ABSTRACT:

BACKGROUND: Hypopituitarism refers to complete or partial failure of pituitary hormones secretion that has a wide range of clinical manifestations which require hormone replacement to eliminate or minimize the symptoms and clinical signs of specific hormone deficiencies. We aimed to identify clinical presentation and management of hypopituitarism in pediatric age group.

PATIENTS & METHODS: This is a case series study involving 35 patients who were diagnosed to have hypopituitarism due to different causes at Endocrine Clinic of Tripoli-Children Hospital from 2000 to 2010. Data were collected from patient’s hard records in the clinic, which include age at presentation, sex, clinical presentation, associated illness, height, weight, extent of pituitary hormone deficiencies, pituitary imaging findings and hormone replacement status.

RESULTS: Out of 35 patients 54.3% were males, 45.7% were females with median age at presentation (10±4.5) years. The most common clinical manifestation was short stature (68.6%) followed by hypoglycemia (14.3%) and delayed puberty (8.6%). 11.4% had Craniopharyngioma. MRI showed normal pituitary in 40% of patients, pituitary hypoplasia in 45.7%. Biochemically, growth hormone (GH) deficiency was evident in 82.9%, low TSH in 17.1%, low T4 in 14.3%, low serum cortisol level in 20%, low ACTH in 11.4%, low FSH in 8.6%, and low LH in 5.7%. The result also showed that 5.3% of males had low testosterone level and 18.8% of females had low estrogen level. Hormonal replacement included GH therapy (85.7%), thyroxine (62.9%), cortisol (45.7%) and sex hormone (31.4%).

CONCLUSION: Most common clinical presentation of hypopituitarism was short stature. Symptoms of patients with hypopituitarism improved by appropriate hormonal replacement according to their needs.

KEYWORDS: Hypopituitarism/Libya, Pan Hypopituitarism, pediatrics, short stature, hypogonadism.

INTRODUCTION

Hypopituitarism refers to complete or partial failure of secretion of anterior and/or posterior pituitary hormones. There are different causes of hypopituitarism include gene defect or mutations [1, 2]. Pituitary adenoma and Craniopharyngioma are the most common tumors that cause hypopituitarism [3]. Inflammatory lesions of the pituitary gland and Lymphocytic hypophysitis classically presents with partial hypopituitarism [4].


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Hypopituitarism is a common complication of irradiation administered for head and neck tumours, intracranial malignancy or as adjunctive cranial irradiation for acute lymphoblastic leukaemia [5]. Severe accidental or inflicted childhood traumatic brain injury (TBI) appears to be a cause of pituitary dysfunction in large population of children one year after the injury, the prevalence of endocrine dysfunction in these patients ranges from 15-68% [6, 7], an enlarged empty sella may be presents with hypopituitarism. The multiple aspects of normal pituitary function serve to predict the wide range of clinical manifestations of hypopituitarism which are determined by the severity, extent and duration of the condition. Onset may be in childhood or adult life and is generally permanent, requiring one or more specific hormone replacements. Acute Adrenocorticotrophic hormone deficiency cause fatigue, weakness, nausea, vomiting, and circulatory failure while chronic deficiency causes Tiredness, pallor, anorexia, nausea, weight loss, myalgia and hypoglycaemia. Gonadotropins deficiency presented with delayed puberty in adolescents and impaired fertility in males and amenorrhrea in females. Thyroxine hormone deficiency cause fatigue, cold intolerance, constipation, weight Gain, dry skin and growth retardation. Growth hormone deficiency cause growth impairment, antidiuretic hormone cause polyuria and polydipsia [8-10]. Basal concentrations of the anterior pituitary hormones should be measured by serum samples were taken unstressed, with no physiological or pharmacological manipulation, between 7 and 9am. Dynamic pituitary function tests may assess the hypothalamic-pituitary unit (e.g. insulin tolerance test, glucagon and arginine tests) [9]. Magnetic resonance imaging (MRI) is the optimum method of imaging, with computerized tomography (CT) as an acceptable alternative [3].

Hypopituitarism is usually permanent. Replacement therapy is achieved by administering target hormones. The aim of hormone replacement is to safely eliminate or minimize the symptoms and clinical signs of specific hormone deficiencies [11].

Our aim to describe the clinical presentation and its management of hypopituitarism in Tripoli Children Hospital.

