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WITWATERSRAND,
JOHANNESBURG

An Audit of Hypopituitarism in Paediatric Patients Seen at Chris Hani Baragwanath Academic Hospital from January 2011 to December 2021

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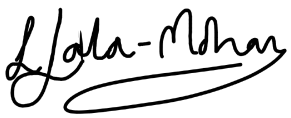
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics.

Johannesburg, August 2024

Declaration

I, Larissa Lala-Mohan, declare that this Research Report is my own work. It is being submitted for the Degree of Master of Medicine in Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Dr Larissa Lala-Mohan

26 August 2024, Johannesburg

Dedication

I would like to dedicate this to my family who have been with me every step of the way.

To my husband, I do not have the words to accurately express how grateful I am for everything that you do for me. You are my shining star.

To my mum, thank you for all the love, guidance, support and academic help through the years.

To my sister, thank you for being amazing and being my right hand girl.

To the rest of my family and friends, thank you for all your love and encouragement.

To all the children with Hypopituitarism - I hope this work goes on to help you in the future.

Acknowledgements

I would like to express my sincerest gratitude to Professor Kebashni Thandrayen. Thank you for affording me the opportunity to undertake this task and I am extremely grateful for your assistance on the entire course of this research journey. Thank you for your invaluable time, guidance, dedication and esteemed contribution to this Research Report. I appreciate your unwavering support and thank you so much for being a wonderful role-model.

I would like to commend my husband, Yatin Badal, for the unparalleled technological contribution to this report. Thank you for writing immaculate code to perform the data extraction, making the graphs and figures, and assisting in all technical aspects. Thank you for all the hours of time, energy and brain power you have put into this - I am eternally grateful for you.

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List of Abbreviations

ACTH	Adrenocorticotropic hormone
ANOVA	Analysis of Variance
BMI	Body mass index
CHBAH	Chris Hani Baragwanath Academic Hospital
CPHD	Combined Pituitary Hormone Deficiency
FSH	Follicle-stimulating hormone
GH	Growth hormone
GHRH	Growth-hormone-releasing hormone
GnRH	Gonadotropin-releasing hormone
HAZ	Height-for-age z-score
HC	Head circumference
HCZ	Head circumference z-score
HPA	Hypothalamic-pituitary axis
IGF-1	Insulin-like growth factor 1
IGFBP-3	Insulin-like growth factor-binding protein 3
IQR	Interquartile range
LH	Luteinizing hormone
LFT	Liver function test
MRI	Magnetic Resonance Imaging
rGH	Recombinant growth hormone
SD	Standard deviation
TSH	Thyroid-stimulating hormone
T4	Thyroxine
WAZ	Weight-for-age z-score
WHZ	Weight-for-height z-score
U&E	Urea and electrolytes

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Author's Guidelines for Intended Journal

This Master of Medicine in Paediatrics will be submitted for examination in the 'Submissible Format.' The Manuscript will be submitted to the Journal of Endocrinology, Metabolism and Diabetes of South Africa (JEMDSA). The link to the guidelines for submission to this journal can be found online at https://ojs.sabinet.co.za/index.php/jemdsa/about/submissions.

Manuscript in Submissible Format

Abstract

Background

Congenital hypopituitarism is a rare but important condition, as normal pituitary function is crucial for neurocognitive development, growth, metabolism, homeostasis and puberty progression.

Objectives

To describe the demographics, anthropometry, clinical presentation, MRI findings, biochemical abnormalities, bone age and response to treatment of children with congenital hypopituitarism.

Methods

A retrospective, descriptive study from 1 January 2011 to 31 December 2021 of paediatric endocrine clinic patients at CHBAH (n = 46).

Results

Two-thirds of patients had panhypopituitarism and the remainder had hypopituitarism. The mean age at presentation was 4.7 years (SD ± 5.3). The male:female ratio was 3.6:1 and the majority were Black (97.8%). The most common presentation was short stature (70%) and pituitary stalk interruption syndrome (45.3%) on MRI. The height-for-age z-score was -4.2 (SD ± 2.1) at baseline and -1.7 (SD ± 1.9) at year 7 on treatment ($p < 0.05$) for those that received recombinant growth hormone. The mean delay in bone age was 2.6 years (SD ± 2.4) before growth hormone initiation. The most common complication was hypoglycemia (43.5%).

Conclusion

Hypopituitarism is a rare disease that requires early detection. Intervention with growth hormone replacement has shown a significant improvement in HAZ achieving a normal range for the majority of treated patients.

Keywords: Hypopituitarism, Panhypopituitarism, Pituitary, Growth, Height

Introduction

Hypopituitarism is the partial or complete loss of anterior and posterior pituitary gland function, caused by pituitary or hypothalamic disorders.[1] This is a rare disorder, with a varied presentation.[2] The diagnosis of hypopituitarism is made on history, examination, biochemical investigations, provocative testing of the hypothalamic-pituitary axis and genetic testing as well as Magnetic Resonance Imaging (MRI) findings of abnormalities of the hypothalamus or pituitary gland.[3] Any disease process affecting either the gland or stalk of the pituitary, or the hypothalamus can lead to hypopituitarism.[2] The pituitary gland is vital for homeostasis, reproduction and the regulation of growth, by the release of its hormones.[3] Hypopituitarism is defined as a deficiency in one or more hormones produced by the anterior pituitary or released from the posterior pituitary gland.[4] Combined Pituitary Hormone Deficiency (CPHD) involves two or more hormone deficiencies[5], while panhypopituitarism is defined as a deficiency of three or more pituitary hormones.[6]

In the United States of America, the incidence of hypopituitarism is reported to be 4.2 per 100 000 children per annum with the prevalence being 45.5 per 100 000 children,[3] however there is a paucity of data in South Africa.

Hypopituitarism is either congenital or acquired.[3,7,8] It can therefore present in the neonatal period through to adolescence and into adulthood.[2,9] The disorder can be divided into primary and secondary hypopituitarism. Disorders of the pituitary gland itself cause primary hypopituitarism, whereas secondary hypopituitarism is due to abnormalities of the hypothalamus or the pituitary stalk, which interrupts the nerve or vascular connections to the pituitary gland, and thus, reduces the secretion from the pituitary gland.[1,9,10] Acquired causes of hypopituitarism include trauma, infection and inflammation, auto-immune processes, infiltration, tumours, radiation and post-chemotherapy.[8,10] For the purpose of this study, the congenital causes of hypopituitarism will be investigated. These include genetic disorders like septo-optic dysplasia, *PIT1* and *PROP1* mutations and pituitary stalk interruption syndrome; genetic syndromes like Pallister-Hall syndrome (hypothalamic hamartoma with polydactyly); and developmental central nervous system defects like holoprosencephaly, anencephaly and pituitary hypoplasia or aplasia. [1,3,9,11]

The clinical features vary based on the number of hormones involved, as well as the extent of the resultant deficiencies.[8] Infants with multiple hormonal deficiencies usually present in the neonatal period, as opposed to children presenting later on in childhood with growth failure or delayed puberty.[3,9] Septo-optic dysplasia is the term used to describe the phenomenon when two or more of pituitary hormones are deficient, midline brain defects are present and there is optic nerve hypoplasia.[3,12] Hypopituitarism can be life-threatening in the case of adrenocorticotropic hormone (ACTH) deficiency and thus early diagnosis is key. Appropriate hormone replacement therapy in all cases is vital to ensure prevention of unnecessary morbidity and mortality for these patients.[2,4]

The hormones from the anterior pituitary get released in a pulsatile fashion, and every hormone has a different circadian pattern, thus hormonal treatment must reflect this pattern.[3,4] Treatment includes: thyroid hormone replacement, growth hormone replacement, hydrocortisone, vasopressin replacement, gonadotropin-releasing hormone (GnRH) agonists or exogenous gonadotropins.[9] These children require holistic care from a multi-disciplinary team.[3,8] They need to be followed up regularly, and require a full pituitary hormone work-up at diagnosis and then annually thereafter, as children with one hormonal abnormality can subsequently develop others.[3] These children should also have regular neurodevelopmental assessments and visual field testing.[3] Psychosocial management is also a vital part of holistic management. In a study by Koa et al. children with hypopituitarism were found to have a significantly lower quality of life into their adulthood as compared to their healthy counterparts.[13] Children in the study were shorter and more overweight, had more childhood behavioural problems, were less educated, had higher unemployment rates, lower marital rates and lower incomes and had fewer children compared to healthy controls.[13,14]

The rationale for conducting this study is that there is a paucity of knowledge as well as clinical and genetic research surrounding hypopituitarism in South Africa. Even though the condition is rare, it is nonetheless an important disease process, as normal pituitary function is crucial for neurocognitive development, growth, metabolism and homeostasis as well as the onset of puberty, all of which are of utmost importance for growing children.

Methodology

Aim

To review hypopituitarism in paediatric patients seen at the paediatric endocrine clinic at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2011 to December 2021.

Objectives

1. To describe the demographics, anthropometry, clinical presentation, MRI findings and biochemical abnormalities of paediatric patients seen at the paediatric endocrine clinic at CHBAH with hypopituitarism
2. To assess bone ages before, during and/or after treatment
3. To review treatment prescribed and response to treatment by documenting the changes in height-for-age (HAZ) and weight-for-age z-scores (WAZ) or body mass index (BMI) z-scores, thyroid function tests, cortisol and insulin-like growth factor-1 (IGF-1) levels
4. To quantify how many patients achieved a HAZ of > -2 with growth hormone treatment as a measure of a good outcome

Study Design

This is a descriptive study conducted through a retrospective review of medical records of paediatric patients with congenital hypopituitarism at the paediatric endocrine clinic at CHBAH.

Study Population and Sample Size

The study population consisted of all children under the age of 18 that were attending the paediatric endocrine clinic at CHBAH, a tertiary institution, with the diagnosis of congenital hypopituitarism from 1 January 2011 to 31 December 2021 until their last follow up. The sample size was 46 patients.

Inclusion Criteria

All children under the age of 18 years with the diagnosis of hypopituitarism (two or more pituitary hormone deficiencies) attending the paediatric endocrine clinic at CHBAH from 1 January 2011 to 31 December 2021 were included in the study.

Exclusion Criteria

Patients with isolated growth hormone deficiency as well as patients with acquired causes of hypopituitarism were excluded from the study.

Data Collection

Data were collected from patient records, and entered onto a data collection sheet and then extracted into an Excel spreadsheet. The data collected included demographics, age of referral, mode of referral, anthropometry at presentation with z-scores, presenting clinical features, MRI findings, as well as bone ages before and during treatment. At each follow-up, data were collected for biochemical markers including insulin-like growth factor 1 (IGF-1), thyroid-stimulating hormone (TSH), thyroxine (T4), cortisol, growth hormone (GH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, oestrogen and testosterone, serum osmolality, urine osmolality, urea and electrolytes (U&E) and liver function test (LFT). Other data collected included anthropometry, Tanner pubertal staging, episodes of adrenal crisis, episodes of hypoglycemia with or without seizures, treatment prescribed (recombinant growth hormone (rGH), levothyroxine, hydrocortisone, desmopressin) as well as compliance with treatment. Data for follow up visits were collected for six-monthly visits in the first two years and then annually thereafter.

Statistical Analysis

Data was analysed with Stata/SE version 18 as well as Statistica version 14.0.1 (Statsoft USA). The data is described using descriptive statistics. Categorical variables are reported as percentages and frequencies. Chi-square and Fisher's exact tests were performed for comparative analyses. Continuous variables are reported as means and standard deviations (SD), and medians with interquartile ranges (IQR). The Mann Whitney U Test was used to compare continuous variables between growth hormone treated and naive patients. The Student's t-test for dependent samples was used to compare HAZ and WAZ scores between

each year on growth hormone therapy. For mean changes in anthropometric z-scores from baseline until seven annual follow-ups on growth hormone therapy, Friedman analysis of covariance (ANOVA) and Kendall Coefficient of concordance was performed.

Ethical considerations

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate number M230437). Permission was also granted to conduct research by the Head of Department of Paediatrics and Chief Executive officer at CHBAH.

Results

There were 46 patients with hypopituitarism that presented to the paediatric endocrine clinic at CHBAH from 2011 to 2021. Of these, two-thirds had panhypopituitarism (n=31) and one third had CPHD (n=15). The mean age of the patients at presentation was 4.7 years (SD ± 5.3) with a median age of 2.3 years (IQR 0.2 - 7.4). A large proportion of patients presented before the age of one year (43.5%), with 28.2% presenting between one to six years, 15.2% presenting from seven to twelve years and 13.1% being older than twelve years at presentation. The majority of patients were male (male : female ratio of 3.6 : 1) and 97.8% of the patients were of the Black race. The majority of patients resided in Gauteng (81.4%), followed by North West at 9.3%, with smaller populations hailing from Limpopo, Eastern Cape and Lesotho. Of the patients residing in Gauteng, 29 out of the 35 patients (82.9%) live in central Johannesburg (Table 1).

In terms of the origin of referrals, 13 (28.3%) of the patients were referred from the General Paediatrics Wards at CHBAH, followed by 10 (21.7%) referrals from clinics and another 10 (21.7%) referrals from peripheral hospitals, followed by 8 (17.4%) patients from the Neonatal Unit at CHBAH as shown in Table 1.

