Original Article

Clinical spectrum of hypopituitarism in India: A single center experience

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ABSTRACT

Objectives: There is paucity of information regarding clinical profile of hypopituitarism from India. We report the clinical profile of hypopituitarism from a tertiary center in North India. **Materials and Methods:** This study was carried out in patients attending our endocrine center between January 2010 and December 2011. All new patients were studied prospectively and those registered before January 2010 retrospectively. Relevant clinical, hormonal, and imaging data were collected. Dynamic testing for pituitary functions was carried out as necessary. Hormonal deficiencies were defined as per prevailing recommendations. **Results:** This study included 113 subjects. The mean age was 38.6 ± 17.8 years (range, 4 – 76 years). There were 78 (69%) males and 35 females (31%). There were 22 subjects aged ≤18 years (childhood and adolescence) and 91 adults (>18 years). Visual disturbances were the most common presenting complaint (33%), though headache was the most common symptom (81%). Fifteen percent presented with pituitary apoplexy. Tumors comprised of 84% of cases. Hypogonadism (97%) was the most common abnormality seen followed by hypothyroidism (83.2%), hypoadrenalism (79.6%), growth hormone deficiency (88.1% of the 42 patients tested), and diabetes insipidus (13.3%). Panhypopituitarism was seen in 104 (92%) patients. There were no cases of hypopituitarism secondary to traumatic brain injury, subarachnoid hemorrhage, central nervous system infections, or cranial irradiation to extrasellar tumors. **Conclusion:** The most common cause of hypopituitarism at tertiary care center is pituitary tumors and the commonest presenting complaint is visual symptoms. Panhypopituitarism is present in 92% cases.

Key words: Hypopituitarism, pituitary macroadenoma, Sheehan syndrome

Introduction

There is scant data on hypopituitarism from India despite estimated total prevalence of pituitary disorders to 4 million in the year 2000.[1] It is at best limited to case series involving childhood hypopituitarism,[2] Sheehan syndrome,[3,4] post radiotherapy,[5] pituitary adenomas,[6] or tubercular meningitis (TBM).[7] A study from Spain documented an incidence and prevalence of hypopituitarism to be 4.21 and 45.5 cases per 100 000 population, respectively.[8] Hypopituitarism follows a smoldering course unless it has an onset with pituitary apoplexy; hence, more often it is likely to be missed.[9] Hypopituitarism is associated with increased mortality with cardiovascular cause being the major culprit.[9] It becomes important to diagnose and treat this entity, especially in subjects who are at risk. There is paucity of data on hypopituitarism in India; hence, we studied the clinical profile of hypopituitarism at a tertiary care center in North India.

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Materials and Methods

The patients attending Endocrinology Department of this tertiary care center between January 2010 and December 2011 were included in this study. A total of 8 623 new cases and 26 113 old patients attended outpatient department (OPD) of endocrinology during study period and 517 179 OPD patients of whole hospital. New patients registered from January 2010 were studied prospectively and relevant clinical, hormonal, and imaging data were collected. Data

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were collected retrospectively for those patients who had registered prior to January 2010. There were 154 cases of hypopituitarism, of which 41 cases were excluded as they were part of our previous study on treatment of growth hormone deficiency (GHD) and were <18 year of age.[10]

Hypopituitarism was defined as deficiency of one or more pituitary hormone and panhypopituitarism was defined as deficiency of three or more pituitary hormones.[11,12]

Hormone levels were measured using commercial kit provided by Immunotech, Beckman Coulter Company, France. Secondary hypothyroidism was defined as low free thyroxine (FT4, normal 0.8-2.1 ng/ml) with low or inappropriately normal thyroid-stimulating hormone (TSH, normal 0.5-6.5 μIU/ml). A peak stimulated cortisol (after adrenocorticotropic hormone [ACTH] stimulation) <18 μg/dl constituted adrenal insufficiency. GHD was defined when peak stimulated growth hormone (GH) level was <10 ng/ml in children and adolescent (≤18 years) and <5 ng/ml in adults (insulin tolerance test and/or clonidine stimulation test).[12] GHD was also defined as low age- and sex-matched insulin-like growth I (IGF-I) in presence of panhypopituitarism.[12] However, all adult patients were not assessed for GHD as we are not presently treating GHD in adult due to financial constraints and due to lack of IGF-1 in-house assay in institution. Secondary hypogonadism in male was defined as low total testosterone (<3 ng/ml) and low or inappropriately normal luteinizing hormone (LH, normal 3-10 IU/l) and follicular-stimulating hormone (FSH, normal 3-10 IU/l) with clinical symptoms. Similarly, secondary hypogonadism in female was defined as low estradiol (<45 pg/ml) and low or inappropriately normal LH and FSH with amenorrhea. Hyperprolactinemia was defined as prolactin levels more than 20 ng/ml.