PATIENTS & METHODS

This is a case series of thirty-five patients who were referred to the Endocrine Clinic at Tripoli Children Hospital between 2000 and 2010. All of the children were diagnosed to have hypopituitarism due to different causes. Hypopituitarism was defined as deficiency of one or more pituitary hormone & pan-hypopituitarism was defined as deficiency of three or more pituitary hormones [10]. Data were collected from patient's hard records in the clinic, which include age at presentation, sex, clinical presentation, associated illness, height, weight, extent of pituitary hormone deficiencies, pituitary imaging findings and hormone replacement status.

Hormone levels were extracted from the patients' records. Secondary hypothyroidism was defined as low Thyroxine (T4, normal 58-161 nmol/l) with low or inappropriately normal thyroid-stimulating hormone (TSH, normal 0.5-6.5 μIU/ml). Low cortisol and ACTH level was taken to indicate secondary adrenal insufficiency. GHD was defined on basis of peak stimulated growth hormone (GH) level < 7 ng/ml by insulin tolerance test [12]. Hypogonadism in male was defined as low total testosterone (<3 ng/ml) and low or inappropriately normal luteinizing hormone and follicular-stimulating hormone (LH, normal 3-10 IU/l) (FSH, normal 3-10 IU/l) with clinical symptoms. Hypogonadism in female was defined as low estradiol (<45 pg/ml) and low or inappropriately normal LH and FSH.

STATISTICAL ANALYSIS

Descriptive statistics were used and all results are presented as frequencies, median, means±standard deviation and percentages. Statistical analysis was performed using statistical software (SPSS).

RESULTS

This study included 35 patients; 19 (54.3%) were males and 16 (45.7%) were females. The median age at presentation was 10±4.5 years. There was no death during the time of study. The most common clinical manifestation was short stature 68.6%, followed by hypoglycaemia 14.3%. 8.6% of the patients presented with delayed puberty and 20% had other symptoms. 11.4% of the patients had brain tumors, 8.6% had learning disabilities and 25.7% had other illness including cerebral palsy, epilepsy, congenital heart disease, urinary tract infection, cleft palate. Pituitary imaging showed normal pituitary in 40% of patients, pituitary hypoplasia in 45.7%, empty sella in 8.6%, and pituitary mass in 5.7% of all patients (Table 1).
Table 1: Patients Profile (Tripoli children hospital 2000-2010).

<table>
<thead>
<tr>
<th>Patient Characters</th>
<th>No (%)</th>
<th>Patient Characters</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age on presentation</strong></td>
<td></td>
<td><strong>Height</strong></td>
<td></td>
</tr>
<tr>
<td>0 – 5 years</td>
<td>10 (28.6%)</td>
<td>Below 3rd centile</td>
<td>24 (68.6%)</td>
</tr>
<tr>
<td>6 – 10 years</td>
<td>9 (25.7%)</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>16 (45.7%)</td>
<td>Below 3rd centile</td>
<td>13 (37.1%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td>Associated illness</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (54.3%)</td>
<td>Brain tumor</td>
<td>4 (11.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (45.7%)</td>
<td>Mental retardation</td>
<td>3 (8.6%)</td>
</tr>
<tr>
<td><strong>Presentations</strong></td>
<td></td>
<td>Other illness</td>
<td>9 (25.7%)</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>3 (8.6%)</td>
<td>MRI/CT scan finding</td>
<td></td>
</tr>
<tr>
<td>Short stature</td>
<td>24 (68.6%)</td>
<td>Normal</td>
<td>14 (40%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>5 (14.3%)</td>
<td>Pituitary hypoplasia</td>
<td>16 (45.7%)</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>7 (20%)</td>
<td>Mass</td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Empty sella</td>
<td>3 (8.6%)</td>
</tr>
</tbody>
</table>

When we looked at the laboratory findings, we found that 82.9% of the children had GH deficiency, 17.1% had low TSH, 14.3% had low T4, 20% had low cortisol level, 11.4% had ACTH deficiency, 8.6% had low FSH and 5.7% had low LH. The result also showed that about 5.3% of the males had low testosterone and about 18.8% of the females had low estrogen (Figure 1).

