Original Article

Clinical Presentations, Hormonal Evaluation and Imaging Abnormalities in Patients with Multiple Pituitary Hormone Deficiency : A Single-centre Experience from Rural West Bengal

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Purpose of The Study : A plethora of conditions are associated with multiple pituitary hormone deficiency (MPHD). Aetiologies and clinical spectrum of MPHD in the developing countries are varied and quite different from that in the West. Tumours of the hypothalamo-pituitary (HP) region are the dominant cause of MPHD in the tertiary care referral centres, not only in the Western World, but also in India. There is real paucity of information regarding clinical profile and aetiology of MPHD from rural India.

Methods : We analysed the presenting manifestations, hormonal parameters and imaging abnormalities in all patients of MPHD (n=53), evaluated in the Department of Medicine, Midnapore Medical College & Hospital between January 2016 to December 2018.

Findings : Hypogonadism was the most common (54.7%) clinical manifestation of hypopituitarism in this study. Repeated hospitalization with spontaneous hypoglycaemia, recurrent hyponatremia and refractory anaemia were also common in this cohort. Vasculotoxic snake (viper) bite (VSB) was the commonest aetiology (30.2%) of MPHD overall, while Sheehan's syndrome (SS) dominated in females. Patients of VSB were exclusively male, with the youngest one being 13-year old. Majority of these patients (87.5%) underwent several sessions of haemodialysis following the bite. 61.5% of SS delivered at home, and almost 92% had had severe post-partum haemorrhage requiring transfusion support. All patients of VSB had hypogonadism and hypoadrenalism, while all but one case of SS had cortisol deficiency. Agalactia was universal in SS. Empty sella on magnetic resonance imaging (MRI) was the dominant abnormality (52.8%) encountered, while 3 patients had normal MRI findings.

Implications : Hypopituitarism is often unrecognized; hence remains untreated, as primary care physicians are unaware of the varying clinical manifestations of MPHD. They need to be sensitised to have a high index of suspicion in appropriate clinical settings.

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Key words **: Multiple pituitary hormone deficiency, Hypopituitarism, Vasculotoxic snake (viper) bite, Sheehan's syndrome, Hypophysitis**

Multiple pituitary hormone deficiency (MPHD), also termed combined pituitary hormone deficiency (CPHD), is used to describe the condition associated with deficiency of more than one hormone, produced from the pituitary gland. Impaired pituitary hormone production, often described as hypopituitarism, results from a plethora of acquired and inherited conditions, and has an approximate global prevalence of 1 in 2200[1]. The aetiology of MPHD varies greatly not only between countries, but also among centres within a country, due to referral bias, age of the participants and sex-ratio of the study population. Majority of studies, particularly those from the Western World documented an unequivocal predominance of tumours in the hypothalamo-pituitary (HP) region as the underlying cause of MPHD. In the Dutch National Registry, one of the largest databases of adult onset growth hormone deficiency (GHD), the dominant causes of MPHD were pituitary tumours and/or their treatment and craniopharyngiomas, involving ~60% of patients[2]. Similar observation was noted in adult onset hypopituitarism database from Serbia (n=512; tumours: 61%) and Spain (n=209; tumours: 55%)[3,4]. There are only a handful of population-based studies related to the aetiology of MPHD from our country. A single-centre study (n=113) from North India has also found tumours in overwhelming majority (84%) of patients with

Editor's Comment :

- **In rural West Bengal, VSB and SS are commonest cause of hypopituitarism in males and females, respectively.**
- **Hypogonadism, spontaneous hypoglycaemia, recurrent hyponatremia, and refractory anaemia are the dominant clinical manifestations in these patients.**
- **Hypoadrenalism due to secondary adrenal insufficiency is almost universal in hypopituitarism following VSB or SS.**
- **Acute kidney injury necessitating haemodialysis and post-partum haemorrhage are the predictors of future hypopituitarism in VSB and SS, respectively.**
- **Majority of the primary care physicians are unaware of this entity, and the condition remains undiagnosed with resultant morbidity, poor quality of life and excess mortality.**

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hypopituitarism attending a tertiary clinic[5]. In contrast, a study conducted at a tertiary care hospital in Eastern India noted tumours responsible for 45% cases of adult onset hypopituitarism, highlighting the centre-specific differences in aetiology[6].

