the Independent t-test or Mann-Whitney U test.

Categorical data were analysed using the Chi squared test or Fisher exact test. When three or more groups were compared, analysis of variance was used. To compare pre and post-treatment data, the paired t-test was used. A two-tailed p-value of <0.05 was considered statistically significant.

7.5 Results

Patient Characteristics

After screening one hundred (100) patients with dynamic testing of somatotrophic axis, thirteen patients (7 female) qualified to receive treatment with GHR. Mean age at time of starting GHR was 56 years (range 32 to 73 years). In most patients, site of aneurysm rupture was located in the anterior circulation (69.2%) and in the majority of patients treatment was via the endovascular route (61.5%). Clinical and radiological severity of SAH is detailed in Table 7.1.

Two patients were on other hormone replacement. One patient was diagnosed with Klinefelter's syndrome during the screening phase. He was commenced on testosterone replacement 3 months prior to starting GHR. One patient was already established on oestrogen therapy prior to participation in the study and this was continued during the study period.

Furthermore, one patient was diagnosed with new onset diabetes mellitus during screening. He required optimisation of his glycaemic control during the study period including commencement of a Sodium Glucose Cotransporter-2(SGLT-2) inhibitor therapy and this may have influenced blood pressure results. Otherwise no other patients received any new medication that may have impacted blood pressure, glycaemic control or lipid prolife during the study period. Two patients declined to complete the exercise testing procedure at the end of the 36 week period. Of note, Glasgow Outcome Score (GOS) for both these patients was 4.

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Patient number	Gender	Age (years)	Age at time of SAH (years)	Relevant Co-morbidities	Lipid Lowering Therapy	Antihypertensive therapy	Antidiabetic therapy	Site of aneurysm	Management of Aneurysm	WFNS	Fisher Grade	GOS score	Weight (kg)	BMI (kg/m2)	Waist Hip Ratio	Other hormone replacement
1	F	64		Hypercholestrolaemia	N	N	N	Basilar	Endovascular coiling	1	4	5	70.1	24.5	0.90	N
2	M	49		HTN, Hypercholestrolaemia	N	Y	N	Anterior Communicating Artery	Endovascular coiling	1	1	5	100.2	37.5	1.04	N
3	M	49		HTN, Diabetes	N	Y	Y*	Internal Carotid Artery and Anterior Communicating Artery†	Endovascular Coiling‡	1	1	4	91.5	29.7	0.99	N
4	M	32		HTN, Klinefelters syndrome**	N	N	N	Posterior Communicating Artery	Endovascular Coiling	1	Unavailable	5	95.6	29.5	0.97	Y*
5	F	54		HTN	N	Y	N	Posterior Communicating Artery	Endovascular Coiling	1	4	5	107.9	40.1	0.88	N
6	M	55		HTN, Hypercholestrolaemia	Y	Y	N	Middle Cerebral artery	Surgical Clipping	2	3	4	97.5	31.5	1.02	N
7	F	63		NA	N	N	N	Perimesencephalic	None	1	Perimesencephalic	5	90.9	35.0	0.93	N
8	F	55		HTN, Hypercholestrolaemia, Primary Hypothyroidism	N	Y	N	Anterior Communicating Artery	Endovascular Coiling	2	4	4	67.5	29.1	0.95	Y**
9	M	65		HTN, IHD, AF	Y	Y	N	Perimesencephalic	None	1	Perimesencephalic	5	96.6	32.7	1.07	N
10	F	61		HTN, Hypercholestrolaemia	Y	Y	N	Posterior Communicating Artery	Endovascular Coiling	1	1	4	72.9	30.7	0.99	N
11	F	52		NA	N	N	N	Perimesencephalic	None	1	Perimesencephalic	5	79.1	33.3	0.90	N
12	F	53		HTN	N	Y	N	Anterior Communicating Artery and Basilar Artery†	Endovascular Coiling‡	1	2	5	79.7	30.4	0.96	N
13	M	73		NA	N	N	N	Anterior Communicating Artery	Surgical Clipping	2	2	5	85.5	28.1	0.93	N

Table 7.1.

Baseline characteristics of study patients *Patient diagnosed with diabetes at study screening **Patient diagnosed with Klinefelter's syndrome during study screening phase †Multiple aneurysm, unable to identify site of bleeding ‡Multiple coiling procedures

Cardiorespiratory fitness

There was a positive correlation between peak GH achieved on screening GST(mcg/L) and relative VO_2 peak(ml/min/kg) prior to GH treatment (r=0.558, p=0.047) (Figure 7.1). Complete pre and post treatment maximum oxygen uptake results were available for 11 patients. After 36 weeks of treatment with GHR, during CPET there was a 9.3% improvement in maximum speed achieved (mean change 0.28 ± SD 0.36km/hr, p=0.044), however improvement relative VO_2 peak (mean change 2.23 ± SD 3.36ml/min/kg, p=0.053), total ambulatory time (mean change 1.40 ± SD 1.52min, p=0.108) and maximum gradient achieved (mean change 0.4 ± SD 2.6%, p=0.642) was not significant. Pre and post treatment markers of cardiorespiratory fitness were not significantly associated with site of aneurysm, aneurysm treatment procedure, Fisher Grade, WFNS score or GOS score.

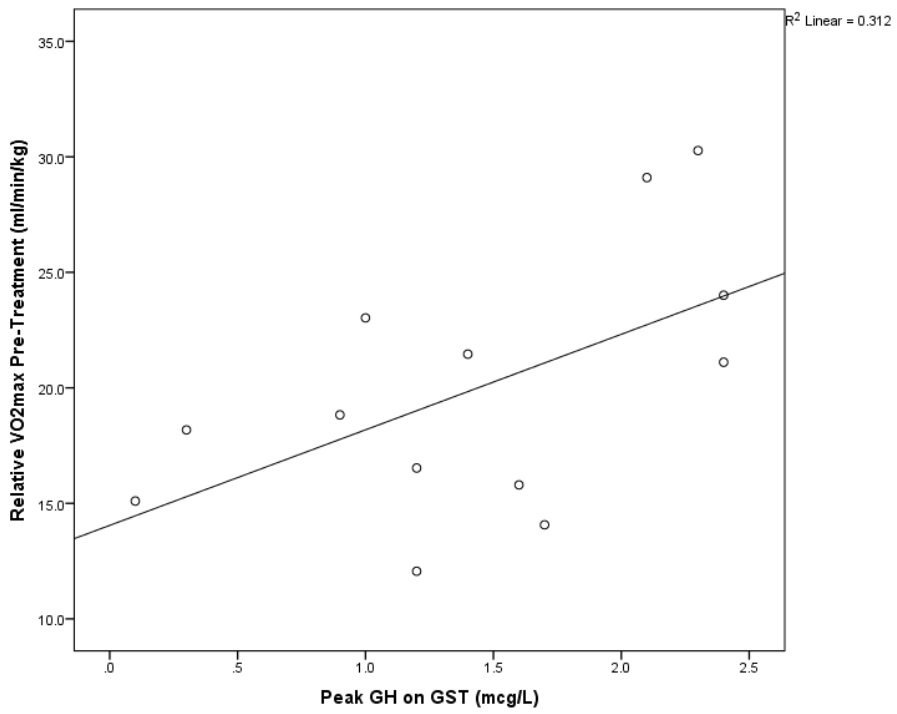

Figure 7.1. Graph showing correlation between Pre-Treatment Relative VO2max (ml/min/kg) and Peak Growth Hormone Level achieved during screening Glucagon Stimulation Test (GST). (r=0.558, p=0.047).

Table 7.2.
Pre and Post-Treatment Cardiorespiratory Testing Results. Results exclude two participants who declined repeat CPET testing.

	Mean Pre-Treatment	Range Pre-Treatment	Mean Post-Treatment	Range Post-Treatment	Δ Mean	95% Confidence Interval	Δ Mean (%)	P-value
VO2max (ml/min)	1900.3 ± SD 606.2	1084 – 2983	2039.5 ± SD 469.5	1498 – 3049	139.2 ± SD 264.0	-38.2 – 316.5	7.33	0.111
VO2max (ml/min/kg)	20.94 ± SD 5.51	16.35 – 30.43	23.17 ± SD 4.57	12.06 – 30.27	2.23 ± SD 3.36	0.03 – 4.49	10.65	0.053
TAT (min)	9.4 ± SD 4.39	6.00-17.00	10.8 ± SD 4.65	5.00 – 18.00	1.40 ± SD 1.52	-0.48 – 3.28	14.89	0.108
Maximum Gradient (%)	13.0 ± SD 2.6	7-15	13.6 ± SD 2.5	9-15	0.4 ± SD 2.6	-1.5- 2.3	2.99	0.642
Maximum Speed (km/hr)	3.01 ± SD 0.85	2.0 -4.2	3.3 ± SD 0.99	2.0 -4.8	0.28 ± SD 0.36	0.01-0.57	9.30	**0.0436**

Metabolic parameters

At baseline there was a gender difference in terms of weight (men vs women, 94.8 vs 81.2kg, p=0.049) and WHR (men vs women, 1.00 vs 0.93, p=0.012). There was no significant correlation between peak GH on GST and pre-treatment weight (r=0.102, p=0.740), BMI (r=0.097, p=0.751) or WHR (r=0.008, p=0.978).

