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Research Article

Autoimmune hypophysitis: a study of natural course

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ABSTRACT

Background: Autoimmune hypophysitis is a rare autoimmune endocrinopathy. Literature on natural history of autoimmune hypophysitis is scarce.
Methods: We prospectively studied patients with autoimmune hypophysitis between January 2013 to June 2015 and all subjects were followed for at least 6 months. Autoimmune hypophysitis was diagnosed based on clinicoradiologic findings. All patients diagnosed with autoimmune hypophysitis were followed every three monthly with evaluation for pituitary functions and six monthly with gadolinium enhanced MRI of pituitary. Deficient hormones were replaced and none of the patients were treated with immunosuppressive therapy or surgery.
Results: Ten cases of autoimmune hypophysitis were diagnosed during the study period. Adrenocorticotropin deficiency was the most common (7/10) followed by thyroid stimulating hormone and gonadotropins (each in 5). Pituitary enlargement and stalk thickening were the most common imaging findings. Three patients had recovery of one hormone in each and none of the patients had progression of mass or new hormone deficiency on follow-up.
Conclusions: The study describes natural history of autoimmune hypophysitis in 10 patients from a single center. We suggest against the routine use of immunosuppressive therapy or surgery in patients with autoimmune hypophysitis.

Keywords: Autoimmune hypophysitis, Lymphocytic hypophysitis, Empty sella, Stalk thickening

INTRODUCTION

Autoimmune hypophysitis is a rare autoimmune endocrinopathy. It is possible that the prevalence of autoimmune hypophysitis is underestimated.[1,2] The reported incidence of autoimmune hypophysitis is one in nine million.[3] A recent study reported an estimated incidence of autoimmune hypophysitis in India as 2.4 per ten million population.[4] Increasing recognition of the disease is contributing for the recent increase in the incidence. In addition to the spontaneously occurring autoimmune hypophysitis cases, a large number of iatrogenic cases have been reported with the use of CTLA4 antibody, ipilimumab. Hypophysitis has been reported in up to 17% melanoma cases treated with ipilimumab.[5] With the increasing use of ipilimumab in the treatment of melanoma, addition of these iatrogenic autoimmune hypophysitis cases may further increase the incidence of autoimmune hypophysistis.

Previously, more than half (57%) of the cases in women were reported to be associated with pregnancy.[6] Lately, most of the studies have reported less association with pregnancy with greater proportion of cases being reported outside the peripartum period.[4,7] A large multicenter study from Germany reported association with pregnancy in only 11% (6/54) of female cases, whereas another large single center study from India reported association with pregnancy in only one of 21 female cases.[4,7] Although, the female predominance persists, the female to male ratio has also decreased in recent studies.[7] Interestingly, hypophysitis associated with CTLA4

antibodies and IgG4 related disease has been reported to be more common in males.[8,9]

The autoimmune etiology of autoimmune hypophysitis is supported by many findings. Histopatholgy is characterised by diffuse infiltration with T and B lymphocytes without a dominant subset which is typical of autoimmune diseases.[6] Presence of other immune response mediator cells like plasma cells, eosinophils, histiocytes and macrophages provide additional support for the autoimmune etiology of hypophysitis.[6] Presence of pituitary antibodies has been demonstrated in variable proportion (10-80%) of subjects with autoimmune hypophysitis.[10,11] Association of the disease with HLA markers like DQ8 and DR53 has been reported with an odd's ratio of 23.1:1 for DQ8. The latter finding may provide a noninvasive way of differentiating autoimmune hypophysitis from other pituitary mass lesions and may obviate the need for biopsy in atypical cases.[12] Moreover hypophysitis is increasingly recognised as a part of IgG4 related disease, further strengthening the role of autoimmunity in the pathogenesis of hypophysitis. [13]

Autoimmune hypophysitis can be classified into lymphocytic hypophysitis (LYH), granulomatous hypophysitis (GRH), and xanthomatous hypophysitis (XH). It is not clear whether these are truly distinct entities or only different expressions of the same disease, since they share clinical and radiological features and can only be distinguished from each other by histological examination.[6]

