

Clinical characteristics of pituitary hormone deficiency in children: A single centre experience

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(Index words: multiple pituitary hormone deficiency, neonatal risk factors, brain imaging, brain tumours, radiotherapy)

Abstract

Background: The clinical presentation of hypopituitarism varies from asymptomatic to circulatory compromise. The late diagnosis may cause significant mortality and morbidity. There is scant data on the clinical profile.

Method: A cross-sectional descriptive analysis was carried out on diagnosed children with hypopituitarism at the endocrinology unit of Lady Ridgeway Hospital for Children, Sri Lanka, from 2013-2021. The presence and progression of pituitary hormonal deficiency were ascertained.

Results: Out of the total 94 children with hypopituitarism, 52 had congenital hypopituitarism with a median presenting age of 5.86 years (IQR 3-9). Short stature was the commonest presentation (59.6%). Multiple pituitary hormone deficiency (MPHD) was seen in 27 (51.91%). MPHD was associated with the presence of postnatal risk factors (OR 2.036, 95% CI 1.94-3.786) and MRI Imaging abnormalities in hypothalamic-pituitary morphogenesis (OR 1.768, 95% CI 1.087-2.874). 90.4% with GHD, 46.2% with ACTH deficiency, and 40.4% with TSH deficiency had the mean age of presentation 6.54 years, 6.11 years, and 5.56 years respectively. Of the children above 13 years, 57% showed hypogonadism. Hypoplastic anterior pituitary (40.4%) was the commonest MRI abnormality.

Out of the 42 children with brain tumours, 25 (59.52%) had craniopharyngioma, and 13 (31%) had Medulloblastoma, while MPHD was seen in 32 (76.2%). Hormone deficiency at the presentation was seen in 57.1%.

Conclusion: Comprehensive evaluation and periodic screening are mandatory for the timely diagnosis of MPHD.

Introduction

The pituitary gland is the prime endocrine organ in the body involved in regulating growth, metabolism, stress response, and puberty through a complex signalling system [1]. Hypofunction could be due to a congenital or an acquired cause and can present either as isolated pituitary hormone deficiency (IHD) or multiple pituitary hormone deficiencies (MPHD) [2].

Hypopituitarism was first described by Simmonds in 1914 [2]. Growth hormone deficiency is the most common deficiency, usually presenting with short stature after infancy [3]. However, additional hormone deficiencies can be developed over time [4].

Genetic defects in the signalling cascade and transcriptional factors responsible for pituitary cell differentiation and proliferation lead to congenital hypopituitarism with or without an associated syndrome [5]. The incidence of congenital hypopituitarism is 1:4000-1:10000 live births [6]. Their genetic heritability and phenotypic presentation are variable. Septo-optic dysplasia (SOD) is a well-known aetiology for congenital hypopituitarism, which is diagnosed clinically with the presence of two or more features from the clinical triad of hypopituitarism, optic nerve hypoplasia, and midline defects of the brain [7].

Acquired aetiologies equally contribute to morbidity and mortality. The majority of acquired hypopituitarism in children is due to brain tumours, particularly craniopharyngioma. Traumatic brain injury, radiation-induced injury, infarctions, and infections are other known aetiologies. Receiving radiotherapy increases the risk of developing subsequent hypopituitarism in children who underwent surgical resection of sellar tumours. The

Ceylon Medical Journal 2023; **68**: 12-17

DOI: <https://doi.org/10.4038/cmj.v68i1.9502>

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development of post-irradiation hypopituitarism is dose-dependent, and growth hormone deficiency is the initial manifestation. 30-60% of children who received a radiation dose above 30Gy develop MPPHD during the first 10 years of follow-up [8]. Additionally, these are associated with extra seller morbidity, including visual field defects, metabolic derangement, and neurological damage [9,10].

Magnetic resonance imaging (MRI) is the imaging technique of choice. It will help finding the aetiology in acquired causes and revealing abnormalities of morphogenesis correlated with underlying genetic abnormality [11, 12,13].

Clinical presentation can be varied and nonspecific depending on the underlying aetiology, severity of dysfunction, rapidity of onset and progression, and the deficient hormones. Undiagnosed pituitary hormone deficiency, particularly adrenocorticotrophic deficiency, is associated with life-limiting consequences whilst hypothyroidism may result in poor neurocognitive development. Children with congenital hypopituitarism may have apnoea, hypoglycaemia, and neonatal cholestasis in the perinatal period but are left undiagnosed most of the time [1]. Further, undiagnosed dysfunction may increase morbidity and mortality in the immediate post-surgical period following the resection of brain tumours [14].

