Case Report

Spontaneous Intracerebral Hemorrhage in Auto Immune Polyglandular Syndrome Type 2/ Schmidt's Syndrome - A case report

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Abstract

The Autoimmune Polyglandular Syndromes (APS) are clusters of endocrine abnormalities that occur in discreete patterns in subjects with immune dysregulation and that permit treatment and anticipation of associated systemic or other hormonal deficiencies. Three major entities are recognized, APS1, APS2 and APS3. APS2/ Schmidt's Syndrome is characterized by Addison's Disease and Autoimmune Hypothyroidism and/or Type 1 diabetes mellitus. It is a rare to have a clinical presentation of spontaneous intracerebral hemorrhage occurring with Auto immune polyglandular syndrome type 2/Schmidt's syndrome. We report a case of 60 years old female, who presented with vomiting and loose motions - 4 episodes of one day duration. She had hyperpigmentation of the skin and mucous membranes of 8 years duration and weight loss of 15 kg in last 8 years. On day 3 of admission, patient developed left hemiparesis with right facial LMN nerve palsy and right lateral rectus palsy due to intracerebral hemorrhage. She was a known case of Addison's disease on steroids, Hashimoto's thyroiditis with hypothyroidism on eltroxin. She stopped her medications for the last three months. We are herewith reporting a rare case of spontaneous intracerebral hemorrhage occurring with Auto immune polyglandular syndrome type 2/Schmidt's syndrome. An extensive search for non-hypertensive causes of intracerebral hemorrhage was negative.

Key words

Auto immune Polyglandular Syndrome (APS) type 2, Schmidt's syndrome, Hashimoto's thyroiditis, Hypothyroidism, Addison's disease, Addison's crisis, Spontaneous intra cerebral hemorrhage.

Introduction

The autoimmune polyglandular syndromes are clusters of endocrine abnormalities that occur in discrete patterns in subjects with immune dysregulation and that permit treatment and anticipation of associated systemic or other hormonal deficiencies. There are five types of APS.

APS Type 1/ APECED is a syndrome characterized by chronic muco-cutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency, as well as ectodermal dystrophy and a host of other endocrine and non-endocrine tissue involvement in autoimmune destructive processes.

APS Type 2 and APS Type 3 are both due to mutations in the HLA DQ/DR regions which regulate antigen presentation to T-cell receptors; APS2 is characterized by, Addison Disease, Auto immune Hypothyroidism and/or Type 1DM , whereas APS3 is similar but without Addison disease. In keeping with other autoimmune disorders, these entities are more frequent in females, whereas APS1 has no sexual predominance [1].

APS Type 4 consists of combinations of autoimmune diseases not fitting into the previous categories. APECED/XLAAD/XPID (Type 5), consists of immune dysfunction, diarrhea and polyendocrinopathies commonly type 1 diabetes mellitus (**Table - 1)**.

Table – 1: Comparison of the main features of different APS main features of autoimmune polyglandular syndromes [2]. APECED, autoimmune-polyendocrinopathy-candidiasis-ectodermal dystrophy; APS, autoimmune polyglandular syndrome; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X linked; XLAAD, X linked autoimmunity-allergic dysregulation syndrome; XPID; X linked polyendocrinopathy immune dysfunction and and diarrhea [2].

APS Type 1/APECED	2 of 3 present from: mucocutaneous candidiasis Hypoparathyroidism Addison's disease
APS type 2/Schmidt's syndrome	Addison's disease AND Autoimmune thyroid disease AND/OR Type 1 diabetes mellitus
APS type 3/thyrogastric syndrome	Autoimmune thyroid disease AND Other autoimmune disease (EXCLUDING Addison's disease)
APS type 4	Combinations of autoimmune disease not fitting into the previous categories
IPEX/XLAAD/XPID	Immune dysfunction, diarrhoea and polyendocrinopathies, commonly type 1 diabetes mellitus

An adrenal crisis in an adult is defined as an acute deterioration in health status associated with absolute hypotension (systolic blood pressure <100 mm Hg) or relative hypotension

(systolic blood pressure ≥20 mm Hg lower than usual), with features that resolve within 1 to 2 hours after parenteral glucocorticoid administration i.e., a marked resolution of hypotension within 1 hour and improvement in clinical symptoms over a period of 2 hours [1].