Table 7.3 displays the changes in metabolic parameters before and after treatment with GHR. After 36 weeks of GHR, significant difference was observed for reduction in weight (mean -2.9kg ±SD 3.5, p=0.012), with subsequent change in BMI (mean -0.8 ± SD 1.2, p=0.015). We note greatest weight loss occurred in the youngest patient in our cohort (13.2kgs), however even when this patient was excluded, the weight loss remained statistically significant (mean 2.0± SD 1.7kg, p=0.002) in the cohort. There was a reduction in systolic blood pressure (mean -6mmHg ± SD 10, p=0.044), however if the patient who received a SGLT2 inhibitor during the study period was excluded, this reduction was no longer significant (p=0.091). Change in HDL-C and HbA1c was not significant.

There was a negative correlation between age and percentage of weight loss after 36weeks on GHR (r=-0.671, p=0.012)(Figure 7.2). Pre and post treatment metabolic variables were not associated with site of aneurysm, aneurysm treatment procedure, Fisher Grade, WFNS score or GOS score.

Table 7.3.

Pre and Post Treatment Results for Metabolic Parameters. A statistically significant decrease in weight and BMI was observed. Reduction in systolic blood pressure was no longer significant after excluding the patient who received SGLT2 inhibitor therapy during the study period.

**Measurements from 12 patients*

***Measurements from 11 patients*

	Mean Pre-treatment	Mean Post-Treatment	Mean Change	P-value
Weight (kg)	87.5± SD 12.8	84.6 ± SD 12.2	-2.9 ± SD 3.5	**P=0.012**
BMI (kg/m2)	31.7 ± SD 4.0	30.9 ± SD 4.2	-0.8 ± SD 1.2	**P= 0.015**
WHR	0.964 ± SD 0.06	0.960 ± SD 0.06	0.004 ± SD 0.04	P=0.793
Systolic BP	131 ± SD 13	125 ±SD 17	-6 ± SD 10	**P=0.044**
Diastolic BP	82 ± SD 5	80 ± SD 7	-2 ±SD 5	P=0.211
Total Cholesterol*	5.1 ± SD 1.2	5.2 ± SD 1.3	0.1 ± SD 0.6	P= 0.58
HDL-C*	1.21 ± SD 0.25	1.32 ± SD 0.42	-0.11 ± SD 0.18	P=0.063
Cholesterol/HDL-C*	4.3 ± SD 1.1	4.2 ± SD 1.4	0.17 ± SD 0.76	P=0.466
HbA1c **	40.4 ± SD 7.6	40.6 ± SD 9.1	0.2 ± SD 2.8	P=0.828

7.6 Discussion

As far as we are aware, this is the first study to assess the effect of GHR on cardiorespiratory fitness and metabolic parameters exclusively in SAH survivors. Prior to treatment with GHR there was a positive correlation between the relative VO_2 peak achieved during baseline CPET and peak serum GH level at screening GST in our cohort. This is consistent with the effect of GHD on cardiorespiratory fitness in patients who have acquired GHD from other aetiologies(20, 22, 25, 34). As such, low levels of GH, may further compound impaired cardiorespiratory fitness in SAH survivors with GHD.

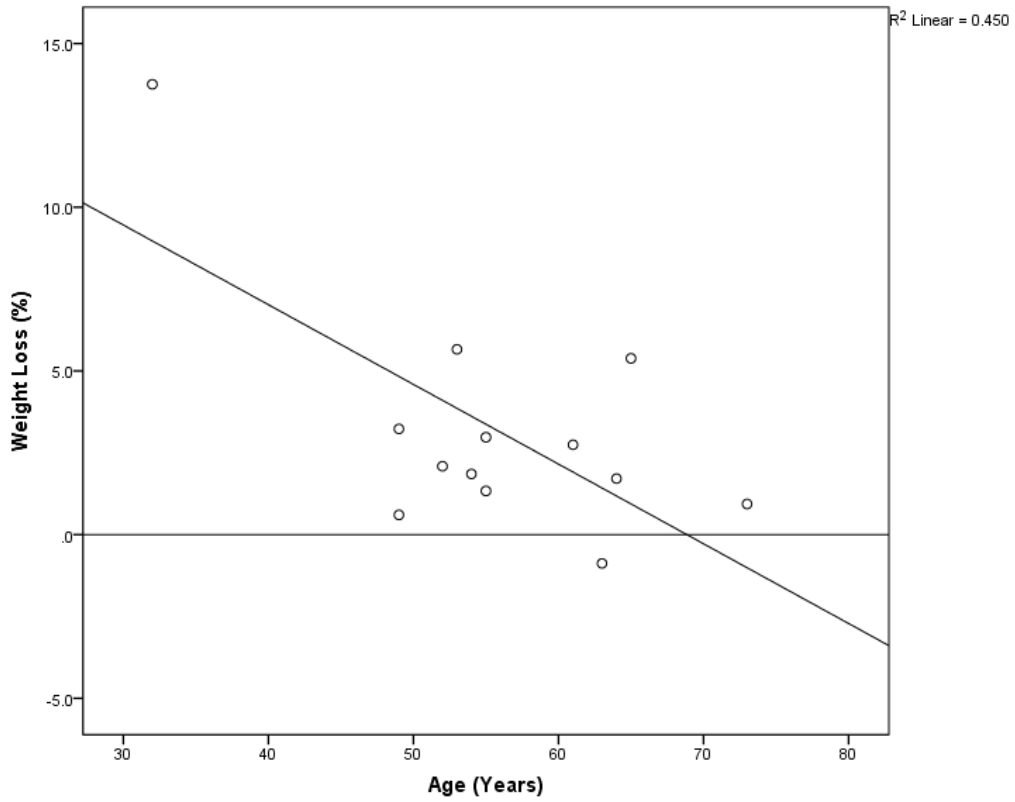

Figure 7.2. Graph showing correlation between percentage weight loss during study period and patient age. (r=-0.671, p=0.012)

After 36 weeks of treatment with GHR, we observed significant improvement in maximum speed achieved (9.3%) during CPET. Improvement of $VO_{2\ peak,}$ total ambulatory time and maximum gradient achieved was not statistically significant. Again we are not aware of any publications reporting on interventions that improve cardiorespiratory fitness in SAH patients. In the TBI and ischaemic stroke population, adoption of a dedicated exercise training programme alone can improve cardiorespiratory fitness however these studies were not designed to tease out the effect GH status on fitness(39-41). Whether or not exercise training in isolation can have the same impact on SAH patients with GHD is unknown. Regardless, from this study we have demonstrated that there is potential to improve some parameters of cardiorespiratory fitness in SAH survivors with GHD and these changes can be demonstrated over a 36 week period.

Although previous analysis of the KIMS database (a pharmoco-epidemiological survey of hypopituitary adults with GHD) did now show any significant change in BMI for the cohort in total with one year of GHR, a significant reduction was demonstrated in patients with BMI>30(-0.3±1.9kg/m2, p<0.05)(26). The mean BMI at baseline in our cohort was 31.7kg/m2 and we observed a mean reduction in BMI of 0.8 ± SD 1.2kg/m2 (p=0.015) after 36 weeks of treatment.

Reduction in weight was not mirrored by improvement in WHR in this cohort. Nevertheless, it may be that measurement of WHR in isolation is insensitive to mild alterations of body composition in our population, and more formal methods of measuring body fat and lean body mass are required. Additionally previous studies in the pituitary population, demonstrating reduced WHR, total body fat and improved lean body mass and lipid profile with GHR, used GHR at higher doses as compared to our study(18, 42, 43). In the pituitary population, replacement with physiological doses of GHR is associated with more modest changes in body composition(44).

Crucially, most patients in our cohort did not require supplementation with other hormones, with GHD being the only deficiency detected. Recent analysis of the Dutch National Registry of GH Treatment in Adults revealed that patients with isolated GHD (IGHD) demonstrated milder impairment in metabolic profile as compared to patients with multiple pituitary hormone deficiency (MPHD)(31) Significant improvement in body composition and lipid profile is mainly observed in patients with multiple pituitary hormone deficiency (MPHD)(18, 22, 26, 27). Conversely, patients with isolated GHD (IGHD) exhibit less of an improvement with GHR than patients with MPHD(31, 45). The lack of change in WHR and lipid profile in our cohort therefore may be reflective of this. Nonetheless, it is not unreasonable to postulate that the changes in BMI themselves will have consequences on the long term cardiovascular risks for these patients.

From this, it is clear that there is the potential to improve cardiorespiratory fitness and BMI in SAH survivors who have GHD. However it is not possible to quantify how much of this is due to GHR, given several limitations of this study.

Firstly the lack of a control group is a weakness of our study. We cannot exclude the possibility of a placebo-effect accounting for the results observed. However it is important to appreciate the feasibility of enrolling a control group of patients, including the ethics of

administrating placebo in this specific patient group especially given that national guidelines already allow for GHR in this patient population. As highlighted by previous authors, randomised controlled trials involving GH treatment are unethical and impractical(31) (44). With specific reference to fitness, it is noteworthy that no patients participated in a regular exercise programme during the study period. Although it is likely that frequent engagement with the same study physician during the trial period is likely to increase motivation, it is not clear whether this in itself can account for the magnitude of improvement in physical endurance observed.