Table 1: Demographics, province of residence and place of referral

	N (%)
Race	
Black	45 (97.8)
Coloured	1 (2.2)
Sex	
Male	36 (78.3)
Female	10 (21.7)
Province of residence	
Gauteng	35 (81.4)
North West	4 (9.3)
Limpopo	2 (4.7)
Eastern Cape	1 (2.3)
Lesotho	1 (2.3)
Referral	
General Paediatrics Wards	13 (28.3)
Clinics	10 (21.7)
Peripheral Hospitals	10 (21.7)
Neonates	8 (17.4)
General Practitioner	2 (4.4)
Other	3 (6.5)

At presentation, the mean WAZ of the patients was -3.0 (SD ± 2.9), HAZ was -3.5 (SD ± 2.3), WHZ (weight-for-height z-score) was 0.6 (SD ± 2.5) with a BMI of -0.3 (SD ± 2.1), indicating that the majority of patients were severely underweight for age and severely stunted, but not wasted. As detailed in Table 2, the anthropometric measurements at baseline between the patients who received rGH, and those who did not, were not significantly different.

Table 2: Age and anthropometry at presentation

	All patients at presentation	Growth hormone treatment cohort at baseline	Growth hormone naive cohort at baseline	*p*-values
Age (Decimal years)				
N	46	34	12	
Mean (SD)	4.7 (± 5.3)	4.8 (± 5.1)	4.3 (± 6.1)	0.60
Median (IQR)	2.3 (0.2 - 7.4)	3.7 (0.2 - 7.4)	1.2 (0.1 - 7.0)	0.59
Weight (kg)				
N	46	34	12	
Mean (SD)	12.2 (± 10.4)	12.8 (± 11.1)	10.5 (± 8.2)	0.63
Median (IQR)	9.8 (3.7 - 15.9)	10.5 (3.7 - 17.0)	9.0 (3.9 - 12.0)	0.63
Height (cm)				
N	46	34	12	
Mean (SD)	79.6 (± 28.6)	80.9 (± 29.2)	75.9 (± 27.7)	0.56
Median (IQR)	77.0 (52.2 - 99)	81.5 (52.2 - 100)	70.5 (52.2 - 91.1)	0.56
Head circumference (cm)				
N	38	28	10	
Mean (SD)	43.8 (± 7.5)	44.0 (± 7.8)	43.1 (± 7.1)	0.70
Median (IQR)	45.5 (36 - 49)	46.3 (36.0 - 50.0)	43.2 (36.0 - 48.5)	0.72
WAZ				
N	46	34	12	
Mean (SD)	-3.0 (± 2.9)	-3.0 (± 2.7)	-3.1 (± 3.5)	0.87
Median (IQR)	-2.45 (-4.0 - -1.1)	-2.4 (-3.8 - -1.2)	-2.9(-5.7 - 0.2)	0.87
HAZ				
N	46	34	12	
Mean (SD)	-3.5 (± 2.3)	-3.6 (± 2.2)	-3.4 (± 2.6)	0.89
Median (IQR)	-3.41 (-5.4 - -1.67)	-3.5 (-5.1 - -1.7)	-3.4 (-5.7 - -1.6)	0.89
WHZ				
N	42	31	11	
Mean (SD)	0.6 (± 2.5)	0.7 (± 2.7)	0.0 (± 1.6)	0.89
Median (IQR)	0.45 (-0.8 - 1.43)	0.4 (-0.5 - 1.6)	0.5 (-1.1 - 1.4)	0.90
BMI				
N	46	34	12	
Mean (SD)	-0.3 (± 2.1)	-0.3 (± 2.2)	-0.4 (± 1.9)	0.81
Median (IQR)	-0.17 (-1.1 - 1.23)	-0.1 (-1.1 - 1.2)	-0.4 (-2.0 - 1.4)	0.82
HCZ				
N	38	28	10	
Mean (SD)	-0.8 (± 2.0)	-1.0 (± 1.9)	-0.5 (± 2.4)	0.39
Median (IQR)	-0.96 (-2.3 - 0.76)	-1.1 (-2.4 - 0.8)	0.1 (-1.8 - 1.0)	0.38

The most common clinical presentation was short stature seen in 32 (70%) patients. This was followed by hypoglycemia seen in 26 (56.5%) patients and 22 (47.8%) patients presented with a micropenis or cryptorchidism. Twenty one (45.7%) patients had dysmorphic features, which included frontal bossing, low set ears, midface hypoplasia, a flat nasal bridge, cherubic facies and hypertelorism (Table 3).

Table 3: Reason for referral and presenting features

	N (%)
Short stature	32 (70)
Hypoglycaemia	26 (56.5)
Micropenis/cryptorchidism	22 (47.8)
Seizures	11 (23.9)
Developmental delay	10 (21.7)
Prolonged neonatal jaundice	8 (17.4)
Delayed puberty	7 (15.2)
Intellectual impairment	6 (13)
Visual problems	4 (8.7)
Obesity	3 (6.5)
Hypotonia	1 (2.2)
Headaches	0 (0)
Adrenal crisis	0 (0)
Dysmorphic features:	21 (45.7)
Frontal bossing	6 (13.1)
Low set ears	5 (10.9)
Midface hypoplasia	5 (10.9)
Flat nasal bridge	5 (10.9)
Cherubic facies	5 10.9)
Hypertelorism	5 (10.9)
Epicanthic folds	4 (8.7)
Clinodactyly	4 (8.7)
Micrognathia	3 (6.5)
Microcephaly	2 (4.4)
Scaphocephaly	2 (4.4)
Brachydactyly	1 (2.2)
Widely spaced nipples	1 (2.2)
Intermediate fontanelle	1 (2.2)

Thirty-one out of the forty-six patients had Magnetic Resonance Imaging of the brain with pituitary views, based on accessibility and resource limitation, and it was diagnostic in 87% of patients in whom scans were done. Fourteen (45.3%) of these scans revealed pituitary stalk interruption syndrome. An ectopic posterior pituitary was seen in four (12.9%) patients and hypoplasia of the anterior pituitary with an ectopic posterior pituitary in two (6.5%) patients. A hypoplastic anterior pituitary, ectopic suprasellar pituitary gland and empty sella turcica were MRI findings in single patients (3.2%). Extra-pituitary manifestations on MRI were found in four (12.9%) patients, including bilateral optic nerve hypoplasia, para-encephalic cyst, normal pituitary gland with hypoxic-ischemic changes and cerebral malformation with an absent corpus callosum. Four (12.9%) patients had normal MRI findings (Table 4).

Table 4: Magnetic Resonance Imaging findings

MRI findings (N = 31)	N (%)	Panhypopituitarism	CPHD
Pituitary stalk interruption syndrome	14 (45.3)	14	0
Ectopic posterior pituitary	4 (12.9)	2	2
Hypoplasia of the anterior pituitary with an ectopic posterior pituitary	2 (6.5)	1	1
Hypoplastic anterior pituitary	1 (3.2)	1	0
Ectopic suprasellar pituitary gland	1 (3.2)	0	1
Empty sella turcica	1 (3.2)	1	0
Normal pituitary gland with hypoxic-ischemic changes	1 (3.2)	0	1
Bilateral optic nerve hypoplasia	1 (3.2)	1	0
Bilateral hypoplastic optic nerves and para-encephalic cyst	1 (3.2)	1	0
Cerebral malformation with absent corpus callosum	1 (3.2)	1	0
Normal	4 (12.9)	1	3
Not imaged	15	8	7

All patients with pituitary stalk interruption syndrome on MRI had panhypopituitarism. Singular findings on MRI of hypoplastic anterior pituitary and empty sella turcica were also seen in patients with panhypopituitarism. Patients whose MRI findings were in keeping with septo-optic dysplasia such as bilateral optic nerve hypoplasia and cerebral malformation with an absent corpus callosum, were also associated with panhypopituitarism (Table 4).

Blood sampling done at the time of a hypoglycemic episode, also known as a critical sample, was conducted in 22 out of the 46 patients (47.8%) at a mean age of 1.3 years (SD ± 2.4), with a median of 0.17 years (IQR 0.8 - 1.6). The median values for glucose was 2 mmol/L (IQR 1 - 2.4), growth hormone was 0.6 µg/L (IQR 0.2 - 3.8), cortisol was 66 nmol/L (IQR 12 - 157), insulin was 5.5 pmol/L (IQR 1.4 - 13.9), c-peptide was 0.1 nmol/L (IQR 0.1 - 0.1) and lactate was 1.2 mmol/L (IQR 0.8 - 2.2), all being below the normal reference range of values in the face of hypoglycemia, with growth hormone and cortisol being pathologically low (Table 5).[15,16]

Table 5: Critical samples conducted

	N	Mean (SD)	Median (IQR)
Age conducted (Years)	22	1.3 (± 2.4)	0.17 (0.8 - 1.6)
Glucose (Neonate: 2.5 - 5.5 mmol/L; Child: 3.0 - 6.1 mmol/L)	22	1.9 (± 1.2)	2 (1 - 2.4)
Growth hormone (>7 µg/L)	19	1.7 (± 1.9)	0.6 (0.2 - 3.8)
Cortisol (Increase above basal level > 280 nmol/L)	18	174.7 (± 325.9)	66 (12 - 157)
Insulin (15.9 - 180.6 pmol/L)	21	7.6 (± 5.5)	5.5 (1.4 - 13.9)
C-peptide (<0.2 nmol/L)	17	0.1 (± 0.1)	0.1 (0.1 - 0.1)
Lactate (<2 mmol/L)	14	1.5 (± 0.9)	1.2 (0.8 - 2.2)

*Normal reference range in brackets [15,16]

Clonidine stimulation tests were performed in 14 out of the 46 patients (30.4%) by means of oral clonidine given at 0.15mg/m^2, to stimulate growth hormone release pharmacologically. The mean age was 9.7 years (SD ± 4.1) with a median of 10.1 years (IQR 6.6 - 12.8). Out of the 14 patients, 5 patients were primed (35.7%), and the test was confirmatory for growth hormone deficiency in 100% of patients. Table 6 details values for growth hormone, blood glucose, IGF-1 and cortisol at 30 minute intervals as the test was conducted, indicating a lack of surge in the growth hormone value, in keeping with a growth hormone deficiency.

Table 6: Clonidine stimulation tests conducted

		0 mins	30 mins	60 mins	90 mins	120 mins
Growth hormone (> 7 µg/L)	N	14	11	14	13	13
	Mean (SD)	0.4 (± 0.4)	0.6 (± 0.7)	1.3 (± 2.3)	1.9 (± 2.9)	1.3 (± 2.3)
	Median (IQR)	0.2 (0.1 - 0.6)	0.3 (0.1 - 0.7)	0.2 (0.1 - 1.0)	0.6 (0.2 - 1.7)	0.3 (0.2 - 1.0)
Blood glucose (3.0 - 6.1 mmol/L)	N	10	7	8	8	9
	Mean (SD)	4.2 (± 0.8)	4.6 (± 1.3)	4.9 (± 1.4)	4.6 (± 2.4)	4.6 (± 1.1)
	Median (IQR)	4.5 (4.2 - 4.7)	4.4 (3.8 - 5.9)	4.8 (4.1 - 6.0)	4.3 (2.6 - 5.7)	5.0 (4.4 - 5.0)
IGF -1 (nmol/l)*	N	8	2	2	2	3
	Mean (SD)	10.7 (± 15.0)	10.9 (± 11.7)	12.7 (± 14.3)	2.4 (± 2.1)	10.0 (±8.5)
	Median (IQR)	4.8 (2.9 - 10.9)	10.9 (2.6 - 19.2)	12.7 (2.6 - 22.9)	2.4 (2.2 - 2.6)	8.0 (2.6 - 19.3)

*Normal reference range in brackets. See IGF-1 reference range values on page 38.[15,16]

Four patients had a glucagon stimulation test performed (glucagon given at 0.03mg/kg intravenously) at a mean age of 3.7 years (SD ± 2.1) and median of 3.8 years (IQR 1.7 - 5.6). The mean baseline growth hormone value was 2.3 µg/L (SD ± 4.1) with a median of 0.25 µg/L (IQR 0.1 - 6.4). Growth hormone values trended downward at each 30 minute mark, with a mean of 0.2 µg/L (SD ± 0.1) and a median of 0.2 µg/L (IQR 0.1 - 0.3) at 120 minutes after the administration of glucagon.

The cohort of patients who did not receive growth hormone therapy showed mean HAZ measurements that worsened with time (Figure 1). At presentation, the mean HAZ was -3.4 (SD ± 2.6) with a median of -3.3 (IQR -5.7 - -1.5), whereas at year three, the mean HAZ score was -4.5 (SD ± 0.8) with a median of -4.7 (-5.1 - -3.8). Conversely, the HAZ scores for

the cohort of patients on growth hormone therapy improved over time (Figure 2). At presentation, the mean HAZ was -4.2 (SD ± 2.1) with a median of -4.3 (IQR -6.1 - -3.2), whereas by year seven, the mean HAZ improved to -1.7 (SD ± 1.9) with a median of -1.7 (IQR -2.9 - -0.8). Statistical significance was shown when comparing years 1, 2, 3, 4, 5 and 7 to baseline; year 2, 3, 5, 6, 7 to year 1; and year 7 to year 2. The WAZ scores for the cohort that received rGH also improved with a mean WAZ at baseline of -2.8 (SD ± 2.8) and median of -2.3 (IQR -3.9 - -1.5), reaching a mean of 0.1 (SD ± 2.2) and a median of 0.2 (IQR -0.8 – 1.8) by year 7 on rGH, with a p-value of < 0.01 when comparing year 7 to baseline and year 7 to year 2; and a p-value of < 0.001 when comparing year 7 to year 1 on rGH (Table 7 and Figure 3).

