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A RARE INCIDENTAL CASE OF IATROGENIC CUSHING'S SYNDROME DUE TO METFORMIN USAGE IN WOMAN WITH TYPE 2 DIABETES MELLITUS: A SINGLE CENTER SCREENING STUDY

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ABSTRACT

Cushing syndrome is caused by prolonged exposure to high circulating levels of cortisol. The most common cause of cushingoid features is iatrogenic corticosteroid use, while some herbal preparations can also increase circulating corticosteroid levels leading to Cushing syndrome. Actual incidence and prevalence of Cushing syndrome are not known. The best therapy of iatrogenic Cushing's syndrome is to taper exogenous steroids. Chronic exposure to steroids can suppress the adrenals functioning and it can take several months for normal adrenal functioning to recover. On under-going clinical rotations in general medicine wards, we retrieve a case of 45 years old female patient presented with complaints of chest pain and headache, giddiness since 1 week, two episodes of vomiting, burning sensation in chest (epigastric region). Patients medical history was reported as shortness of breath since 20 years and current conditions were reported as hypertension and type-2 diabetes mellitus. Past medication history was reported as metformin for diabetes and amlodipine for hypertension since 10 years. Patient presented with events alopecia, weight gain, hearing impairment and fell down due to B/L-cataract while upon treatment with suspected drug metformin. Finally, patient was diagnosed with Metformin Induced Cushing Syndrome that was done depending upon casualty assessment between reported events and suspected drug is probable. However, further studies were warranted for establishing mechanism.

KEYWORDS: Adreno cortico hormone, Cushing syndrome, Metformin, Cortisol, Naranjo's scale WHO-UMC Karch and Lasagna scale severity, Predictability and Probability.

INTRODUCTION

Cushing's disease (CD) is a rare pathology characterized by uncontrolled ACTH secretion from a pituitary adrenocorticotroph adenoma that leads to an increase in cortisol production by the adrenal glands. It is a serious condition characterized by metabolic derangements that may include visceral adiposity, hepatic steatosis, dyslipidaemia, and diabetes mellitus. Cushing syndrome is caused by prolonged exposure to high circulating levels of cortisol.[1] The most common cause of cushingoid features is iatrogenic corticosteroid use, while some herbal preparations can also increase circulating corticosteroid levels leading to Cushing syndrome. Cushing syndrome can be interchangeably known as hypercortisolism. Adrenocorticotropic hormone (ACTH)-dependent cortisol excess due to a pituitary adenoma is called Cushing disease, and it is responsible for 80% of endogenous Cushing syndrome.[2,3] Actual incidence and prevalence of Cushing syndrome are not known. The prevalence of the disease is highly variable across different ethnic and cultural groups depending upon the frequency and a spectrum of the medical conditions requiring steroid based therapy. However, of the known cases iatrogenic hypercortisolism outweighs the endogenous causes, of the endogenous causes pituitary mediated ACTH production accounts for up to 80% of cases of hypercortisolism, followed by adrenals, unknown source and ectopic ACTH production secondary to malignancies.[4] The best therapy of iatrogenic Cushing's syndrome is to taper exogenous steroids. Chronic exposure to steroids can suppress the adrenals functioning and it can take several months for normal adrenal functioning to recover. Therefore,

steroids should be slowly tapered allowing adrenal functioning to recover. Hypercortisolism due to Cushing disease or adrenal tumour or ectopic tumour is best treated with surgical resection. Radiotherapy is recommended in Cushing disease after failed transphenoidal surgery or in Cushing disease with mass effect or invasion of surrounding structures.[5] Cortisol, which is a steroid hormone, regulates a wide range of body processes, but it displays its main effect after food intake. It seems to contribute to glucose intolerance and to reduce insulin sensitivity. In the liver, chronic hypercortisolism impairs fasting and postprandial glucose. Cortisol exacerbates gluconeogenesis and hepatic glucose output through both direct and indirect effects. Early diagnosis can reduce disease-related complications and improve life expectancy in CD patients, and DM is one of its most frequent although underestimated complications. Appropriate treatment is based on antidiabetic medication and, first and foremost, treating the underlying disease.[6]