Results

There were 154 subjects (30 new and 124 old) with hypopituitarism. Hypopituitarism was present in 0.44% of OPD cases (4.4/1 000 endocrine OPD cases) and three cases/million of whole hospital OPD patients. Of these, 113 patients were included in further analysis. The mean age was 38.6 ± 17.8 years (range, 4 – 76 years). There were 78 (69%) males and 35 females (31%). There were 22 subjects aged ≤18 years (childhood and adolescence) and 91 adults (>18 years). The chief presenting features of these patients are shown in Table 1. Visual disturbances were the most common presenting feature seen in 33% of the patients, though headache was the most common symptom observed in 81% of patients but was presenting complaint in 12.4% cases only. Acute presentation with apoplexy was seen in 15% of the patients. Those with pituitary adenoma had apoplexy as presenting feature in 18.6%.

The etiology of hypopituitarism is shown in Table 2. Tumors comprised 84% of the cases. Pituitary macroadenoma was the cause of hypopituitarism in 75 patients (66.4%). Of these, 47 patients had non-functioning adenoma (62.6%), 24 had acromegaly (32%), three had macroprolactinoma [Figure 1] (4%), and one had Cushing's disease. Other pituitary tumors were craniopharyngiomas (18 cases), one case each of intrasellar germ cell tumor [Figure 2] and granular cell tumor of neurohypophysis [Figure 3]. The latter two tumors were diagnosed by their immunohistochemistry characteristics. Non-tumor causes were seen in 16% of the patients. Sheehan's syndrome was documented in six patients (5.3%). There were few rare cases of hypopituitarism which we came across. Recurrent pituitary abscess was seen in one patient who had panhypopituitarism.[13] Snake bite (hemotoxic) was seen in one patient, she had presented with multiorgan failure and panhypopituitarism was diagnosed when she was evaluated for secondary hypothyroidism about two years after snake bite. Panhypopituitarism due to isolated lymphocytic hypothalamitis in a 16-year-old girl was also observed and reported by us.[14] There were two siblings

Table 1: Chief presenting feature of the patients with hypopituitarism

Presentation	Number (%)
Vision disturbance	38 (33)
Pituitary apoplexy	17 (15)
Headache	14 (12.4)
Acromegaly	13 (11.5)
Raised intracranial tension	9 (8)
Hypothyroidism	5 (4.4)
Short stature	5 (4.4)
Secondary amenorrhea	3 (2.7)
Failure of lactation	3 (2.7)
Diabetes insipidus	1 (0.9)
Pituitary incidentaloma	1 (0.9)
Ptosis	1 (0.9)
Delayed puberty	1 (0.9)
Hydrocephalus	1 (0.9)
Renal stone	1 (0.9)

Table 2: Etiology of hypopituitarism

Etiology	Number (%)
Pituitary macroadenoma	75 (66.4)
Other sellar/suprasellar tumors	20 (17.7)
Sheehan syndrome	6 (5.3)
Familial hypopituitarism	2 (1.8)
Idiopathic hypopituitarism	2 (1.8)
Hypophysitis	2 (1.8)
Empty sella syndrome	2 (1.8)
Snake bite	1 (0.9)
Pituitary abscess	1 (0.9)
Thalassemia major	1 (0.9)
Dandy Walker syndrome	1 (0.9)

with deficiency of GH, TSH, LH, FSH, and ACTH with a novel PROP-1 mutation (unpublished data). We detected adrenal insufficiency and GHD in a six-year-old boy with sacral agenesis.[15]

Hypogonadism (97%) was the most common abnormality seen followed by hypothyroidism (83.2%), hypoadrenalism (79.6%), GHD (88.1% of the 42 patients tested), and diabetes insipidus (13.3%). Hypogonadism, hypothyroidism, and hypoadrenalism were symptomatic in 88.7%, 59.6%, and 32.2% [Table 3]. Panhypopituitarism was seen in 104 (92%) patients. The distribution of hypopituitarism according to sex is shown in Table 4.