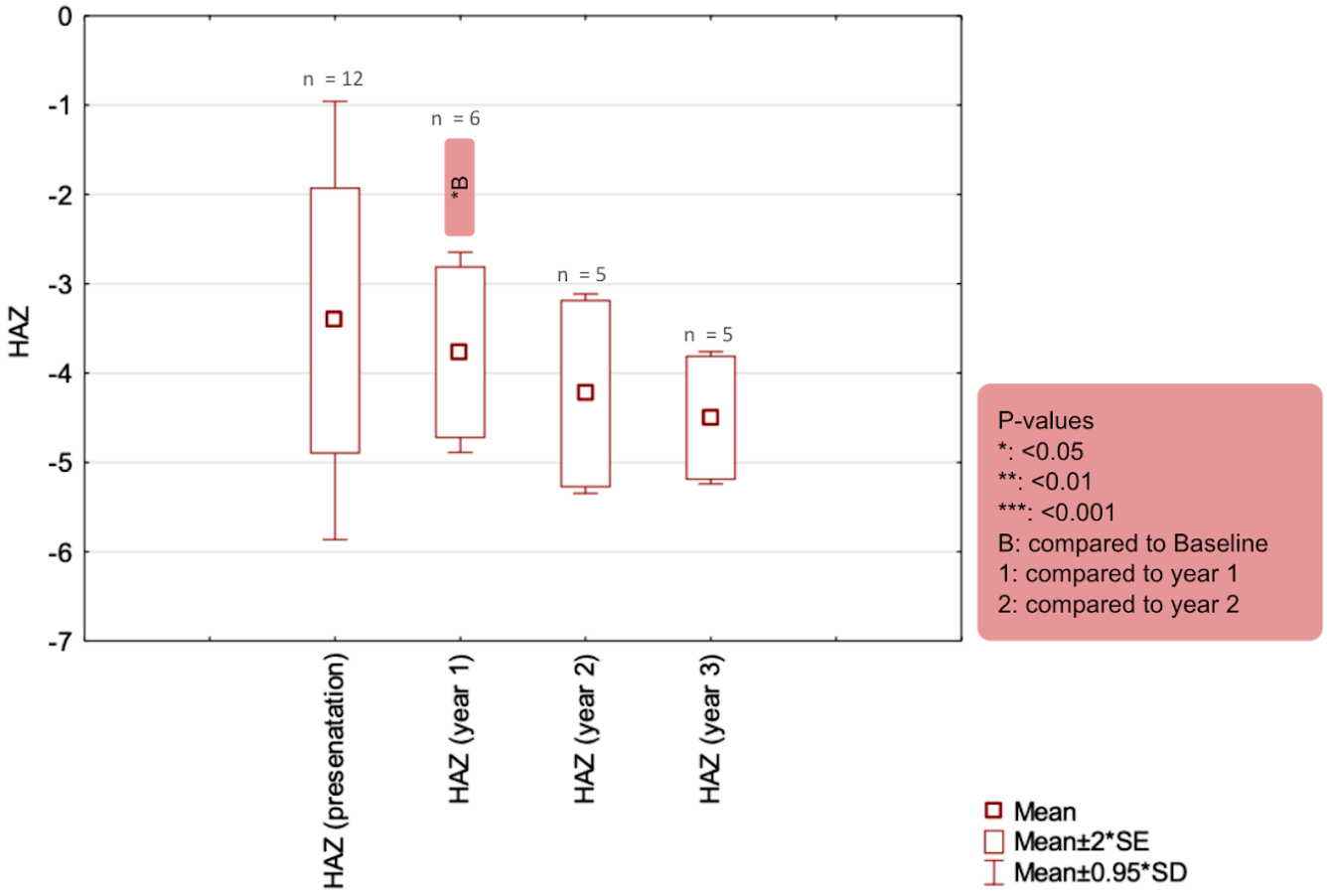

Figure 1: Mean HAZ over time for growth hormone naive patients

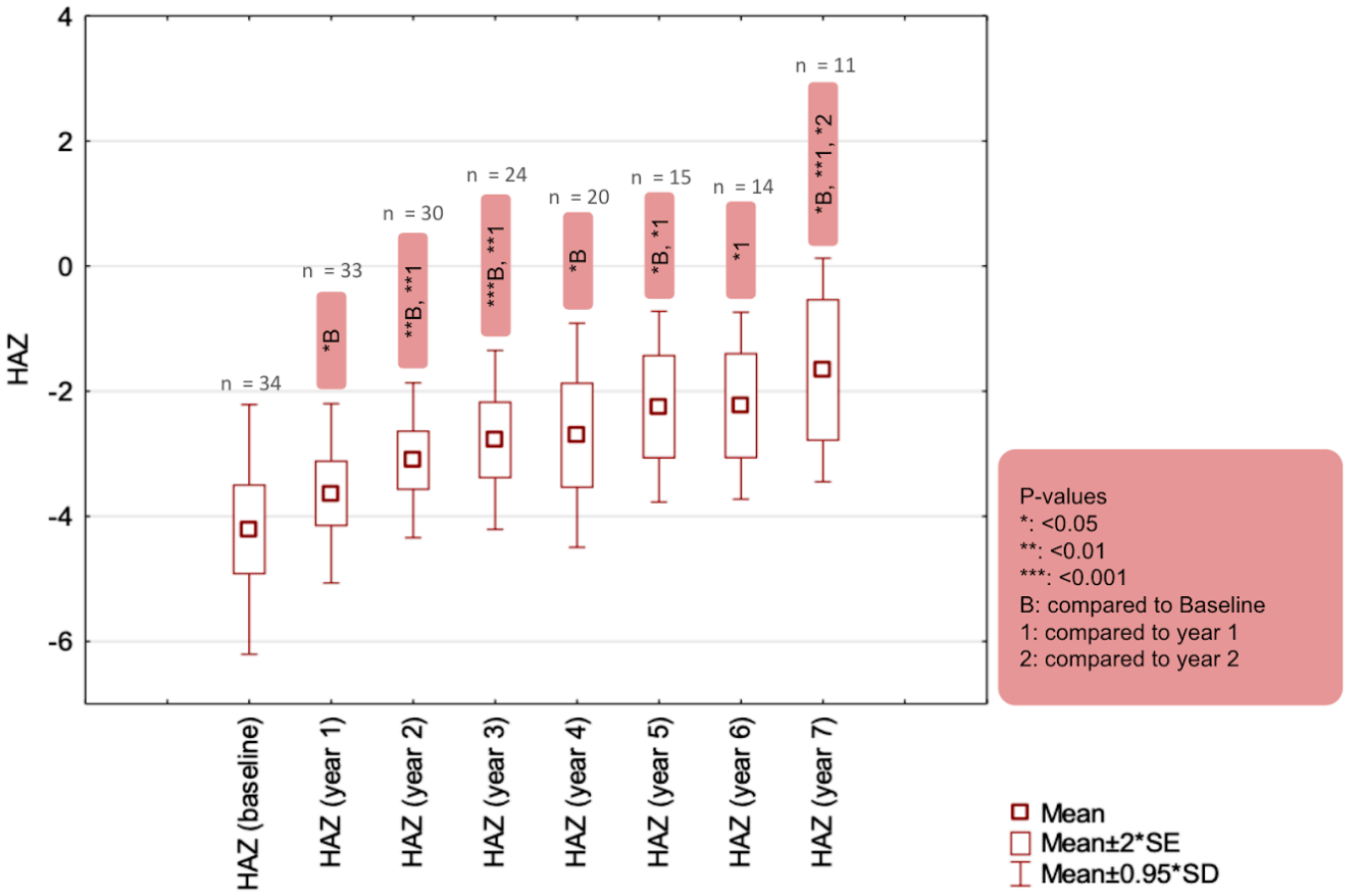

Figure 2: Mean HAZ over time for patients on growth hormone therapy

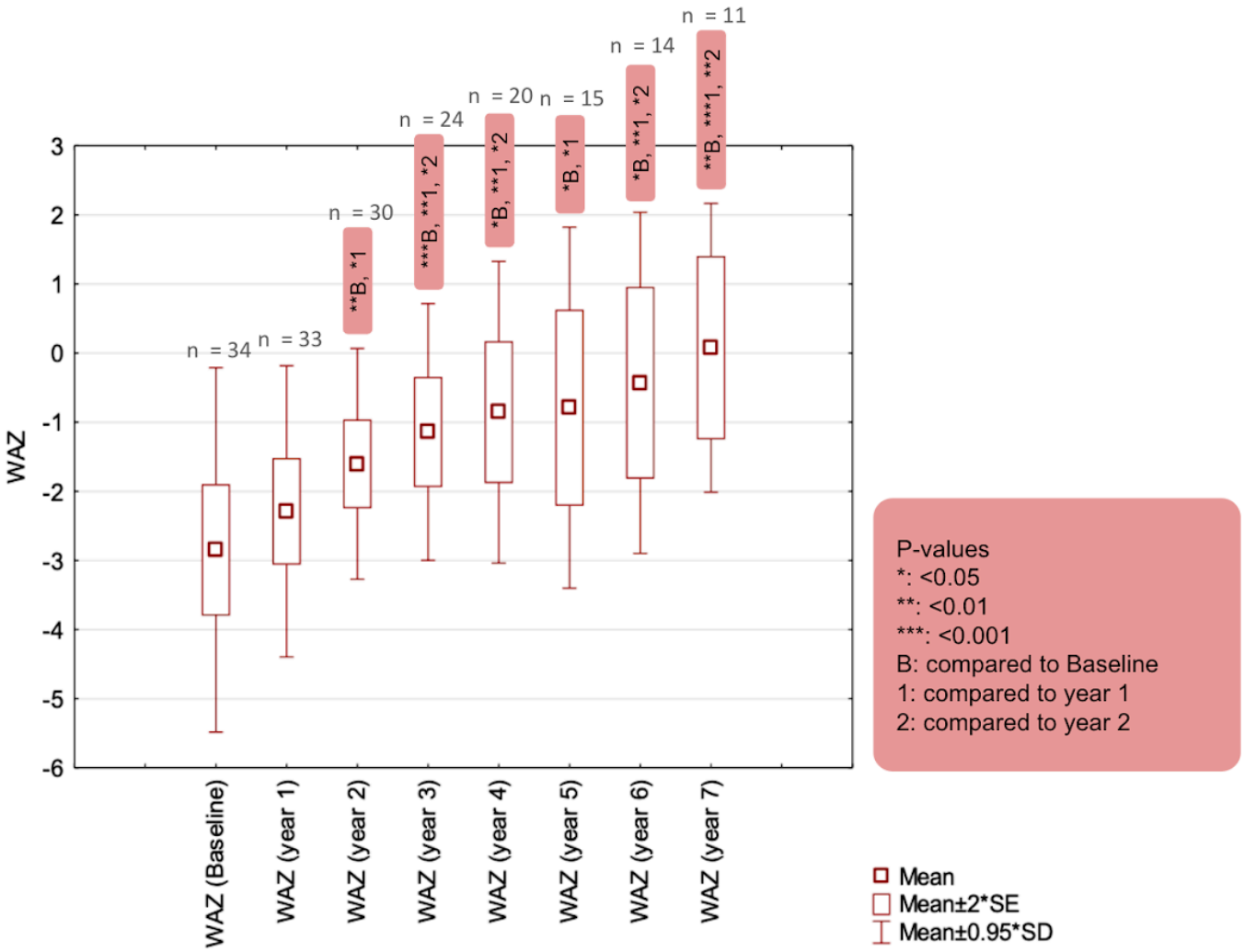

Figure 3: Mean WAZ over time for patients on growth hormone therapy

In the cohort of patients that received rGH therapy (Table 7), the IGF-1 values trended upward as therapy on rGH progressed, with a baseline mean of 9.7 nmol/L (SD ± 12.3) and median of 4.3 nmol/l (IQR 3.2 – 8.8) and by year eight on rGH treatment the mean was 26.7 nmol/l (SD ± 2.9) with a median of 26.7 nmol/l (IQR 25.6 – 27.7). As the levothyroxine dose increased over time, the TSH decreased with a baseline mean of 1.56 mIU/L (SD ± 1.75) and median of 0.5 mIU/L (IQR 0.05 - 2.9) to a mean at year eight of 0.04 mIU/L (SD ± 0.06) and a median of 0.01 mIU/L (IQR 0.01 – 0.01). The T4 value remained in the normal range with a baseline mean of 14.3 pmol/L (SD ± 5.8) and median of 13.1 pmol/L (IQR 9.5 – 18.1), to a mean of 15.8 pmol/L (SD ± 6.8) and a median of 16.8 pmol/L (IQR 16.1 – 20.1) at year eight (Table 7). The mean baseline cortisol level was 170.2 nmol/L (SD ± 196.8) with a median of 91 nmol/L (IQR 42 - 216). All study patients were pre-pubertal at presentation and had undetectable or low LH, FSH, oestrogen and testosterone values prior to the induction of

puberty. All study patients also had normal urea and electrolytes, as well as normal liver function test results.

Growth hormone, levothyroxine and hydrocortisone are the mainstays of treatment. During the first eight years on rGH, the highest dosage (mg/kg) was during year one of treatment with a mean of 0.027 (SD ± 0.009) and median 0.025 (IQR 0.024 - 0.029) (Table 7). By year eight, the dose had dropped to a mean of 0.022 (SD ± 0.005) and median of 0.023 (IQR 0.018 - 0.025). The mean levothyroxine dose (ug/kg) also decreased over time with a baseline mean of 3.3 (SD ± 2.2) and median of 3.4 (IQR 1.9 - 4.4), to a mean of 2.5 (SD ± 0.6) and median of 2.5 (IQR 1.9 – 3.1) by year eight (Table 7). The hydrocortisone dose (mg/m^2) at baseline was a mean of 17.2 (SD ± 6.2) and median 16.8 (IQR 12.5 - 20.0) and also decreased with time to a mean of 8.5 (SD ± 2.6) and median of 9.1 (IQR 5.6 - 10.7) by year eight (Table 7).

