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Case Report Open Access

Atypical Presentation of Giant Prolactinoma: Case Report and Review of Literature

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Abstract

Background: Prolactin is a well-known hormone that mainly functions as a milk producer. Its secretion by lactotroph cells in the pituitary gland (anterior pituitary) is under regulation by different effectors, mainly by Dopamine. However, under non-physiologic circumstances, Prolactin can be over secreted (hyper-prolactinemia) either due to primary (such as pituitary adenoma) or secondary (such as hypothyroidism, infections and systemic diseases) causes. Since prolactin has actions on glucose and lipid metabolisms, hyper-prolactinemia can result in insulin resistance and worsening of lipid profile. In case of prolactinoma, Prolactin can be co-secreted with Growth Hormone in 25% of cases (since lactotroph cells as well as somatotroph cells share common genetic origin), which can have a detrimental additive effect on insulin sensitivity and lipid profile.

Case description: We describe a case of a young male patient with background of type 2 diabetes mellitus (T2DM) (which was not well controlled on oral hypoglycemic agents) and dyslipidemia (which was controlled with Atorvastatin) presented with progressive nausea, vomiting, dizziness and abdominal pain and was admitted initially as a case of DKA. After induction of therapy, the patient was stabilized but then his mental status deteriorated significantly. Computerized Tomography (CT) of the head revealed a giant pituitary mass. Hormonal workups were immediately sent which showed markedly elevated prolactin (PRL) level and slightly elevated growth hormone level as well as IGF-1. The elevation of PRL along with the findings of Magnetic Resonance Imaging (MRI) of pituitary gland, confirmed the diagnosis of giant invasive prolactinoma, which explained his insulin resistance and therefore his presentation.

Conclusion: DKA is a rare presentation of pituitary prolactinoma and should be considered if occurred in a patient with co-existing CNS manifestations.

Keywords: Prolactinoma; Growth hormone; Diabetic ketoacidosis

Introduction

Prolactin (PRL), is a 198 amino acid polypeptide (21,500 KD) protein that is weakly homogenous to Growth Hormone (GH) and Human Placental Lactogen (HPL), reflecting a common cellular origin. All of these hormones work through the type 1 cytokine receptor superfamily which results in intracellular domain phosphorylation followed by tyrosine kinase mediated signal transduction [1].

In case of hyper-prolactinemia, there is an increased amount of PRL level mainly, either due to a primary pituitary adenoma arising from pituitary lactotroph cells or secondary to hypothyroidism which might indirectly lead to a micro or a macro-adenoma. Other causes include the effect of various drugs and finally due to mass effect on the pituitary stalk [2].

PRL circulates in our body in two forms which are transcribed by two different transcriptional sites at chromosome 6. One of them represents pituitary secretion while the other reflects prolactin secretion by other tissues including adipocyte cells. Several literatures supported that PRL exerts myriad of effects on adipose tissue and its related hormones including inhibition of Interleukin-6 (IL-6), adiponectin and possibly leptin. It can also induce adipolysis and therefore inhibits adipogensis. These actions of PRL contributed to metabolic syndrome and insulin resistance in prolactinoma patients [3,4].

The association between hyper-prolactinemia and insulin resistance has been described widely in the literature. This could be secondary to the hypo-gonadism which is not uncommon in hyper-prolactinemic patients or due to prolactin hormone itself. In a study conducted by Dos Santos Silva et al. which compared the various components of metabolic syndrome (waist circumference, Body Mass Index (BMI), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Triglyceride level (TG) and Homeostasis Model of Insulin Resistance Index (HMOIR) before and after the treatment of hyper-prolactinoma patients. The study showed a significant reduction in HMOIR, glucose, LDL, and TG after six months of treatment. These findings were observed in both Eugonadal and hypogonadal patients highlighting the intrinsic capacity of prolactin to cause metabolic syndrome [5].

Furthermore, Growth Hormone (GH) is known to cause insulin resistance that might lead to overt diabetes and the need for insulin treatment. Several mechanisms have been proposed for this action. These include the release of high levels of cytokines such as IL-6 and Tumor Necrosis Factor-Alfa (TNF-a), reduction in Adiponectin and enhanced lipolysis [6].

After literature review, there has previously been only one case report describing a mixed PRL and GH secreting adenoma in a patient who presented with DKA [7].

Case Presentation

A 62 year-old Indian male, presented to Emergency Department in Dec/2014 because of progressively worsening nausea, vomiting, dizziness and abdominal pain which started 3 days prior to his

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presentation. Furthermore, he reported some weakness on his legs especially at the left side lately, which affected his daily activity. The patient was known to have T2DM, not well controlled on oral hypoglycemic agents (HbA1c was 7.9 in April/2014), hypertension and dyslipidemia both were well controlled (TG was 1.64 mmol/cholesterol: 5.11 mmol/l /LDL=2.8 mmol/l/HDL=1.57, all in April/2014).