Secondly, the sample size of this study may not have been adequate to detect minor changes in metabolic parameters during the study period. SAH in itself is a relatively infrequent event(46) and furthermore the incidence of GHD in SAH survivors is not high. To be able to recruit enough patients for a sufficiently powered study with a control arm will require screening of a large amount of patients with SAH (in our cohort 100 patients underwent dynamic testing of somatotrophic axis), which is virtually impossible in a single neurosurgical centre. Undoubtedly this will incur significant burden on finances and resources.

Frequently it is recommended that two baseline exercise tests are carried out to account for the effect of learning(47), yet it has been shown that this is not always necessary(48, 49). Given the relatively long interval between testing procedures, the effect of learning is likely to be minimal on cardiorespiratory parameters in our study population. Furthermore the difficulty and safety of carrying out exercise testing, what more repeatedly in the SAH population must be appreciated. Not only do these patients frequently have mild physical impediments such as impaired balance, altered gait and high levels of fatigue, they also commonly suffer from low mood and high levels of anxiety, making the treadmill procedure very challenging. Both patients who declined repeat exercise testing in our cohort, cited this procedure as being too strenuous.

Lastly, the clinical and radiological severity of SAH in our patient population was relatively mild. As such it is possible that the baseline cardiorespiratory fitness and metabolic

parameters is overestimated in our study population. Given this, it is possible that the impact of GHR is also underestimated.

In spite of some of the limitations, there are several significant findings from this study that are necessary to report. We are not aware of any interventions in the SAH population that demonstrated a similar impact as that observed in our cohort. The effect of GHR in this patient population not only has the potential to improve health but also consequently day-to-day functioning and overall quality of life.

7.7 Conclusion

In this cohort, severity of GHD (as measured by GST) is correlated with baseline cardiorespiratory fitness. After 36 weeks of GHR, there were improvements in some metabolic markers in our cohort. Limitations in our study did not make it possible to draw firm conclusions about the effect of GHR in this patient population, however fortifies the need for further larger studies assessing the effectiveness of GHR in improving metabolic and cardiorespiratory fitness in SAH patients. GHR could have a potentially vital role in the rehabilitation process of SAH patients with GHD.

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Chapter 8

The Impact of Growth Hormone Replacement on Quality of Life and Mood in Patients with Growth Hormone Deficiency Following Subarachnoid Haemorrhage.

8 Chapter 8 The Impact of Growth Hormone Replacement on Quality of Life and Mood in Patients with Growth Hormone Deficiency Following Subarachnoid Haemorrhage.

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8.1 Preface

Even though there is an increasing appreciation that quality of life and mood remains impaired in survivors of subarachnoid haemorrhage, there is a lack of knowledge about interventions that can improve this. Some of the mood and psychosocial symptoms reported by SAH patients, resemble that of adults with untreated growth hormone deficiency. Although Growth Hormone Replacement can ameliorate these symptoms in adults with growth hormone deficiency from other aetiologies, whether this is possible in SAH patients is unclear. This chapter will investigate if Growth Hormone Replacement can improve perceived quality of life and mood in patients who have developed growth hormone deficiency after subarachnoid haemorrhage.

8.2 Abstract

Objective

To investigate if Growth Hormone Replacement (GHR) can improve Quality of Life (QoL) and mood in patient who have developed Growth Hormone Deficiency (GHD) after Subarachnoid Haemorrhage (SAH).

Methods

After screening 100 SAH patients, 13 patients qualified for treatment GHD. Patients were treated with GHR for 36 weeks. Quality of life and mood was assessed before and after GHR. This was assessed using QoL-AGHDA questionnaire, WHO-QoL Bref questionnaire and the HADS questionnaire. Patients without GHD were required to complete QoL-AGHDA questionnaire at baseline and again at 36 weeks to provide a comparator group.

Results

Prior to treatment, there was a negative correlation between peak GH achieved during screening GST and QoL-AGHDA questionnaire in patients with GHD (r= -0.596, p=0.032). After 36 weeks of GHR, patients with GHD demonstrated improvement in QoL-AGHDA score (mean change -10 ± SD 8, p=0.001), WHO-QoL Bref Physical Health Domain score (pre vs post-treatment, 10 ± SD 3 vs 13 ± SD 3, p=0.015), Psychological Health Domain score (pre vs post-treatment, 11 ± SD 2 vs 14 ± SD 2, p=0.018) and Social Relationships Domain score (pre vs post-treatment, 11 ± SD 4 vs 16 ± SD 4, p=0.024). When compared to patients without GHD, improvement in QoL-AGHDA score remained significant (mean score after 36 weeks GHD vs control, 10 vs 15, p<0.001). Improvement in HADS depression score was also demonstrated (pre vs post-treatment 10± SD 4 vs 6± SD 6, p=0.016).

Conclusion

GHR is associated with improved perception of quality of life and mood in patients with GHD after SAH. As far as we are aware no other intervention has been reported to cause a similar effect in SAH survivors. Clinicians should be encouraged to screen symptomatic patients for GHD.

8.3 Introduction

Improved survival in patients with subarachnoid haemorrhage over the past three decades (1) due to the introduction of neurovascular procedures and enhanced neurointensive care, has unveiled the long term sequalae of this life changing event. It is now well recognised that despite minimal physical disability and favourable neurological outcome as measured by the GOS and MRS, impaired quality of life is experienced by a significant proportion of survivors(2-5). Discrepancy between the clinicians impression of 'good clinical outcome' versus that of the patients and carer clearly exists(6). Although only 5-10% of SAH survivors report physical disability(7), impaired health related quality of life (HRQoL) is detected in up to 55% of patients(8). A meta-analysis revealed that predictors such as age, gender, severity of SAH and clinical severity at time of admission to hospital had a negligible effect on patient reported health related quality of life(8).

The prevalence of depression post SAH is between 33%- 47%(2, 9-11) and is higher than in age matched controls(10). Between 27% and 54% of survivors suffer from anxiety(11, 12) with post-traumatic stress disorder (PTSD) becoming increasingly recognised in this patient

group(13-15). The prevalence of both anxiety and PTSD is higher than that of the general population. More importantly anxiety and depression in the SAH population is not correlated to the degree of physical disability, but are predictors of poor functional outcome(15-17).

Hypopituitarism is increasingly recognised as a consequence of SAH with GHD being the most common hormone deficiency. Strikingly the cognitive, emotional and psychosocial consequences in SAH survivors resemble that of patients with untreated hypopituitarism, specifically untreated GHD(18).

Since the seminal publication of McGauley et al., (1989)(19) it is now well established that growth hormone deficiency in adults is associated with impaired quality of life as compared to matched controls in the population(20-23). Adults with GHD also suffer higher levels of anxiety and depression as compared to the general population(20, 24-26). Replacement of growth hormone in adults has been shown to improve quality of life(27). Additionally alleviation of mood symptoms is seen with GHR(28, 29).

Although it may be possible that there is a cohort of SAH patients who may benefit from GHD, the evidence for GHR in adults is mainly derived from patients who have developed GHD from pituitary tumours of the treatment thereof. Unlike pituitary tumours, subarachnoid haemorrhage is a sudden, potentially life threatening catastrophe that requires urgent treatment. High levels of post-traumatic stress disorder is detected in this patient population, which is probably due to a combination of experiences surrounding diagnosis, but also on-going anxiety about recurrent events(13-15). There is no doubt that this contributes to impaired mood and poor perception of quality of life in these patients(15). As far as we are aware there are no published studies to date assessing the impact of GHR exclusively in SAH survivors. Given all of this, whether patients with SAH will experience these same benefits of GHR as other patients is unknown. Despite of this lack of evidence, in the United Kingdom, GHR is indicated in this patient population when GHD is present to improve quality of life. We therefore propose to assess the impact of GHR on quality of life or mood in SAH survivors with GHD.

8.4 Subjects and Methods

Patient recruitment

This is a single centre prospective study assessing the impact of Growth Hormone Replacement(GHR) in patients newly diagnosed with Growth Hormone Deficiency (GHD) following Subarachnoid Haemorrhage (SAH). Patients who sustained a SAH between 2006 and 2014 were invited to participate. A total of one hundred patients were screened for growth hormone deficiency using the glucagon stimulation test (GST) and the arginine stimulation test (AST) to confirm isolated GHD. Details about the screening procedure are presented in a separate publication. From this screening protocol, 13 patients qualified for GHR.

To comply with national guidelines, patients were included if they scored ≥11 points on the QoL-AGHDA questionnaire at screening visit. If other hormone deficiencies were detected, this was replaced (where appropriate) and patients were required to be on stable hormonal replacement for at least 3 months prior to commencing GHR.

Methods

Prior to commencing GHR, all subjects were required to complete assessments of quality of life (QoL) and mood at baseline. Quality of life was assessed by completion of the QoL-AGHDA questionnaire and the WHO-QoL Bref questionnaire. The Hospital Anxiety and Depression Scale (HADS) was used to assess mood.

GHR was commenced at a dose of 0.2mg/day subcutaneously in males and 0.3mg/day subcutaneously in women in keeping with current guidance. Dose of GH was titrated with the aim of keeping the serum IGF-1 in the upper third of the age and gender specific reference range, if tolerated by the patient. All patients received treatment with GHR for a period of 36 weeks in keeping with national clinical practice guidelines(30). After commencing GHR patients were reviewed by the clinician at week 4, 8, 12, 24 and week 36. Patients were assessed for side-effects of GHR and subject diary was reviewed to determine compliance with treatment as well as any new medication or health conditions since the previous visit.