The majority of patients were compliant with their treatment, ranging from 50% to 85.3%, but this is obviously a limitation as it relies on patients' verbal reports and is both subjective and retrospective.

Table 7: Age, biochemistry, treatment and compliance as per year on growth hormone treatment

		Year on growth hormone treatment								
		Baseline	1	2	3	4	5	6	7	8
Age (years)	N	34	34	31	26	21	16	15	12	7
	Mean (SD)	6.2 (±5.0)	7.2 (±5.0)	8.3 (±4.9)	9.5 (±4.9)	9.5 (±4.6)	9.5 (±3.6)	10.3 (±3.6)	11.1 (±3.4)	12.4 (±2.5)
	Median (IQR)	5.2 (2.2 -9.5)	6.2 (3.0 – 10.8)	7.0 (4.2 – 11.8)	8.8 (5.3 – 12.8)	7.4 (6.2 – 13.0)	8.1 (6.9 – 12.4)	9.0 (7.8 – 11.6)	10.1 (8.9 – 11.8)	11.8 (11.0 – 13.8)
IGF-1 (nmo/L)	N	17	14	13	9	8	5	4	7	2
	Mean (SD)	10.1 (±12.3)	9.5 (±9.9)	20.8 (±17.9)	17.6 (±13.8)	22.9 (±36.1)	25.1 (±8.5)	18.9 (±6.2)	20.1 (±16.7)	26.7 (±2.9)
	Median (IQR)	4.3 (3.2 – 8.8)	5.60 (3.3 – 10.3)	13.7 (7.5 – 38.3)	17.9 (4.5 -28.1)	8.2 (3.1 - 23.6)	17.6 (20.0 - 25.4)	17.7 (15.1 - 21.5)	25.6 (4.1 - 34.4)	26.7 (25.6 – 212)
TSH (mIU/L)	N	28	20	26	18	16	15	13	11	5
	Mean (SD)	1.56 (±1.75)	1.21 (±1.93)	0.89 (±1.30)	0.66 (±1.75)	0.34 (±0.84)	0.57 (±0.89)	0.55 (±1.05)	0.28 (±0.68)	0.04 (±0.06)
	Median (IQR)	0.5 (0.05 - 2.9)	0.08 (0.01 - 2.23)	0.18 (0.01 - 1.58)	0.01 (0.01 - 0.33)	0.01 (0.01 - 0.06)	0.01 (0.01 - 0.93)	0.12 (0.01 - 0.69)	0.02 (0.01 - 0.05)	0.01 (0.01 – 0.01)
T4 (pmol/L)	N	29	20	26	19	15	15	13	11	5
	Mean (SD)	14.3 (±5.8)	16.7 (±6.7)	15.9 (±6.0)	16.6 (±7.4)	16.7 (±7.6)	15.0 (±5.8)	14.1 (±6.0)	16.0 (±4.2)	15.8 (±6.8)
	Median (IQR)	13.1 (9.5 – 18.1)	15.3 (11.0 - 19.8)	14.4 (12.4 - 19.0)	16.3 (13.2 - 18.4)	16.2 (13.5 - 20.4)	13.9 (11.2 - 20.1)	11.4 (10.5 - 19.2)	16.9 (14.4 - 19.4)	16.8 (16.1 – 20.1)
rGH (mg/kg)	N		34	31	26	21	16	15	12	7
	Mean (SD)		0.027 (±0.009)	0.025 (±0.006)	0.025 (±0.005)	0.024 (±0.008)	0.026 (±0.005)	0.025 (±0.005)	0.024 (±0.006)	0.022 (±0.005)
	Median (IQR)		0.025 (0.024 - 0.029)	0.025 (0.022 - 0.028)	0.024 (0.022 - 0.027)	0.025 (0.022 - 0.027)	0.026 (0.024 - 0.029)	0.025 (0.022 - 0.026)	0.024 (0.019 - 0.028)	0.023 (0.018 - 0.025)
Levothyroxine (ug/kg)	N	29	28	25	20	18	15	14	11	6
	Mean (SD)	3.3 (±2.2)	3.3 (±2.1)	3.4 (±2.2)	3.0 (±2.1)	3.0 (±2.0)	3.4 (±2.0)	3.2 (±1.8)	2.5 (±0.7)	2.5 (±0.6)
	Median (IQR)	3.4 (1.9 - 4.4)	3.4 (2.0 - 5.0)	3.3 (2.0 - 4.5)	2.9 (2.0 - 3.7)	2.9 (2.2 - 3.4)	3.1(2.0 - 4.1)	2.8 (2.3 - 3.5)	2.2 (1.9 - 3.5)	2.5 (1.9 – 3.1)
Hydrocortisone (mg/m^2)	N	21	19	17	14	12	10	9	8	3
	Mean (SD)	17.2 (±6.2)	14.7 (±4.3)	13.3 (±3.1)	12.0 (±2.4)	11.4 (±2.9)	10.8 (±2.8)	10.5 (±3.6)	8.9 (±2.8)	8.5 (±2.6)
	Median (IQR)	16.8 (12.5 - 20.0)	15.1 (12.1 - 16.1)	13.7 (10.9 - 14.8)	12.5 (9.9 - 13.6)	11.4 (8.8 - 13.8)	11.4 (8.1 - 12.7)	10.9 (7.1 - 14.4)	8.7 (6.3 - 11.6)	9.1 (5.6 – 10.7)
Compliance	Yes	29 (85.3%)	26 (78.8%)	20 (66.7%)	19 (79.2%)	13 (70%)	10 (66.7%)	10 (71.4%)	7 (63.7%)	3 (50%)

*See TSH and T4 reference range values on page 38

To assess a positive outcome, the proportion of patients that achieved HAZ scores greater than -2 were assessed per year on rGH treatment and results are depicted in Figure 4. A large number of patients presented during the neonatal period with normal lengths for their age at birth, and their HAZ worsened as they grew from birth and then improved on rGH. At baseline, 29.4% of patients had a HAZ of greater than -2, and at one year on rGH treatment, this number dropped to 14.7%, but then increased steadily from 15.2% at year two to 63.7% by year eight on rGH treatment. Although this trend is marginally significant, the small number of patients limit meaningful comparisons (p = 0.072) as shown in Figure 4.

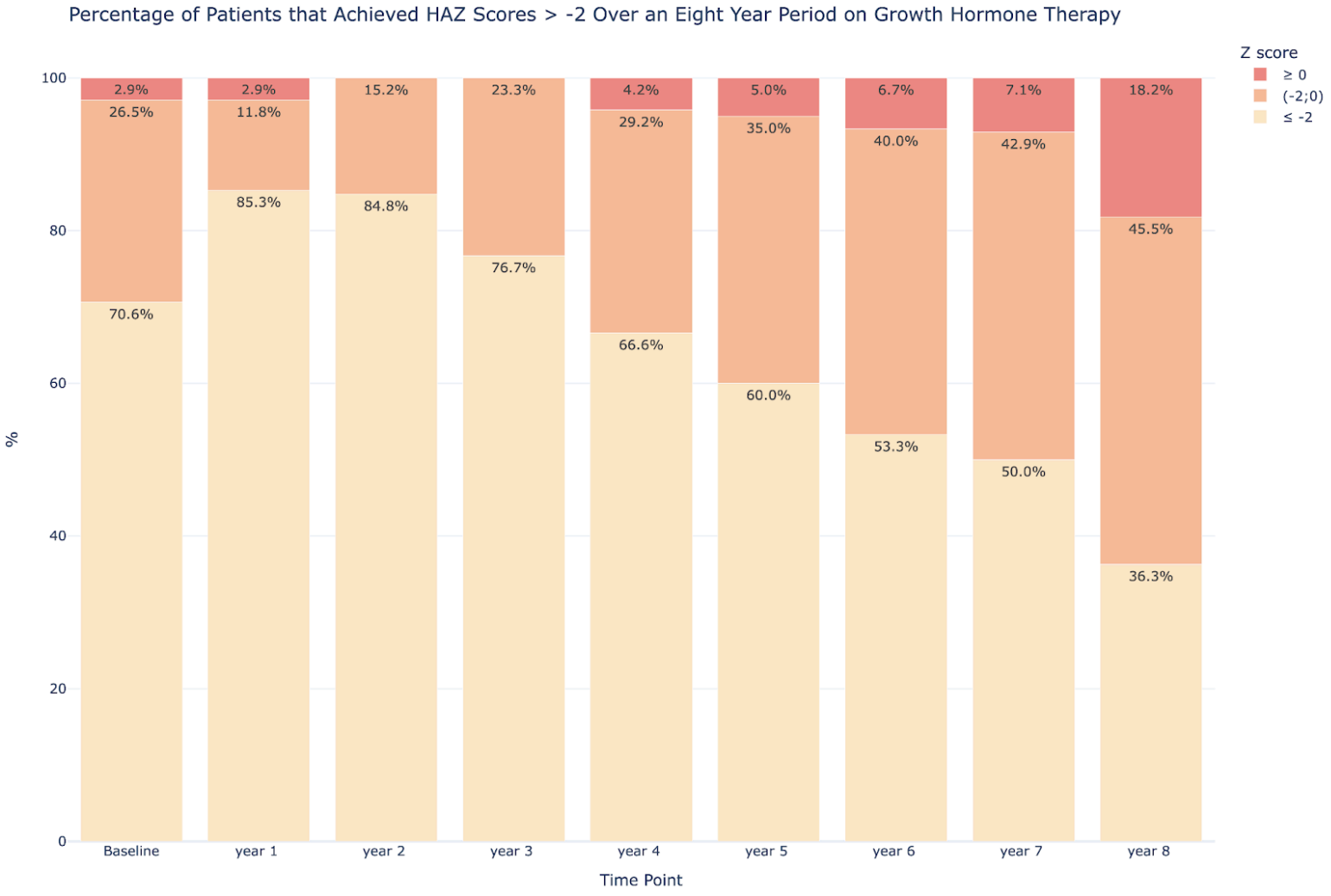

Figure 4: The percentage of patients that achieved HAZ > -2 over an eight year period on growth hormone therapy

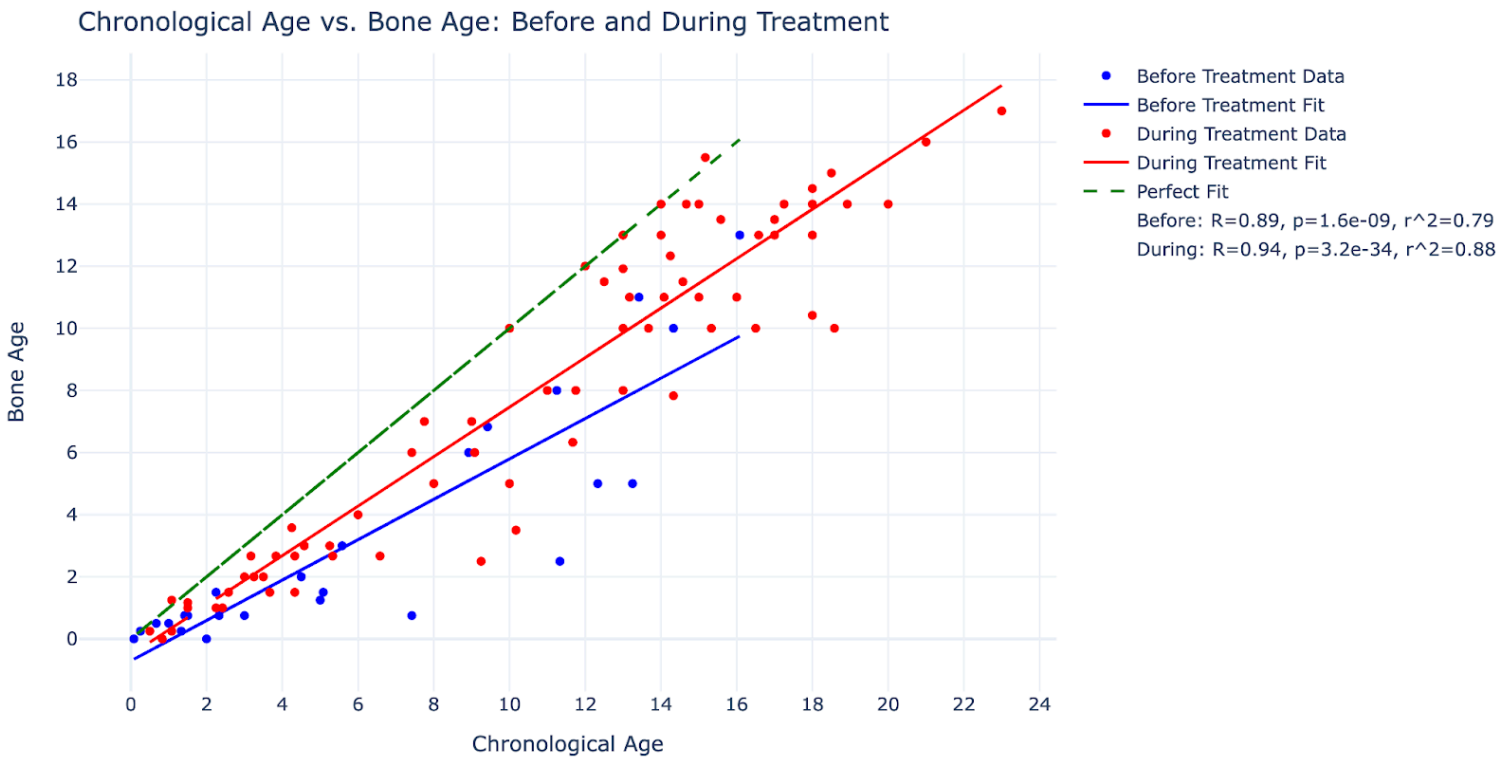

Figure 5: Chronological age vs bone age before and during growth hormone treatment

The mean delay between bone age and chronological age before treatment was 2.6 years (SD ± 2.4) with a median of 2.4 years (IQR 0.67 - 3.4), and improved to a mean of 1.2 years (SD ± 1.3) with a median of 0.8 years (IQR 0.3 - 1.4), after one year on rGH therapy. Only one patient (2%) did not have a delay in bone age before treatment and was started on rGH based on neonatal hypoglycemia. Figure 5 depicts the bone age as compared to the chronological age before rGH initiation as well as during treatment. This figure demonstrates that the difference between bone age and chronological age is smaller on treatment as compared to before treatment, with the treatment line being closer to the line of best fit, where chronological and bone age are equal. The 'During Treatment' line has an r^2 of 0.88 and a statistically significant p-value of <0.00001, whereas the 'Before Treatment' line has an r^2 of 0.79 and a statistically significant p-value of <0.00001, demonstrating the positive impact rGH has on growth.