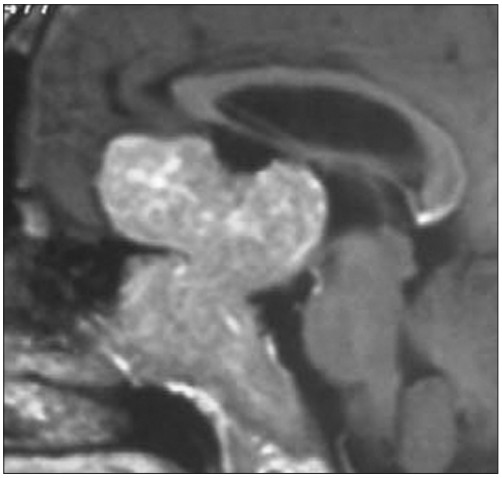

Figure 1: T2-weighted magnetic resonant imaging of sella showing a giant macroprolactinoma in a male presenting with bitemporal hemianopia and headache. His initial prolactin level was 16 000 ng/ml. He underwent debulking surgery followed by dopamine agonist therapy

All patients with a tumor underwent surgery. Forty-four (46.3%) and 20 (21%) of these patients received conventional radiotherapy and gamma knife surgery, respectively, for residual/recurrent lesion. Table 5 shows the pattern of hypopituitarism according to the treatment offered. Amongst those who underwent surgery alone for adenoma, 94.7% had panhypopituitarism compared to 97.7% and 85.7% in those who received additional conventional radiotherapy and gamma knife surgery, respectively. Deficiencies of all the hormones were seen in 18 (16%) patients and combination of hypogonadism, hypothyroidism, and hypoadrenalism was seen in 62 (55%) patients.

The children and adolescents comprised 19.5% of the patients. Among this group, 73% had a tumor as a cause for hypopituitarism and the most common tumor was craniopharyngioma (87.5%). In this group, all but one child with somatotroph adenoma had GHD, 95% had hypoadrenalism, 86% had hypothyroidism, 32% had DI, and 86% had panhypopituitarism.

Magnetic resonance imaging (MRI) was performed in all patients. Ninety-five (84%) patients had sellar/parasellar mass. Eight patients (7%) had empty sella and one sibling of familial hypopituitarism had enlarged sella.

Discussion

In this study, we present data regarding spectrum of hypopituitarism for which data from India is scant. The most common cause for hypopituitarism is sellar/suprasellar

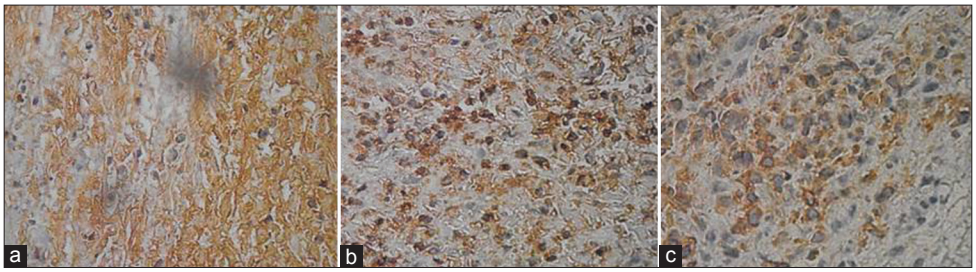

Figure 2: The immunohistochemistry confirming the diagnosis of intrasellar germinoma, (a) positive for CD68, (b) positive for cytokeratin, (c) positive for epithelial membrane antigen

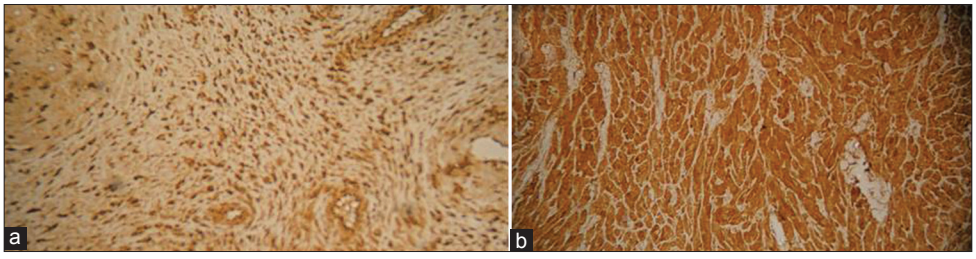

Figure 3: Immunohistochemistry of granular cell tumor of neurohypophysis confirming the diagnosis, (a) Positive for S100, (b) positive for neuron-specific enolase