Hence the knowledge of early predictive factors and temporal pattern of development of deficiencies is essential and will shed some light for the treating clinician to draw the appropriate management plan, timely diagnosis, and initiation of therapy. Early initiation of treatment gives better treatment outcomes, particularly in gaining final adult height and neurocognitive development. The proper implication of therapy will reduce the risk of cardiovascular mortality during adult life [15].

Methods

A descriptive cross-sectional study was conducted among 94 children with pituitary hormone deficiencies followed up at the endocrine unit of Lady Ridgeway Hospital from 2013-2021. Children with at least one confirmed pituitary hormone deficiency were recruited. Data were collected using an interviewer-administered data collection tool.

Basal values and appropriate dynamic stimulatory tests, where necessary, were carried out to confirm the endocrine dysfunction. Analysis was done with chemiluminescence immune assays. Growth hormone deficiency was diagnosed with a glucagon or clonidine stimulation test when the peak growth hormone value was less than 7ng/ml [16]. Luteinizing hormone (LH) level less than 0.2 IU/L was considered hypogonadotropic hypogonadism in children with absent secondary sexual

characteristics at 13 years in girls and 14 years in boys. The sensitivity of the assay for both LH and follicle stimulating hormone (FSH) was 0.10 IU/L. Children were assessed six monthly for developing an additional pituitary hormonal deficiency. MRI brain and pituitary was conducted on all participants and was reported by a consultant radiologist who is well experienced in paediatric radiology.

Descriptive statistics were described with median with interquartile range. The associations were statistically evaluated with odds ratios and their confidence interval. SPSS (statistical packages for social service) version 22 was used to analyse.

Ethics approval for this study was obtained from the Ethics Review Committee, Sri Lanka College of Paediatricians. (Ref. NoSLCP/ERC/2020/17)

Results

Ninety-five children were identified with hypopituitarism, and one was excluded due to inadequate data on dynamic hormonal testing (55 males and 39 females). Congenital hypopituitarism was diagnosed in 55.3% (n=52), while the rest were diagnosed with an acquired pituitary hormonal deficiency. The population's median age was 10.5 years (IQR 8.31-13.5). Ten fulfilled criteria for Septo-optic dysplasia (Figure 1).

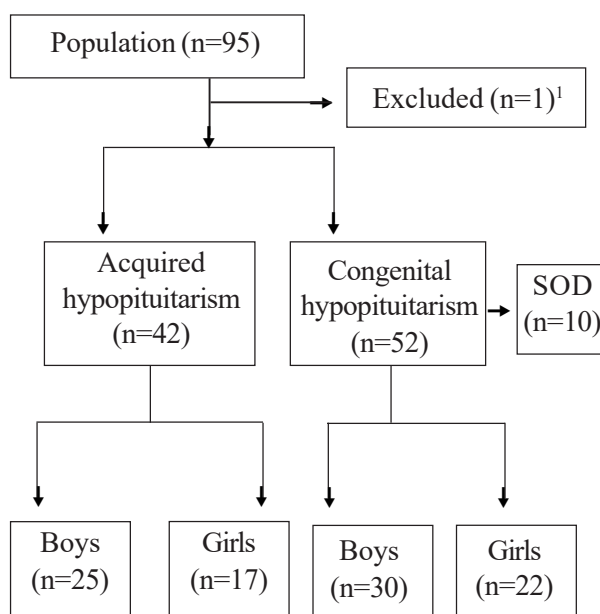


Figure 1. **Characteristics of the data evaluated for pituitary hormone deficiency. SOD= Septo-optic dysplasia, ¹lost the records of dynamic hormone testing.**

Congenital hypopituitarism

Clinical characteristics

Thirty (57.7%) boys and 22(42.3%) girls had congenital hypopituitarism with a median presenting age of 5.87 years (IQR 3-9). Eight (15.38%) were diagnosed during infancy.

Thirty-eight-point five percent (n=20) had low birth weight (< 2.5 kg). Seventy-four-point six percent were delivered at term. Eight (15.4%) were born to primi mothers whose median maternal age was 31 years (IQR 25.6-33). Mothers of 7 children (13.3%) had experienced first trimester vaginal bleeding. Fifty-three point eight percent (n=28) had at least one neonatal risk factor. The frequency of prolonged (> 2 weeks) neonatal jaundice and neonatal hypoglycaemia were 34.6% (n=18) and 28.8% (n=15) respectively (Table 1). Fifty-one-point five percent (n=24) of boys with hypopituitarism had micropenis (SPL < 2.5 cm) during infancy.