As the natural history of the disease is becoming clearer, conservative approach with replacement of deficient hormones and close follow-up with periodic imaging is the most preferred line of management.[4] A recent study from Germany also suggests against routine use of immunosuppressive therapy or surgery in the management of autoimmune hypophysitis.[14]

Autoimmune hypophysitis is well known for its diagnostic difficulties. It is a great masquerade and often closely mimics pituitary adenoma leading to inadvertent surgeries.[15] Although, a set of radiological findings may differentiate hypophysitis from pituitary adenoma, diagnosis of the former condition requires a high index of suspicion. On the other hand, almost half of the autoimmune hypophysitis cases are associated with ACTH deficiency leading to adrenal insufficiency which could be life threatening.[6] Hence, it is very important to make appropriate and timely diagnosis of the condition. Hence, we have studied the presenting features, hormonal and imaging characters and outcome of autoimmune hypophysitis patients at our institution.

METHODS

This prospective study was conducted at Vydehi Institute of medical sciences and research center, Bangalore, India. The study was approved by the institutional ethics committee and a written informed consent was obtained by all participants. Subjects were recruited between January 2013 to June 2015 and all subjects were followed for at least 6 months.

Autoimmune hypophysitis was diagnosed based on clinic radiologic findings.[16] All patients diagnosed with autoimmune hypophysitis were followed every three monthly with evaluation for pituitary functions and six monthly with gadolinium enhanced MRI of pituitary. At diagnosis all patients were evaluated with automated perimetry; if found abnormal automated perimetry was repeated every month till normalisation of visual fields.

Evaluation of pituitary function included free thyroxine (FT4), free tri-iodothyronine (FT3), thyroid stimulating hormone (TSH), serum 8:00 am cortisol [supplemented with adrenocorticotropic hormone (ACTH) stimulation tests if serum 8:00 am cortisol is between 5-14 µg/dl], follicular stimulating hormone (FSH), leutinising hormone (LH), prolactin and estradiol. Thyroid stimulating hormone deficiency was diagnosed when FT4 is low with low, inappropriately normal or slightly elevated TSH (<20 µIU/ml). Adrenocorticotropic hormone deficiency was diagnosed if cortisol is low (serum 8:00 am cortisol is <5 µg/dl or ACTH stimulated serum cortisol is <18 µg/dl) with low or inappropriately normal ACTH. Hypogonadotropic hypogonadism (gonadotropin deficiency) was diagnosed if oligoamenorrhea or low estradiol with low or inappropriately normal FSH and LH. Hyperprolactinemia was diagnosed when serum prolactin is >25 ng/ml in women and >20 ng/ml in men whereas hypoprplactinemia was diagnosed when serum prolactin is < 5 ng/ml in women and <3 ng/ml in men. Diabetes insipidus (DI) was diagnosed when urine osmolality was <300 mOsm/L with concomitant serum osmolality >295 mOsm/L or after water deprivation test when a serum osmolality of >295 mOsm/L is associated with urine osmolality of <400 mOsm/L (complete DI) or 401-800 mOsm/L (partial DI). In patients with DI, central nature of DI was confirmed by positive response to vasopressin (increase in serum osmolality). Hormonal assessment was performed by chemiluminiscence method using Unicel DxC 600 Synchron®, Beckman Coulter Ireland Inc.

MRI pituitary images were closely examined for nature of enlargement (symmetric vs asymmetric), enhancement (homogenous vs hetrogenous), stalk thickening, stalk deviation, optic chiasm compression, sellar floor erosion, dark parasellar sign and parasellar extension. Anterior autoimmune hypophysitis was defined as at least one anterior pituitary hormonal deficiency with imaging evidence of anterior pituitary involvement but no evidence of DI or loss of pituitary bright spot on imaging. Clinical or laboratory evidence of DI or loss of pituitary bright spot on imaging with no evidence of anterior pituitary hormonal deficiencies or imaging findings suggestive of anterior pituitary involvement is considered autoimmune infundibuloneuro hypophysitis. A

combination of anterior and posterior pituitary involvement is diagnosed as autoimmune panhypophysitis.