Table 3: Spectrum of pituitary hormone deficiency

Hormone deficiency	Symptomatic (%)	Asymptomatic (%)	Total (%)
Hypogonadism*	86 (88.7)	11 (11.3)	97 (97)
Hypothyroidism	56 (59.6)	38 (40.4)	94 (83.2)
Adrenal insufficiency	29 (32.2)	61 (67.8)	90 (79.6)
Growth hormone deficiency#	42 (100)	0	37 (88.1)
Diabetes insipidus	13 (100)	0	15 (13.3)

*13 children were prepubertal and gonadal axis cannot be commented, #Growth hormone was tested in 42 patients

Table 4: Distribution of pituitary deficiency in males and females

Pituitary dysfunction	Male (%)	Female (%)
Hypogonadism	68 (97)	29 (97)
Hypothyroidism	98 (87)	26 (74)
Hypoadrenalism	72 (77)	30 (86)
Panhypopituitarism	72 (92)	33 (94)

tumors which is consistent with the prevalent data. Bates *et al*.[16] reported tumors in 89% of their hypopituitarism series which is similar to that seen in our series. However, etiology has been more diverse in our series.

Chatterjee *et al*. have described the largest published series of adult hypopituitarism (82 cases) till date in India.[17] Hence, present study is the largest series of adult hypopituitarism (91 cases). They noted pituitary adenoma in 37.8%, Sheehan's syndrome in 27%, snake bite in 14.6%, suprasellar lesion in 7.3%, and empty sella in 7.3%. Lower incidence of Sheehan's syndrome in our study may be due to availability of free obstetrical care to our population at service hospitals and better socioeconomic strata of our sample population. The high incidence of snake bite could be due to geographical variations in snake bite pattern. They found hypocortisolism in 81.7%, hypothyroidism in 63.4%, hypogonadism in 78%, and GHD in 64.6% of their patients. This study is in contrast to our observations.

A study among non-Cushing's pituitary macroadenoma from India observed hypothyroidism, hypoadrenalism, and hypogonadism in 24%, 54%, and 52% of patients, respectively, at initial presentation but a significant proportion of them went onto recover their pituitary functions after intervention.[6] However, a majority of them were evaluated before receiving radiotherapy and also had a short follow-up period. In contrast, the incidence of hypothyroidism, hypoadrenalism, and hypogonadism was 87%, 72%, and 100%, respectively, in present series. Radiotherapy was administered to 53% of these patients and most of them were on long-term follow-up and these could explain the high incidence of hypopituitarism.

From India, another study studied incidence of hypopituitarism in patients who had received cranial irradiation for extrasellar tumors.[5] The author showed that pituitary dysfunction was common in these patients. However, in our study, we did not come across any case of hypopituitarism due to cranial irradiation for extrasellar tumors. This suggests that hypopituitarism after radiotherapy for extrasellar tumors are often missed as cases are under follow-up at oncology center and do not come to attention for non-specific symptoms due to hypopituitarism. Though recommendations for evaluation of pituitary function following cranial radiation exist,[18] it is not often followed.

We came across a case of hypopituitarism due to snake bite. It has been estimated that 2 00 000 people are bitten by venomous snake (viperidae family is a major contributor) in India every year.[19] Clinicians treating snake bites from tropical countries like ours need to be aware of this entity and these patients should be under long-term follow-up to document any pituitary insufficiency. The presentation can be acute like apoplexy or chronic as seen in our patient who was diagnosed two years after the event. Only a handful cases have been reported from India till date.[17,20-24]

Another common cause in the developing countries is Sheehan's syndrome. There have been few case series of this entity from India.[3,4] Patients can have a varied spectrum of pituitary dysfunction in Sheehan syndrome from panhypopituitarism to isolated hormone deficiency and from acute presentation to a chronic form. In their seminal work, Zargar *et al*.[3] described the clinical profile of Sheehan's syndrome. They reported 149 patients with Sheehan's syndrome and estimated total cases of this entity to be 38 691 in Kashmir valley. They documented one, two, three, four, and five pituitary hormone deficiencies in 17.4%, 23.5%, 18.8%, 17.4%, and 22.8%, respectively. We diagnosed six cases of Sheehan's syndrome and all had panhypopituitarism. Hypogonadism and hypoadrenalism were universal and hypothyroidism was present in four. None of them had diabetes insipidus. All had chronic form and MRI showed empty sella in all.