At the end of the 36 weeks on GHR, all patients were required to complete the QoL-AGHDA questionnaire, WHO-QoL Bref questionnaire, and HADS questionnaire. In keeping with national guidance, if patients demonstrated an improvement on the QoL-QGHDA

questionnaire by at least 7 points, continued treatment with GHR after completion of the study was offered. These patients were referred to the Department of Endocrinology at Salford Royal NHS Foundation Trust for on-going follow-up and monitoring of GHR after the end of the study period.

Patients with normal GH levels detected during the screening phase were requested to complete a QoL-AGHDA questionnaire, 36 weeks after their original study visit. This was to control for the possible change in QoL-AGHDA score over time.

Assessment of Quality of Life Assessment

The QoL-AGHDA questionnaire (Quality of Life Assessment of Growth Hormone Deficiency in Adults) is a validated disease-specific questionnaire used to assess the impact of growth hormone deficiency on quality of life in adults. It compromises 25 questions with a 'yes' or 'no' response and a higher score indicates a worsening impairment of quality of life. In the United Kingdom, GHR is indicated in adults with severe GHD who score ≥11 on QoL-AGHDA questionnaire(30).

WHO-QoL Bref questionnaire is an abbreviated version of the WHO-QoL 100 questionnaire, which is designed to assess a patient's perception of their well-being. This self-administered questionnaire contains 26 items and has been demonstrated as a reliable method of assessing quality of life in the SAH population(31). Raw scores for each domain were transformed to 4-20 scores according to guidelines, making this comparable to WHO-QoL 100. Given the impact of GHR specifically in energy and sleep, questions assessing both these domains were reviewed separately as well.

Assessment of Mood

Hospital Anxiety and Depression (HADS) Questionnaire is a validated questionnaire that allows the clinician to detect symptoms of anxiety or depression in patients(32, 33). It contains 14 items; 7 pertaining to anxiety and 7 pertaining to depression, and is self-administered by the patient.

Statistical Analyses

Data analysis was carried out using IBM SPSS Statistics 22 (IBM SPSS Statistics for Windows, Version 20 NY, USA; 2011). Descriptive statistics is used to present baseline demographics. Non-categorical data were analysed using the Independent t-test or Mann-Whitney U test. Categorical data were analysed using the Chi-squared test or Fisher exact test. Where three

or more groups were compared, analysis of variance was used. To compare pre and post-treatment data, the paired t-test was used. To compare outcomes from treatment group and control group, ANCOVA analysis with Bonferroni correction was used. A two-tailed p-value of <0.05 was considered statistically significant.

8.5 Results

Patient Characteristics

After screening one hundred (100) patients with dynamic testing of somatotrophic axis, thirteen patients (7 female) qualified to receive treatment with GHR. Mean age at time of starting GHR was 56 years (range 32 to 73 years). In most patients, site of aneurysm rupture was located in the anterior circulation (69.2%) and in the majority of patients treatment was via the endovascular route (61.5%). Clinical and radiological severity of SAH is detailed in Table 8.1.

Two patients received other hormone replacement. One patient was diagnosed with Klinefelter's syndrome during the screening phase and was commenced on testosterone replacement prior to GHR. One patient was post-menopausal and already on oestrogen therapy prior to participation in the study. This was continued during the study period. None of the patients were commenced on mood altering or sleep enhancing medication during the study period. A total of thirty-two patients (32) with normal GH levels returned the repeat QoL-AGHDA after 36 weeks.

Weight and BMI

At baseline there was a gender difference in terms of weight (men vs women, 94.8 vs 81.2kg, p=0.049) but not BMI (men vs women, 31.5 ± SD 3.4 vs 32.0 ± SD 4.7, p=0.843). After 36 weeks of GHR, statistically significant difference was observed for change in weight (mean -2.9kg ±SD 3.5, p=0.012), with subsequent change in BMI (mean -0.8 ± SD 1.2, p=0.015) (Table 8.2). We note greatest weight loss occurred in the youngest patient in our cohort (13.2kgs), however even when this patient was excluded, the weight loss remained statistically significant (mean 2.0± SD 1.7kg, p=0.002).

QoL-AGHDA score

At baseline, patients with GHD had higher QoL-AGHDA score than patients without GHD (mean score GHD vs control, 20 vs 16, p=0.015). In patients with GHD, there was a significant negative correlation between peak GH achieved during GST and baseline QoL-AGHDA score (r= -0.596, p=0.032) (Figure 8.1). After 36 weeks of treatment with GHR, there was a statistically significant improvement in QoL-AGHDA score in patients with GHD (mean change -10 ± SD 8, p=0.001) (Table 8.2).

QoL-AGHDA scores after 36 weeks revealed a significant improvement in patients who had received GHR as compared to the control group (mean score after 36 weeks, GHD vs control, 10 vs 15, p<0.001).

There was no significant correlation between change in weight and change in QoL-AGHDA score after 36 weeks of GHR. On univariate analysis there was no statistically significant difference for both pre and post-treatment AGHDA score in terms of gender, site of aneurysm, treatment modality, Fisher grade, WFNS score and GOS score.

WHO-QoL Bref Score

At baseline, in patients with GHD, there was a positive correlation between peak GH achieved during GST and pre-treatment WHO-QoL Bref Energy Score (r=0.623, p=0.023). Prior to treatment with GHR, women demonstrated lower scores in the Psychological Health Domain (women vs men, 8 ± SD 4 vs 12 ± SD 2, p=0.041) and Social Environment Domains (women vs men, 7 ± SD 4 vs 14 ± SD 2, p=0.005) as compared to men.

After 36 weeks of treatment with GHR, there was significant improvement in WHO-QoL Bref Physical Health Domain score (pre vs post-treatment, 10 ± SD 3 vs 13 ± SD 3, p=0.015), Psychological Health Domain score (pre vs post-treatment, 11 ± SD 2 vs 14 ± SD 2, p=0.018) and Social Relationships Domain score (pre vs post-treatment, 11 ± SD 4 vs 16 ± SD 4, p=0.024)(Table 8.2). Score for the Energy Question and Sleep Question also improved significantly after 36 weeks. There was no significant correlation between change in weight and change in Physical Health Domain score after 36 weeks treatment. Post-treatment scores for all domains did not differ significantly between genders.

On univariate analysis there was no statistically significant difference for both pre and post-treatment WHO-QoL Bref scores in terms of site of aneurysm, treatment modality, Fisher grade, WFNS score and GOS score.

Hospital Anxiety and Depression Scale

In patients with GHD, there was a significant negative correlation between peak GH levels achieved during GST and HADS Depression score prior to treatment with GHR (r=-0.62, p=0.024)(Figure 8.2). There was a statistically significant gender difference in baseline HADS Depression score (women vs men, 13± SD 3 vs 8 ± SD 4, p=0.018). After 36 weeks of GHR, there was a significant improvement in HADS Depression score and no gender difference was observed (Table 8.2). There was no significant correlation between change in weight and improvement in HADS Depression score. On univariate analysis there was no statistically significant difference for both pre and post-treatment HADS scores in terms of site of aneurysm, treatment modality, Fisher grade, WFNS score and GOS score.

Patient number	Gender	Age (years)	Site of aneurysm	Management of Aneurysm	WFNS	Fisher Grade	GOS score	Weight (kg)	BMI (kg/m2)	Waist Hip Ratio	Other hormone replacement
1	F	64	Basilar	Endovascular coiling	1	4	5	70.1	24.5	0.90	N
2	M	49	Anterior Communicating Artery	Endovascular coiling	1	1	5	100.2	37.5	1.04	N
3	M	49	Internal Carotid Artery and Anterior Communicating Artery†	Endovascular Coiling‡	1	1	4	91.5	29.7	0.99	N
4	M	32	Posterior Communicating Artery	Endovascular Coiling	1	Unavailable	5	95.6	29.5	0.97	Y*
5	F	54	Posterior Communicating Artery	Endovascular Coiling	1	4	5	107.9	40.1	0.88	N
6	M	55	Middle Cerebral artery	Surgical Clipping	2	3	4	97.5	31.5	1.02	N
7	F	63	Perimesencephalic	None	1	Perimesencephalic	5	90.9	35.0	0.93	N
8	F	55	Anterior Communicating Artery	Endovascular Coiling	2	4	4	67.5	29.1	0.95	Y**
9	M	65	Perimesencephalic	None	1	Perimesencephalic	5	96.6	32.7	1.07	N
10	F	61	Posterior Communicating Artery	Endovascular Coiling	1	1	4	72.9	30.7	0.99	N
11	F	52	Perimesencephalic	None	1	Perimesencephalic	5	79.1	33.3	0.90	N
12	F	53	Anterior Communicating Artery and Basilar Artery†	Endovascular Coiling‡	1	2	5	79.7	30.4	0.96	N
13	M	73	Anterior Communicating Artery	Surgical Clipping	2	2	5	85.5	28.1	0.93	N

Table 8.1

Baseline demographics of patients in this cohort. Patient diagnosed with Klinefelter's syndrome and received testosterone replacement therapy. **Patient post-menopausal receiving oestrogen therapy

†Multiple aneurysms, unable to identify site of bleeding. ‡Multiple coiling procedures