Upon presentation, the patient looked well, not in distress, conscious, alert and oriented. His Body Mass Index (BMI) was 38 Kg/m^2. Examinations were unremarkable except for signs of dehydration and bilateral mild lower limbs weakness. Initial labs showed Random Blood Sugar (RBS) of 29.6 mmol/L, Arterial Blood Gases (ABG) showed wide anion gab metabolic acidosis with serum B hydroxybutyrate of 5.6 mmol/l (normal range from 0-1 mmol/l). These findings were consistent with DKA. Other investigations showed HBA1C of 13.9, cholesterol of 5.46, TG of 2.86, HDL of 1.13 and LDL of 3.04.

The patient was started on insulin drip and fluid hydration as per Intensive Care Unit (ICU) protocol which led to improvement of DKA quickly. However, on the second day, the patient's mental status started to alter and he became profoundly confused as well as disoriented. CT scan oh head showed large intra and suprasellar mass lesion composed mainly of solid components with some cysts located at the periphery, compressing the lateral as well the third ventricle causing hydrocephalus, extends to cavernous sinus and encasing the carotid arteries bilaterally. Magnetic Resonance Imaging (MRI) was done later, which confirmed the findings of CT scan, showed a large intra and suprasellar mass measuring around 6.7 × 4.3 × 4.5 cm. (Figures 1 and 2. MRI/T1 (coronal/sagittal views): showing pituitary mass with bony destruction and compression of optic chiasm) [8].

Hormonal workup showed a markedly elevated serum PRL level of 154497 mIU/L (normal level is 212-424 mIU/l in males). Serum Follicular Stimulating Hormone (FSH) and Luteinizing Hormone (LH) both were less than 0.5 IU/L, serum testosterone was 0.29 nmol/l (normal level from 10-35) consistent with hypogonadotropic hypogonadism. Thyroid function tests revealed a Thyroid Stimulating Hormone (TSH) of 0.43 mIU/L (normal from 0.45-4.5 mIU/L), free thyroxine of 10.4 Pmol/L (normal 9-20 Pmol/L). The GH was slightly elevated at 19.9 mcg/L (normal level 0-10 mg/L) and the Insulin growth factor-1 (IGF-1) was found to be 190 ng/mL (normal 55-185 ng/ml), random serum cortisol level was 73 nmol/L.

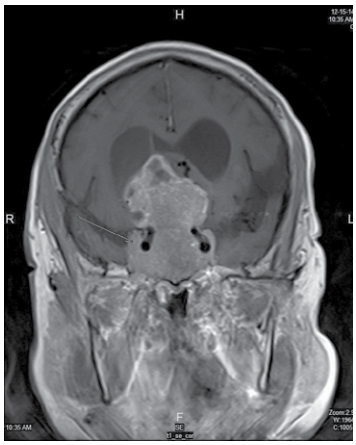

Figure 1: MRI/T1 (coronal view) showing pituitary mass (suggestive of macroprolactinoma) with bony destruction and compression of optic chiasm.

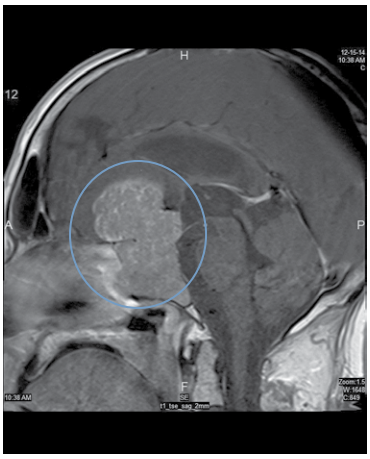

Figure 2: MRI/T1 (sagittal view) showing pituitary mass (suggestive of macro-prolactinoma) with bony destruction and compression of optic chiasm.

The patient's clinical picture and imaging were suggestive of an invasive giant prolactinoma. Therefore, the patient was started on cabergoline (0.5 mg twice weekly), L-thyroxine and steroids. The patient's condition markedly improved and he completely regained his full consciousness. Follow up with his physical examination was remarkable for bilateral temporal hemianopia and bilateral lower limbs weakness, which could be explained by the obstructive hydrocephalus and mild cerebral edema. After a week, serum PRL level dropped to 67817 mIU/L and the patient was able to stand and walk with assistance. Upon discharge, the patient was given basal-bolus insulin regimen and was planned for MRI pituitary and hormonal studies after 8 weeks with follow-up appointment in diabetic clinic.