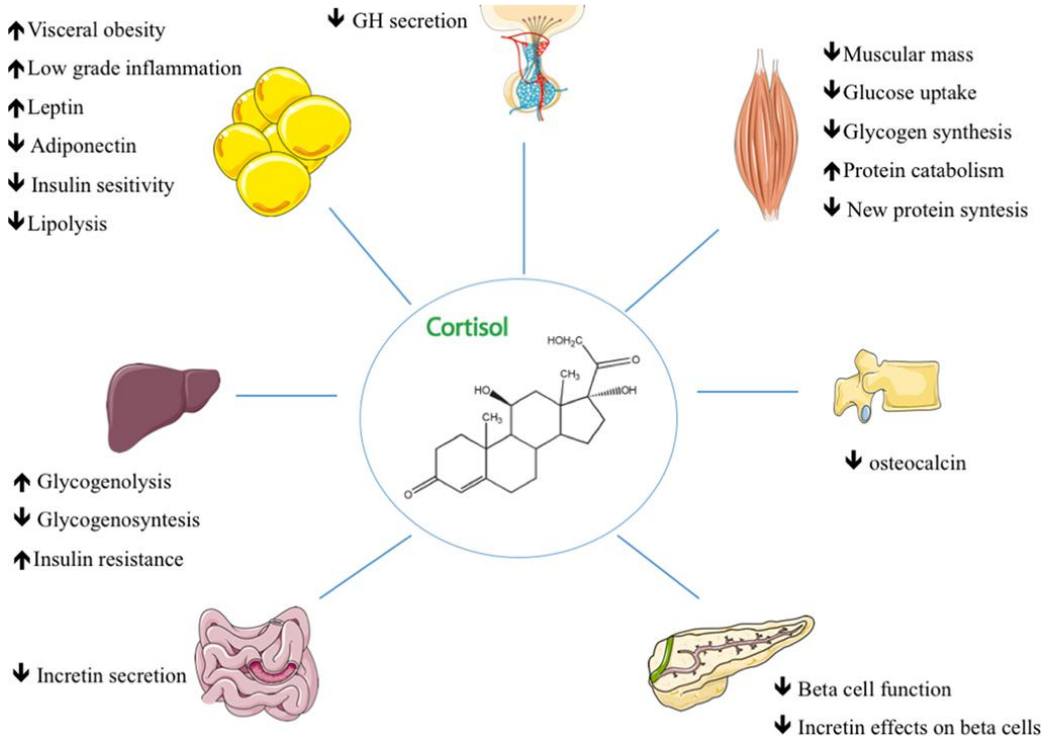

Figure: The main mechanisms of action in glucocorticoid-induced diabetes and their effects on target tissues in Cushing's disease.

Transphenoidal surgery remains the most effective treatment to control both cortisol and glucose metabolism as it can guarantee long-term remission in a high percentage of patients, but other options need to be considered when it is ineffective or unfeasible. With the exception of pasireotide, all cortisol-lowering medications have been shown to be effective in reducing to some degree the severity of hyperglycemia[7]. Due to its action on peripheral insulin sensitivity, which is the primary mechanism responsible for glucose intolerance in CD, metformin represents the mainstay of antidiabetic treatment. When treatment intensification becomes necessary, incretin-based therapies may represent a useful option. Beyond glucocorticoid excess, other factors implicated in DM development such as age, genetic predisposition, and lifestyle variables combined with the duration and degree of hypercortisolism, may contribute to impaired glucose tolerance.[8]

CASE REPORT

A 45-year-old female patient was brought to the Rajiv Gandhi Institute of Medical Science tertiary care teaching hospital, Kadapa, India. On the day of admission, patient was presented with the complaints of chest pain and headache, giddiness since 1 week, two episodes of vomiting, burning sensation in chest (epigastric region). Patient had similar complaints for the past 2 years. Medical history was reported as shortness of breath since 20 years and current conditions were reported as hypertension and type-2 diabetes mellitus and treated with tablet metformin 500 mg twice daily and tablet amlodipine 5 mg once daily for approximately ten years. Patient reported with alopecia, weight gain, hearing impairment and fell down due to B/L-cataract. During the hospitalization, Patient was treated with syrup sucralfate, ondansetron, paracetamol, dulcolax, norfloxacin, citralka, amlodipine, metformin, H. mistard, H. Actrapid, H. Insultard, iron folic acid, budecort, nebulization with asthalin, atorvastatin. Patient was diagnosed as Metformin Induced Cushing Syndrome.