The bulk of patients (97.8%) were pre-pubescent at presentation with a Tanner stage 1, with the exception of one male patient who presented at 15.3 years of age from the Adult Endocrine Clinic with Tanner stage 1 external genitalia and Tanner stage 2 pubic hair. Three females progressed into puberty, of which all of them progressed spontaneously without the need for oestrogen therapy. Ten male patients progressed into puberty, of whom nine required testosterone replacement therapy for induction or progression of puberty, while one entered into spontaneous puberty, and progressed unaided. Figure 6A and 6B demonstrate the progression through the Tanner stages for males and females respectively. The mean age at which testosterone replacement therapy was initiated was 17.8 years (SD ± 1.8) with a median of 18.6 years (IQR 17.4 - 19.4). Out of the nine males on testosterone replacement therapy, only five progressed to Tanner stage 2, three remained pre-pubertal, and only one progressed to Tanner stage 3 for external genitalia. All nine males who received testosterone replacement therapy progressed past Tanner stage 2 for pubic hair with two progressing to stage 3, four progressing to stage 4 and three progressing to stage 5. The one male that progressed through puberty spontaneously from 14.6 years reached a Tanner stage 2 for external genitalia and a Tanner stage 4 for pubic hair before defaulting. Of the three females who progressed into puberty, the first progressed to Tanner stage 3 for both breast development and pubic hair, the second patient progressed to Tanner stage 5 for both breast development and pubic hair and the third patient reached Tanner stage 3 for breast development and Tanner stage 2 for pubic hair before being transferred to the adult unit. The mean age in which females progressed into puberty was 12.6 years (SD ± 3.2) with median of 10.8 years (IQR 10.7 - 13.6), and a mean of 17 years (SD ± 2.2) with a median of 17 years (IQR 15.2 - 18.6) for males (Figure 6A and 6B).

	Age at TRT initiation		Tanner Stage				
			1	2	3	4	5
Patient 1	17.4y	G		18.3			
		P		17	17.6	18.3	19.4
Patient 2	19.5y	G					
		P		15.2	15.8		
Patient 3	16.2y	G		16.5			
		P		16.5	17.4	19.3	
Patient 4	19y	G					
		P		19.8	20.8		
Patient 5	19.3y	G		16.8			
		P		14.5	16.8	22.5	25.3
Patient 6	14y	G					
		P		14	14.9	16	
Patient 7	18.6y	G		18.6			
		P		18.6	19.5	26.3	27.6
Patient 8	17.6y	G		17.2	18.3		
		P		17.8	18.0	18.3	
Patient 9	19.3y	G		26.3			
		P		20.4	25.2	27	
Patient 10	nil	G		14.6			
		P		14.6	15.4	16.5	

G: External genitalia
P: Pubic Hair
B: Breast development
TRT: Testosterone replacement therapy
Each cell value represents the age at which each Tanner stage was reached

Figure 6A: Progression of puberty in males with Tanner staging

		Tanner Stage				
		1	2	3	4	5
Patient 1	B		10.8	14.8		
	P		13.5	14.3		
Patient 2	B		10.8	11.4	13	16.1
	P		12	14	15.1	16.2
Patient 3	B		16.3	19.3		
	P		19.4			

G: *External genitalia*
P: *Pubic Hair*
B: *Breast development*
Each cell value represents the age at which each Tanner stage was reached

Figure 6B: Progression of puberty in females with Tanner staging

Looking at the complications of hypopituitarism, none of the patients had an adrenal crisis on presentation, but four (8.7%) of the patients had an adrenal crisis at some point during the course of their disease, with one patient having three episodes while the other three patients had one episode each. Twenty (43.5%) patients experienced hypoglycemia with or without seizures during the course of their disease. The highest number of episodes experienced by a single patient was eight, with the mode being one episode experienced by ten patients. None of the patients developed diabetes insipidus.

Discussion

This study, conducted at a paediatric endocrine unit in South Africa, illustrates the presentation, biochemical and radiological observations, as well as the management and treatment outcomes of a primarily Black paediatric patient group with hypopituitarism. These findings are pertinent due to the paucity of data on hypopituitarism in a semi-urban area and middle-income country. It has been demonstrated that panhypopituitarism is more common than CPHD, and the majority of our population were Black males. By year eight on rGH treatment, 63.7% of the cohort had achieved a normal height. The most frequent MRI finding was pituitary stalk interruption syndrome (45.3%). Timely diagnosis and individualised management strategies are essential for achieving positive outcomes in the treatment of hypopituitarism. There is still a wealth of knowledge to be uncovered in this field.

Hypopituitarism has a male predominance seen across the board in multiple different studies. Jakobsen et al. found 68.6% of their cohort in Denmark to be males[5], similar to Hassan et al. with 64.7% being males in their Sudanese study[17]. Our study revealed a higher male predominance of 78.3% with a male:female ratio of 3.6:1, similar to the findings of Kornete et al. in Latvia, at 78.2%.[18] Reasons accounting for a male predominance include X - linked genetic factors, as well as the fact that males demonstrate signs of hypovirilization, resulting in earlier detection and investigation compared to females. Short stature is also of greater concern in male patients and would spur a higher chance of referral and follow up.[5] The mean age of the patients at presentation was 4.7 years (SD ± 5.3) with a median age of 2.3 years (IQR 0.2 - 7.4) which is younger than the findings of Jakobsen et al, who found a median age at diagnosis of 6.2 years (IQR 0.01 - 19).[5]

Even though the majority of patients were referred from the general paediatrics wards at CHBAH (28.3%), a considerable number of patients were referred from the Neonatal Unit (17.4%). A large proportion of our patients (43.5%) in the study were less than a year old at presentation, demonstrating that many of these patients presented early on in life. Jakobsen demonstrated similar findings with a peak diagnosis before the age of one, with smaller peaks at age 6, 11 and 14 years.[5] This is reassuring as a timely diagnosis allows for earlier commencement of hormonal replacement therapy.[19]

The anthropometry on presentation demonstrated that patients were severely stunted, and thus severely underweight for age, but not wasted, with a normal BMI and normal head circumference. There was no significant difference in the baseline anthropometry between the cohort of patients who received rGH versus those that did not. It is therefore a fair comparison to track the HAZ over time between the two groups, as detailed below.

In our study, the most common clinical finding at presentation was short stature seen in 32 (70%) patients. Of the male patients, 61% presented with a micropenis or cryptorchidism. Other common features included hypoglycemia and seizures. BenRajab et al. had similar findings with short stature being the most common clinical presentation at 68.8% followed by hypoglycemia and delayed puberty.[19] A common triad seen in our neonatal population includes hypoglycemia, neonatal jaundice and hypovirilization in our male population. Similar results were reported by Hietamaki, who identified a neonatal phenotype in 66% of their study participants. This phenotype included: hypoglycemia associated with an apnoea or seizure, hypoglycemia requiring intravenous dextrose for more than three days or persistent hypoglycemia past day three of life; prolonged neonatal jaundice; and a male genital phenotype of cryptorchidism or micropenis.[20] A recommendation would be that if a patient fulfils two out of the three features of this triad, a high index for suspicion of hypopituitarism should be maintained, prompting further investigation.

Dysmorphic features were also seen in a substantial number of patients (45.7%), leading one to consider a genetic or syndromic cause of hypopituitarism in these patients. The dysmorphic features noted in our study were frontal bossing, low set ears, midface hypoplasia, a flat nasal bridge, cherubic facies, hypertelorism, epicanthic folds, clinodactyly, micrognathia, microcephaly and scaphocephaly. Hietamaki found that many patients presented with dysmorphism as well, namely craniofacial abnormalities in 27% of patients and eye abnormalities in 33% of patients in their study.[20]

Panhypopituitarism (three or more pituitary hormone deficiencies) was more prevalent, seen in 67% of our patients, with only 33% having CPHD (two pituitary hormone deficiencies). This distribution contrasts with the findings of Hietamaki, where panhypopituitarism was diagnosed in only 30% of patients.[20] Interestingly, isolated growth hormone deficiency preceded the development of hypopituitarism in 14% of patients in Hietamaki's study. This

highlights the importance of annual screening in individuals with one hormonal deficiency, as they are at risk of developing additional hormonal deficiencies over time.[20]

Our study revealed that 67.4% of patients underwent MRI of the brain with pituitary views, and among those who had this imaging, 45.3% showed evidence of pituitary stalk interruption syndrome. These findings suggest that pituitary stalk interruption syndrome is a prevalent and significant aetiology of hypopituitarism. The next most common finding was an ectopic posterior pituitary gland. As expected, all patients that had pituitary stalk interruption syndrome on MRI had panhypopituitarism. Wang et al. demonstrated that more severe forms of pituitary stalk interruption syndrome correlated with more frequent and worse pituitary hormone deficiencies.[21] Our study had three (9.7%) MRI findings consistent with septo-optic dysplasia, that is bilateral optic nerve hypoplasia in two MRIs and cerebral malformation with an absent corpus callosum in the third MRI. Of the MRIs that were conducted, 74.2% showed pituitary manifestations, 12.9% had extra-pituitary manifestations and 12.9% were normal. Hietamaki's study included 41 patients who had MRIs, of which all patients had abnormalities,[20] in contrast to our study. Ninety percent of the MRIs in their study had classic pituitary abnormalities, which is higher than our study. Fifty-one percent of MRIs in their study showed pituitary stalk interruption syndrome, with a posterior ectopic pituitary gland being the second most common finding, mirroring the findings of our study. Septo-optic dysplasia was more prevalent in their study at 27%, and was found to be associated with schizencephaly, local polymicrogyria and local cortical structural abnormalities.[20] Kornete's study revealed that in the CPHD group, a normal MRI finding was the most prevalent, consistent with our findings. However, unlike our study, a hypoplastic anterior pituitary was the second most common finding. In contrast, the panhypopituitarism group exhibited a hypoplastic anterior pituitary as the most frequent finding, with an abnormal pituitary stalk as the second most common observation.[18] Kornete, however, did not group all the features of pituitary stalk interruption syndrome together, therefore, the frequency of this syndrome cannot be adequately assessed and compared to our study.[18] These results demonstrate the importance of pituitary imaging in early diagnosis, and also in prediction of hormonal deficiencies that are present and will become apparent as the child ages. Even though it is an expensive modality, it is at the cornerstone of management of patients with hypopituitarism. Shelton et al. explains that pituitary abnormalities detected on screening MRI are 100% sensitive and 92% specific indicators of hypopituitarism in children who present with optic nerve hypoplasia,[22] making it an invaluable investigation. For the

patients in our study who did not have an MRI conducted, access to this modality as well as resource limitation was the main reason why it was not done. Availability, access and cost of MRI remains a huge barrier in low and middle income countries.[23]

Critical samples were performed at the time of hypoglycemia in nearly half of the patients, and were suggestive of hypopituitarism in all patients. All patients were hypoglycemic at the time with low growth hormone, cortisol, insulin and C-peptide values. The lactate levels were normal. With a normal physiological response to hypoglycemia, insulin production should be suppressed which would result in low insulin, and C-peptide levels and an increase in fatty acid oxidation. Counterregulatory hormones, such as cortisol and growth hormone, should rise.[24] In growth hormone deficiency, the hypoglycemia is due to decreased lipolysis and decreased glycogenolysis. In cortisol deficiency the hypoglycemia is as a result of increased insulin sensitivity, decreased endogenous glucose production and increased glucose oxidation. To note, the counterregulatory hormone response involving growth hormone and cortisol may not peak at the same time as the blood glucose level drops, and as such, additional investigations must be done to evaluate for growth hormone or cortisol deficiency if the levels do not rise sufficiently when hypoglycemic.[25]

Provocative testing of the hypothalamic-pituitary axis is an important investigation in diagnosing growth hormone deficiency. The usual provocative stimuli include clonidine, glucagon, insulin-induced hypoglycemia, levodopa, arginine and growth-hormone-releasing hormone (GHRH).[25] In our study, the most frequently conducted investigation was the clonidine stimulation test, with only a few patients having had a glucagon stimulation test. Clonidine is a selective alpha-agonist and it acts as a stimulus for growth hormone release via GHRH secretion.[26] Yackobovitch-Gavana et al. found the clonidine stimulation test to be more effective than the glucagon stimulation test in testing the GH – IGF-1 axis in the diagnosis of growth hormone deficiency in children as clonidine is less affected by the pubertal status and therefore has a lower error rate across all age groups.[26] In our study, the test confirmed a growth hormone deficiency in all patients on whom it was conducted as there was a lack of surge in the growth hormone value as the test progressed. A peak GH response of < 3 μg/L suggests GH deficiency, 3 - 7 μg/L suggests partial GH deficiency and > 7 μg/L is a normal response.[16] The highest mean growth hormone value in our study was 1.9 μg/L at 90 minutes which is suggestive of growth hormone deficiency. This finding is in

keeping with literature as growth hormone deficiency is the most common abnormality noted, and often the first deficiency in hypopituitarism.[18,19] Priming with sex hormones is a valuable way in provoking the axis, with 35.7% of the patients in our study getting primed. Sex hormones increase growth hormone secretion by regulating the amount of GHRH that gets secreted. As per guidelines, girls older than 11.5 and boys older than 13.5 years of age who are prepubescent are primed with sex hormones, that is β-estradiol two days before testing in females and testosterone intramuscularly 10 days before the test in males.[26]