Table 1. Antenatal and neonatal factors and development of multiple pituitary hormone deficiency

<i>Anti-natal and Neonatal risk factors</i>	<i>Frequency of (n=27)</i>	<i>MPHD</i>
Recurrent neonatal hypoglycaemia	15/27	55.6%
Prolonged neonatal jaundice	14/27	51.9%
Micropenis	10/16	62.5%
Young maternal age (< 30years)	13/27	48.1%
1 st trimester vaginal bleeding	04/27	14.8%
Low birth weight (< 2.5 kg)	11/27	40.7%
Primi mother	05/27	18.5%

Short stature was the commonest presentation (59.6%, n=31). Other presentations were hypoglycaemia and micropenis, which accounted for 17.3% (n=9) and 5.7% (n=3), respectively. Infants were commonly referred due to hypoglycaemia 50% (n=4) and micropenis 25% (n=2).

The frequency and age of diagnosis of pituitary hormone deficiencies are described in table 2. Of the children above 13 years (n=7); 57% showed hypogonadotropic hypogonadism. All of them were females.

Table 2. Frequency and age of diagnosing pituitary hormone deficiency

<i>Hormone deficiency</i>	<i>Frequency</i>	<i>The median age of diagnosis</i>
GH deficiency	90.4%	6.33 years (IQR 3.25-9)
ACTH deficiency	46.2%	Six years (IQR 2.37-9.75)
TSH deficiency	40.4%	Six years (IQR 2.25- 8.125)
DI	7.7%	6.33 years (IQR 3.75- 11.04)

MPHD was seen in 27(51.91%). Majority presented with short stature (37%; n=10) and hypoglycaemia (33.33%; n=9). The median age of presentation was 4.25 years (IQR 0.8-7.5). GHD was the most prevalent deficiency (88.9%; n=24). The most common additional hormone deficiency was ACTH deficiency (81.5%; n=22), followed by TSH deficiency (74.1% n=20). Children with postnatal risk factors (neonatal hypoglycaemia/ prolonged neonatal jaundice) showed a significantly higher risk of developing MPHD (OR 2.036, 95% CI 1.94-3.786).

The commonest isolated hormone deficiency was GHD (92%; n=23). Thyroxin deficiency and ACTH deficiency were 4% (n=1) each. The median age of referring for endocrine care was eight years (IQR 3.625- 9.65).

Eighteen (34.6%) had evidence of phenotypic variants on the clinical examination, and 16 (88.89%) of them were diagnosed with MPHD. Midfacial hypoplasia (15; 83.34%) was the commonest. Polydactyly, central incisor, cleft lip and cardiac defects were other less common associations which accounted for 3.8% each.

Thirty-two (61.5%) children showed developmental abnormalities on MRI brain imaging. Hypoplastic anterior pituitary was the most prevalent, followed by ectopic posterior pituitary (Table 3). Imaging abnormalities were significantly associated with MPHD (OR 1.768, 95% CI 1.087-2.874).

Table 3. The common MRI brain and pituitary abnormalities

<i>MRI brain findings</i>	<i>Frequency</i>
Anterior pituitary hypoplasia	21/32 (65.62%)
Ectopic posterior pituitary	16/32 (50%)
Pituitary stalk abnormalities	07/32 (21.87%)
Absent septum pellucidum	06/32(18.75%)
Agenesis of corpus callosum	05/32 (15.62%)
Optic nerve hypoplasia	05/32 (15.62%)

Ten children had fulfilled the criteria for SOD. Six (60%) had optic nerve hypoplasia, and 9 (90%) had midline brain defects. All the features of the triad were seen in 50% (n=5).

Acquired hypopituitarism

Forty-two children (male = 25) with brain tumours presented with acquired hypopituitarism. The median age of presentation was 7.5 years (IQR 5.18-10.25). The median follow-up time was four years (IQR 2.375-5.5). Craniopharyngioma 59.52% (n=25) was the commonest brain tumour that led to hypopituitarism. Medulloblastoma 31% (n=13) was the next commonest and germ cell tumour (n=3; 37.1%), optic glioma (n=1; 2.4%) were the other brain

tumours caused pituitary hormone deficiencies. Ninety-two-point eight percent (n=39) underwent complete or partial tumour resection, while 64.1% (n=25) of them received adjuvant radiotherapy. Radiotherapy alone was given to 3 (7.1%).