RESULTS

A total of 10 cases of autoimmune hypophysitis were diagnosed during the study period. Anorexia (n=7), weight loss (7), nausea (n=7), vomiting (n=6), polyuria and polydipsia (n=2), headache (n=5) and visual field defect (n=1) were the presenting symptoms in our patients. There were seven women and three men with mean age of 38.1±13.45 years. Three women presented during the peripartum period. Associated autoimmune conditions (autoimmune hypothyroidism and celiac disease in one each) were diagnosed in two patients (Table 1).

Table 1: Clinical characteristics of autoimmune hypophysitis patients in the study.

Sex /Age	Hormonal axis involved	Associated features	Relation with pregnancy	Reversal of hormones
M/57	ACTH, TSH, Gn			
F/52	ACTH, Gn	Hypoprolactinemia		Gn
M/58	ACTH, TSH Gn			
F/22	ADH, Gn	Celiac disease	+	
F/30	ACTH, TSH			TSH
F/28	ACTH	Primary hypothyroidism	+	
F/42	ACTH			ACTH
F/24	ADH		+	
F/36	ACTH, TSH	Hyperpolactinemia		
M/32	TSH, Gn			

ACTH: adrenocorticotropic hormone, ADH: antidiuretic hormone, Gn: gonadotropins, TSH: thyroid stimulating hormone

ACTH deficiency was the most common (7/10) followed by TSH and gonadotropin deficiency (5/10 each). Two patients had diabetes insipidus; hyperprolactinemia and hypoprolactinemia were found in one patient each (Table 1).

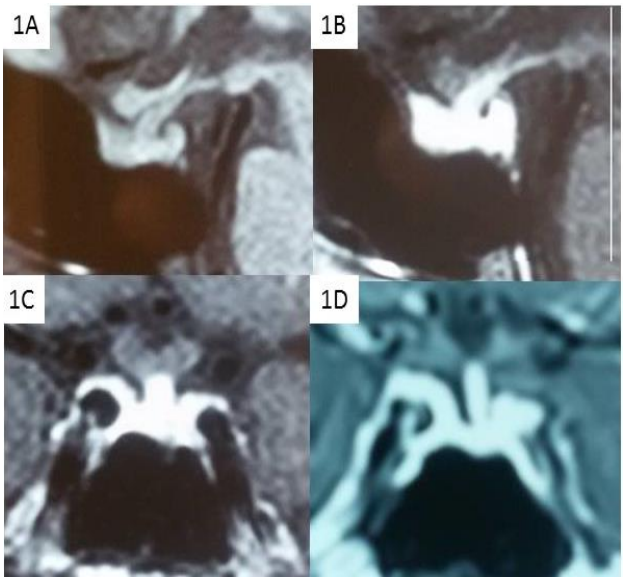

Figure 1: Magnetic resonance imaging feature of case 1 at diagnosis which showed a normal sized pituitary measuring 0.7X0.6 cm with stack thickening and diffuse intense homogenous enhancement at diagnosis (1A, 1B and 1C which was transformed to partial empty sella 1 year later (1D).

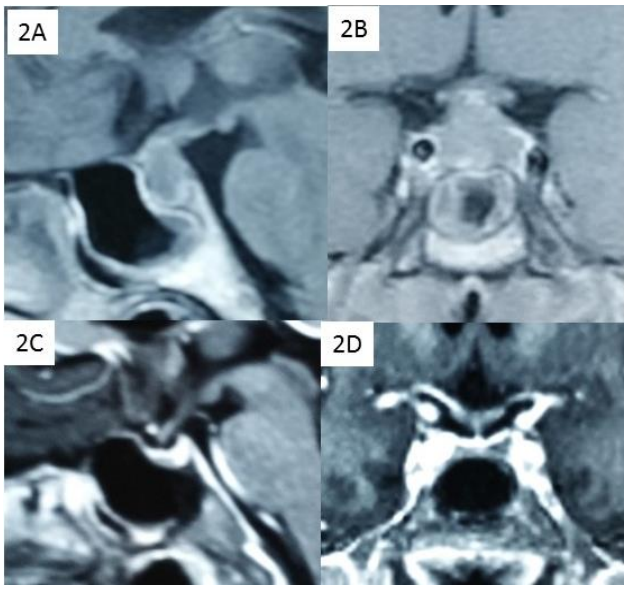

Figure 2: Magnetic resonance imaging feature of case 3 at diagnosis which showed a large mass measuring 2.1X1.7cm with stack thickening at diagnosis (2A and 2B) which was rapidly transformed to empty sella at 3 months of follow-up (2C and 2D).