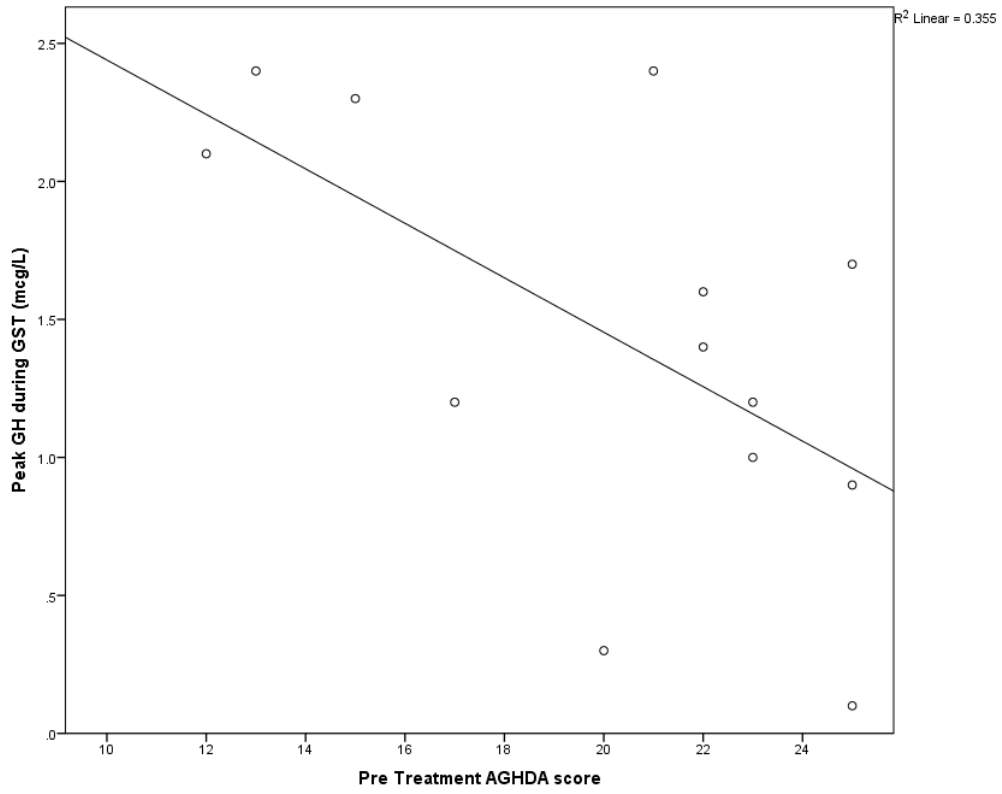

Figure 8.1 Graph showing correlation between peak GH level achieved during GST and QoL-AGHDA score prior to treatment with GHR (r= -0.596, p=0.032)

Table 8.2

Pre and post treatment measurement of weight, BMI, QoL-AGHDA score, WHO-QoL Bref score and HADS score. *Paired readings from 12 patients.

	Mean Pre-treatment	Mean Post-Treatment	Mean Change (SD)	P-value
Weight (kg)	87.5± SD 12.8	84.6 ± SD 12.2	-2.9 ± SD 3.5	**P=0.012**
BMI	31.7 ± SD 4.0	30.9 ± SD 4.2	-0.8 ± SD 1.2	**P= 0.015**
QoL-AGHDA	20 ± SD 5	10 ± SD 9	-10 ± SD 8	**P=0.001**
WHO-QOL Bref 1 Physical*	10 ± SD 3	13 ± SD 3	3 ± SD 3	**P=0.015**
WHO-QOL Bref 2 Psychological*	11 ± SD 2	14 ± SD 2	3 ± SD 3	**P= 0.018**
WHO-QOL Bref 3 Social Relationships	10 ± SD 5	15 ± SD 4	5 ± SD 6	**P=0.011**
WHO-QOL Bref 4 Environment	16 ± SD 2	16 ± SD 4	1 ± SD 3	P=0.443
WHO-QOL Bref Energy	2 ± SD 1	3 ± SD 1	1 ± SD 2	**P=0.008**
WHO-QOL Bref Sleep	2 ± SD 1	3 ± SD 1	1 ± SD 2	**P=0.025**
HADS Anxiety	10 ± SD 4	7 ± SD 5	3 ± SD 6	P=0.085
HADS Depression	10 ± SD 4	6 ± SD 6	4 ± SD 6	**P=0.016**

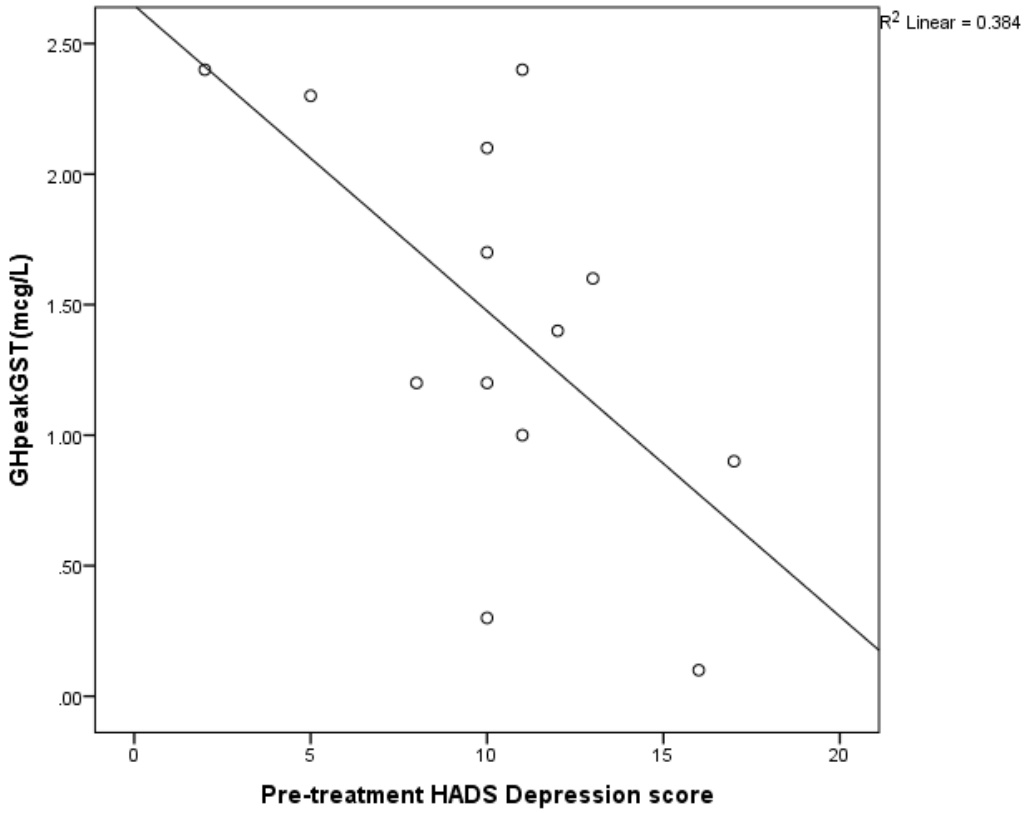

Figure 8.2 Graph showing correlation between peak GH level achieved during screening GST and HADS Depression score prior to GHR in patients with GHD(r=-0.62, p=0.024).

8.6 Discussion

As far as we are aware this is the first study reporting on the impact of GHR on quality of life and mood exclusively in survivors of SAH with GHD. Prior to treatment, we demonstrated a positive correlation between peak GH level achieved during screening GST and QoL-AGHDA score, indicating that severity of GHD impacts perceived quality of life in this patient population. A positive correlation between peak GH level during screening GST and pre-treatment WHO-QoL Bref Energy Score was observed in our cohort. This is consistent the known effect of GHD on energy levels in other patient cohorts(24, 34, 35). Although HIPS study (Hypopituitarism in Patients with Subarachnoid Haemorrhage, Screening and Treatment) concluded that GHD was not an important determinant of pathological fatigue in their SAH cohort, the study did demonstrate that in patients without GHD, fatigue levels (as measured by the Fatigue Severity Scale) improved to approximately normal levels after 6

months, whereas in patients with GHD this persisted in the pathological range(36). Clearly, in a subset of SAH survivors, GHD can compound some of the neuropsychological consequences.

In an analysis of the KIMS database, Gardner et al., showed that pre-treatment QoL-AGHDA score in Traumatic Brain Injury survivors were higher than patients with non-functioning pituitary adenoma (13.8 vs 9.7, p=0.004)(37). Mean baseline QoL-AGHDA score in our cohort was 20. This worse perception of quality of life is not surprising given that it is probably reflective of the difference in underlying pathology. As previously discussed, very few pituitary tumours present as an emergency. Conversely, most patients with ruptured aneurysmal subarachnoid haemorrhage have minimal prodrome and require treatment on an urgent basis. Patients progress through the initial treatment pathway rapidly, with limited time to understand and come to terms with their diagnosis. Worse perception of quality of life in our cohort as compared to that reported in the TBI population is not clear, but may be in part due to selection bias. It is not unreasonable to postulate that SAH patients who perceived their quality of life to be good, were perhaps less willing to participate our study. The mean QoL-AGHDA score of the whole cohort that was screened (100 SAH survivors) was 14 (range 0-25) is probably in keeping with this (data not presented).