In our study, 34 patients (74%) received rGH therapy, and 12 (26%) did not. This allows us to compare anthropometry over time for each group. Patients did not receive rGH for several reasons, including caregiver refusal, unsuitability due to severe global developmental delay or neurological conditions, and limited resources in settings where rGH was reserved for more appropriate candidates. Additionally, some patients defaulted on follow-up visits early in their care, preventing the initiation of rGH treatment. For the first three years of follow up, the HAZ score in the growth hormone naive cohort worsened over time from a mean z-score of -3.4 (SD ± 2.6) with a median of -3.3 (IQR -5.7 - -1.5), to a mean of -4.5 (SD ± 0.8) with a median of -4.7 (IQR -5.1 - -3.8). The converse was observed for the cohort that received rGH as their HAZ improved over time from severely stunted to normal height, with a mean of -4.2 (SD ± 2.1) and a median of -4.3 (IQR -6.1 - -3.2) at presentation to a mean of -1.7 (SD ± 1.9) with a median of -1.7 (IQR -2.9 - -0.8) by year seven on rGH treatment. All comparisons between baseline and year 1 to 5 as well as baseline to year 7 were statistically significant, but the most significant comparison (p-value < 0.001) was between year 3 on rGH treatment compared to baseline. Kornete et al. observed a considerable improvement in the HAZ after just one year of rGH treatment, with a HAZ of -3.0 in their CPHD group and -2.8 in their panhypopituitarism group, to -2.4 and -1.8 respectively after one year on rGH treatment. In the CPHD cohort, the median growth rate was 9.0 cm with a median weight gain of 4.8 kg, and in the panhypopituitarism cohort, the median growth rate was 11.7 cm with a median weight gain of 2.9 kg after a year on treatment. They, however, did not see an improvement in WAZ measurements after a year on rGH treatment.[18] Bar et al. also had positive findings with an improvement in the HAZ after one year on rGH treatment of 1.2 standard deviations, and 1.7 standard deviations after two years on treatment.[27] In our study, the WAZ improved from moderately underweight for age, to normal weight for age with a mean of -2.8 (SD ± 2.8) and median of -2.3 (IQR -3.9 - -1.5), reaching a mean of 0.1 (SD ± 2.2) and a median of 0.2 (IQR

-0.8 – 1.8) by year 7. Comparisons between year 7 and 1, and year 3 and baseline were the most significant (p-value < 0.001). Literature demonstrates that the HAZ should improve the most significantly during the first three years on rGH therapy, as seen in our study, with a gradual decline thereafter.[28] Hage et al. recommends that response to rGH therapy is considered poor if the z-score improvement is less than 0.4 for the first year on treatment. Reasons for this include compliance issues, improper administration, hypothyroidism, complete osseous maturation as well as the presence of growth hormone antibodies.[29] In that regard, our study had a good outcome with an improvement in the HAZ score of 0.6 in one year on rGH therapy.

Hietamaki assessed a group of patients who started to growth falter during the first six months of life and were subsequently started on rGH therapy. The mean birth length z-score was -0.4. The median age at which growth faltering was noticed was 0.3 years with a HAZ of -3.0. The median time to start rGH treatment from the time growth faltering was noticed was 1.9 years. At the last height measurements, the HAZ had improved to -0.6 at a median age of 16.7 years.[20] This study demonstrates that these patients were born with a normal length and experienced growth faltering within the first few months of life. It also demonstrates that there is a lag in time from noticing the pathology to investigation and management. This phenomenon should inspire earlier detection and management.

The aim of growth hormone therapy is to achieve a normal height (HAZ score > -2). By year eight on rGH therapy, only 63.7% of patients had normal HAZ scores, being suboptimal, mostly attributed to compliance issues. Maghnie et al. found that the median duration of rGH therapy in males was 11.5 years and 8.8 years in females with the z-score of final adult height being -0.7 in males and -0.8 in females, demonstrating that patients with hypopituitarism can reach a normal final height on appropriate therapy.[30] The cost implication of this in South Africa is quite significant as each centimetre of height achieved with rGH treatment would cost approximately R127 000 to R181 000.[31] This limits successful treatment for our patients, which may be remedied by the advent of more affordable growth hormone therapy.

The medical treatment for hypopituitarism seeks to replace deficient hormones and is comprised of growth hormone replacement, thyroid hormone replacement, hydrocortisone, vasopressin replacement and sex hormone replacement.[9] Our study revealed that the highest

rGH dose was during year one of treatment with a mean of 0.027 mg/kg/day (SD ± 0.009), which is 0.189 mg/kg/week, with the dose dropping to 0.022 mg/kg/day (SD ± 0.005) by year eight. The recommended optimal dose of rGH to treat hypopituitarism is 0.022 to 0.035 mg/kg/day with a maximum dose of 0.3 mg/kg per week.[27] Our study's dosages were at the lower range of normal, with the capacity to increase the dose for optimal results. Reasons for suboptimal dosage include not increasing the dose as per weight increases during follow-ups. Maghnie reported a median dose of rGH of 0.18 mg/kg/week, being similar to our study, with similar outcomes.[30] De Castro et al. had higher rGH doses of 0.27 mg/kg/week and observed a better growth velocity in the first year of treatment, with 76.6% of patients having a good response to treatment.[32] Along with the rGH dose, the levothyroxine and hydrocortisone doses also decreased over time. The levothyroxine dose was adjusted to thyroid function tests. The majority of patients remained euthyroid on the medication, and thus, their thyroid hormone replacement requirements decreased with time. The highest hydrocortisone dose (mg/m^2) was also on initiation with a mean of 17.2 (SD ± 6.2) which is higher than the recommended dosage, and decreased to a mean of 8.5 (SD ± 2.6) by year eight. The usual starting dose of hydrocortisone is 9 - 12 mg/m^2 in neonates, and is then titrated with age. The dose is higher in neonates as compared to infants and older children as they have higher cortisol secretion rates.[33] None of the patients in our study required Desmopressin for the treatment of diabetes insipidus.

Biochemically, IGF-1 values improved with time on rGH, reflecting the success of the treatment in this cohort. On levothyroxine, the TSH and T4 values were indicative of patients generally being euthyroid and compliant with treatment. The mean baseline cortisol level was low with a mean of 170.2 nmol/L (SD ± 196.8), representing ACTH deficiency. Low LH, FSH, oestrogen and testosterone values were noted in the group at baseline due to patients being pre-pubertal prior to the induction of puberty. These sentiments are echoed by Braslavsky et al. who explained that a serum LH and testosterone surge is a discernible sign of postnatal GnRH activation in males and thus, repeatedly low concentrations of these hormones are indicative of hypogonadotropic hypogonadism in boys under 6 months of age.[34] Findings also have to take compliance into account, as this is the biggest reason laboratory measurements do not correlate to treatment administered and the expected outcome. Our study had varying levels of compliance ranging between 50 to 85.3%, but may be unreliable due to the subjective nature of gauging compliance from patients.

Bone age is an important investigation that is carried out in patients with hypopituitarism, more specifically, with growth hormone deficiency. The mean delay between bone age and chronological age before treatment was 2.6 years and improved to 1.2 years after a year on rGH treatment. Kornete et al. found that the mean difference was 1.6 years in the CPHD group, and 2.1 years in the panhypopituitarism group, before treatment initiation,[18] with similar findings from Bar et al. with a delay of 2.1 years in the combined CPHD/panhypopituitarism group.[27] Both of these studies demonstrate a shorter delay compared to our study. The majority of patients' bone ages did not catch up to their chronological ages on rGH therapy. An improvement was however noticed, as evidenced by the increase in correlation between bone age and chronological age before and on treatment ($r^2 = 0.79$ before treatment, improving to 0.88 on treatment). Reasons to explain why bone age did not converge to chronological age could be due to the fact that patients that were responding well to rGH therapy did not have X-rays done to check their progress, whereas the patients who were non-compliant or had a poor response to treatment were the ones on whom X-rays were done. This translates into the poor outcomes being reflected only. Added to this, poor compliance amongst the cohort also explains suboptimal results.

All patients were prepubescent at presentation with the exception of one male referred at the age of 15.3 years from Adult Endocrine Clinic (97.8%). Of note, all three females progressed into puberty spontaneously, whereas 90% (9/10) of males required medical induction of puberty. Added to that, the females also progressed through puberty a lot earlier as compared to their male counterparts. One female had pituitary stalk interruption syndrome, while the other had an ectopic posterior pituitary on MRI. This demonstrates that even though the females had severe forms of hypopituitarism as well, they still fared better than the males. The mean age at which testosterone replacement therapy was initiated was 17.8 years (SD ± 1.8), with males progressing through puberty from a mean age of 17 years (SD ± 2.2). Females began the progression at a mean age of 12.6 years (SD ± 3.2), which is significantly younger. Hietamaki demonstrated contrasting results compared to our study, where females were the recipients of sex steroid replacement therapy in 53% of the cases, and induction was started at a mean age of 14.1 years (SD ± 1.9) for both males and females.[20] Maghnie demonstrated that the mean age of patients at the start of pubertal induction with sex steroid replacement therapy was considerably lower and more physiologically correct in their study as compared to the standard in other studies they researched, at a median age of 14 years in

males and 13.5 years in females, versus 18.5 to 20.5 years in males and 18.5 to 19.5 years in females in the other studies. They found that an earlier induction of puberty did not affect patients' final adult height before age 18, but height was moderately increased if induction was started after 18 years old.[30] Their study aimed to decrease the side effects of prolonged rGH treatment as well as the negative psychological impact on adolescents due to the delay in their secondary sexual characteristics.[30] This study deviates from the norm, with competitive results, suggesting that this is a potential area for greater research to be conducted.

The most frequent complication was hypoglycemia with or without seizures experienced by 20 (43.5%) patients during the course of their disease, with an adrenal crisis occurring infrequently in only four (8.7%) patients. Interestingly, none of the patients developed diabetes insipidus. Ravichandran et al. had similar findings regarding diabetes insipidus, but explains that there are a few studies, albeit rare, in which diabetes insipidus is seen in pituitary stalk interruption syndrome due to the osmo-receptor dysfunction.[35] A reason for the low incidence of diabetes insipidus in our study was that the patient population encompassed congenital, instead of acquired hypopituitarism. Hassan's study included patients with acquired hypopituitarism, largely secondary to craniopharyngiomas, and found that nearly all patients who had a tumour resection surgery had at least temporary vasopressin deficiency.[17] Radiation also increases the risk of diabetes insipidus, of which none of our patients were exposed to.[17]

Congenital hypopituitarism can be caused by genetic variants of the genes involved in the embryological development of the midbrain and the pituitary gland, namely *HESX1, LHX3, LHX4, POU1F1, PROP1, SIX6, OTX2, PITX2, GLI2,* and *SOX3*.[5] Syndromic as well as non-syndromic causes of congenital hypopituitarism exist, with autosomal as well as X-linked patterns of inheritance being implicated.[36] Unfortunately, the cost and intricate technology required to investigate these patients is not feasible in our population. As a result, we do not know the frequency nor type of mutations that exist in our population. At least four of our patients had features consistent with a syndromic form of hypopituitarism. Septo-optic dysplasia requires at least two of the three criteria to be met: optic nerve hypoplasia; pituitary hormone abnormalities; and midline brain defects including agenesis of the septum pellucidum or corpus callosum.[37] The aetiology is multifactorial and includes viral infections, environmental teratogens, vascular or degenerative damage and antenatal exposure to drugs and alcohol, along with mutations in *HESX1, SOX2* and *SOX3* genes.[17,36] Three patients

(6.5%) in our study had septo-optic dysplasia, two of which had bilateral optic nerve hypoplasia and the third who had a cerebral malformation with an absent corpus callosum. Literature describes the incidence to be 1 in 10 000 to 1 in 50 000 live births,[38] with an unknown incidence in our population. One female patient presented with pituitary stalk interruption syndrome as well as a Mullerian duct abnormality of uterine hypoplasia and agenesis of right ovary on MRI, along with dysmorphic features of midface hypoplasia, widely spaced nipples, hypertelorism, flat nasal bridge and epicanthal folds, also in keeping with a syndromic form of hypopituitarism. The international GENHYPOPIT network conducted whole genome sequencing and discovered that the prevalence of identified mutations was 7.3% in index cases and 29.5% in familial cases. Of note, 3.8% of mutations were found in patients with pituitary stalk interruption syndrome. *PROP1* was the highest implicated mutation in non-syndromic hypopituitarism in neonates with a higher prevalence from consanguineous parents due to its recessive nature of inheritance.[39] Features, in unison, suggestive of an underlying mutation are combined pituitary hormone deficiency, greater patient-parent height difference, low growth hormone peak and young age.[40] This range of features provides a good assembly of patients to begin genetic investigation on, once technology and funding improve in our setting.

Limitations

Limitations of our study stem from its reliance on patient clinical records, which may affect the robustness of our results, as they are contingent upon the accuracy and completeness of the recorded information. Assessment and efficacy of treatment administered is difficult to ascertain as adherence remains a large barrier to good outcomes in our setting. Following the transfer of our patients to the Adult Endocrine Unit, a lack of continuity in follow-up resulted in uncertainty regarding the completion of puberty and fertility potential for our patients.