On imaging, seven patients had mild to moderate enlargement of the pituitary which included six patients with isolated anterior pituitary hormone deficiencies, one with combined anterior pituitary hormone deficiency and diabetes insipidus (Table 2). Stalk thickening was appreciable in six patients (Table 2). Imaging

characteristics of case no 1, 3 and 4 have been depicted in Figure 1, 2 and 3 respectively. None of the patients had asymmetric enlargement, stalk deviation, sellar floor invasion or parasellar extension.

Two patients, including the one with visual field defects, had enlargement of pituitary abutting optic chiasm. In addition to both patients with diabetes insipidus, another patient with no laboratory/clinical evidence of diabetes insipidus also had loss of posterior pituitary bright spot.

Table 2: Imaging characteristics of patients with autoimmune hypophysitis in the study.

Pituitary size at diagnosis (cm)	Duration of disappearance of enlarged pituitary [Months]	Stalk thickening	Empty sella at last follow-up
0.7X0.6	NA	+	+
1.4X1.2	24	+	
2.1X1.7	3	+	+
1.3X1.0	No change at 6 months	+	
1.4X0.9	9	+	
1.2X0.9	9		
1.3X1.1	18	+	
0.7X0.5	NA		
0.7X0.6	NA		+
1.5X1.1	16		

During a follow-up period of months, recovery of hormonal axis was observed in three patients. Each patient had recovery of only one hormone and recovery was observed in ACTH, TSH and gonadotropins. None of the patients developed new hormone deficiency on follow-up.

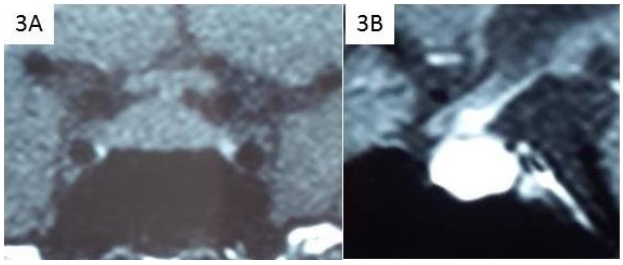

Figure 3: Magnetic resonance imaging feature of case 4 at diagnosis which showed a mildly enlarged pituitary measuring 1.3X1.0 cm with stack thickening and diffuse intense homogenous enhancement at diagnosis (3A and 3B). This patient had no change in imaging characters at 6 months (not shown in figure).

During follow-up, six of the seven patients with pituitary enlargement at diagnosis had regression of the mass lesion; two of these had developed partial empty sella. The time period for disappearance of the lesion ranged from 3 months to 24 months.

In one patient with enlargement of the pituitary abutting optic chiasm at diagnosis, there was rapid transformation to empty sella. Another patient who had normal pituitary size at diagnosis also had developed complete empty sella at last follow-up. None of the patients had progression of mass on follow-up. Stalk thickening had normalised in five patients at last follow-up. All patients were managed with replacement of deficient pituitary hormones alone. The patient with primary hypothyroidism was continued on levothyroxine and the patient with coeliac disease was continued on gluten free diet. None of the patients were neither treated with supraphysiological doses of corticosteroids or other immunosuppressive agents nor underwent surgery.

DISCUSSION

This study describes clinical features, hormonal deficiencies and imaging characteristics at presentation and changes in hormonal axes and imaging characters during follow-up of 10 cases of autoimmune hypophysitis. Since all patients in our study were managed without immunosuppressive therapy or surgery, the study represents the natural history of autoimmune hypophysitis.