Adrenal crises is the most severe manifestation of adrenal insufficiency, but they share symptoms with milder hypoadrenal states. These symptoms include anorexia, nausea, vomiting, fatigue, postural dizziness, abdominal pain, limb and back pain, and impaired consciousness. Shared biochemical perturbations include hyponatremia, hyperkalemia and hypoglycemia [1].

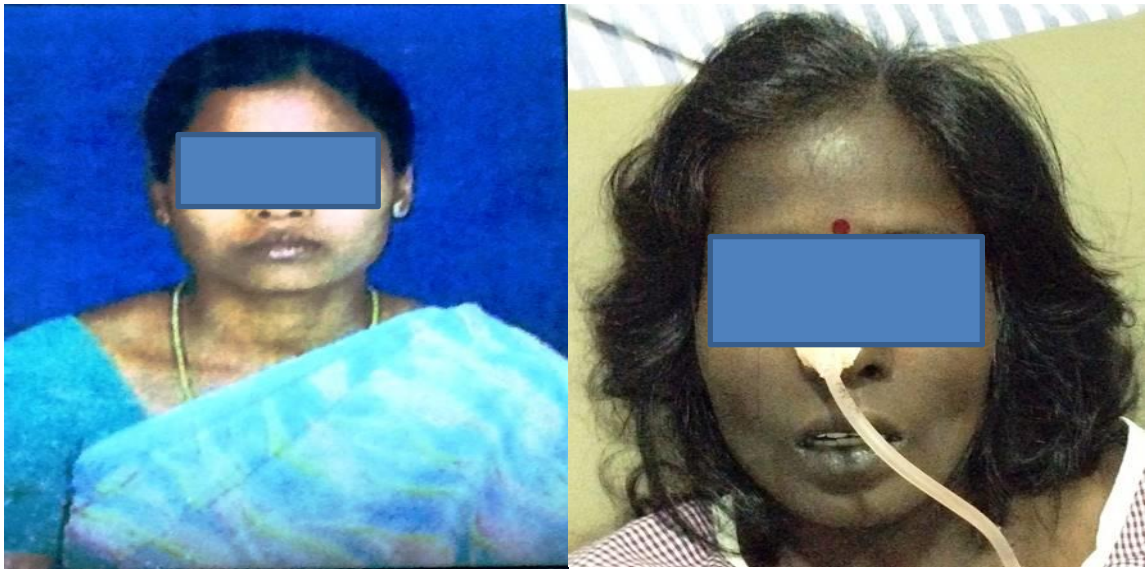
Adrenal crises arise from an absolute or a relative deficiency of cortisol, an endogenous glucocorticoid, Cortisol has a circulating half-life of 90 minutes; hence, tissues become deficient within several hours after cortisol deprivation. At the cellular level, loss of cortisol depresses the action of activator protein 1 (AP-1) and nuclear factor κB (NF-κB), leading to the unfettered activation of genes that produce inflammatory proteins, since the normal cortisol inhibition of the binding of NF-κB to the glucocorticoid receptor is lost [2]. Furthermore, mineralocorticoid deficiency, which is prominent in primary but not secondary adrenal insufficiency, is likely to exacerbate adrenal crises through sodium and water loss and potassium retention [3]. APS2/Schmidt's Syndrome is characterized by Addison Disease and Autoimmune Hypothyroidism and/or Type 1 diabetes mellitus. It is a rare to have a clinical presentation of spontaneous intracerebral hemorrhage occurring with Auto immune polyglandular syndrome type 2/Schmidt's syndrome. In one case report, the coagulation studies revealed severe hypofibrinogenemia and prolonged prothrombin time related to vitamin K-dependent coagulation factor deficit and the Clotting abnormalities cleared in 4 months of treatment with hydrocortisone. Glucocorticoids are potent regulators of fibrinogen synthesis, increasing fibrinogen secretion. They concluded that primary adrenocortical insufficiency induced this hemorrhagic diathesis leading to spontaneous intracerebral hemorrhage, which was not reported in literature earlier [5].

Case report

Day - 1

60 years female presented with vomitings and loose motions 4 episodes of one day duration. Hyperpigmentation of the skin and mucous membranes of 8 years duration, she had weight loss of 15 kg of 8 years duration (**Photo – 1**)

Photo – 1: Patient – 2012 and 2020.



