



Unconsciousness in a 29-Year-Old Woman with 8 Weeks Amenorrhea

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Abstract

Auto Immune Hypophysitis (AIH) affects women of reproductive age group presenting in early or late pregnancy. ACTH followed by TSH and gonadotropin is the sequence of hormone deficiencies. Steroids form the main stay of the treatment. They recover in 6-9 months. Surgery is rarely required. This report discusses conception in a patient with missed diagnosis of AIH. 29-year women with 8 weeks amenorrhea (G2P1L1A0) presented with unconscious state in the emergency room. Four years back, in 8th month of first pregnancy she had headache and weight loss which continued one year postpartum. Her cycles resumed 3rd month postpartum and was regular till present conception. She breastfed for 18 months. Random blood sugar was 22 mg/dl with normal electrolytes, liver and thyroid functions. Paired 8 am cortisol-ACTH was 0.13 ug/ml - 4.87 pg/ml. Incremental response of plasma cortisol after ACTH stimulation was absent. Adrenal and thyroid autoantibodies were negative. MRI of sella revealed a small pituitary gland with signal changes in pars intermedia and infundibulum, interpreted as sequel of prior apoplexy or AIH. Other anterior pituitary functions were normal. She was supplemented with high dose steroids and carried the pregnancy to 33.4 weeks and delivered a healthy male child. Repeat MRI 6 weeks postpartum revealed an increase in size of pituitary gland with normal posterior pituitary signal and stalk enhancement. CT adrenal-small size gland measuring 1 mm × 1.5 mm. To the best of our knowledge this is the first reported case of untreated AIH resulting in successful spontaneous conception, diagnosed and treated leading to normal delivery with resumption of cycles postpartum.

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Introduction

Auto Immune Hypophysitis (AIH) commonly affects women of reproductive age group presenting with temporal relation to early or late pregnancy. They usually present with headache and visual disturbances. ACTH deficiency is the commonest followed by TSH and the gonadotrophins. Steroids form the main stay of treatment and they recover in 6 to 9 months. Surgery is rarely required. There are very many reports of autoimmune hypophysitis patients treated and later conceiving with successful pregnancy. We present a rare case of, conception in a patient with missed diagnosis of autoimmune hypophysitis, presenting with unconsciousness in 8 weeks of pregnancy. The case was evaluated and treated. Later patient delivered a healthy baby. Mother breast fed the infant and later resumed her menstrual cycles.

Case Presentation

A 29-year old woman with 8 weeks amenorrhea (G2P1L1A0) presented to the emergency room with a history of unresponsive state in the early morning. She had a recent history of vomiting and vaginal spotting three days prior and the urine pregnancy test was positive. The patient's BMI-19.10 Kg/m², heart rate 86/min and blood pressure 90/50 mm/Hg. Four years ago, in the 8th month of 1st pregnancy, she had headache with weight loss (8 Kg) which continued until one-year postpartum. She delivered a male child at term and breast fed for 18 months. Menstrual cycles resumed 3rd month post-partum and was regular until her 2nd conception. After her 1st delivery she has been complaining of weakness, lethargy, fatigue, weight loss and anorexia. After her 2nd conception she had been having nausea and vomiting. Her Random blood sugar was 22 mg/dl, TSH: 4.18 uIU/mL; T4:9.77 ug/dL; T3:1.410 ng/mL; electrolytes (Serum Sodium and potassium 130.43, 4.45 mmol/l respectively) and Liver aminotransferase levels were normal. Random plasma cortisol was <0.4 ug/dL. Urine specific gravity 1030. Ultrasound of the abdomen and pelvis did not reveal any significant finding other than a gravid uterus. No adrenal lesion could be seen.



Figures 1: Non-Contrast MRI dated 21 Aug 2018. 1A) Sagittal T2W image shows a focal hyperintensity in the pars intermedia (white arrow) with overall small size of the gland; 1B) Sagittal T1W image shows a focal hyperintensity in the pars intermedia (white arrow), with bright in the stalk (arrowhead); 1C) Coronal T1W image shows loss of normal posterior pituitary bright signal (small white arrow) with bright signal in the stalk (arrowhead).



Figures 2: MRI Contrast Scan dated 18 March 2019. 2A) Sagittal T1W image shows normalization of the gland size (white arrow) with normal posterior pituitary bright signal; 2B) Coronal T1W image shows thickened stalk in the superior portion (white arrow) and 2C) Sagittal post contrast T1W image shows focal nodular thickened and enhancing stalk in the superior aspect (white arrow).