Case Discussion

Lactotroph cells are unique among anterior pituitary tumors since they are under inhibition of dopamine. Other hormones can modulate PRL secretions such as Thyroid Releasing Hormone (TRH), Vasoactive Intestinal Peptide (VIP) and enkephalin which can stimulate PRL secretion while glucocorticoids and thyroxine weakly inhibit PRL secretion [9]. On the contrary, somatotroph cells (which constitute about 50% of the cells in the anterior pituitary) are regulated mainly by Growth Hormone Releasing Hormone (GHRH) which is the primary regulator for these cells. Like the lactotroph cells, somatotroph cells are under regulation of other hormones as well. These include L-arginine, dopamine, and hypoglycemia which are potent stimulator for GH secretion and can be used as a diagnostic tool for GH deficiency. Somatostatin, on the other hand, is considered to be a potent inhibitor for GH secretion.

Since lactotroph cells as well as somatotroph cells share a common genetic origin, prolactinoma is associated with secretion of GH in about 25% of cases [10]. On the contrary, synchronous pituitary adenoma such as the presence of somatotroph and lactotroph adenoma is exceedingly rare [11].

The association between prolactinoma and worsening of metabolic profile as well as cardiovascular mortality was reported in the literature. A study made by Bahceci et al. which observed the insulin sensitivity and serum PRL level in obese as well as non-obese females who had Polycystic Ovary Syndrome (PCOS). The study demonstrated a

statistically significant difference in the mean of serum insulin as well as insulin sensitivity in hyper-prolactinemic patients compared to normo-prolactinemic at non-obese arm of the study [12].

In another study, which evaluated the effect of prolactinoma treatment on metabolic profile for 14 patients, showed a positive correlation between serum PRL level and various components of metabolic profile. The decrease in body weight, waist circumference and LDL levels was observed after the reduction of serum prolactin level [13].

Since insulin resistance is the main contributing factor in T2DM, those patients unlikely present with DKA. However, in the setting of various hormonal derangement, those patients might be prone to this. The association between excessive GH secretion and DKA has been reported in the literature. The review of 860 cases of acromegaly patients over 32 years at Toranoman hospital in Tokyo; who underwent trans-sphenoidal surgery for somatotroph adenoma showed that about 1% of patients with acromegaly presented with DKA as their first presentation. None of those patients had Diabetes Mellitus (DM) nor had positive antibodies for type 1 DM [14].

Furthermore, Palakawong et al. described a case of 23 year-old male patient presented with DKA and was found to have acromegaly. Initially, he was treated with Trans-sphenoidal surgery, followed by bromocriptine, octreotide and then pegvisomant which resulted in complete normalization of GH and IGF-1 and thus a complete resolution of his diabetes [15].

Another case made by Carrasco de la Fuente et al. which described a 54 year-old female lady who presented with DKA. The patient was having the clinical picture of acromegaly. Hormonal workup had shown clinically significant elevation of GH, IGF-1 and mildly elevation of PRL level (microprolactinoma). Eventually, the Patient was found to have mixed prolactinoma with somatotroph adenoma. The excessive amount of GH was mainly the contributing factor for insulin resistance and DKA presentation [7].

We report a case of an Indian male patient, with a history of T2DM, partially controlled with oral an hypoglycemic agent (his HBA1c was 7.9%) who was admitted as a case of DKA with worsening of his glycemic control and lipid profile. Imaging as well as hormonal studies were found to be consistent with pituitary invasive macroprolactinoma. In the absence of various kinds of stressors such as infections, myocardial infarction and stroke, the markedly elevated prolactin level was the major culprit for worsening of his lipid profile, insulin resistance and finally DKA.

Moreover, the elevation of GH level as well as IGF1 is mostly due to co-secretion from the lactotroph cells in prolactinoma. This with the presence of hypo gonadotropic hypogonadism, both was contributing factors for insulin resistance in this patient.

Finally, prolactinoma is one of the pituitary tumors that significantly respond well to medical therapy. This has been demonstrated in various studies. In a study published by Cho et al. which demonstrated the effect of cabergoline in the treatment of giant invasive prolactinoma? The study has shown significant reduction in serum prolactin level and tumor size after couple of months of treatment [16].

Conclusion

Prolactinoma presents with central nervous system symptoms (CNS) such as bilateral temporal hemianopia, diplopia and headache, or secondary to the physiological effects of excess prolactin which is a common presentation of prolactinoma in females. Males usually presents with CNS symptoms since sexual dysfunction and decreased libido are the sole manifestations of prolactin excess in men that are usually overlooked. However, DKA is a rare presentation of pituitary prolactinoma and should be considered if occurred in a patient with co-existing CNS manifestations.

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