There was no history of fever, cough, chest pain, breathlessness, palpitations, pedal edema, surgery, seizures, loss of consciousness, pain abdomen, blood in stools or any indigenous drug intake. There was no history of bleeding diathesis. There was no history of blood transfusions.

Past history

Patient was a known case of Addison's disease on steroids, and Hashimoto's thyroiditis with hypothyroidism on eltroxin. She stopped her medications for the last three months. No history of HTN, or NIDDM, No history of contact with TB. No history of Asthma, Epilepsy, Cerebro vascular accident, myocardial infarction. No history of any bleeding diathesis.

On examination

Patient was drowsy, moderately built and nourished, no pallor, no icterus, no clubbing, no koilonychias, and no enlarged lymph nodes. Temperature was 95.0F, PR 120/min regular, BP 80/60 mmHg, Respiratory Rate 20 breaths per minute. Cardiovascular system and respiratory system examination was normal clinically, there was hyperpigmentation of skin and mucous membranes, no neurocutaneous markers, no petechiae, no ecchymosis, no bruises, no thyromegaly, skull and spine was normal, no trophic ulcers. No neurological deficit, we thought of Adrenal insufficiency with hypothyroidism.

Day - 3

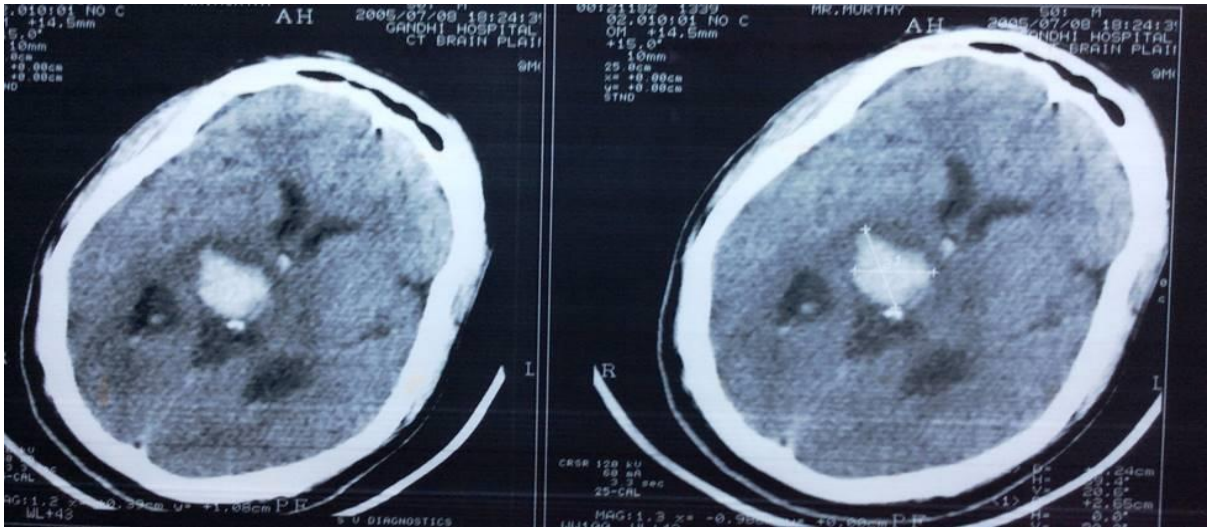
On day 3 of admission, patient developed left hemiparesis with Right LMN type of facial palsy and Right lateral rectus palsy.

Neurological Examination

Patient was comatose, Cranial nerve examination revealed Right LMN type of facial palsy and Right lateral rectus palsy.

Motor system exam; Nutrition: Normal, Bulk: Bilaterally Symmetrical. There was hypotonia in left upper and lower limbs. The power in left sided limbs was 3/5. No wasting of small muscles of hand, no abnormal movements, No incoordination of movements of right side, Coordination could not be tested as the patient was in coma. Reflexes: Superficial reflexes Normal, abdominal reflex present, Corneal and conjuctival Absent on right side. There was extensor plantar reflex on left side. Deep Tendon Reflexes were absent on left side. Sensory system: could not be tested. There were no cerebellar signs, no signs of meningeal irritation, no papilloedema, skull and spine normal. The examination of cardio vascular system and respiratory system was normal (**Photo – 2**).