Pituitary abscess is another rare cause of hypopituitarism. We previously reported one case of recurrent pituitary abscess[13] with panhypopituitarism. The pus from the abscess of this patient was sterile and no cause could be ascertained in him. Dutta *et al*.[25] reported four cases

Table 5: Treatment modality and occurrence of hormone deficiency in tumoral cause of hypopituitarism

Treatment (n)	Hypothyroidism (%)	Hypogonadism (%)	Hypoadrenalism (%)	Panhypopituitarism (%)
Surgery (38)	30 (79)	33 (87)	30 (79)	35 (92)
Sx+CRT (44)	41 (93)	38 (86)	35 (80)	43 (98)
Sx+GKS (14)	11 (76)	13 (93)	10 (71)	12 (26)

Sx: Surgery, CRT: conventional radiotherapy, GKS: gamma knife surgery

of pituitary abscess and all had presented with systemic manifestations in addition to endocrine dysfunction. Our patient did not have any systemic symptoms. In the largest series of pituitary abscess published till date, the authors report that abscess can be successfully treated but the accompanying hypopituitarism is usually irreversible.[26]

Traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) are being more frequently reported as etiology of hypopituitarism.[27] The incidence of traumatic brain injuries is 150/100 000 in India.[28] Post-traumatic hypopituitarism is observed in about 5.4 to 40% of patients with a history of TBI usually presenting as an isolated deficiency in most cases.[29,30] Hypopituitarism has been observed in 19% of patients with ischemic stroke and 47% of patients with SAH, presenting as an isolated deficiency in most cases.[31] However, there were none with TBI or SAH in our cohort. This could be due to lack of awareness in clinicians attending these patients. Efforts need to be made to sensitize the clinicians about the existence of hypopituitarism in this subset of patients as advocated by a consensus guideline.[32]

Central nervous infections, known to have high incidence in developing countries, are known to cause hypopituitarism. In a recent study from India, hypopituitarism was observed in about 30% of newly diagnosed TBM.[7] The study stated TBM to be a severe stressful condition and conveniently used the controversial cortisol cut-off values for diagnosing adrenal insufficiency. The thyroid dysfunction could well be interpreted as sick euthyroid syndrome. Nevertheless, the study highlights the need to consider hypopituitarism in central nervous system (CNS) infections. Again, we did not have CNS infections as a cause of hypopituitarism in our series.

The etiology of hypopituitarism differs in childhood and non-tumor causes are more common than in adults. We previously reported treatment response to growth hormone therapy in 71 patients;[10] hence, those cases (41 cases) which belonged to this center's endocrine OPD were excluded from the study. Among these children, 61 had abnormalities in hypothalamo-pituitary axis as a cause of GHD. Idiopathic GHD was reported in 73% which included 9.8% of combined pituitary hormone deficiency and 12.6% had GHD secondary to tumor/ structural lesion. Excluding subjects with genetic causes of hypopituitarism, craniopharyngioma is the most common cause of hypopituitarism in children rather than pituitary adenoma. One needs to consider congenital structural disease like Dandy Walker syndrome as a cause of pituitary dysfunction which has not been reported previously.

Contrary to the belief that hypophysitis occurs in middle-aged women, we previously reported a case of isolated lymphocytic hypothalamitis with panhypopituitarism in a 16-year-old girl.[14] Familial hypopituitarism due to transcription factor defects is now a well-recognized entity[33,34] and we documented two siblings with a novel PROP-1 mutation. The interesting fact was the deficiency of all the anterior pituitary hormones and early onset of corticotrophin deficiency in them.

We found that the most common presentation was due to compression symptoms rather than endocrine dysfunction. The fact highlights the subtleness in the clinical profile of patients with pituitary dysfunction and also underlines the need for dedicated evaluation of pituitary functions in those at risk of developing the same.

We noted acute presentation in the form of apoplexy in 15% of patients. Compared to one of the largest case series of classic pituitary apoplexy,[35] we documented a very high rate of pituitary dysfunction—hypothyroidism (82.3% vs 45%), hypoadrenalism (70.5% vs 58%), hypogonadism (88.2% vs 43%), and diabetes insipidus (23.5% vs 6%). All had panhypopituitarism. This could be explained by delay in diagnosis of the subjects with pituitary adenomas.

Conclusions

This is the largest reported series of hypopituitarism from India. The most common cause of hypopituitarism at tertiary care center is pituitary tumors and presenting complaint is visual symptoms. Panhypopituitarism is present in 92% cases. Though tumors comprise of the majority of the cases, one needs to be aware of Sheehan's syndrome and snake bite as a cause of hypopituitarism in our country. The study was also significant for not documenting any case of hypopituitarism secondary to

"emerging" causes like TBI and SAH. Hypopituitarism needs to be diagnosed and treated early to prevent associated morbidity and mortality.

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