Clinical manifestations of MPHD depend upon several factors like underlying aetiology, number of pituitary cell lines affected, magnitude of hormone deficiency, and rapidity of onset and disease progression. Symptoms and signs of hypopituitarism, particularly early in the course of disease are non-specific and often subtle, resulting in delay in diagnosis and appropriate management. Adrenocorticotrophic hormone (ACTH) deficiency makes them vulnerable, particularly during acute stress and intercurrent illnesses[7]. Patients with undiagnosed, hence untreated MPHD, have a poor quality of life and are at increased risk of mortality both in short term and due to cardiovascular disease in the long run. Untreated gonadotropin deficiency has also been identified as an independent risk factor for excess mortality[8,9]. This is particularly important in countries like India, where Sheehan's syndrome (SS) and vasculotoxic snake (viper) bite (VSB), conditions often associated with combined ACTH and gonadotropin deficiencies, contribute to a sizable portion of cases with hypopituitarism[6]. The adverse consequences of hypopituitarism can be mitigated to a large extent by early diagnosis and appropriate management. We conducted this study to look for clinical manifestations and underlying aetiologies of MPHD in a group of population from relatively poor socio-economic stratum, residing in a region of India with limited access to tertiary health care facility.

Materials and Methods

In this hospital record based retrospective study, data of 53 patients with a confirmed diagnosis of MPHD, either attending the Endocrinology clinic or discharged from the in-patient department (IPD) of Department of Medicine, Midnapore Medical College & Hospital between January 2016 to December 2018 were analysed. The study was approved by the Institutional Ethical Committee (Memo No. MMC/IEC-2019/193 dated 28/01/2019). We looked into the different aetiologies of hypopituitarism and characterized the clinical presentation and biochemical profile of these patients.

Clinical presentations, relevant information including number of prior hospitalization, traumatic brain injury (TBI), history of VSB, acute kidney injury (AKI) after VSB, number of haemodialysis (HD) sessions, history of cranial surgery and/or radiation, history of stroke were noted for all. Female participants were also evaluated for menstrual history, childbirth, post-partum haemorrhage (PPH), blood transfusion (BT) and agalactia.

Cortisol, free thyroxine (FT4), thyroid stimulating hormone (TSH), prolactin, and insulin like growth factor 1 (IGF1) were measured in all patients from serum samples collected between 8:00-9:00 AM after an overnight fast. Patients with AM cortisol between 5-14.5 μg/dl underwent ACTH stimulation. Due to non-availability of Synacthen (tetracosactide acetate), we used twenty-five units of Acton Prolongatum® (Ferring pharmaceuticals, available as 5 ml vial with concentration of 60 units/ml) injected intramuscularly, and sample was collected after 60 minutes; a cortisol concentration of less than 18 μg/dl was considered as hypocortisolism[10]. Serum testosterone was measured only in males after the age of 14 years from samples collected in fasting state between 8:00-9:00 AM. FSH was measured in males with low testosterone, and in females after 13 years of age with history of oligo-amenorrhoea. Polyethylene glycol (PEG) precipitation test was performed in cases with high prolactin.

All hormonal assays were performed by chemiluminescent immunoassay (CLIA). Cortisol, FT4 and TSH assays were performed in ADVIA Centaur CP system (SIEMENS). Testosterone, IGF1, FSH, and prolactin were measured in cobas e 411 analyser (Roche Diagnostics). Magnetic resonance imaging (MRI) of the HP region was performed using SIGNA Explorer, 60 cm 1.5T system (GE Healthcare).

Hypophysitis was diagnosed based on the radiological score proposed by Gutenberg et. al. that showed a sensitivity of 92%, a specificity of 99%, a positive predictive value of 97%, and a negative predictive value of 97% for the diagnosis of autoimmune hypophysitis[11]. All such patients underwent routine cerebrospinal fluid (CSF) analysis, and estimation of adenosine deaminase (ADA), angiotensin-converting enzyme (ACE), β-human chorionic gonadotropin (hCG) and α-fetoprotein (AFP) in CSF in addition to measurement of serum immunoglobulin G4 (IgG4) level. Idiopathic intracranial hypertension (IIH) was suspected in presence of empty sella (ES), dilated optic nerve sheaths, protrusion of optic nerve papilla into the posterior globes, and compressed ventricles and CSF cisterns on MRI[12].