<u>Photo – 2</u>: CT brain on day 3: CT Brain showed Intra Cerebral Hemorrhage Rt. Pontine region.



Her investigations were as follow: Hb: 11gm%, WBC: 7000 per cumm, N - 74, L - 24, B - 0, E - 2, M - 0; Platelets: 2.44 lac/cumm, ESR: 05 mm, Bleeding Time – 4 mts, Clotting Time – 6 mts, Prothrombin Time - 12 seconds, RBS: 124 mg/dl, Complete urine examination: Normal, serum electrolytes: Serum sodium – 128 mmol/L, serum potassium 6.9 mmol/L, Blood urea – 20 mg/L, serum creatinine - 0.8 mg/dl, C reactive protein (CRP) was elevated at 24 mg/L, The Morning cortisol was low at 0.81 µg/L (reference range 2.30-11.9 µg/L), The baseline adrenocorticotropic hormone (ACTH) was markedly elevated at 220 pmol/L (reference range 2–11 pmol/L). FT3 – 0.70 pg/ml, FT4 - 0.15 ng/dl, T.S.H – 165 uIU/ml, TPO – 390 (Positive) (Reference Normal range - TPO – > 60 (Positive) < 60 (Negative)), Anti Tg Ab – 298 (Positive) (Reference Normal range - Anti Tg Ab – > 34 (Positive) <34 (Negative)), Anti ds DNA – 351(Positive) (Reference Normal range - Equivocal – 201 – 300, Mod. Positive – 301 – 800, Strong Positive - > 800), X – ray chest PA view - NAD, ECG - low voltage complexes.
CT scan Brain - revealed pontine hemorrhage, USG of Thyroid – Normal Study, FNAC of thyroid – revealed Hashimoto's thyroiditis, USG - Abdomen - Normal Study, CT Abdomen - Normal Study.

A diagnosis of APS 2 was made with the features of CVA –Rt. Pontine Hemorrhage with Lt. Hemiparesis with Rt. 6^{th} and 7^{th} LMN Palsies, Addison's Disease in Addison's crisis, Hashimoto's thyroiditis with Hypothyroidism.

The management of the patient consists of

1) Volume replenishment and rehydration, glucocorticoid replacement therapy initially with injectable hydrocortisone 100 mg bolus and 100-200 mg hydrocortisone over 24 h, till patient stabilizes.
2) Once acute crisis is over chronic replacement therapy is required for lifetime. Hydrocortisone orally 10-mg/m2/24 hours in three-divided dose is sufficient. Prednisolone (20 – 25% of hydrocortisone dose) may be used, divided twice daily.
3) Mineralocorticoid replacement therapy can be initiated once the daily hydrocortisone dose has been reduced to < 50 mg because at higher doses hydrocortisone provides sufficient stimulation of mineralocorticoid receptors. Initial dosing is about 1-150 µg daily.
4) Adrenal androgen replacement is an option in patients with lack of energy, loss of libido. The dose is 25-50 mg dehyrdo-epiandrosterone once daily.
5) All patients need to be counselled for the need for doubling of glucocorticoid oral dose in times of stress and urgent hospitalization.
6) Calcium supplements should be added to patients receiving oral glucocorticoid dose of 30 mg or more as bone metabolism will be affected.

Response to therapy

Assessment of adequacy of glucocorticoid replacement is clinical, and not by biochemical measures. Adequate treatment results in disappearance of weakness, return of appetite and sense of well-being, and weight returns to normal.

The hyperpigmentation invariably improves but may not entirely disappear.

Chronic overdose with glucocorticoids leads to obesity, short stature and osteoporosis. Adequacy of mineralocorticoid replacement may be determined by assessment of blood pressure, electrolytes, and upright plasma rennin levels.

Hypertension and hypokalemia result if the fludrocortisone dose is excessive [6, 7].

Hypothyroidism may mask the Addison's disease. Hence, in patients with autoimmune polyglandular syndrome type 2, thyroxine replacement without adequate steroid

replacement may result in acute addisonian crisis.