![Hormonal levels](image)

**Figure 1: Hormonal levels (Tripoli children hospital 2000-2010).**

When we looked at the hormonal replacement therapy, we have found that 85.7% of all patients were given GH, 62.9% were given thyroxine, 45.7% were given cortisol, 11.4% (4 males) were given HCG, 17.1% (6 males) were given testosterone, 14.3% (5 females) were given estrogen and 17.1% (6 females) were given combined estrogen and progesterone (Figure 2). The relation between the clinical presentation and different

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age groups was statistically insignificant (Table 2), which also showed insignificant relation between clinical presentation of patients and gender.

![Figure 2: Hormonal replacement therapy (Tripoli children hospital 2000-2010)](image)

Table 2: Relation of clinical presentations with age and gender.

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Total</th>
<th>0 – 5 (Count (%))</th>
<th>6 – 10 (Count (%))</th>
<th>&gt; 10 (Count (%))</th>
<th>Males Count (%)</th>
<th>Females Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short stature</td>
<td>24</td>
<td>7 (29.2%)</td>
<td>6 (25%)</td>
<td>11 (45.8%)</td>
<td>17 (70.8%)</td>
<td>7 (29.2%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>5</td>
<td>3 (60%)</td>
<td>1 (20%)</td>
<td>1 (20%)</td>
<td>2 (40%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (100%)</td>
<td>2 (66.7%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>7</td>
<td>4 (57.1%)</td>
<td>2 (28.6%)</td>
<td>1 (14.3%)</td>
<td>4 (57.1%)</td>
<td>3 (42.9%)</td>
</tr>
</tbody>
</table>

DISCUSSION

This study reports our experience with childhood-onset cases of hypopituitarism in Tripoli Children Hospital. We showed that more than a quarter of patients presented at age of 0-5 years and another quarter presented between 6 and 10 years. However, hypopituitarism in children is not a common occurrence, but with the advent of newer diagnostic techniques the diagnosis can be made more frequently at an early age; [13,14].

Familial cases of hypopituitarism are extremely rare and could be autosomal recessive, dominant or x-linked recessive [15]. There is a single report of a Libyan family with a familial hypopituitarism. The family in this report had combined pituitary hormone deficiency in two cases [16]. However, in Childhood cases, one must consider whether the hypopituitarism has its origin before or at birth or is acquired at any time after birth. The younger the child is at the time of presentation, the more likely the etiology is to be congenital and needs earlier hormonal replacement therapy [17].

The age at presentation in our study was 10±4.5 years; males and females were almost equal in number. Abhay Gundurthi et al in their study in India [18], found a mean age of 38.6±17.8 years, with a male preponderance (69%). There were 22 subjects aged ≤18 years (childhood and adolescence) and 91 adults (>18 years) [18]. This study may not represent a good
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comparison with ours because of including adults and not just children.

Short stature is one of classical presentation of hypopituitarism. Our study showed that the most common presentation was short stature followed by hypoglycemia. Pan-hypopituitarism was diagnosed in Ullah et al study [19] in only 2.7 % (n=73) as cause of short stature due to Craniopharyngioma in early childhood. Bhadada et al [20] reported panhypopituitarism only in 1.1% (n=352). Brasel et al [13] reported a group of seventy-five patients in whom hypopituitarism was the most common cause of short stature, seconded by hypothyroidism. Hypoglycemia was one of presenting symptoms among young age group in our study. Braslavsky [21] showed that pituitary insufficiency in the first months of age is a life threatening disorder, usually evidenced by nonspecific signs such as hypoglycemia, cholestasis or poor feeding.

Some of our patients presented with hypogonadism supported with other studies which suggested that delayed puberty and sexual infantilism could be presenting symptoms [22,24]. The majority of MRI findings in this study was normal or evidence of pituitary hypoplasia; which is not going with other studies which reported that brain tumors (most commonly Craniopharyngioma) were the most common finding in MRI [13-18,25]. Though CT-scan was conducted in some of our cases instead of MRI, the latter is considered the standard pituitary imaging modality [26].