MPHD was seen in 32 (76.2%). Hormone deficiency at presentation was seen in 57.1% (n=24), of which 87.5% were craniopharyngioma, all children with germ cell tumours (n=3) and 96% (24/25) with craniopharyngioma developed MPH. D.

ACTH (n=29, 69%) and TSH (n=27, 64.3%) deficiencies were the commonest, followed by GH (n=23, 54.8%) deficiency and DI (n=21, 50%). Of the 12 children above 13 years of age, 7 (58.34%) developed hypogonadotropic hypogonadism requiring pubertal induction. Eighty percent (n=8) showed isolated growth hormone deficiency following receiving cranial radiation after Medulloblastoma excision. The median lapse of developing growth hormone deficiency was 2.5 years (IQR 1-3.5). ACTH and TSH deficiency were commonly diagnosed before the intervention or after immediate postoperative, whereas DI was diagnosed during 0-1 week post-operatively. Additional hormonal deficiencies were detected at the routine follow-up visits, while none presented with endocrine emergencies.

Sixty-six-point seven percent (n=28) had disease-related extra pituitary morbidity. Common complications and their frequencies were as described in table 4. During the follow-up, 15 (35.7%) had a residual tumour, and 3 (7.1%) developed recurrence.

Table 4. Extra pituitary morbidity of brain tumours

<i>Morbidity</i>	<i>Frequency</i>
Hydrocephalus requiring shunt insertion	47.6% (20)
Obesity	31% (13)
Radiation-induced thyroiditis	23.8% (10)
Visual defects	19% (8)
Neurological weakness	16.7% (7)

Discussion

This study describes the clinical spectrum of acquired and congenital pituitary hormone deficiency, which is a common disease in paediatric endocrinology, with a nonspecific presentation and scant data. Undiagnosed deficiencies may lead to life-threatening complications. Enhanced knowledge would help to reduce disease-related morbidity and mortality. This is the first Sri Lankan paediatric study and the largest South Asian paediatric cohort.

In this study, a significant gender predominance

was not evident, even though the percentage of boys was slightly higher in both sub-categories. It is consistent with the well-known varied genetic inheritance and the sporadic origin [17]. The clinical profile of hypopituitarism varies from asymptomatic to circulatory collapse. In our series, it extended from isolated short stature to refractory epilepsy due to recurrent hypoglycaemia. The majority presented at the pre-school age with short stature compared to their peers despite more than one-third of them having documented recurrent hypoglycaemia, prolonged jaundice, or micropenis during their neonatal life. The presence of postnatal risk factors displayed a significant association with evolving MPH. D. The frequencies were even slightly higher compared to the other European studies [17]. Hence, more attention should be paid to those infants to assess the possibility of hypopituitarism which may be life-threatening if left undiagnosed and untreated. We suggest including pituitary hormone function assessment as a routine investigation in prolonged jaundice evaluation panel in infants.

Reduced vascular supply secondary to maternal smoking and recreational drug abuse (potent vasoconstrictors), first trimester vaginal bleeding, intrauterine growth restriction, prematurity, and hypoxia was previously described as a postulation of congenital hypopituitarism even though significant association with antenatal risk factors was not demonstrated in this cohort of children [19]. One limitation of the present study was the unavailability of data on maternal smoking and substance abuse. However, as a significant percentage showed anterior pituitary hypoplasia and pituitary stalk abnormalities on MRI imaging, this vascular hypothesis cannot be excluded.

The absence of postnatal gonadotrophin surge resulted in micropenis [20,6] and was detected in more than fifty percent of children who had delayed puberty secondary to hypogonadotropic hypogonadism. In this context, micropenis carries a significant positive predictive value of developing delayed puberty with hypogonadism in later life. However, isolated GHD can also be present as micropenis [6]. Inadequately elevated postnatal serum LH and testosterone will provide additional support to establish the probability of hypogonadism as it further indicates GnRH activity in postnatal life [20,6]. Early diagnosis will alleviate the adverse effects of delayed puberty, like deranged bone health and emotional distress.

The commonest isolated hormone deficiency was growth hormone deficiency which agreed with other studies [4]. However, the most frequent additional hormone deficiency was ACTH in this cohort, whereas it was TSH in the Japanese and Italian multicentre cohorts [3,17]. A temporal relationship in developing additional hormone deficiency was not evident.

Most children with MPH. D. showed phenotypic variants on clinical examination. Thus, a thorough physical examination may provide a clue to the presence of MPH. D. or the risk of progressing into MPH. D. in later life.