Observations

The study cohort consisted of 53 patients with male (n=31) to female (n=22) ratio of 1.4. The mean age of the study population was 40.5 (±14.6) years (range: 7-65 years). 6 of them (11.3%) belonged to an age group below 18 years, and 47 subjects (88.7%) were of more than 18 years of age. The clinical presentations have been summarized in Table 1.

The most common clinical feature in this population was loss of secondary sexual characters (54.7%), elicited from history and/or clinical examination, performed at presentation. Symptoms, which were potentially life-threating, like severe hypoglycaemia (second in order) and recurrent hyponatremia (fifth in order), requiring repeated hospitalisation were observed in 34% and 22.6% of the cohort, respectively. Another 4 (7.5%) patients had history of frequent hospitalisation only for BT. Overall, 31 patients (58.5%) had previous episodes of hospitalization (<5 times: 18 patients; 5-10 times: 10 patients; >10 times: 3 patients); however, the diagnosis of MPHD had been missed during those occasions.

In our study, 16 subjects (30.2%) (all of them were male, youngest one was of 13 years of age) had history of VSB in the past, and 14 out of these 16 subjects (87.5%) required HD due to AKI (Table 2). 17 female subjects (32% of the entire cohort and 77.3% of the total female population) had secondary amenorrhoea, while another 12 (54.5% of the female population) had agalactia

with secondary amenorrhea since last childbirth. Only one lady had agalactia, but with preserved menstrual cycles. Out of 13 patients of SS, definite diagnosis was made within 5 years of the responsible obstetric event in 1 (7.7%), between 5-10 years in 4 (30.8%), 10-20 years in 4 (30.8%) and more than 20 years in another 4 (30.8%) patients.

The patient with acromegaly had haemoglobin (Hb) level of 20.1 gm/dl secondary to polycythaemia. The mean Hb concentration in the rest of the cohort was 9.9 (±1.4) gm/dl. One patient had pancytopenia and another one had β-thalassemia major. Hyponatremia (<135 mmol/L) was observed in 24 (45.3%) and hypokalemia (<3.5 mmol/L) in 3 subjects (5.7%). Low FT4 (<0.8 ng/dl) was encountered in 32 patients (60.4%), and 13 of them (40.6% of those with low FT4) had TSH below reference range (<0.5 μIU/ml). Low AM cortisol (<5 μg/dl) was seen in 44 patients (83%). Peak cortisol of more than 18 μg/dl following ACTH injection was noticed only in 7 patients. All patients of VSB, hypophysitis, and all but one patient of SS had ACTH deficiency, either low AM cortisol or failed ACTH stimulation test. The hormonal parameters have been summarized in Tables 3&4. Among 29 male patients, 28 (96.6%) had low testosterone (<300 ng/dl). The median value of testosterone was 43 ng/dl. The median value of FSH was 2.65 mIU/ml, consistent with the diagnosis of hypogonadotropic hypogonadism. Only 6 patients had (11.3%) elevated monomeric prolactin and the median value of serum prolactin was 5.18 ng/ml. IGF1 was below age and sex specific reference ranges in 39 patients (73.6%) while one patient had elevated IGF1. Median value of serum IGF1 was 73.85 ng/ml.

Majority of the patients had abnormal appearances of the HP region on MRI (Table 5) (Figs 1&2). Empty sella with varying thickness of the remaining pituitary tissue was the commonest abnormality noted (28 patients, 52.8% of the cohort). Only 3 patients (5.66%) had apparently normal looking HP region. Hypophysitis was diagnosed retrospectively in 1 lady with ES, whose previous MRI was consistent with hypophysitis[11]. One male with hypophysitis presented with diabetes insipidus. Pituitary transcription factor defect was considered in 3 subjects with MPHD presenting during childhood and adolescence periods. The commonest aetiology of MPHD in our study was VSB (Table 6).