The great danger in APS2 is the treatment of a presenting hypothyroidism without recognizing coexisting hypoadrenalism. This precipitates Addisonian crisis by two mechanisms. First, hypothyroidism reduces cortisol clearance. Second, hypothyroidism reduces the metabolic rate thereby reducing the need for cortisol. The increased metabolic rate accompanying thyroxine replacement increases the cortisol requirements that cannot be provided by the failing adrenals. The addition of thyroid hormone replacement increases cortisol clearance, thus decreasing circulating cortisol availability. Patients may die from ensuing Addisonian crisis.

Research indicates that autoimmune processes commonly attack multiple endocrine organs, although this may not result in sufficient damage to produce clinical symptoms. Physicians should be alert to the potential for additional endocrine conditions, particularly adrenal failure, in all patients with autoimmune endocrine diseases, especially those with insulin-dependent diabetes and autoimmune thyroid conditions [8]. It is also important to recognize the concept of normalization of hypothyroidism with cortisol replacement in patients with Addison's disease otherwise they may go into adrenal crisis [9].

Treatment given

Inj. Cortisol 100 mg bd
Tab. Eltroxin 100 mcg 1 daily
Tab. Nimodip 30 mg 2 TID
Inj Mannitol 10% 100 ml iv TID
Inj. Ampicillin 500mg iv QID
Inj. Amikacin 500 mg iv BD
Inj. Metrogyl 500 mg iv TID
Inj. Optineuron 1 amp iv OD
I.V. fluids – Normal saline as needed
Physiotherapy

Discussion

The type 2 autoimmune polyglandular syndrome is the most frequent autoimmune polyglandular syndrome, with underlying pathologies that develop years to decades apart in an affected individual. Our patient was a middle-aged woman with spontaneous intra cerebral hemorrhage, precisely at the peak of APS type 2 incidence with the coexistence of Addison's disease and Hypothyroidism.

Approximately 50% of patients with adrenal insufficiency have other autoimmune diseases associated with it, and thyroid disease is the most frequent of them - however, only 1% of patients with autoimmune thyroid disease have adrenal insufficiency [3]. Adrenal insufficiency is the first manifestation in 50% of cases. It appears simultaneously with diabetes mellitus or autoimmune thyroid disease in 20% of cases, and after these pathologies in approximately 30%.

The early diagnosis of Addison's disease significantly reduces the morbidity and mortality. Since the clinical presentation can be inaccurate and nonspecific in most cases, the diagnosis is delayed. The concept of APS consists in the fact that a patient with autoimmune disease has a higher probability of developing a new autoimmune disease than the general population.

In view of the possibly long time interval between the manifestation of the first and further autoimmune endocrinopathies, regular and long-term observation of patients with endocrine autoimmune disorders is necessary.

Spontaneous intra cerebral hemorrhage - primary adrenocortical insufficiency induces hemorrhagic diathesis leading to spontaneous intracerebral hemorrhage. This was not reported in Addison's disease earlier. Primary adrenocortical insufficiency should be considered as a rare potential cause of non-hypertensive intracerebral hemorrhage [5]. Exhaustive research for non-hypertensive causes of intracerebral hemorrhage was negative. Initial coagulation studies disclosed severe hypofibrinogenemia and prolonged prothrombin time related to vitamin K-dependent coagulation factor deficit but in our case the coagulation studies were normal.

Conclusion

Its less frequent clinical presentation is the combination of spontaneous intra cerebral hemorrhage with Addison's disease and Autoimmune Hypothyroidism. We are herewith reporting a rare case of spontaneous intracerebral hemorrhage occurring with Auto immune polyglandular syndrome type 2/ Schmidt's syndrome. Adrenal crises arise from an absolute or a relative deficiency of cortisol due to non-adherence to treatment or due to lack of follow up. In this case, patient stopped treatment. With stressful insults such as infection, surgery or other trauma may precipitate adrenal crisis with catastrophic collapse in affected individuals. Hence it is necessary to have regular and long-term observation of patients with endocrine autoimmune disorders [10]. Exhaustive search for non-hypertensive causes of intracerebral hemorrhage is necessary. In one of the studies Initial coagulation profile disclosed severe hypofibrinogenemia and prolonged prothrombin time related to vitamin K-dependent coagulation factor deficit [5]. But in this case the coagulation studies were normal.

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