In our cohort, after 36 weeks of treatment with GHR, we demonstrated a significant improvement in quality of life as measured by the QoL-AGHDA questionnaire and WHO-QoL Bref domains of Physical Health, Psychological Heath and Social Relationships. When controlled for patients without GHD, the improvement in QoL-AGHDA score remained significant. Furthermore, our cohort demonstrated a significant improvement in the domains of Energy and Sleep. This is consistent with the observed effect of GHR on other patient populations and demonstrates that SAH patients can also experience the benefits of GHR(19, 35, 38-43).

The observed mean improvement in QoL-AGHDA score was 10 points after 36 weeks of treatment. Again this is greater than that observed for the TBI and NFPA population in the KIMS database after 12 months (TBI vs NFPA, 5.0 vs 3.5, p=0.04)(37). It may that SAH survivors derive greater benefit of GHR due to poorer baseline however we note that in spite of this, post-treatment QoL-AGHDA score in our cohort was higher than both TBI and NFPA patients in the KIMS database after 1 year of treatment(37).

At baseline, there was a negative correlation between peak GH level on GST and pre-treatment HADS Depression score. It may be that in the SAH population the severity of GHD can be linked to the severity of mood symptoms. After 36 weeks of GHR, scores of the HADS depression component improved significantly.

There was no correlation between improvements in quality of life, perception of physical health or mood, with reduction in weight after 36 weeks of GHR in this cohort. As such, these positive neuropsychological changes that occur after GHR are independent of alterations in physical health. One study reported significant improvement in emotional reaction scores within one month GHR treatment, suggesting that it was too early for physical changes to occur in this time and that GH might itself have a role in mood regulation(35). The role of growth hormone in the control of mood remains largely unclear however given the presence of GH and IGF receptors in the brain; one can postulate that this might be due to its direct effects on the central nervous system.

Although we have demonstrated a clear potential to improve well-being in a proportion of SAH patients, there are some limitations to our study. Firstly the lack of a 'true' control group, means that we are unable prove causality between the outcomes observed and GHR. In a real-life study however, administrating a placebo-drug into a control group of participants, especially in this patient population who already suffer from high levels of distress is not feasible and more importantly, unethical. We did attempt to control for the possibility that a patients perception of quality of life may change over time, by comparing QoL-AGHDA score of patients with and without GHD. Comparisons between these two groups, still demonstrated that the improvement in QoL-AGDHA score with GHR in the GHD group was significant. Furthermore, it may well be that some of the effect observed may be due to frequent engagement of the GHD patients with the study team during the study period, however it is unlikely that this would cause the degree of improvements observed. None of the patients reported participation in a regular exercise programme during the study period. Therefore the improved perception of energy and physical health observed in our cohort is less likely to be due to actual increased activity level, but instead more likely due the direct neuropsychological effect of GHR.

Secondly, the short duration of follow up in our study population, does not enable us to draw any conclusions about the long term effects or side-effects of GHR in this patient population. To what degree the observed improvement continues and whether perception

of quality of life approaches that of the normal population will need a longer period of monitoring. How this observed improvement in quality of life and mood translates into change in functional outcome and independence remains to be seen.

Thirdly, we acknowledge the relatively small size of our study population, however this problem is inherent to this patient group. One hundred SAH survivors were screened with two dynamic pituitary tests, and from this, thirteen patients were identified as suitable to received GHR. Clearly, to be able to secure a sizeable treatment population for a study setting, would require screening of a very large number of SAH survivors, beyond the capacity of a single tertiary centre. This in itself incurs substantial monetary and logistical costs. Regardless, we feel that the outcomes of our study are of potential therapeutic significance and as such our results require reporting. We are not aware of any current interventions that demonstrate an effect to a similar degree in improving quality of life and mood in SAH patients.

Based on these findings, although assessment of pituitary function is not routinely carried out after SAH, we would encourage clinicians to screen for GHD in this patient population. It may not be feasible to screen all patients for pituitary dysfunction, however clinicians should have a high index of suspicion in patients exhibiting signs and symptoms that mimic GHD. Further analysis into how these patients can be identified prior to biochemical testing is required.

8.7 Conclusion

From our study, it is clear that SAH patients can derive the same benefit of GHR as other patients with GHD. This is reflected in improvement in quality of life and symptoms of low mood. GHR provides an exciting therapeutic option to dramatically improve wellbeing in a sub-group of SAH survivors. Given this, we would encourage the screening of GHD in suitable SAH survivors.

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Chapter 9

Conclusion

9 Chapter 9 Conclusion, Evaluation of Findings and Discussion

9.1 Preface

This final chapter summarises the findings of all preceding chapters. In this chapter, the analysis of the findings will be discussed pertaining to whether the initial hypotheses have been adequately addressed. Emerging themes from the overall results will be presented. Issues arising during the process of this thesis development will be addressed. This will conclude with a discourse about how the results of the thesis can affect clinical practice and further studies arising as a consequence.

9.2 Review

Evaluation of Chapter 4 – Pituitary Apoplexy-Bespoke Patient Management Allows Good Clinical Outcome

The purpose of this chapter was to assess if modern management of pituitary apoplexy resulted in good visual and endocrine outcomes. To do this, rates of visual symptoms and hypopituitarism in patients managed with emergency surgery, elective surgery and patients managed conservatively. At presentation there was no significant difference in terms of hypopituitarism between all three groups of patients. Although there was a higher rate of ophthalmoplegia and reduction in visual acuity in the emergency surgery group at baseline, this was not significant. Visual outcomes were good in all three groups. At follow up, no significant difference in terms of hypopituitarism was detected between the groups, but crucially, the rate of hypopituitarism was very high (73-91%). Contrary to some reports in the literature, no superiority in terms of endocrine outcomes was conferred by any particular treatment method(1, 2). The chapter discusses the reasons potential for endocrine recovery is limited in this pathology. Treatment should be directed at restoring vision and not instead attempting to re-establish endocrine function.

Evaluation of Chapter 5 – Variables Associated With Hypopituitarism in Patients With Non-Functioning Pituitary Adenoma

As the main goal of surgical resection in non-functioning pituitary adenomas is to preserve or restore visual function(3, 4), this type of pituitary lesion provides a good model to assess

clinical factors that may contribute to pituitary dysfunction and its potential for recovery. Establishing the 'true' rate of hypopituitarism post-surgically in patients with NFPA is not easy due to the various reasons discussed earlier. The aim of this chapter was to report on the variables related to pre and post-operative hypopituitarism in a modern case-series. Furthermore, change in individual hormone axis was reported to assess if this was the same in all patients. Review of 150 patients who underwent transsphenoidal surgery, revealed that the rate of hypopituitarism pre-operatively in this cohort was 67.4%. On univariate analysis, patients who were eupituitary were more likely to be female, have smaller tumour size, experience no endocrine symptoms and have tumours that were detected incidentally. On multivariate analysis, intact pituitary function (eupituitary) was significantly associated with female gender (OR 3.1, p=0.008) and smaller tumour size (giant adenoma OR 0.15, p<0.001). Post-operative hypopituitarism was present in 70.0% of the cohort. On univariate analysis, post-operative hypopituitarism was more likely in men, patients with larger tumours and older patients. Post-operative hypopituitarism was associated with gender (female = OR 0.12, p < 0.001), age (OR 1.05 per year, p =0.004) and having a giant adenoma (OR =6.53, p<0.001). Improvement in pituitary function after surgery was more likely in women (p=0.043) and in patients with higher serum prolactin level at baseline (p=0.023). Men were more likely to experience worsening in pituitary function post-operatively (p=0.031). From this chapter it is demonstrated that there are variables, other than surgical technique, that are associated with hypopituitarism in patients with NFPA. None of the associated variables detected are modifiable and this in itself presents an interesting discussion point. Rather than placing emphasis on innovation to enhance surgical technique, perhaps greater efforts should be focused on understanding how these mechanisms by which the above-mentioned variables exert effect on pituitary function. In the discussion part of this chapter, various postulations are offered but this serves to reflect the gap in the literature. Secondly and perhaps more excitingly, is how we choose to use this increased understanding of the factors associated with hypopituitarism. From a purely clinical view point, rather than 'painting all patients with the same brush', this knowledge will enable clinicians to individualise the risk of hypopituitarism in their patients, making decisions about surgery, radiotherapy or indeed no intervention at all, easier for patients.