Table 1 — *Clinical presentations of the study population (n=53)*

Clinical presentation	Number of patients (n)	Percentage (%)
Loss of secondary sexual characters	29	54.7
Severe hypoglycaemia	18	34
Secondary amenorrhoea	17	32
Agalactia	13	24.5
Recurrent hyponatremia	12	22.6
Headache	8	15
Short stature	6	11.3
Refractory anaemia needing transfusion support	4	7.5
Delayed puberty	3	5.7
Weight gain with pica	1	1.9
Acromegaly	1	1.9
Galactorrhoea	1	1.9
Diabetes insipidus	1	1.9
Visual defect	1	1.9

Table 2 — *Characteristic of patients with viper bite*

	Number of patients (%)
Male	16
Female	0
History of haemodialysis	14
Interval between bite and diagnosis of MPHD (n=16)	
<1 year	2 (12.5)
1-5 years	3(18.8)
5-10 years	9 (56.3)
>10 years	2 (12.5)
Number of haemodialysis sessions (n=14)	
<5	4 (28.6)
5-10	7 (50%)
>10	3 (21.4%)

Discussion

Tumours dominated over other causes like cranial irradiation, traumatic brain injury, SS and lymphocytic hypophysitis in 7708 patients of adult onset GHD (as a component of MPHD) in the KIMS database[13]. However, a difference in aetiology was noted amongst the six largest contributing countries. The Pituitary Study Group of the Society of Endocrinology and Metabolism of Turkey (SEMT) looked into the aetiology of hypopituitarism in 773 patients aged between 16 to 84 years, in nineteen tertiary care institutions. Though non-tumoral causes dominated overall (49.2%), a significant gender deference was noted, and SS contributed to majority of females[14]. The dominant causes of MPHD in our study were VSB (30.2%), tumours (de novo and post-treatment) (26.4%), and SS (24.5%). VSB and SS were encountered exclusively in males and females, respectively. Tumours contributed to ~26% cases (n=14) of MPHD (de novo pituitary macroadenoma:9; post-operative cases of pituitary macroadenoma: 3; craniopharyn-gioma: 1; hypothalamic mass: 1). Of the 9 newly diagnosed cases of pituitary macroadenoma, seven patients had non-functional pituitary adenoma, one had acromegaly and the other one had macroprolactinoma. A study from our part of the country reported SS in 27% and VSB in 14.6% cases of adult with MPHD[6].

Table 3 — *Biochemical parameters of the study population*

Parameters	Mean	Standard deviation
Sodium (mmol/L)	133.9	10.7
Potassium (mmol/L)	4.1	0.5
FT4 (ng/dl)	0.73	0.39
TSH (μIU/ml)	1.97	1.82
A.M cortisol (μg/dl)	3.66	2.97
FSH (mIU/ml) (male)*	3.46	2.49
FSH (mIU/ml) (female)**	3.54	3.53

***Measured in males aged more than 14 years with low testosterone**
****Measured in females after 13 years of age with history of oligo-amenorrhoea.**

Table 4 — *Pituitary hormone deficiency in different aetiologies of MPHD (n=53)*

	Low cortisol (n=46)*	Low FT4 (n=32)	Low IGF1 (n=39)	Low testosterone (n=28)**
Viper bite (n=16)	16	12	11	16
Sheehan's syndrome (n=13)	12	10	10	
Pituitary macroadenoma (n=9)	6	4	7	8
Sequel of pituitary surgery (n=3)	3	2	2	1
Craniopharyngioma (n=1)	1	0	1	1
Hypothalamic mass (n=1)	1	1	1	
Hypophysitis (n=4)	4	2	1	1
Transcription factor defect (n=3)	2	1	3	1
Idiopathic intra-cranial hypertension (n=1)	0	0	1	
Idiopathic hypopituitarism (n=1)	1	0	1	
β-thalassemia major (n=1)	0	0	1	

***Low cortisol includes AM cortisol <5 µg/dl or post-ACTH cortisol <18 µg/dl**
****Only in males above 14 years of age**

Table 5 – *MRI findings in different aetiologies of MPHD (n=53)*

Diagnosis	MRI appearance
Viper bite (n=16)	Partial empty sella: 14; hypoplastic pituitary: 1; normal HP region: 1
Sheehan's syndrome (n=13)	Partial empty sella: 12; hypoplastic pituitary: 1
Pituitary macroadenoma (n=9)	Sellar mass with/without supra & parasellar extension and heterogenous contrast enhancement
Sequel of pituitary surgery (n=3)	Enlarged sella with residual tissue and fibrotic changes with deviation of stalk: 3
Craniopharyngioma (n=1)	Sellar and suprasellar mass with mixed solid and cystic components and calcification
Hypothalamic mass (n=1)	Isointense mass in T1 weighted MRI with intense contrast enhancement
Hypophysitis (n=4)	Diffuse enlargement of the pituitary with stalk thickening and rapid, intense, and homogenous contrast enhancement:3; partial empty sella: 1
Transcription factor defect (n=3)	Hypoplastic pituitary: 3; Absent pituitary stalk & ectopic posterior pituitary bright spot: 1
Idiopathic intra-cranial hypertension (n=1)	Partial empty sella with protruded optic nerve head inside orbit and dilated optic nerve
Idiopathic hypopituitarism (n=1)	Normal HP region
β-thalassemia major (n=1)	Normal HP region