Autoimmune hypophysitis is a condition with female preponderance; the female to male ratio being 8:1.[6] Our patients showed a less female predominance with female to male ratio of 7:3. Our finding is comparable with the recent report from Germany, in which 71% of the study population were female.[7]

Symptoms of sellar compression, represented by headache and visual disturbances, are the most common and usually the initial complaint.[4,6,7] However in our study, five patients had headache and only one had visual field defect. The most common presentation in our study was symptoms suggestive of ACTH deficiency (anorexia, weight loss, nausea and vomiting). A recent study has reported weight gain as manifestation of autoimmune hypophysitis in 18% patients but in our study none had weight gain.[7] In our study, ACTH was the most common hormonal deficiency followed by TSH, gonadotropins. A large review including 371 cases, report similar findings with ACTH followed by TSH deficiencies as the most common hormonal abnormalities.[6]

In contrast, a recent study has reported gonadotropin deficiency followed by antidiuretic hormone deficiency as the most common hormonal deficiencies in patients with autoimmune hypophysitis.[7] Growth hormone deficiency is the least common hormonal deficiency. However, we have not studied growth hormone status in our patients.

The most common radiological finding in autoimmune hypophysitis is enlarged pituitary mass, which is associated with stalk thickening and intense, homogenous enhancement after gadolinium injection.[4,6,7] It is often

confused with pituitary adenoma unless there is high index of suspicion.[15] These characteristic imaging findings or presence of a mild-moderately enlarged pituitary associated with hormonal deficiencies, especially ACTH and/or TSH deficiencies should suggest the possibility of autoimmune hypophysitis instead of pituitary adenoma.

Recovery from the hormone deficiency was seen in three cases; ACTH, TSH and gonadotropins recovered in one case each. All those who had the recovery of hormonal axis had normal sized pituitary on imaging at the time of axis recovery whereas none of the three patients who had empty sella over time had recovery of the hormonal axis. Hence, development of empty sella may be a negative indicator of hormonal recovery.

In all except one with pituitary enlargement at diagnosis, mass regressed and on conservative management. The only patient with no change in pituitary mass size had only 6 months of follow-up. Regression of mass in most of our patients without immunosuppressive therapy or surgery suggests against the routine use of these therapies in patients with autoimmune hypophysitis. Previously, surgery was the most commonly reported treatment modality, most probably due to less recognition of the disease leading to misdiagnosis as pituitary adenoma or to achieve histopathological diagnosis.[6]

However, with better understanding of the natural course of the disease, replacement of deficient hormones is now the most preferred therapy. A recent multicenter study from Germany has also reported results encouraging this approach. In that study, with replacement of hormonal deficiencies alone, almost half of the cases regress, one fourth stabilize whereas another one fourth may progress. Immunosuppressive therapy (most often with glucocorticoids), although produces excellent initial results, long term success rate was poor with recurrence or progression of the disease. Moreover, use of immunosuppressive therapy was associated with side effects in 63% cases. Surgery was also not a perfect therapy; it was also associated with failure rates of 25%.[14] If surgery is considered, the aim of the surgery should be to debulk the mass and not complete hypophysectomy.

Two patients had associated other autoimmune disorders. One had Hashimoto's thyroiditis which has been reported to be the most commonly associated autoimmune disorder.[6,7] One patient had coeliac disease. Although rare, coeliac disease has been reported previously with autoimmune hypophysitis.[17]

The study is limited by small number of subjects; however, for a rare disorder like autoimmune hypophysitis, a study of ten patients from a single center provides useful information. Another limitation of the study was lack of histopathological diagnosis in all patients. Although, it is the gold standard in the diagnosis, recent reports recommend diagnosis based on clinicoradiological findings. In our study all patients had clinicoradiological findings consistent with autoimmune hypophysitis.

CONCLUSION

The study describes natural history of autoimmune hypophysitis in ten cases. The diagnosis of autoimmune hypophysitis requires high index of suspicion. All patients who present as pituitary macroadenoma, especially those who manifest hormonal deficiencies with a relatively smaller pituitary mass or those who present in the peripartum period should be suspected to have autoimmune hypophysitis. In the absence of evidence of optic chiasm compression, appropriate hormone replacement with follow-up at regular intervals should be the line of management and routine use of immunosuppressive therapy or surgery are not suggested.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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