CASE REPORT

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Hyperpigmentation with Acute Delirium and Idiopathic Intracranial Hypertension: Suspect Addison's Disease

Namita Soni, Umesh Malu**, Akhil Raghavan***, Abhishek Sharma****, Megha Varghese*****

Abstract

Addison's disease, presents with a wide variety of signs and symptoms making diagnosis challenging. The neuropsychiatric symptoms are well documented but not fully understood. Addison's disease (AD) associated with idiopathic intracranial hypertension (IIH) has been seen in children but there are very few cases reported in adults. We are presenting a case of 19-year-old lady of Addison's crisis admitted with neuropsychiatric symptoms and had IIH on investigations which improved on treatment.

Key words: Addison's disease (AD), Addison's crisis (AC), Idiopathic Intracranial Hypertension (IIH), neuropsychiatric symptoms, hyperpigmentation.

Introduction

Addison's disease (AD), also referred as primary adrenal insufficiency, is a rare autoimmune disorder affecting males and females equally, with a prevalence rate of 100 - 140 cases per million. AD is characterised by impairment of the adrenal glands, which prevents enough cortisol, aldosterone, and androgen production in human body[1]. The usual signs and symptoms of AD include persistent fatigue, nausea, vomiting, loss of weight, anorexia, hypotension, hyponatraemia, hyperkalaemia, hypoglycaemia, intra- and extra-oral skin pigmentation (bronzing of skin). Neuropsychiatric symptoms include psychosis and mood disturbances which are the unusual presentations during addison's crisis, hence making the diagnosis more challenging.

The clinical syndrome of idiopathic intracranial hypertension (IIH) without any evidence of vascular lesions or space-occupying lesions, without enlargment of the cerebral ventricles, and without a known cause is known as IIH. The syndrome is usually associated with obesity or a number of medications, such as the oral contraceptive pill, amiodarone, cyclosporin, systemic and topical steroids, and antibiotics (nitrofurantoin, and tetracyclines)[2]. However, underlying endocrine conditions such as Cushing's disease, hyperthyroidism, or the injection of thyroxine or growth hormone rarely cause IIH[3]. Though cases of IIH associated with AD in children have been reported, there are only few cases documented of this association in adults[4]. Here we are presenting a case of Addison's disease associated with IIH and neuropsychiatric symptoms.

Case history

A 19-year-old lady presented to the emergency department in a state of altered sensorium, complaining of severe headache. She had an episode of vomiting in the emergency room. On eliciting history, it was revealed that she had an episode of fever 5 days back, 2 episodes of vomiting and since then she was experiencing headache which became very severe last night. The patient was in a state of altered sensorium since last night in the form of extreme irritability and psychosis. No history of convulsions. On leading questions, her husband told that since the past 7 - 8 months they noticed darkening of her skin all over the body. (Fig. 1) which was fair 7 - 8 months back (Fig. 2) for which she visited many local doctors but it was not resolved. There was also a history of easy fatigability, loss of interest in surroundings, abnormal behaviour like agitation, salt craving, increased sensitivity to spicy food, loss of appetite, and weight loss since past 5 - 6 months.

She was married 3 years back (non-consanguineous marriage) and delivered a healthy boy via caesarean section 1 - 1/2 years back. Following this, she took 2 injections of depo medroxyprogesterone acetate as contraceptive 3 months apart with the last dose being administered 8 months back. She was not having any comorbidities, and was not taking any other medications. No history of tuberculosis in the past was found.

On vital examination, she was afebrile with a pulse rate of 62 bpm, Blood pressure of 84/60 mmHg, respiratory rate of 16/min with 97% oxygen saturation on room air. Random Blood sugar was 84 mg/dL.

Associate Professor, **Assistant Professor, ***Senior Resident, ****Junior Resident, Department of Medicine, MGM Medical College and Hospital, Chhatrapati Sambhaji Nagar - 431 003, Maharashtra.

Corresponding Author: Dr Umesh Malu, Assistant Professor, Department of Medicine, MGM Medical College and Hospital, Chhatrapati Sambhaji Nagar - 431 003, Maharashtra. Phone: 9421480135, E-mail: u.malu1510@gmail.com.

On general examination she was thin built, dark in complexion, had mild pallor, mucous membranes of mouth were also dark. Rest of the general examination was normal. She was delirious, irritable with no signs of neck rigidity, Bilateral pupils were normal in size and normally reacting to light. Bilateral plantars were mute. She was moving all four limbs equally and spontaneously. Fundus examination revealed signs of established papilloedema in both eyes (Fig. 3 and 4).

MRI brain was done which did not reveal any space occupying lesion or oedema.

In view of slowly progressive darkening of skin, altered behaviour, papilloedema, and hypotension, a probable diagnosis of Addison's disease with crisis was made.