Aetiology of MPHD varies depending on age of the study population. In those 6 patients of our study, aged less than 18 years of age, 3 had transcription factor defects, and craniopharyngioma (n=1), hypothalamic mass (n=1) and VSB contributed to MPHD in the remaining 3.

Conditions, which rarely contribute to MPHD in the western world, often are the dominant causes of pituitary dysfunction in the developing countries. The list includes VSB, SS and central nervous system (CNS) infections[15]. Hypopituitarism following VSB is common (61%) in patients who develop AKI requiring HD. Increasing number of sessions of HD confers higher risk and cortisol deficiency is the commonest abnormality encountered. Hypopituitarism has been reported as early as 7 days following snake bite[16]. Our findings were consistent with this study as majority of our patients required more than 5 sessions of HD. One of our patients developed severe hypoglycaemia due to hypopituitarism on 5th day after viper bite.

SS is quite prevalent in rural India. The prevalence of SS is about 3% in women above 20 years of age residing in Kashmir valley; and almost two-third of them delivered at home[17]. The diagnosis is often delayed, and the average time lag between the culpable obstetric event and diagnosis was found to be 13 years[18]. Definitive diagnosis of SS was reached after 10 years in 8 (61.5%) of our patients. 12 out of 13 patients of SS (92.3%) had history of PPH, and all of them required BT suggesting severe blood loss. 8 (61.5%) of these ladies had delivered at home. PPH has been reported in 82-100% of patients with SS[18,19]. Frequency of agalactia

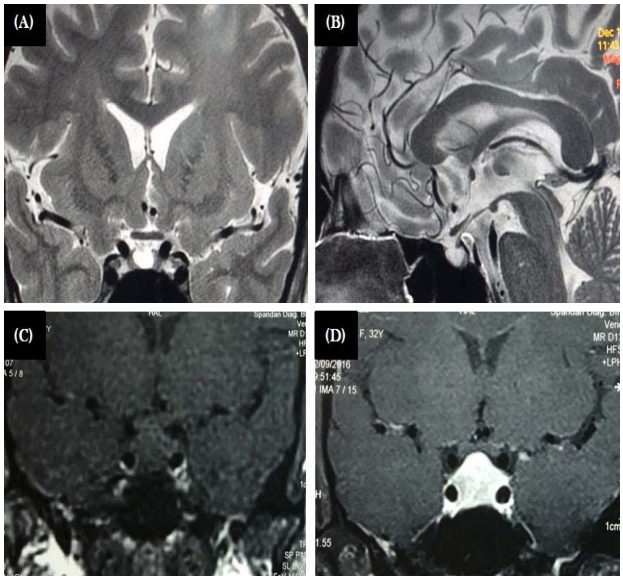

Fig 1 — Upper panel: Partial empty sella in T2 weighted MRI (A: coronal; B: mid-sagittal) from a patient of VSB. Lower panel: Diffuse enlargement of pituitary with stalk thickening (C) and intense homogeneous contrast enhancement (D), suggestive of hypophysitis