Recommendations

This study displays the myriad of further research potential that exists around the topic of hypopituitarism. Since the dose of rGH currently being administered in practice is on the lower end of the spectrum, we recommend increasing the dose in keeping with guidelines. Our study has proven just how fundamental MRI is in diagnosis and management, and thus our hope for the future is to improve accessibility to this modality, with the possibility of screening MRIs in neonates who present with possible features of hypopituitarism. We

recommend following up our paediatric cohort into adulthood, looking at their hormone profile and fertility potential as they age. Conducting genetic research on this topic is vast and untouched in our country and continent and will definitely pave the way to better understanding hypopituitarism in the future.

Conclusion

Hypopituitarism is a rare, but important disease in our paediatric population. Early diagnosis and management enables patients to have the best outcomes with regard to growth, metabolism, homeostasis, neurocognition and pubertal development. Our clinical audit revealed that hypopituitarism is more prevalent in males, and the most common presenting feature was short stature. Early key features include hypoglycemia with poor growth, which should raise a high index of suspicion. MRI is an invaluable tool in diagnosis, with the majority of patients having abnormal pituitary gland findings. The patients were predominantly severely stunted at the onset, but a large proportion achieved normal height with rGH, validating its efficacy. Due to the paucity of data available in our population, the research potential associated with hypopituitarism in the paediatric population is boundless, which will pave the way for us to better understand and help improve the lives of the children that live with this complex disease.

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IGF-1 reference range values [16]

IGF reference range values (nmol/l)

Females		Males	
< 6 years	7 - 21	< 6 years	7 - 21
6 - 7 years	7 - 31	6 - 7 years	7 - 28
8 - 9 years	13 - 46	8 - 10 years	11 - 34
10 - 11 years	22 - 64	11 - 12 years	19 - 52
12 - 13 years	34 - 106	12 - 13 years	34 - 97
14 - 15 years	34 - 82	14 - 15 years	34 - 79
16 - 18 years	28 - 64	16 -18 years	27 - 64

Thyroid function test reference range values[16]

TSH: 0.51 - 4.30 mIU/L

T4: 12.6 - 21.0 pmol/L

Appendix I: Ethics Clearance Certificate

M230437 MED23-01-019

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Larissa Lala-Mohan

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230437 MED23-01-019

NAME: (Principal Investigator)	Dr Larissa Lala-Mohan
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	An Audit of Hypopituitarism in Paediatric Patients seen at Chris Hani Baragwanath Academic Hospital from January 2011 to December 2021
DATE CONSIDERED:	05/05/2023
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Kebashni Thandrayen
APPROVED BY:	CB Penny Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/05/2023 **EXPIRY DATE:** 30/05/2028

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** in April each year until study is closed. Failure to submit annual report will result in ethics clearance certificate suspension. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical). Login to upload signed copy of this ethics clearance certificate prior to commencing with the study https://www.witsethics.co.za/login.aspx

L Lala-Mohan

Principal Investigator Signature

05/06/2023

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

DECLARATION:

Adherence to HREC (Medical) Ethics Application Terms and Conditions

I, the undersigned, hereby declare that I have not collected data/ done secondary data analysis or any other form of research, prior to obtaining clearance certificate from the HREC (Medical) for study no: MED23-01-019.

I have read and understood the terms and conditions on page 8-9 of the HREC (Medical) application form. I confirm that it is my responsibility to ensure that I have received final HREC (Medical) Clearance before commencing any research.

Larissa Lala-Mohan

Name, Surname and Signature

Student/Staff no if applicable: 551969

Date: 05/06/2023

Name, Surname and Signature

Supervisor (if applicable)

Date:

Appendix II: Plagiarism Declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Larissa Lala-Mohan (Student number: 551969) am a student registered for the degree of Master of Medicine in Paediatrics in the academic year 2024.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: L Lala-Mohan Date: 26 August 2024

Appendix III: Turnitin Report

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Page count:	62
Word count:	11,979
Character count:	62,991
Submission date:	25-Aug-2024 04:32PM (UTC+0200)
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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

An Audit of Hypopituitarism in Paediatric Patients Seen at Chris Hani Baragwanath Academic Hospital from January 2011 to December 2021

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics.

Johannesburg, August 2024

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Appendix IV: Data Collection Sheet

Patient 1

Tags Templates

A) Demographics

1. Age:
2. Sex:
3. Race:
4. Place of Residence:
    a. Province:
    b. Town:

B) Referral

1. Clinic:
2. Peripheral hospital:
3. Paediatrician:
4. General Practitioner (GP):
5. Other:

C) Anthropometry at presentation

Weight:

Height:

Head Circumference:

Weight-for-age z score:

Height-for-age z score:

Weight-for-height z score:

BMI (z score):

Head Circumference z score:

D) Presenting features

- ☐ Short stature
- ☐ Obesity
- ☐ Hypoglycemia
- ☐ Prolonged neonatal jaundice
- ☐ Seizures
- ☐ Headaches
- ☐ Visual problems
- ☐ Delayed puberty
- ☐ Developmental Delay
- ☐ Intellectual Impairment
- ☐ Dysmorphism

  Specify features:
- ☐ Adrenal crisis
- ☐ Other:

E) MRI findings

F) Bone Age

Before Rx:

During Rx:

- 12 months:
- 18 months:
- 24 months:
- 36 months:
- 48 months:
- 60 months:

G) Critical Sample

Age that it was done:

Glucose(mmol/L):

Growth hormone(µg/l):

Cortisol(nmol/l):

H) Biochemical Markers, Anthropometry and Treatment

	At presentation	Follow up 1 @ 6m	Follow up 2 @ 12m	Follow up 3 @ 18m	Follow up 4@ 24 m	Follow up 5 @ 36m	Follow u 48m
Age							
Weight							
Height							

IGF-1							
TSH							
T4							
Cortisol							
GH							
FSH							
LH							
Prolactin							
Oestrogen							
Testosterone							
Serum osmolality							
Urine Osmolality							
Na							
K							
Cl							
Bicarb							
Urea							
Creat							
Total Bili							
Conj Bili							
Total Protein							
Albumin							
ALP							
GGT							
ALT							
AST							
WFA z score							
HFA z score							
WFH z score							
BMI z score							
HC z score							
Tanner staging: breast development							
Tanner staging: testicular volume							
Tanner staging: pubic hair							
Episodes of adrenal crisis							
Episodes of hypoglycemia with or without seizures							
Growth Hormone Dose: (mg)							
Eltroxin: Dose (ug)							

Covocort Dose:(mg)							
DDAVP Dose: (mg)							
Compliance:							

I) Clonidine Stimulation Test

Age when it was conducted:

Was the patient primed:

	0 mins	30 mins	60 mins	90 mins	120 mins
Growth hormone (µg/l)					
Blood glucose (mmol/L)					
IGF-1 (µg/l)					
Cortisol (nmol/l)					

Confirmatory for Growth Hormone deficiency:

J) Final Diagnosis

K) Notes

Appendix V: Protocol

An Audit of Hypopituitarism in Paediatric Patients Seen at Chris Hani Baragwanath Academic Hospital from January 2011 to December 2021

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Paediatric Endocrinologist
Chris Hani Baragwanath Academic Hospital
Faculty of Health Sciences
University of the Witwatersrand
This Research Project will be used toward a higher degree as it is my Master of Medicine Research

Table of Contents

Abbreviations

FSH: Follicle stimulating hormone

LH: Luteinizing hormone

GH: Growth hormone

ACTH:Adrenocorticotropic hormone

TSH: Thyroid stimulating hormone

IGF-1: Insulin-like growth factor 1

GnRH: Gonadotropin-releasing hormone

IGFBP-3: Insulin-like growth factor-binding protein 3

Introduction

The pituitary gland is vital for homeostasis, reproduction and the regulation of growth, by the release of its hormones.(1) Hypopituitarism is the partial or complete loss of anterior and posterior pituitary gland function, caused by pituitary or hypothalamic disorders.(2) This is a rare disorder, with a varied presentation.(3) The diagnosis of hypopituitarism is made on history, examination, biochemical investigations, provocative testing of the hypothalamo-pituitary axis and genetic testing as well as Magnetic Resonance Imaging findings of abnormalities of the hypothalamus or pituitary gland.(1) Any disease process affecting either the gland or stalk of the pituitary, or the hypothalamus can lead to hypopituitarism.(3) Isolated pituitary hormone deficiency indicates that one pituitary hormone is affected. If two or more pituitary hormones are affected, this known as multiple pituitary hormone deficiency. A reduction in all pituitary hormones is termed panhypopituitarism. (4,5)

Epidemiology

In the USA, the incidence is reported to be 4.2 per 100 000 children per annum with the prevalence being 45.5 per 100 000 children.(1) Congenital Growth Hormone deficiency has a reported incidence of 1 in 4 000 to 1 in 10 000 live births. (1) Australian data looking at hospitalizations between 2001 and 2014 found that there were 3 779 admissions for hypopituitarism and adrenal insufficiency in the paediatric population,

equating to 48.7 admissions/million/year.(1) Growth hormone deficiency is the most common pituitary hormone deficiency in children, and occurs more commonly in males as compared to females.(1) GENHYPOPIT study by Jullien et al. (2020) looking at primary hypothyroidism found that 24% of patients were diagnosed in the neonatal period, 28% during childhood, 32% during adolescence and 7.2% during adulthood, with 8.8% that data was not available for.(5)

Physiology

Located in the sella turcica, the pituitary gland comprises of two lobes both with its own embryological origin.(6) The adenohypophysis, made up by the anterior and intermediate lobe, is developed from oral ectoderm. The anterior lobe contains 5 cell types and produces 6 hormones.(7) The intermediate lobe has melanotrophs, releasing pro-opiomelanocortin. The neurohypophysis, the posterior lobe, is derived from neural ectoderm and contains axons of neurons.(1,8) Their cell bodies sit in the hypothalamus and secrete oxytocin and vasopressin.(1) The table in Appendix 1 details the hormones produced by the pituitary gland, as well as their origin and action.(1,7)

Both the production and release of hormones from the pituitary gland is tightly controlled by a negative feedback loop, as well as inhibitory and stimulatory hormones that are released by the hypothalamus.(8) Damage to either the hypothalamus or the pituitary gland elicits pituitary hormone deficiency. (1,9)

Aetiology

Hypopituitarism is either congenital or acquired.(1,4,7) It can therefore present in the neonatal period through adolescence and into adulthood.(3,9) The disorder can be divided into primary and secondary hypopituitarism. Disorders of the pituitary gland itself causes primary hypopituitarism, whereas secondary hypopituitarism is due to abnormalities of the hypothalamus or the pituitary stalk, which interrupts the nerve or vascular connections to the pituitary gland, and thus, reduces the secretion from the pituitary gland. (2,8,9) Acquired causes of hypopituitarism include trauma, infection and

inflammation, auto-immune processes, infiltration, tumours and post-chemotherapy. (7,8)

For the purpose of this study, the primary or congenital causes of hypopituitarism will be investigated and are listed below:(1,2,9,10)

- Congenital
    - Genetic disorders: septo-optic dysplasia, PIT1 and PROP1 mutations, interrupted pituitary stalk
    - Genetic syndromes: i.e. Pallister-Hall syndrome (hypothalamic hamartoma with polydactyly)
    - Developmental central nervous system defects: holoprosencephaly, anencephaly, pituitary hypoplasia or aplasia

Clinical Presentation

The clinical features are extremely varied, based on the number of hormones involved, as well as the extent of the deficiencies.(7) Infants with multiple hormonal deficiencies usually present in the neonatal period, as opposed to children presenting later on in childhood with growth failure who usually have an isolated growth hormone deficiency.(1,9) Septo-optic dysplasia is the term used to describe the phenomenon when two or more of pituitary hormones are deficient, midline brain defects are present and there is optic nerve hypoplasia.(1,11) Hypopituitarism can be life-threatening in the case of ACTH deficiency and thus early diagnosis is key. Appropriate hormone replacement therapy in all cases is vital to ensure prevention of unnecessary morbidity and mortality for these patients. (3,6)

Neonatal Period

Hypopituitarism symptoms in the neonatal period are non-specific. These include hypoglycemia, prolonged neonatal jaundice, hyponatraemia, poor weight gain, apnoeas, poor feeding, recurrent sepsis, jitteriness, seizures, lethargy and acute collapse due to ACTH deficiency with hypotension. (1,7,9)

Childhood

The clinical presentation of one or multiple deficiencies in pituitary hormones can include short stature, weakness, hypoglycaemia,, sweating, headaches, confusion, and seizures; hypogonadism, presenting with delayed puberty and infertility; adrenal crisis, presenting with severe hypotension, and shock; as well as osteoporosis with increased fracture risk.(3)

Investigations

Hypopituitarism can be diagnosed with a thorough history, examination, baseline biochemical investigations, provocative testing of the hypothalamic-pituitary axis, genetic testing as well as MRI.(1)

Baseline Biochemical Investigations (1,7,9)

- U&E and LFT: hyponatraemia secondary to ACTH and cortisol deficiency or hypernatraemia due to diabetes insipidus
- 8am cortisol: usually low
- Prolactin: high/low/normal
- Free thyroxine and TSH - low thyroxine and low/normal/slightly increased TSH
- GH: In children, GH stimulation testing should be done instead, because of the circadian nature of GH production and its variable nocturnal peak levels
- IGF-1 and IGFBP-3: Due to its low sensitivity and specificity for GH deficiency, it cannot be used alone, but can be used as a guide

Dynamic Tests(1,7,12,13)

- Growth Hormone Stimulation test (Clonidine Stimulation test): Provocative GH testing is indicated in children with a poor height velocity as well as a low height for age Z score (taking into account their mid-parental target height).
- Critical sample done at the time of hypoglycemia (glucose < 2.7mmol/l) to establish hypopituitarism: glucose, growth hormone and cortisol.