Fig. 1: *Current photograph - dark skin.*

Fig. 2: *Easker photograph - fair skin.*

Routine labs, serum cortisol and serum ACTH levels were sent and injection hydrocortisone was given stat and 6 hourly to the patient. She was hydrated well. Injectable painkiller, antibiotic, and antiedema drug acetazolamide was started. Irritability of patient reduced within 6 hours. A lumbar puncture was done. Opening pressure of CSF was 30 mm of water.

She was re-evaluated the next morning. Now, she was conscious, oriented to time, place and person. Both pupils were normal sized reacting to light. She had normal vision with full bilateral eye movements. All limbs were moving equally.

Lab investigations revealed hyponatraemia – serum sodium 125 meq/L, with serum cortisol level 0.17 ug/dL and serum ACTH - 112 pg/mL. Lab investigations (Table I) combined with signs and symptoms edged towards a diagnosis of primary adrenal insufficiency. CECT (Abdomen + Pelvis) done which was within normal limits.

The relatives were counselled about the need for 21-alpha hydroxylase antibodies testing; the confirmatory test for autoimmune Addison (primary adrenal insufficiency) but could not be done due to non affordability.

She responded dramatically to steroids with symptomatic improvement seen within 24 hours of initiation of treatment. She regained normal sensorium, with no further complaints of headache, fever or nausea.

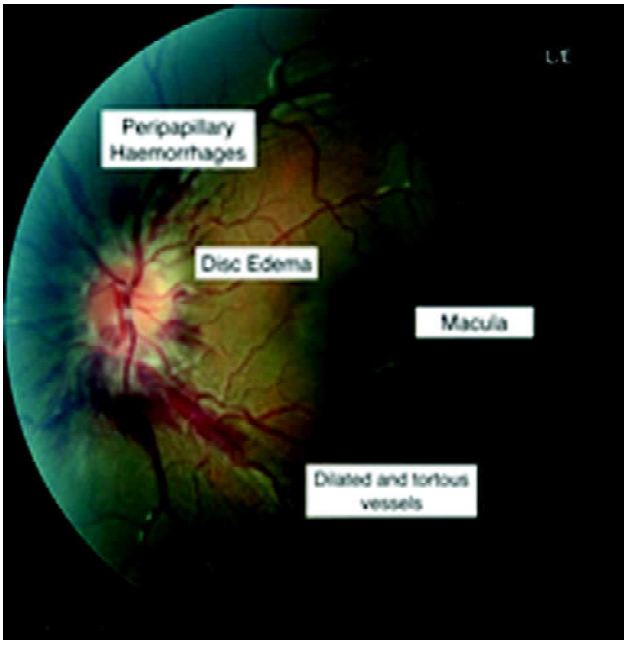

Fig. 3: *Papilloedema left eye.*

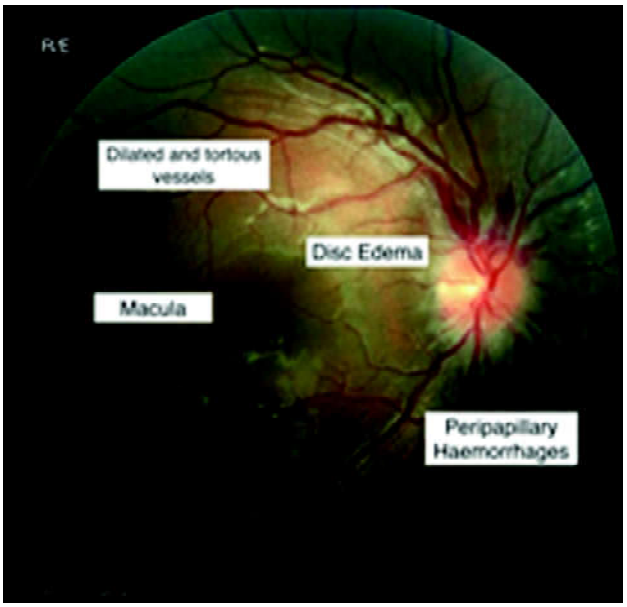

Fig. 4: *Papilloedema right eye.*

Table I:

Labs Parameter	Values
Haemoglobin	9.2 g/dL
Serum Sodium	125 meq/L (low)
Serum Potassium	3.2 meq/L
Serum Cortisol	0.17 μg/dL (low)
Serum ACTH	64.7 (Increased)
RFT/LFT/TFT	Within Normal Limits

Discussion

Addison's disease has an unusual presentation with a wide range of signs and symptoms, which can be confounding and often delay a definitive diagnosis.