Patient's Investigations

Parameter	Observed value
Hb	10g/dl
Total count	8,900cells/cu mm
Total Bilirubin	0.6mg/dl
Direct Bilirubin	0.1mg/dl
Indirect Bilirubin	0.5mg/dl
Creatinine	0.7mg/dl
RBS	178mg/dl
Urea	10mg/dl
Fasting blood sugar levels	150mg/dl
Post Prandial Blood Sugar	264mg/dl

ADR Analysis

However, upon analyzing the product information of anti-diabetic drugs, it was found that the most suspected drug (Metformin) induced Cushing syndrome. However further assessment was done by performing causality assessment with the standard methods such as Naranjo's scale, Karch and Lasagna scale and WHO-UMC causality assessment system[9]. Upon assessment of the reported event, there is a probable causal relationship between medical and medication history for the reported event which were represented in the below table 1. We made a further assessment on the severity, predictability and preventability through Modified Hartwig and Siegel severity scale, Schumock and Thornton Preventability Scale which were represented in the below table 2. Outcome of the suspect drug was reported as drug withdrawn and outcome of the event was reported as recovering. However, patient was treated with supportive therapy for the developed event.[10]

Table 1: Causality assessment.

Naranjo's scale	WHO-UMC	Karch and Lasagna scale
Probable	Probable	Probable

Table 2: Severity, Predictability and Probability.

Severity	Predictability	Preventability
Level 4b	Type-B	Definitely preventable

DISCUSSION

A literature search was done for Metformin and Cushing syndrome was conducted using PubMed, Embase etc. Search was done by using suitable medical subject headings (MESH) terms. Few articles were identified with relevant significant information. Cortisol is a steroid hormone produced by the zona fasciculata of the adrenal cortex. After production, the cortisol is carried to different parts of the body by cortisol binding protein, almost 90% of cortisol binds to these (CBG) protein and has a bioavailability of 60% to 100%. Synthetic corticosteroids have varying bioavailability and potency, but all affects in similar pathways. It is a catabolic hormone which is released under stressful conditions. The excess of cortisol results in an increased rate of gluconeogenesis, glycogenolysis and increased insulin resistance.[11]

Cortisol is a steroid hormone, and it directly affects the transcription and translation of enzyme proteins involved in the metabolism of fats, glycogen, proteins synthesis and Kreb's cycle. It promotes the production of free glucose in the body, elevating glucose levels, while simultaneously increasing insulin resistance. The destruction of protein yields amino acids which are used in gluconeogenesis,[12] The prolonged catabolism of proteins causes purplish striae of the torso, osteoporosis and poor wound healing. All these processes involve collagen which is a three amino based protein. High cortisol levels also cause immune disruptions. This hormone leads to a decrease in lymphocyte levels and increases the neutrophils. This mechanism explains the typical picture of raised TLC where there is decreased lymphocyte number and increased neutrophils. The corticosteroids mediate the downregulation of NF-kappaB, regulation of AMP kinase, glycogen phosphorylase, superoxide dismutase and many other enzymes. Cortisol inhibits the production of IL-2, TNF alpha, IFN alpha, and gamma. Metformin is a commonly used ant diabetic drug that has been widely used to control the hyperglycaemia that occurs in patients with Cushing's disease, which is secondary to both cortisol excess and pasireotide treatment.[13]

In a research study, author investigated whether metformin exerts an anti-tumour effect by directly targeting pituitary corticotroph tumours and exploring the underlying mechanisms. Using the mouse corticotroph tumour cells, AtT20 cells, author report that metformin inhibited cell proliferation, promoted cell apoptosis and decreased ACTH secretion but did not block the cell cycle in cells. Author concluded that, Metformin inhibits cell proliferation and induces apoptosis in AtT20 cells by activating AMP-activated protein kinase (AMPK)/ mammalian target of rapamycin (mTOR) and inhibiting IGF-1R/AKT/mTOR signaling pathways. Metformin may have direct antitumor activity against pituitary corticotroph tumours.[14] In another study, research scholars investigated the anti-diabetic mechanism of Metformin in-vitro and in-vivo. The fluctuation of the metabolite cortisol indicated that neuroendocrine system was involved in anti-diabetic effect of Metformin. Actually it was found that

Metformin induced (AMPK)/liver X receptor α (LXRα) phosphorylation, followed by pro-opiomelanocortin (POMC) suppression in rat pituitary cells. It is confirmed that, this result by administering Metformin in animals. It was noted that, cortisol stimulates gluconeogenesis, author propose the anti-hyperglycaemic effect of Metformin is attributed to reduced POMC/ adrenocorticotropic hormone (ACTH)/cortisol levels following AMPK/LXR α phosphorylation in the pituitaries.[15]

CONCLUSION

We concluded that upon assessment with causality scales there is a probable causal relationship with the suspect drug and the reported event. De-challenge was identified as positive. While upon review of the published literatures, very few articles were retrieved with limited information which was not sufficient for correlation. Exact mechanism was not known. However, further studies were warranted for establishing the association.

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DECLERATION OF INTERESTS

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the case reported.

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