This study showed that most of the patients had GH deficiency which presented as short stature, followed by hypothyroidism, hypoadrenalism. Hypogonadal males and females were also observed but with low percentage. The study of Brasel et al [13], reported that 24% of the children in their study had panhypopituitarism and the rest had hypopituitarism in one or more than hormones. GH deficiency was only seen in one case in Brasel et al study, the same study showed that five children had TSH deficiency and 15 partial evidence of TSH deficiency [13]. Higher percentage of hypothyroidism (40%) was reported by Hubble [27]. Many studies revealed an association between gonadotropin hormones deficiency and brain tumor [13,25,28]. The management of hypopituitarism should focus on the cause of the problem and physiological hormonal replacement to maintain normal body functions. The current study reported that most of the patients were received GH and thyroxin with good response. Patients with delayed puberty were given, testosterone, HCG for hypogonadal males, estrogen and progesterone for hypogonadal females, Kim [29] also reported that when gonadotropin deficiency occurs in a male patient, it is important to administer testosterone orally or intramuscularly and to adjust the dose by closely monitoring the clinical response of the patient and his testosterone concentrations. For female patients, estrogen and progesterone should be alternately administered and gonadotropin should be prescribed when the patient wishes to conceive [29]. Unfortunately, we have no data about reproduction ability of hypogonadal males and females as all referred to adult endocrine services at 20 years old but all have signs of puberty with good response to replacement therapy before referral to adult endocrine center. This indicates the lack of coordination of services and data flow between adult and pediatric endocrinology departments.

CONCLUSION

The most common clinical presentation of hypopituitarism were short stature and hypoglycemia followed by hypothyroidism, hypoadrenalism and delayed puberty. The GH, cortisol, TSH and T4 were the most affected hormones. Brain MRI is important in determining the etiology. Appropriate hormonal replacement and, direct treatment of the cause is crucial in management of children with hypopituitarism. All these children need referrals to a reproductive endocrinologist as fertility issues arise.

LIMITATION OF THE STUDY

The number of patients included in this study is small and no available data about long term follow up at adult endocrine services especially about reproduction capability.

ACKNOWLEDGMENT

We wish to thank our patients and their parents who agree to involve in this study

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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ملخص باللغة العربية

اعراض وعلاج نقص إفراز الغدة النخامية في مستشفى الأطفال طرابلس 2000-2010

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رقم الهاتف: 00218925252661

المقدمة:
نقص نشاط الغدة النخامية يشير إلى فشل كامل أو جزئي في إفراز هرمونات الغدة النخامية، وتظهر بعلامات سريرية تتعلق من نقص هرمون معين. وتشمل الدراسات تحديد الأعراض السريرية وكيفية علاج نقص نشاط الغدة النخامية في الأطفال.

الطرق:
هذه دراسة تشمل 35 مريضا تم تشخيص إصابتهم بقصور الغدة النخامية لعوامل مختلفة في عيادة الغدد الصماء في مستشفى الأطفال طرابلس من 2000 إلى 2010. تم جمع البيانات من سجلات المرضى في العيادة، والتي تشمل العمر الذي ظهرت فيه العراض، والجنس، الأعراض السريرية، والطول، والوزن، ومدى القصور في هرمون الغدة النخامية، نتائج التصوير للغدة النخامية، والموروثية، والهرمونات التي تم إعطائها كعلاج.

النتائج:
من بين 35 مريضا 54.3% ذكور، 45.7% إناث مع متوسط العمر عند التشخيص كان 10 ± 4.5 سنوات (13 يومًا - 17 عامًا). وكان من بين الأعراض السريرية الأكثر شيوعا قصر القامة (68.6%) تلتها هبوط السكر في الدم (40%)، وقصر النوم (31.4%)، وتأخير سن البلوغ (8.6%). وتأخر في نمو الورك (14.3%) ونحو 11.4% من المرضى، ونقص هرمون النمو (14.3%)، ونقص هرمون الغدة الدرقية (17.1%)، وانخفاض مستويات هرمون التستوستيرون (18.8%)، وانخفاض مستويات الهرمونات الجنسية (31.4%) في الحالات.

الاستنتاج:
كان العرض السريري الأكثر شيوعا من قصور الغدة النخامية قصر القامة، واتخاذ التدابير اللازمة للمرضى الذين يعانون من نقص نشاط النخامية، وحول العلاج الاستبدالي بهرمون النمو (85.7%)، والثروكسين (62.9%)، والكورتيزول (45.7%)، والهرمون الجنسي في (45.7%) من الحالات.

الكلمات المفتاحية: نقص أفرز الغدة النخامية / ليبيا، عموم نقص النخامية، طب الأطفال، قصر القامة، قصور الغدة النخامية.