Basal paired ACTH and cortisol levels, an ACTH stimulation test was performed to assess the adrenal glands reserve and MR imaging of the Sella without contrast (because of pregnancy), was performed. The results revealed low cortisol and ACTH levels (Paired 8 AM plasma cortisol 0.13 ug/ml-ACTH - 4.87 PG/ML), lack of incremental response in plasma cortisol after ACTH stimulation (Basal and stimulated cortisol every 30 min for 2 h was <0.4 ug/ML). The Anti Adrenal antibody-negative, Antibodies TPO: <0.8 IU/ml and Anti Thyroglobulin Antibody (Anti Tg): <6.4 IU/ml. MRI findings showed a small pituitary gland (AP 7.4 × CC 2.8 × ML 9 mm), signal changes in the pars intermedia and infundibulum and lack of normal posterior pituitary signal (interpreted as a sequel of prior apoplexy or autoimmune hypophysitis) (Figure 1a-1c). Further hormonal tests of anterior pituitary function showed; TSH: 4.18 uIU/mL; serum Prolactin - 42.71 ng/ml; Growth Hormone (GH) - 0.83 ng/ML; IGF Binding protein-3 - 4.73 ng/ml; IGF-1 - 71.8 ng/ml. The GH, IGF levels and serum prolactin were normal. She had normal HbA1c and parathormone levels.

The constellation of findings, lethargy, weight loss from the peripartum period of first pregnancy, resumption of menstrual cycles and subsequent conception along with low paired cortisol-ACTH values, favored a diagnosis of peripartum Autoimmune Hypophysitis (AIH) which had presumably started after the first pregnancy. She was supplemented with high dose steroid (up to 40 mg of hydrocortisone/day). She carried the pregnancy to 33.4 weeks and spontaneously delivered a healthy male child (Weight 1.63 kg, Length 42 cm; Head circumference 30.5 cm. APGAR SCORE 1 and 5 min - 8/10 and 9/10), and is being breast fed. After 8 months her menstrual cycles resumed. MRI of the Sella was performed 6 weeks post-partum with contrast which showed an increase in size of the pituitary gland with normal posterior pituitary signal and mild increased stalk enhancement (AP:12.2 × CC 4 × ML 12.2 mm) (Figure 2a-2c). CT scan of the adrenal glands showed significantly small sized adrenal glands with

the limb thickness measuring only 1mm and body thickness of 1 mm to 1.5 mm.

Discussion

The clinical presentation of anorexia, weakness, lethargy, fatigue, weight loss, and lack of stamina, along with hypotension, mild hyponatremia and hypoglycemia typically suggest adrenal insufficiency. Some of the symptoms of adrenal insufficiency are mirrored by pregnancy. In this background biochemical diagnosis of mild adrenal insufficiency can be challenging. Hypercortisolism may be primary or secondary. Paired early morning ACTH along with cortisol is recommended for diagnosis of adrenal insufficiency. A value of <5 mcg/dl of cortisol confirms hypercortisolism accompanied by >2-fold the upper limit of ACTH.

The total and free plasma cortisol, ACTH, CRH, urinary free cortisol and Cortisol Binding Globulin (CBG) increases by 12th week of pregnancy until mid-gestation in healthy pregnancy. The values are three-fold above the levels of non-pregnant women. Maternal adrenal reserve accounts for 90% to 95% of free cortisol up to 33 weeks of gestation. There are trimester specific cut-offs for stimulated cortisol values 25, 29 and 32 ug/dL in the first, second and third trimester respectively [1]. The low paired cortisol-ACTH levels with lack of adrenal response to ACTH could be explained as secondary adrenal insufficiency as a result of autoimmune hypophysitis untreated for a long period leading to “lazy adrenals”. Also, hyponatremia is less pronounced in secondary adrenal insufficiency.

This patient conceived spontaneously, had normal thyroid function and no adrenal pathology on ultrasound imaging, autoimmune polyglandular syndrome was initially ruled out. This left the possibility of a hypothalamus-pituitary axis aetiology with the possibilities being Sheehan’s syndrome and autoimmune hypophysitis. The preserved gonadal function as evidenced by uneventful previous

pregnancy, breast feeding post-partum, resumption of menstrual cycles and a spontaneous second conception made the possibility of Sheehan's syndrome unlikely. Her autoantibodies to adrenal and thyroid glands (to further rule out autoimmune polyglandular syndrome-APS) was negative. A Magnetic Resonance Imaging (MRI) of the sella was performed (Figure 1a-1c). Contrary to autoimmune thyroid diseases in the puerperium, autoimmune adrenal failure in puerperium has not been reported. Though in Addison's disease there is chronic anovulation leading to infertility unless properly treated, there are reports of fertility in untreated Addison's disease [2].

Typically, AIH presents with hypopituitarism and pituitary mass. AIH is rare in children and seniors. It affects the reproductive age group and has a temporal relation with pregnancy-late pregnancy and early post-partum. The anterior pituitary deficiencies are in order of ACTH>TSH>LH/FSH in AIH. In pituitary tumors, surgery or radiotherapy the sequence of deficiencies is GH>LH/FSH>TSH=ACTH [3]. Autoimmune hypophysitis is classified based on,