MRI

MRI brain is the gold standard in terms of imaging for hypopituitarism.(1) The hypothalamus, pituitary gland and surrounding structures can be well visualized.(14) Anatomical abnormalities like corpus callosum dysplasia, optic nerve hypoplasia and posterior pituitary ectopia can be noted.(1) Brain tumours can also be recognized to exclude the acquired causes.(5) A normal MRI finding does not, however, exclude hypopituitarism.(8)

Management

Medication

The hormones from the anterior pituitary get released in a pulsatile fashion, and every hormone has a different circadian pattern, thus hormonal treatment must reflect this pattern.(1,6) Treatment includes: Thyroxine, growth hormone replacement, hydrocortisone, vasopressin replacement, GnRH agonists or exogenous gonadotropins. (9)

With regard to growth hormone therapy, a positive effect on height was seen. In a study conducted by Finkelstein et al, at one year of growth hormone treatment, the growth velocity was significantly higher in the treatment versus the control group at 2.53 cm/year. With regard to the height standard deviation score, the growth hormone treatment group was greater than that of the control group by 0.60 SD after 1 year of treatment. (15) Indications for growth hormone therapy include children with growth hormone deficiency, Prader Willi Syndrome, Turner's syndrome, small for gestational age children with failure of catch-up growth, chronic renal failure and idiopathic short stature. Growth hormone therapy is contraindicated in children with an active malignancy. (16) Although rare, side effects of growth hormone include intracranial hypertension, breast tenderness, gynaecomastia, and slipped capital femoral epiphysis.(17) The cost of growth hormone in South Africa is quite expensive. Each inch of height achieved with growth hormone treatment would cost approximately R323 500 to R462 000. (18)

General Management

Children with hypopituitarism must be cared for by a multi-disciplinary team. They must be given an emergency bracelet with the medication they would need.(1,7) They must also have a clear emergency plan in place for when they become acutely ill. These children are prone to hypoglycemia due to GH and ACTH deficiency. They should therefore be educated on signs of hypoglycemia and the management thereof. The risk of hypoglycemia with GH deficiency usually resolves once GH has been adequately replaced, but children with ACTH deficiency have an on-going risk of hypoglycemia, especially when ill. They need to be taught to double their hydrocortisone dose in times of a fever, trauma or when undergoing surgery.(1) Children with hypopituitarism need have follow up appointments 3 to 6 monthly, and have their height and weight plotted, as well as their growth velocity assessed. They need a full pituitary hormone work-up at diagnosis and then annually thereafter, as children with one hormonal abnormality can subsequently develop others. These children should also have regular neurodevelopmental assessments and be sent for visual field testing regularly.(1) Psychosocial management is also a vital part of holistic management. In a study by Koa et al. children with hypopituitarism were found to have a significantly lower quality of life into their adulthood as compared to healthy counterparts.(19) Children in the study were shorter and more overweight, had more childhood behavioural problems, were less educated, had higher unemployment rates, lower marital rates and lower incomes and had fewer children compared to healthy controls. (19,20)

Rationale

Clinical reporting of endocrine disorders, more specifically hypopituitarism is much fewer in the developing world as compared to the developed countries. This is a direct reflection on the resources and facilities available for diagnosis. In South Africa (SA), particularly, there is sparse information and clinical or genetic research on hypopituitarism in a predominantly black population. It may be an uncommon condition and as far as I am aware, the incidence or prevalence in SA is unknown. Nonetheless, it is an important disease process, as normal pituitary function is crucial for neurocognitive

development, growth, metabolism and homeostasis as well as the onset of puberty, all of which are of utmost importance for our growing children.

Aim

To review hypopituitarism in paediatric patients seen at the paediatric endocrine clinic at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2011 to December 2021.

Objectives

1. To describe the demographics, anthropometry, clinical presentation, MRI findings and biochemical abnormalities of paediatric patients seen at the paediatric endocrine clinic at CHBAH with hypopituitarism
2. To assess bone ages before, during and/or after treatment
3. To review treatment prescribed and response to treatment by documenting the changes in height and weight for age z scores or BMI z scores, thyroid function tests, cortisol and IGF-1 levels
4. To quantify how many patients achieved a height-for-age z score of ≥ -2 and >0 with growth hormone treatment as a measure of a good outcome

Methodology

Study design

The study will be a retrospective and descriptive study. The research will be conducted by reviewing patient files from those patients seen between 1 January 2011 to 31 December 2021 at the paediatric endocrine clinic at CHBAH and inputting data into a data collection sheet. (Appendix A) Data will then be captured electronically and analysed.

Study Population

The study will be conducted at CHBAH in the Division of Paediatric Endocrinology. The study population will comprise of all children under the age of 18 that were attending the paediatric endocrine clinic with the diagnosis of hypopituitarism from 1 January 2011 to 31 December 2021 until their last follow up on 30 June 2022.

Sample Size

The sample size is 70 paediatric patients with hypopituitarism seen at the paediatric endocrine clinic at CHBAH from 1 January 2011 to 31 December 2021.

Inclusion criteria

All children under the age of 18 years with the diagnosis of hypopituitarism (two or more pituitary hormone deficiencies) attending the paediatric endocrine clinic at CHBAH from 1 January 2011 to 31 December 2021.

Exclusion criteria

- Isolated GH Deficiency
- All children with acquired causes of hypopituitarism: trauma, infection/inflammation, infiltration, CNS tumours, post cranial radiation, post chemotherapy, primary hypothyroidism, neurosecretory dysfunction and severe psychosocial deprivation.
- Patients whose files contain missing or incomplete data

Data Collection and Handling

Files of patients with hypopituitarism seen at CHBAH from January 2011 to December 2021 will be retrieved from the paediatric endocrine clinic . The investigator will then use the files to populate the data collection sheet (Appendix A). An independent person will then check the investigator and audit to see that the data capturing was carried out correctly in order to remove the possibility of human error.

The following parameters or variables will be collected into the data collection sheet (Appendix A):

- Demographics: Age, sex, race, place of residence
- Mode of referral
- Anthropometry with z scores
- Presenting clinical features
- MRI findings
- Bone age: before and during treatment
- Biochemical markers: Insulin-like growth factor 1(IGF-1), thyroid stimulating hormone (TSH, Thyroxine (T4), Cortisol, Growth Hormone (GH), Follicle stimulating hormone (FSH), Luteinizing Hormone (LH), Prolactin, Oestrogen and testosterone, serum osmolality, urine osmolality, Urea and electrolytes (U&E), Liver Function Test (LFT)
- MRI findings
- Tanner staging
- Episodes of adrenal crisis or hypoglycemia with/without seizures
- Treatment prescribed: Growth hormone, Eltroxin, Covocort, DDAVP
- Compliance with treatment

The biochemical markers at the first visit will be compared to the results at the 6, 12, 18, 24, 36, 42 and 60 month follow up or longer if available. Response to treatment will be ascertained by looking at intervalled height-for-age z scores, weight-for-age z scores or BMI z scores, thyroid function tests, cortisol and IGF-1 levels.

Statistical Analysis

Data will be entered into an excel spreadsheet and thereafter imported into Statistica version 13.3 (https://statistica.software.informer.com) for data analyses. The data will be described using descriptive statistics and measures of central tendency including the mean, median, mode and standard deviation will be used where applicable. The categorical variables will be reported as percentages and frequencies. Chi-square or Fischer exact tests will be performed for the analyses. The continuous variables will be

analysed using the Mann Whitney U test or Student-t test depending on the normal distribution of data. For mean changes in anthropometry or z scores from baseline until 6,12,18, 24, 36, 42 and 60 months follow-up on growth hormone therapy, analysis of covariance or ANOVA will be performed and 2 by 2 post hoc analyses will be applied.

The Kaplan-Meier survival analysis will be applied to investigate the effect of growth hormone therapy on the increase in HAZ scores from baseline and over the specified time periods of treatment to reach a mean Z score of ≥ 0 and > -2.

Anonymity and Confidentiality

For this study, all data will be analysed without using any identifying information. A study identification number will be assigned to each patient to keep them anonymous. Confidentiality will be ensured at all times and the only people accessible to the raw data will be the researcher and the supervisor. All data will be under password protection.

Ethical considerations

This protocol will be submitted to the Human Research Ethics Committee of the University of Witwatersrand for ethics approval, prior to conducting the study. As this is a retrospective study, no informed consent or assent is required. Permission to access patient information will also be obtained from the CEO of CHBAH as well as the Head of Unit of the paediatric endocrine clinic at CHBAH.

Limitations of the study

Since this is a retrospective audit, it relies on good note-keeping in patients files and having all information accessible in the files. If there is data missing, these patients will have to be excluded from the study.

Budget

This project will be funded by the researcher. Costs that will be incurred include those of printing of resources, travelling expenses for meetings with supervisors as well as time required for data collection, analysis and interpretation. A projected budget is R 1000 to cover the above costs.

Project Timeline

Task	April 2022	May 2022	June 2022	July 2022	Aug 2022	Sept 2022	Oct 2022	Nov 2022	Dec 2022	Jan 2023
First draft of protocol										
Revision of protocol										
Submit to PGC and corrections										
Submit to HREC and corrections										
	Feb 2023	Mar 2023	April 2023	May 2023	June 2023	July 2023	Aug 2023	Sept 2023	Oct 2023	Nov 2023
Data Collection and analysis										
First Drafts of research										
Review										
Final Draft & submission										

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Appendix 1: Hormones of the Pituitary Gland

Pituitary Gland				
Anterior lobe	**Cell Type**	**Hormone**	**Action**	**Tissue targeted**
	Somatotrophs	Growth Hormone	Promotion of growth and metabolic action	Liver, bone, adipose
	Thyrotrophs	Thyroid Stimulating hormone	Stimulates thyroxine production	Thyroid gland
	Lactotrophs	Prolactin	Lactation	Breast ductal tissue
	Gonadotrophs	FSH and LH	Stimulates gonadal maturation and hormone cycling	Gonads
	Corticotrophs	Adrenocorticotropic hormone	Stimulates cortisol production	Adrenal cortex
Intermediate lobe	Melanotrophs	Pro-opiomelanocortin, the precursor to melanocyte-stimulating hormone and endorphins	Skin pigmentation	Skin
Posterior lobe	Axonal projections of neurons	Cell bodies sit in the hypothalamus, secrete vasopressin and oxytocin	Vasopressin: reabsorption of water in collecting ducts. Oxytocin: childbirth	

Appendix 2: Data Collection Sheet

Data Collection Sheet

Study no: ▢

A) Demographics

1. Age ____y_____m
2. Sex: Male ⬜ Female ⬜
3. Race: _____
4. Place of Residence: Province _____ Town _____

B) Referral

1. Clinic _____
2. Peripheral hospital _____
3. Paediatrician _____
4. General Practitioner (GP)_____
5. Other _____

C) Anthropometry at presentation

Weight: _____kg

Height:_____cm

Head Circumference: ____cm

Weight-for-age z score: _____

Height-for-age z score: _____

Weight-for-height z score: _____

BMI (z score): _____

Head Circumference z score: _____

D) Presenting features

Short stature ⬜

Obesity ⬜

Hypoglycemia ⬜

Prolonged neonatal jaundice ⬜

Seizures ⬜

Headaches ⬜

Visual problems ⬜

Delayed puberty ⬜

Developmental Delay ⬜

Intellectual Impairment ⬜

Dysmorphism ⬜ Specify features: _____

Adrenal crisis ⬜

Other: _____

E) MRI findings

_____

_____

_____

_____

F) Bone Age

Before Rx: _____

During Rx:

- 12 months _____
- 18 months _____
- 24 months _____
- 36 months_____
- 48 months _____
- 60 months _____

G) Critical Sample:

Age that it was done: _____

Glucose:_____mmol/L

Growth hormone:_____µg/l

Cortisol:_____nmol/l

H) Biochemical Markers, Anthropometry and Treatment

	At presentation	Follow up 1 @ 6m	Follow up 2 @ 12m	Follow up 3 @ 18m	Follow up 4@ 24 m	Follow up 5 @ 36m	Follow up 6 @ 48m	Follow up @7 60m	Last visit
Age									
IGF-1									
TSH									
T4									
Cortisol									
GH									

FSH									
LH									
Prolactin									
Oestrogen									
Testosterone									
Serum osmolality									
Urine Osmolality									
Na									
K									
Cl									
Bicarb									
Urea									
Creat									
Total Bili									
Conj Bili									
Total Protein									
Albumin									
ALP									
GGT									
ALT									
AST									
WFA z score									
HFA z score									
WFH z score									

BMI z score									
HC z score									
Tanner staging: breast development									
Tanner staging: testicular volume									
Tanner staging: pubic hair									
Episodes of adrenal crisis									
Episodes of hypoglycemia with or without seizures									
Growth Hormone Dose: (mg)									
Eltroxin: Dose (ug)									
Covocort Dose:(mg)									
DDAVP Dose: (mg)									
Compliance:									

I) Clonidine Stimulation Test

Age when it was conducted:_____

Was the patient primed? YES ⬜ NO ⬜

	0 mins	30 mins	60 mins	90 mins	120 mins
Growth hormone (µg/l)					
Blood glucose (mmol/L)					
IGF-1 (µg/l)					
Cortisol (nmol/l)					

Confirmatory for Growth Hormone deficiency: YES ⬜ NO ⬜

J) Final Diagnosis

_____

K) Notes

_____

_____

_____

_____

_____