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OPIATE INDUCED ADRENAL INSUFFICIENCY: CASE REPORT

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ABSTRACT

Opiates are commonly used for pain relief and palliation. It is a proof of concept that morphine suppresses the hypothalamic-pituitary-adrenal axis. It can also suppress the pituitary-gonadal axis and cause vague symptoms in the form of tiredness, weakness, dizziness and postural giddiness. Even in short-term use of opiates, secondary and tertiary adrenal failure is a common side effect that remains under recognized among physicians. Even in cases where an accurate diagnosis of adrenal failure is made, a patient may be commenced on a course of steroids, and ceasing opiates is a concept often under-appreciated or forgotten. In this article, we report a patient treated by a rheumatologist for presumed polymyalgia rheumatica. The patient was exposed to multiple expensive investigations and received an unnecessary course of long-term steroid before reaching an accurate diagnosis and morphine ceased with resolution of all symptoms. Clinicians should have a low threshold for diagnosing opiate induced secondary adrenal insufficiency prior to commencing a patient on steroids.

BACKGROUND

Secondary and tertiary adrenal insufficiency is a common condition that is underdiagnosed likely due to its nonspecific symptoms, which include fatigue, muscle pains, abdominal discomfort, postural dizziness due to hypotension, anorexia, and weight loss.[1]

In contrast, primary adrenal insufficiency has more specific manifestations that include mucocutaneous pigmentation and probable signs of autoimmune organ specific disease, premature ovarian failure, pernicious anemia, celiac disease, type 1 diabetes, vitiligo, alopecia, primary hypoparathyroidism, renal tubular acidosis and Sjogren's syndrome.

In this article we report a 55-year-old female treated for presumed polymyalgia rheumatic without improvement of symptoms, despite increasing morphine and prednisolone dose for her poorly controlled symptoms.

Blood tests confirmed secondary adrenal insufficiency. Gradual tapering the dose of prednisolone did not improve her symptoms, so prednisolone was ceased and azathioprine was commenced due to concerns regarding side effects of steroid use.

Synacthen test confirmed secondary adrenal insufficiency, so morphine was tapered gradually. All body aches, postural dizziness, anorexia resolved and the patient started to feel well with improvement in appetite and body weight. Repeat synacthen test returned a result within normal limits.

Secondary adrenal insufficiency due to morphine is not an uncommon disease, underdiagnosed due to the nonspecific symptoms.

CASE REPORT

A South American 55 year old lady presented with muscles aches, anorexia, weight loss of 6kg over a three-month period, dyspepsia and loss of appetite. She had no medical history of note.

Her mother was diagnosed with giant cell arteritis at the age of 60, which is well controlled on 5 mg prednisolone and mycophenolate 250mg BD. Her elder sister was diagnosed with primary biliary cholangitis on ursodeoxycholic acid.

Examination of the patient was unremarkable apart from tenderness on proximal muscles of the arm and legs with subjective weakness.

Routine blood tests showed ESR of 60 mm.hr, CRP 100mg/l.

Liver function test showed alkaline phosphatase 200u/l(normal range 30-110)

GGT 150U/L (normal range 30-60)

Bilirubin 60 umol/L (normal range 15-26)

The following blood tests were either normal or negative:
Urea, creatinine, serology for hepatitis A, B.C, D E, ANA, DNA binding, RF, ACCP, vasculitis screen, immunoglobulin, mitochondrial antibodies, CA19, CA 125, CEA, alpha feto protein, blood culture, procalcitonin.

Ultrasound of the liver did not show any dilation of the biliary ducts and normal liver architecture.

Ultrasound of both temporal arteries were normal and no halo sign.

Pan CT for the body was unremarkable.