A. Anatomy (morphology) whether inflammation involves anterior pituitary (Lymphocytic Adenohypophysitis: LAH), posterior gland and stalk (Lymphocytic Infundibulo Hypophysitis: LINH) or entire gland Panhypophysitis- Lymphocytic Pan Hypophysitis (LPH) [4]. Inflammation involving only anterior pituitary occurs in 65% of cases. It is six times common than involvement of anterior and posterior pituitary together. More than 50% of them are present during pregnancy and post-partum. Involvement of anterior and posterior pituitary are twice as common in women (25%) and neurohypophysis involvement occurs equally in both sexes (10%). AIH commonly presents in the peripartum period beginning with the 3rd trimester of pregnancy. Common symptomatology is headache (40%) and visual disturbances (enlarged pituitary gland-related) in one third of patients or symptoms of anterior pituitary insufficiency in 44% of the cases [3]. Autoimmunity leads to acinar cell destruction which causes the hormonal deficiency resulting in hypoadrenalism, hypothyroidism and hypogonadism. Posterior pituitary may be affected by compression from the anterior pituitary and stalk or directly due to autoimmunity and this leads to polyuria and polydipsia (31% cases) and hyperprolactinemia (18% cases) [3]. The most common hormonal deficiency in AIH is ACTH followed by thyrotropin and gonadotropins [4,5].

B. Aetiological classification is primary and secondary hypophysitis. Primary refers to isolated inflammation of pituitary and secondary refers to cases associated with-immunotherapy drugs, rupture of sella cyst and rarely pituitary adenoma or systemic inflammatory process involving the pituitary gland.

C. Histological classification includes subtypes of lymphocytic, granulomatous, xanthomatous and plasmocytic.

MRI characteristics of AIH are usually a sellar mass typically symmetric and homogenous with an intact sellar floor, suprasellar extension, stalk thickening, precontrast homogeneous signal with homogeneous enhancement with loss of normal posterior pituitary signal. MR imaging follow up of patients with AIH usually showed decreased pituitary volume, a concave pituitary aspect or an empty sella turcica [6]. In pituitary macroadenoma, there is asymmetric sellar mass, often non homogenous with supra sellar extension, stalk displacement, erosion of sellar floor and non-homogenous enhancement on contrast [4].

AIH may spontaneously resolve. Some cases are refractory to treatment and may relapse [7]. In our case, the patient had an AIH peripartum in her 1st pregnancy which probably resolved spontaneously and relapsed in 2nd pregnancy or missed diagnosis in the first pregnancy. During the first trimester of her second pregnancy, her cortisol deficiency was exaggerated and presented as hypercortisolism. The long duration of ACTH deficiency of 4 years between her first and second pregnancies had made her adrenal glands "lazy" and there was no incremental response of her adrenals by the ACTH stimulation. A lack of initial imaging in our case, during peripartum period of the first pregnancy was unfortunate; however the MRI of the pituitary gland in the first trimester did reveal the findings which were inferred to be the sequel of a prior hypophysitis event. Biopsy may not always be necessary for an effective clinical treatment [7,8].

Natural history of AIH is variable. Most patients (72%) improve with high dose glucocorticoids or mass reducing surgeries (rarely), 17% need no medications, 7% die because of irreversible adrenal insufficiency and a few (4%) improve spontaneously. Radiological follow up of AIH show reduction or disappearance of mass (88%), no changes in 12% and empty sella in 10% of patients.

Fertility and pre-conceptual consideration are outlined for patients with primary adrenal insufficiency [9] with steroid dose adaptation (hydrocortisone/fludrocortisone) for different trimesters of pregnancy and during parturition. There are no treatment guidelines for patients conceived with AIH. In this patient, the electrolytes were normal and blood pressures maintained with supplementation of glucocorticoids. Also, hyponatremia is less pronounced in secondary adrenal failure.

Steroids form the mainstay of treatment in AIH. High doses of steroids given during pregnancy to our patient indirectly aided the recovery of AIH as was evidenced by the changes in the pituitary gland on follow up imaging after her 2nd delivery. In some cases, where there is no symptomatic relief of mass effect symptoms, immune suppression (azathioprine, methotrexate, mycophenolate), biological therapies (Rituximab) and even radiotherapy may be considered [10]. Majority of patients recover within 6 to 9 months with therapy and surgical removal is rarely required [10]. AIH has no adverse effects on pregnancy or ability to conceive in future. There are reports of conception after successful treatment of AIH with steroid therapy [11]. There are no reports of conception in patients with missed diagnosis of AIH, later presenting with hypercortisolism in subsequent pregnancy.

In a retrospective analysis [12] (1988-2006) of 15 patients of AIH, there was female preponderance (14 females and one male), with commonest hormone deficiency being ACTH (67%), TSH (53%) and gonadotropin deficiency (40%). Imaging revealed enhancing sellar mass (87%) with stalk thickening (33%). On serial monitoring sellar mass regressed/disappeared without any immunosuppressive treatment. Three patients underwent surgery.

The important points that we would like to highlight in our case are: the importance of a good clinical history coupled with an understanding of the relevance of hormonal tests, supplemented by appropriate imaging will lead one to the diagnosis of AIH. With our patient being pregnant and in her first trimester, we needed to be judicious and careful to come to the diagnosis after having considered relevant differential diagnoses, we had to rely on non-invasive

diagnostic practices (hence she was not subjected to a biopsy) and our primary goal was for our patient to have a healthy pregnancy and a healthy baby.

To the best of our knowledge, this is the first reported case of untreated AIH resulting in a successful spontaneous conception, which was then appropriately diagnosed and treated, to lead to a normal delivery with resumption of menstrual cycle's post-partum.

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