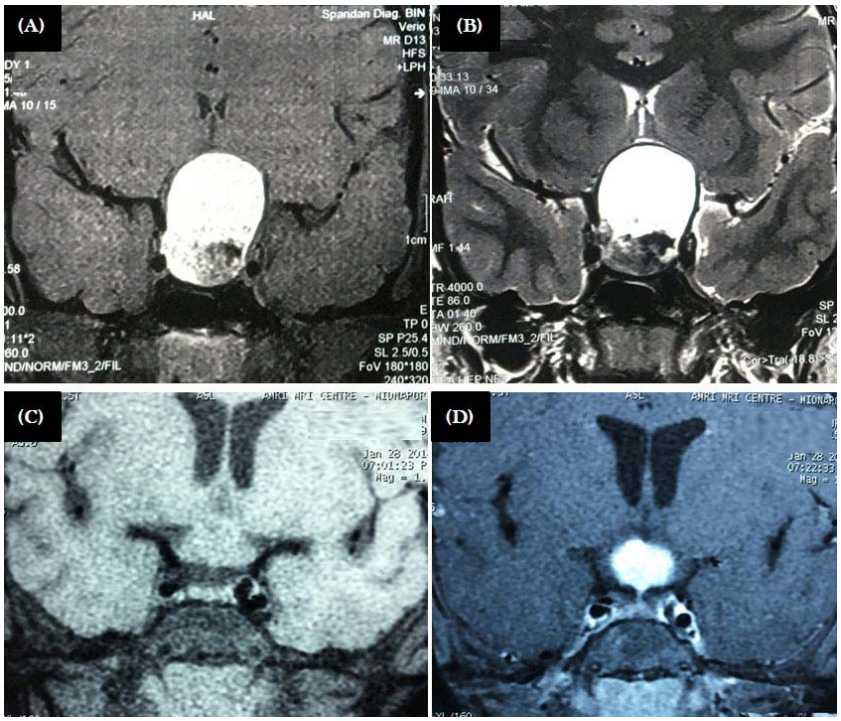

Fig 2 — Upper panel: MRI of patients with craniopharyngioma. Mixed solid-cystic lesion with cystic component being hyperintense in both T1 (A) and T2 (B) weighted sequences
Lower panel: Patient with hypothalamic mass, that is isointense in T1 (C) with intense contrast enhancement (D)

in SS has variably been reported in about 40-67% in studies outside India[18,20]. However, agalactia is much higher in our country and, was seen in 100% of our patients with SS, a finding consistent with another study published from the same geographical region[19]. One patient of SS had preserved gonadotroph functions, as evidenced by cyclic predictable menses, and she conceived spontaneously during follow-up. Spontaneous pregnancy in SS, though rare, has been reported in literature[21].

Hypopituitarism is a frequently overlooked cause of severe hyponatremia (<130 mmol/L). The prevalence of hypopituitarism in patients with "euvolemic severe hyponatremia" is 20% in the Western World, and much higher in India[22]. 22.6% of our patients had been admitted with recurrent severe hyponatremia, and the diagnosis of MPHD was never considered. Another interesting observation we came across was refractory anaemia (in 4 patients) and pancytopenia (in 1 patient) in our cohort. Deficiency of thyroid hormone, testosterone, IGF1, and perhaps cortisol either in isolation or in combination have been found to impair haematopoiesis[23]. Refractory anaemia and pancytopenia have been reported in MPHD, SS in particular and are completely reversible after supplementing the deficient hormone(s)[24,25]. The patient with pancytopenia in our study had SS and the 4 patients with refractory anaemia had hypopituitarism due to VSB. We came across one patient with polycythaemia secondary to GH secreting pituitary macroadenoma[26].

In rare patients with MPHD, no obvious aetiology of hypopituitarism could be identified and such patients have normal morphology of the HP region on MRI. In one of the retrospective analyses (n=230), 21 patients (9%) with hypopituitarism had normal pituitary imaging[27]. Despite extensive work-up definitive diagnosis remained elusive in 2. We came across one such patient in our study, and we used the term idiopathic hypopituitarism for that patient.

To conclude, aetiology of MPHD demonstrate a strong geographical variation and referral bias. In regions with poor obstetric care, SS undoubtedly is the leading cause of hypopituitarism in females, while in rural West Bengal, VSB contributes significantly to MPHD in males. Recurrent hyponatremia, unexplained hypoglycaemia, frequent BT are often the presenting manifestations of MPHD in non-tertiary care centres. Many of these patients remain unrecognized, due to lack of awareness among primary care physicians, rendering them to repeated hospitalization, poor quality of life and high risk of mortality.

Table 6 — *Aetiology of MPHD in the study population (n=53)*

Diagnosis	Number of patients (n)	Percentage (%)
Viper bite	16	30.2
Sheehan's syndrome	13	24.5
Pituitary macroadenoma	9	17
Sequel of pituitary surgery	3	5.7
Craniopharyngioma	1	1.9
Hypothalamic mass	1	1.9
Hypophysitis	4	7.5
Transcription factor defect	3	5.7
Idiopathic intra-cranial hypertension	1	1.9
Idiopathic hypopituitarism	1	1.9
β-thalassemia major	1	1.9

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