Patient was diagnosed with polymyalgia rheumatic and started on 30 mg of prednisolone without improvement. Prednisolone dose was escalated to 50 mg with resolution of her pain, appetite improvement and started regaining weight. Patient was continued on 50 mg prednisolone for 18 months and routine blood testing showed normalization of ESR and CRP, HBA1C raised to 13%. Rheumatologist advised GP to taper the dose of prednisolone by 10 mg every week, and discuss with an endocrinologist regarding hyperglycemia, for which the patient was started on metformin and mixtard insulin. With reduction of the prednisolone to 40 mg, all symptoms returned and Rheumatologist advised to start on Mycophenolate and continue on tapering dose of prednisolone. GP started her on 10 mg oral slow release morphine BD, with the reduced dose of prednisolone. Patient started to improve with increasing dose of morphine to 30 mg BD. Mycophenolate increased gradually to Ig BD, without side effects. Prednisone was tapered to 10 mg daily.

However, after 4 months, the patient started experienced generalised muscle aches, anorexia, loss of weight and severe postural dizziness. The patient was admitted to the hospital for further investigation and consultation from immunology, endocrinology and the pain team.

The patient was cushingoid, experienced flat mood, nonspecific myalgia and severe postural dizziness.

On examination, patient was dizzy with a postural drop of blood pressure from 150/90 supine to 130/75 on standing. The rest of examination was unremarkable. There was no evidence of retinopathy, nephropathy or neuronopathy.

Blood test showed sodium 129 mmol/l (135-145mmol/l), potassium 5.5mmol/L (3.5-5 mmol/l)

The following results returned within normal limits
Calcium, phosphate, urea, creatinine, LFT, thyroid function, chloride, ceruloplasmin, alpha one antitrypsin, HBA1C, iron studies, uric acid, spot urine for sodium, ESR and CRP.

Repeat whole body CT scan were normal.
Endocrinologist arranged a synacthen test. Patient was given 250 ACTH, cortisol was measured at 0, 30, and 60 minutes:
Serum cortisol at 0-minute 80 mcg/dl (normal range 140-690 nmol/l)
Serum cortisol at 30 minutes 100 mcg/dl
Serum cortisol at 60 minutes 550 nmol/l
Results were consistent with secondary or tertiary adrenal insufficiency.
Pituitary CT did not show any pituitary or Sella mass.

Pituitary trophic hormones which included, insulin growth factor, TSH, T3 and T4, FSH, LH, serum estrogen, plasma aldosterone, plasma renin activity, 21 hydroxylase antibodies, all were within normal range.

Therefore, diagnosis was consistent with secondary adrenal failure due to morphine as she was not on steroid for the last 5 months. Morphine was tapered until ceased. Patient was continued on mycophenolate with resolution of all pain and symptoms of tertiary adrenal failure.

Repeat synacthen test was normal.

Patient was discharged from endocrinology, ongoing follow up with immunologist with an aim to taper mycophenolate.

DISCUSSION

Adrenal insufficiency is a common condition which is often not diagnosed in timely manner because of its non-specific symptoms. Failure of timely diagnosis of adrenal insufficiency will expose the patient to serous adrenal crisis should the patient have any illness or surgical procedure.[1]

Adrenal insufficiency could be primary, secondary or tertiary. 40% of patients with primary adrenal insufficiency are autoimmune and 21 hydroxylase antibodies are detected. Once autoimmune adrenal failure had been ruled out, the rest are either genetic or acquired. Genetic types include congenital adrenal hyperplasia, congenital adrenal hypoplasia and adrenoleukodystrophy. The latter two are x linked and affect only males.[2] Organ specific autoimmune disease are associated with the primary autoimmune adrenal insufficiency, which include type 1 diabetes mellites,

pernicious anemia with atrophic gastritis, premature ovarian failure, celiac disease, vitiligo, primary biliary cholangitis, graves and Hashimoto disease Sjogren syndrome and renal tubular acidosis.[3] Primary adrenal failure could be part of autoimmune polyendocrine syndrome type 1 or type 11. Autoimmune polyendocrine syndrome type 1 includes primary adrenal insufficiency, primary hypoparathyroidism and mucocutaneous candidiasis.[4] Autoimmune polyendocrine type 11 includes type1 DM, autoimmune hypothyroidism and hypoparathyroidism, premature ovarian failure.[5] Acquired causes of adrenal failure include infection, in particular TB, infiltration (sarcoidosis, amyloidosis Hemochromatosis), bleeding due to anticoagulation, metastasis, antiphospholipid syndrome, lymphoma infection like HIV, syphilis, histoplasmosis, coccidioidomycosis, cryptococcal infection and histoplasmosis.[6]