MRI brain and pituitary remains the investigation of choice for imaging as it precisely diagnoses abnormalities of the sellar region. The hypoplastic anterior pituitary was the commonest developmental abnormality noted and was consistent with past literature [3]. The developmental abnormalities of the brain and pituitary were associated with progressing into MPH. Hence, it carries an essential prognostic value that alarms the treating clinician to be more vigilant in the routine follow-up to detect progressive hormonal deficiencies.

Besides congenital aetiologies, acquired hypopituitarism also carries a significant disease burden. Despite having multiple aetiologies for acquired hypopituitarism, brain tumours were the commonest cause in our series. There was no gender difference, proving the sporadic origin of brain tumours. Most tumours close to the hypothalamic-pituitary region cause pituitary hormone deficiency upon presentation, with craniopharyngioma being the commonest [18,22,23]. This is possibly due to the mass effect of the tumour that would damage the vascular and neuronal supply of the surrounding tissues and structures. Thus, endocrine evaluation prior to surgery is mandatory.

The survivors of brain tumours continue to have a risk of developing additional hormonal deficiency throughout. Most of the children with craniopharyngioma evolved into multiple pituitary hormone deficiencies during the follow-up in our cohort, which was consistent with the prevalent data [14,23]. This may be due to compromised pituitary reserve and hypothalamic-pituitary neuronal integrity by the tumour or the surgery [14,23].

The median age of diagnosing GH deficiency was 2.5 years, whereas all the other hormonal deficiencies were diagnosed within the 1st year of presentation. The consensus to start GH therapy after the neurosurgical intervention is one year after because increasing IGF1 may affect the recovery by influencing metabolic homeostasis of the body in an acute illness. Thus, the lapse time between screening may have contributed to this time difference.

Cranial irradiation is a well-known cause of hypopituitarism, and the radiosensitivity of pituitary cells differs. Thus, the severity of hypopituitarism is dose-dependent. The low radiation dose of less than 30 Gray mainly affects the somatotrophs, the most abundant and radiosensitive cell in the pituitary, resulting in isolated growth hormone deficiency [8]. In addition to the direct cell damage, it leads to progressive diffuse pituitary fibrosis resulting in progressive pituitary dysfunction [22]. In our series, all the children who received radiotherapy for germ cell tumours developed MPH due to the direct high dose of radiation compared to Medulloblastoma, where the majority developed isolated GHD. Continued screening is mandatory even for children who received cranial irradiation without surgical intervention.

Additionally, brain tumours are associated with long-term metabolic and neurological comorbidities. Nearly two-thirds of children in this cohort had other extra pituitary complications enhancing their morbidity and diminishing quality of life [9]. Despite the benign origin of craniopharyngioma, more than 40% had an unfavourable prognosis with a residual or a recurrence.

Conclusion

This provides the first descriptive data on childhood hypopituitarism in Sri Lanka. Being vigilant on nonspecific neonatal risk factors and periodic screening for other hormone deficiencies will optimise the early identification of pituitary hormone deficiency, reducing disease-related mortality and morbidity. Considering the relatively late presentation of congenital hypopituitarism despite having early neonatal risk factors, we suggest including pituitary hormone assessment as a routine investigation to the prolonged jaundice evaluation panel in infants. The duration of screening for additional hormone deficiency is indefinite. Thus, appropriate transition care is mandatory.

Acknowledgements

We thank parents and patients who participated in this study and Dr. H. Abeysekera, consultant ophthalmologist, Dr. N. Samarasekera and Dr. J. Fernando, consultant radiologists of the Lady Ridgeway Hospital for Children, Colombo.

Abbreviations

ACTH- adrenocorticotrophic hormone
DI- diabetes insipidus
GH- growth hormone
GHD- growth hormone deficiency
GnRH- gonadotropin-releasing hormone
IHD- isolated hormone deficiency
IGF-1- insulin-like growth factor-1
MPHD-multiple pituitary hormone deficiency
MRI- magnetic resonance imaging
SOD- Septo-optic dysplasia
TSH-stimulating thyroid hormone
VP shunt-ventricular peritoneal shunt

Conflict of interests

There are no conflict of interests.

Funding

A self-funded study.

Ethical approval

Ethics approval for this study was obtained from the Ethics Review Committee, Sri Lanka College of Paediatricians. (Ref. No SLCP/ERC/2020/17)

Author contributions

Lakmini BC and Atapattu N designed the study and contributed to data collection and manuscript writing. Rathnayake H contributed to statistical analysis and data interpretation. All authors have read the manuscript and agreed. SPSS data sheets are available for further reference.

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