Evaluation of Chapter 6- The Prevalence of Growth Hormone Deficiency in Survivors of Subarachnoid Haemorrhage- Results from a Large Single Centre Study

In recent years, increasing interest has developed in hypopituitarism as a consequence of subarachnoid haemorrhage. Unfortunately due to heterogeneous testing methods and definitions of hypopituitarism, the reported prevalence of hypopituitarism after SAH in the current literature is highly variable ranging from 0-55%(5-13). The aim of this chapter was to report on the rate of hypopituitarism when rigorous dynamic pituitary function testing and confirmatory testing was used to assess pituitary hormone deficiency. The protocol employed consisted of a screening glucagon test followed by a short synacthen test to confirm cortisol deficiency and arginine stimulation test to confirm growth hormone deficiency. Using this testing protocol, after screening 100 survivors of SAH, hypopituitarism was detected in 19% of patients and growth hormone deficiency was detected in 14% of patients. A significant difference in terms of weight (GHD vs non-GHD, 88.3 ± SD13.3kg vs 72.4 ± SD 14.2kg, $p<0.0001$), BMI (GHD vs non-GHD, 31.9 ± SD 3.9 vs 26.6 ± SD 4.5, $p<0.0001$) and WHR (GHD vs non-GHD, 0.94 ± SD 0.07 vs 0.88 ± SD 0.08, $p=0.08$) between patients who were GHD and those who were GH sufficient was observed. As obesity and central adiposity confound the GH response in a variety of dynamic tests(14-16), it cannot be concluded that the observed difference is due to GHD, even though it is well-established that adults with exhibit increased weight, body fat and central adiposity(17, 18). Primarily, this chapter concluded that the prevalence of hypopituitarism and specifically GHD is relatively low, when rigorous testing methods are employed. Implicit to this, is the requirement of a good understanding of not just how and when different testing methods should be used, but also potential drawbacks of each method. In the concluding remarks of this chapter, the complexities involved in screening all SAH survivors for hypopituitarism is discussed. However, the results of the subsequent chapters of this thesis, dictate that a process of identifying these patients needs to be developed.

Evaluation of Chapter 7 - The Impact of Growth Hormone Replacement on Cardiorespiratory Fitness and Metabolic Parameters in Patients with Growth Hormone Deficiency Following Subarachnoid Haemorrhage

High levels of fatigue, reduced cardiorespiratory fitness and adverse metabolic profile is frequently reported after SAH(19-23). In this chapter the hypothesis that GHR can improve these parameters in patients who have developed GHD after SAH was tested. This is the first study assessing the effect of GHR exclusively in this patient group. Prior to treatment, a correlation between the peak GH level achieved during screening GST and relative VO_2 peak achieved during cardiopulmonary testing was observed (r=0.558, p=0.047). This implies that in this patient group, severity of GHD can affect cardiorespiratory fitness. After 36 weeks of GHR, a significant reduction in weight (mean change -2.9 ± SD 3.5kg, p=0.012) and BMI (mean change -0.8 ± SD 1.2, p=0.015) was observed. During cardiopulmonary exercise testing, participants demonstrated a significant improvement in maximum speed achieved (mean change 0.28 ± SD 0.36km/hr, p=0.044). No significant improvement in waist hip ratio or lipid profile was observed and this may be due to the small study size. Given the lack of a control group, concluding that the effect observed was due GHR was not possible. However the chapter did demonstrate the unquestionable ability to improve cardiorespiratory fitness and certain metabolic parameters in SAH survivors with GHD. Given the potential long term health care implications of these benefits, further studies assessing the specific impact of GHR on cardiorespiratory fitness, fatigue and metabolic profile in this patient group is warranted.

Evaluation of Chapter 8 – The Impact of Growth Hormone Replacement on Quality of Life and Mood in Patients with Growth Hormone Deficiency Following Subarachnoid Haemorrhage

Given that some of neuropsychological symptoms observed in patient after SAH resemble that of adults with growth hormone deficiency, this chapter aimed to address whether GHR in patients who developed GHD after SAH could improve perceived quality of life and mood. This is an important hypothesis to test given that in the United Kingdom, NICE already allows for GHR in SAH patients with GHD, in spite of a clear lack of evidence of benefit in this group.

In this chapter, it was demonstrated that after 36 weeks of GHR, patient experience significant improvement in quality of life as measured by the QoL-AGHDA score (pre-treatment vs post-treatment, 20 ± SD 5 vs 10 ± SD 9, p=0.001), and in the WHO-QoL Bref domains of Physical Health (pre-treatment vs post-treatment score, 10 ± SD3 vs 13 ±SD 3, p=0.015), Psychological Health (pre-treatment vs post-treatment score, 11 ± SD2 vs 14 ± SD 2, p=0.018) and Social Relationships (pre-treatment vs post-treatment score, 10 ±SD 5 vs 15 ± SD 4, p=0.011). There were also significant improvements in the Energy and Sleep Items. Concurrently, the cohort demonstrated an improvement in HADS Depression score at the end of the treatment period (pre-treatment vs post-treatment score, 10 ±SD 4 vs 6 ± SD 6, p=0.016). These changes were not correlated to improvements in weight or BMI during the treatment period, suggesting that the positive neurobehavioural and psychosocial effects of GHR were not completely dependent on its physical effects. Given some limitations, the causality of GHR on the outcomes observed can not be directly assumed. Nonetheless, it is crucial that these results are reported and acknowledged given the potential therapeutic benefit of GHR in a cohort of SAH patients.

Although there is a vast literature on the predictors of poor quality of life and impaired mood in SAH survivos(24-28), the therapeutic options for this patient group is scarce if not ineffective. Certainly there are no interventions that have demonstrated such a degree of improvement in this patient group and GHR may have a role to play in the neurorehabilitation process of some SAH survivors. Routine screening of hypopituitarism and GHD after SAH is not part of standard clinical practice. The results demonstrated in this cohort, provides evidence that clinicians should certainly have an awareness of this, if not incorporate hormonal evaluation as part of their clinical assessment in SAH patients.

9.3 Impact on Clinical Practice and Further Studies

Defining and Diagnosing Hypopituitarism

In reviewing the literature for the production of this thesis, it became apparent that criterion used to define hypopituitarism was not standardised. Predominantly neurosurgical reports, contend with the diagnosis in patients only taking hormonal replacement therapy, whereas endocrine driven series adopt more accurate description of hypopituitarism.

Fundamentally this stems from how hypopituitarism is diagnosed in the literature. Some authors were resigned to simply baseline pituitary function tests, whereas others

incorporated validated dynamic tests. This issue is then complicated by the use, or rather lack of use of confirmatory testing methods. Both these issues were evident in all three patient groups investigated. Unexpectedly this leads to heterogeneous reports on the prevalence of pituitary dysfunction from all aetiologies in the literature.

Consequently teasing out the effect of any intervention of pituitary function is difficult. It is unlikely that reporting of pituitary function will be standardised in the near future, however when analysing data and more crucially when presenting the evidence to patients, this issue should be borne in mind.

Using Dynamic Tests of Pituitary Function

In spite of various advancements in modern clinical endocrinology, methods of diagnosing hypopituitarism have not evolved very much. Gold standard tests for various pituitary axes have remained largely the same, although often for other reasons, derivative testing methods are used. Certainly, as tertiary endocrine centres amass more and more, long term patients, safer and more convenient testing methods gain popularity. In the United Kingdom itself, variability of testing protocols between different centres is well known.

An in depth discussion about the drawbacks of each individual dynamic test of pituitary function is beyond the scope of this thesis. However a good understanding about the potential pit-falls and confounders to the testing protocols used is imperative so as not to draw erroneous conclusions from the data. This is perhaps most important when discussing hypopituitarism in patients with TBI and SAH, as it is only in recent years that pituitary dysfunction has become recognised as a consequence of these pathologies. Given that the mechanism of hypopituitarism from these types of brain injuries continue to go inadequately described, using tests that are both sensitive and specific to pituitary dysfunction in these patient groups is imperative.

From Chapter 6, it was noted that in the SAH population, there was a correlation between peak level of GH achieved during GST with BMI and WHR. To negate the possible confounding effects of BMI on GH response, a further study incorporating the GHRH-arginine stimulation with its BMI specific cut-offs was carried out in all SAH patient diagnosed with GHD described in Chapter 6. Also included were SAH patients diagnosed

with GHD from a previous cohort at Salford Royal NHS Foundation Trust. This study has just completed and is currently in the process of data analysis.

Individualising Patient Care

Chapters 4 and 5 attempt to review variables associated with hypopituitarism one in an emergency situation and latterly in a fairly benign endocrine disease. Often, much emphasis is placed on surgical technique and experience in relation to change in pituitary function. The results from Chapters 4 and 5 show that some of the variables that impact of pituitary function can not be changed. These results and other reports in the literature not only enhance our understanding of the pituitary gland but help us provide better care to our patients. As clinicians, we should attempt to better individualise the risk of pituitary dysfunction in our patients, so as to be able to assist and empower their clinical decision making process. No doubt the prospect of permanent hypopituitarism in a young female who has yet to start a family is very different, from an elderly male who has memory impairment with limited daily activities. A young female who is yet to start a family, may be more reassured by the possibility of recovery of endocrine function (specifically gonadal function) after pituitary surgery. Conversely, surgical decision may be swayed in an elderly patient with memory impairment given significant risk of ACTH deficiency necessitating life-long hydrocortisone replacement and the risks associated with missed doses.

Acknowledging the Long Term Consequences after SAH

In the process of working with just over 100 SAH survivors for the production of this thesis, it has become increasingly clear that there are other cognitive, emotional and personality changes that occur after SAH that cannot be easily quantified by questionnaires. These include becoming increasingly ‘short tempered’, easily upset, greater disinhibition and reduced tolerance to circumstances that might have previously been tolerable. Just because these symptoms are difficult to assess does not minimise their impact on the patients overall health. No doubt this not only affects the quality of life and psychosocial interactions of the patients but also their carers. It would therefore be premature to assume that all these symptoms can be ameliorated with GHR alone. Although an immense amount of

research has been carried out with regards to interventions aimed at improving survival in SAH(29), the same cannot be said for therapies to modulate functional outcomes in SAH patients. Perhaps it is the differing views of successful outcomes between the treating clinicians and patients, that accounts for the lack of investment into potential therapies for the neurobehavioural effects of SAH(30). The opportunity to investigate this unique group of patients reveals on no uncertain terms, that in spite of improved survival with neurosurgical and neurovascular advances, a problem still exists in this patient group. Improving overall outcomes in SAH survivors, requires a paradigm shift toward a holistic health care approach to be adopted by the key-players involved in managing these patients.