Table II:

Symptoms	Incidence
Generalised weakness	>90%
Weight loss	>80%
Gastrointestinal symptoms	>80%
Body aches	18%
Salt craving Hyper pigmentation Syncope Disorientation	12 - 15%
Psychiatric symptoms	Rare

However, the common symptoms are mentioned (Table II) and psychiatric symptoms (sleep difficulties, mood and behaviour abnormalities) are rare. The specific cause of neuropsychiatric symptoms associated with AD is unknown; however, they may be due to abnormalities in electrophysiological, metabolic, and electrolyte imbalance[1]. The profound decrease in glucocorticoids that underlies many of the manifestations of Addison's disease is likely to contribute to the development of neuropsychiatric symptoms. Cortisol, the primary glucocorticoid in the body, is lipid soluble and therefore can diffuse through cell membranes and bind to intracellular glucocorticoid receptors in target cells. Once cortisol is bound to its receptor in the cytoplasm, the hormone-receptor complex translocates to the nucleus where it interacts with regulatory DNA sequences and modifies gene transcription. Glucocorticoid receptors are distributed throughout the brain, but are particularly abundant in the hippocampus. It has been demonstrated that adrenalectomy produces massive granule cell death in the dentate gyrus of the hippocampus. It is possible that granule cell death resulting from cortisol deficiency interrupts the hippocampal tri-synaptic circuit, producing memory impairment and cognitive changes[6,7].

Hyponatraemia occurs in the majority of patients and may contribute to cognitive changes and encephalopathy by causing brain swelling and increased intracranial pressure.

Hyperpigmentation occurs because melanocyte stimulating hormone (MSH) and ACTH share the same precursor molecule, Pro-opiomelanocortin (POMC). Then anterior pituitary POMC is cleaved into ACTH, MSH and beta lipoprotein. The subunit ACTH undergoes further cleavage for production of alpha-MSH, the most important MSH for skin pigmentation. One of the most important distinguishing feature of primary adrenal insufficiency is hyper-pigmentation. Conversely in secondary adrenal insufficiency, the skin has an alabaster like paleness due to lack of ACTH secretion.

The hallmark sign of Primary Addison's disease is hyperpigmentation of the skin due to excessive ACTH production, which in our case served as an important diagnostic clue (Fig. 1).

IIH is defined as the clinical syndrome of raised intracranial pressure, in the absence of space-occupying lesions or vascular lesions, without enlargement of the cerebral ventricles, for which no causative factor can be identified IIH is a diagnosis of exclusion. Persistent headaches, nausea, vomiting are the characteristic signs and symptoms of this condition. It is classically associated with obese females of reproductive age but is also known to occur in children Although IIH is often associated with papilloedema but it is not an absolute requirement to make the diagnosis.

Although the pathogenesis of IIH is unknown, proposed

theories include increased CSF production, decreased CSF absorption, or increased cerebral venous pressure creating resultant rise in CSF pressure. CSF arginine vasopressin (AVP) levels in IIH patients were shown to be higher than healthy controls. This appears to be in accordance with studies that patients with glucocorticoid insufficiency exhibit higher plasma AVP levels and prolonged hypersecretion of AVP despite plasma dilution. Thus, elevated serum and perhaps CSF AVP levels may facilitate IIH in Addison's illness[2,3].

It has also been postulated that IIH arises from an increase in CSF volume secondary to delayed CSF absorption, without ventricular dilatation due to increased resistance of flow across absorptive channels following acute corticosteroid withdrawal. The putative effects of acute withdrawal of steroids implicate the enzyme 11 beta-hydroxysteroid dehydrogenase type1, an enzyme highly expressed in choroid plexus epithelium that converts inactive cortisone to active cortisol. Cortisol can activate mineralocorticoid receptors in the choroid plexus with similar affinity to aldosterone, leading to active sodium secretion by the Na^+/K^+ ATPase at the choroid plexus membrane, movement of sodium ions into the cerebral ventricle, and an osmotic gradient to drive CSF secretion[4].

Similarly there have been case reports showing that after surgical treatment of Cushing's disease, IIH develops as a rare complication. A sudden lowering of supraphysiological levels of glucocorticoids can lead to IIH[4,5].

Zainordin *et al* reported a case of partial adrenal suppression with prolonged use of depomedroxy progesterone acetate (DMPA) for 16 years[8]. DMPA has been identified to have a notable cortisol-like glucocorticoid activity on the hypothalmic-pituitary-adrenal (HPA) axis since the 1970s when patients on DMPA presented with Cushingoid symptoms, such as weight gain, facial swelling and generalised oedema .This cortisol-like effect is believed to exert a negative feedback action on the hypothalamus or the pituitary leading to low plasma ACTH, suppression of adrenal function and decreased cortisol secretion and manifesting as secondary adrenal insufficiency. In our case the patient had received only 2 doses of DMPA and manifested as primary adrenal insufficiency so we can conclude that medroxyprogesterone acetate was not responsible for adrenal insufficiency.

In this case, hyperpigmentation increasing over a period of 7 months served an important initial clue and further lab investigations that revealed hyponatraemia, hypoglycaemia and hypotension consolidated the diagnosis. A dramatic response to steroids with rapid symptomatic improvement within 24 hours justified the diagnosis.

Conclusion

Addison's disease should be considered when hyperpigmentation, hyponatraemia and IIH co-exist. Though acetazolamide is the treatment for IIH, early steroid replacement helps in alleviating symptoms and preventing vision loss, which can be catastrophic for the patient.

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