Primary adrenal insufficiency will affect steroid and mineralocorticoid. Low sodium, mildly elevated potassium, high urea and creatinine, postural dizziness, postural hypotension, pigmentation of the mucous membranes and areas of exposed skin are very sensitive and specific for primary adrenal insufficiency.[6] Patients who present with adrenal crisis may have normal potassium and sodium due to concomitant nausea and vomiting. Patients with primary adrenal insufficiency usually crave for salt.[7] Confirmation of the diagnosis with synacthen test typically shows low cortisol after 30 minutes and after 60 minutes, low plasma aldosterone and increased plasma renin activity.[8]

Treatment for patient with primary adrenal failure is hydrocortisone 15-25 mg daily. 10 mg immediately on waking in the morning and the rest in divided doses over the day, with final dose at least 6 hours prior to bed to avoid insomnia. A patient who works night should take the main dose just before going to work. All patients with primary adrenal failure should take fludrocortisone (0.05- 0.2mg). Children might need higher dose as they are aldosterone resistant.[9] Treatment of patient in crisis involves stat 100 mg IV hydrocortisone, 1 liter saline over one hour followed by continuous slow IV saline and 200mg hydrocortisone infusion over 24 to 48 hours till patient is able to eat and drink.[10] All patients with primary adrenal failure should have a medic alert and education to double the dose of steroid on sick days and before surgical procedures.[11]

In contrast with primary adrenal failure, secondary and tertiary type requires the clinician to have a high index of suspicion because symptoms are very nonspecific, without clear signs other than in extreme stages. The patient could present with loss of appetite and unintentional weight loss, which is often misdiagnosed as an eating disorder. Other nonspecific symptoms include fatigue, muscles and joint pains, which is often misdiagnosed as polymyalgia rheumatica. Physical examination is usually unremarkable, synacthen test will show low cortisol at 0 minutes and 30 minutes with recovery in minute 60. Biochemically ACTH is low, other thyrotropic pituitary hormones are low which includes TSH, LH, FSH, insulin growth factor, and sometimes ADH. Every patient should have MRI for pituitary and Sella. Causes are pituitary adenoma, craniopharyngioma, meningioma, lymphoma, metastasis, Lymphocytic hypophysis's infiltration, like sarcoidosis and haemochromatosis.[12]

Treatment for secondary adrenal insufficiency is replacement with hydrocortisone and other deficient hormones. Fludrocortisone is not required for secondary and tertiary adrenal failure.[13] Patient with secondary adrenal failure could have isolated ACTH deficiency, which is a diagnosis of exclusion.

A patient with Cushings syndrome who receives corticosteroid can develop tertiary adrenal failure. Morning cortisol is low and ACTH either normal or high normal. Treatment would involve a slow taper of steroid. Second most common cause of tertiary adrenal failure is opiates, with which the treatment involves weaning of opiates.

Our patient was diagnosed with tertiary adrenal failure. The patient did not improve with cessation of steroids, prompting us to look at other causes of tertiary adrenal failure. Once morphine was ceased, the patient showed dramatic improvement. Clinicians should have a high index of suspicion in any patient on high dose of morphine, for nonspecific symptoms of tertiary adrenal insufficiency.[14]

CONCLUSION

Opiate induced adrenal insufficiency is very common among inpatients treated for chronic pain, and is often underdiagnosed. Opiate suppresses cortisol secretion by inhibition of hypothalamus and pituitary causing secondary and tertiary adrenal insufficiency. Patients are often subjected to extensive investigations prior to diagnosis. Treatment involves a gradual withdrawal of morphine and steroid administration.

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