9.4 References

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Appendix 1 Publications and Presentations

A1 Publications arising from the thesis

Giritharan S, Gnanalingham K, Kearney T. Pituitary apoplexy - bespoke patient management allows good clinical outcome. *Clinical Endocrinology*. 2016;85(3):415-22.

Giritharan S, Cox J, Heal CJ, Hughes D, Gnanalingham K, Kearney T. The prevalence of growth hormone deficiency in survivors of subarachnoid haemorrhage: results from a large single centre study. *Pituitary*. 2017. Available online 18 August 2017

A2 Related abstracts presented at international meetings

International Society of Pituitary Surgeon (ISPS), 2015

Pituitary Apoplexy –*Oral Presentation*

Aspiring to Excellence: Pituitary Expert Forum, 2015

Pituitary Apoplexy: The Greater Manchester Experience – *Poster Presentation*

Euopean Congress of Endocrinology, 2017

[EP 1022] Non-Functioning Pituitary Adenoma; Outcomes From A Single-Surgeon Case Series- The Manchester Cohort- *Poster Presentation*

A3 Related abstracts presented at national meetings

British Endocrine Society, 2016

Low Risk of Growth Hormone Deficiency Post Subarchnoid Haemorrhage- *Poster Presentation*

The University of Manchester, Institute of Population Health- All Institue Showcase, 2016

Low Risk of Growth Hormone Deficiency Post Subarchnoid Haemorrhage- *Poster Presentation*

Appendix 2

NICE Guidance- Human growth hormone (somatropin) in adults with grothw hormone deficiency (TA64)

- Severe growth hormone deficiency, as defined by a peak growth hormone response of 9mU/Litre (3ng/ml) during an insulin tolerance test or a cross-validated GH response in an equivalent test
- Perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease specific 'Quality of life assessment of growth hormone deficiency in Adults' (QoL-AGHDA) questionnaire.
- Already received treatment for other pituitary hormone deficiencies as required.

Appendix 3

Contraindication to dynamic pituitary testing (specific to Glucagon Stimulation Test)

- Phaeochromocytoma
- Insulinoma
- Prolonged starvation

Appendix 4

Clinical contraindication to GHR

- Idiopathic Intracranial Hypertension
- Evidence of active malignancy
- Pregnant or lactating women or intention to become pregnant
- Critical illness
- Patients with diabetic retinopathy
- Known hypersensitivity to the active substance or to any of the excipients

Appendix 5

Baseline Pituitary Function Tests

Adrenocorticotrophic Hormone (ACTH)
Cortisol
Luteinising Hormone (LH)
Follicle Stimulation Hormone (FSH)
Estradiol/testosterone
Prolactin
Thyroid Stimulation Hormone (TSH)
Thyroid Hormone (T4)
Insulin-Like Growth Factor 1 (IGF-1)

Appendix 6 Questionnaires

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

QoL-AGHDA

Quality of Life

Assessment of GH Deficiency in Adults

Country: .....

Center: .....

Patient number: .....

Patient initial: .....

Visit date: |_|_|_|_|_|_|

LISTED BELOW ARE SOME STATEMENTS that people may make about themselves.

Read the list carefully and put a tick in the box marked YES if the statement applies to you.

Tick the box marked NO if it does not apply to you.

Please answer every item. If you are not sure whether to answer YES or NO, tick whichever answer you think is most true in general.

	YES	NO
I have to struggle to finish jobs	☐	☐
I feel a strong need to sleep during the day	☐	☐
I often feel lonely even when I am with other people	☐	☐
I have to read things several times before they sink in	☐	☐

	YES	NO
It is difficult for me to make friends	☐	☐
It takes a lot of effort for me to do simple tasks	☐	☐
I have difficulty controlling my emotions	☐	☐
I often lose track of what I want to say	☐	☐

	YES	NO
I lack confidence	☐	☐
I have to push myself to do things	☐	☐
I often feel very tense	☐	☐

QoL-AGHDA English
2000-02-17
OR 7064-01

	YES	NO
I feel as if I let people down	☐	☐
I find it hard to mix with people	☐	☐
I feel worn out even when I've not done anything	☐	☐

	YES	NO
There are times when I feel very low	☐	☐
I avoid responsibilities if possible	☐	☐
I avoid mixing with people I don't know well	☐	☐

	YES	NO
I feel as if I m a burden to people	☐	☐
I often forget what people have said to me	☐	☐
I find it difficult to plan ahead	☐	☐
I am easily irritated by other people	☐	☐

	YES	NO
I often feel too tired to do the things I ought to do	☐	☐
I have to force myself to do all the things that need doing	☐	☐
I often have to force myself to stay awake	☐	☐
My memory lets me down	☐	☐

Now please go back to the first question and make sure that you have answered "YES" or "NO" to every question, on all two pages of the questionnaire. Thank you for your help.

QoL-AGHDA English
2000-02-17
OR 7064-01

WHO/MSA/MNH/PSF/97.4
English only
Distr.: Limited

WHOQOL-BREF

PROGRAMME ON MENTAL HEALTH
WORLD HEALTH ORGANIZATION
GENEVA

r office use only

	Equations for computing domain scores	Raw score	Transformed scores*	
Domain 1	(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18 ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐	=	4-20	0-100
Domain 2	Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26) ☐ + ☐ + ☐ + ☐ + ☐ + ☐	=		
Domain 3	Q20 + Q21 + Q22 ☐ + ☐ + ☐	=		
Domain 4	Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25 ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐	=		

* Please see Table 4 on page 10 of the manual, for converting raw scores to transformed scores.

I.D. number

ABOUT YOU

Before you begin we would like to ask you to answer a few general questions about yourself: by circling the correct answer or by filling in the space provided.

What is your **gender**? Male Female

What is you **date of birth**? _____ / _____ / _____
Day / Month / Year

What is the highest **education** you received?
None at all
Primary school
Secondary school
Tertiary

What is your **marital status**?
Single Separated
Married Divorced
Living as married Widowed

Are you currently **ill**? Yes No

If something is wrong with your health what do you think it is?_____illness/ problem

Instructions

This assessment asks how you feel about your quality of life, health, or other areas of your life. **Please answer all the questions.** If you are unsure about which response to give to a question, **please choose the one** that appears most appropriate. This can often be your first response.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last two weeks.** For example, thinking about the last two weeks, a question might ask:

	Not at all	Not much	Moderately	A great deal	Completely
Do you get the kind of support from others that you need?	1	2	3	4	5

You should circle the number that best fits how much support you got from others over the last two weeks. So you would circle the number 4 if you got a great deal of support from others as follows.

	Not at all	Not much	Moderately	A great deal	Completely
Do you get the kind of support from others that you need?	1	2	3	4	5

You would circle number 1 if you did not get any of the support that you needed from others in the last two weeks.

Please read each question, assess your feelings, and circle the number on the scale for each question that gives the best answer for you.

		Very poor	Poor	Neither poor nor good	Good	Very good
1(G1)	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2 (G4)	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last two weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3 (F1.4)	To what extent do you feel that physical pain prevents you from doing what you need to do?	1	2	3	4	5
4(F11.3)	How much do you need any medical treatment to function in your daily life?	1	2	3	4	5
5(F4.1)	How much do you enjoy life?	1	2	3	4	5
6(F24.2)	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7(F5.3)	How well are you able to concentrate?	1	2	3	4	5
8 (F16.1)	How safe do you feel in your daily life?	1	2	3	4	5
9 (F22.1)	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about **how completely** you experience or were able to do certain things in the last two weeks.

		Not at all	A little	Moderately	Mostly	Completely
10 (F2.1)	Do you have enough energy for everyday life?	1	2	3	4	5
11 (F7.1)	Are you able to accept your bodily appearance?	1	2	3	4	5
12 (F18.1)	Have you enough money to meet your needs?	1	2	3	4	5
13 (F20.1)	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14 (F21.1)	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither	Good	Very good

				poor nor good		
15 (F9.1)	How well are you able to get around?	1	2	3	4	5

The following questions ask you to say how **good or satisfied** you have felt about various aspects of your life over the last two weeks.

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16 (F3.3)	How satisfied are you with your sleep?	1	2	3	4	5
17 (F10.3)	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18(F12.4)	How satisfied are you with your capacity for work?	1	2	3	4	5
19 (F6.3)	How satisfied are you with yourself?	1	2	3	4	5
20(F13.3)	How satisfied are you with your personal relationships?	1	2	3	4	5
21(F15.3)	How satisfied are you with your sex life?	1	2	3	4	5
22(F14.4)	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23(F17.3)	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24(F19.3)	How satisfied are you with your access to health services?	1	2	3	4	5
25(F23.3)	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to **how often** you have felt or experienced certain things in the last two weeks.

		Never	Seldom	Quite often	Very often	Always
26 (F8.1)	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	1	2	3	4	5

Did someone help you to fill out this form?.....

How long did it take to fill this form out?.....

Do you have any comments about the assessment?

.....

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THANK YOU FOR YOUR HELP