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Extrapyramidal Symptoms and Insulin Resistance in a Patient on Multiple Antipsychotics Therapy

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ABSTRACT

Background/Objective: Multiple Antipsychotics Therapy promote obesity and insulin resistance. This study aimed to describe a T2DM patient with extrapyramidal symptoms and hyperglycemia who was also on several antipsychotic therapies and to determine whether omission of all antipsychotics along with modification of antidiabetic therapy led to better glycemic control.

Case Report: An uncontrolled T2DM female subject presented with tremor in both hands as well as in the right corner of her lips. She also having comorbid hypertension and hypothyroidism. On examination, she showed no signs of pallor, icterus, clubbing, cyanosis or edema. Central nervous system examination revealed a GCS of 15 and neurological examinations including motor and sensory responses were unremarkable in Nerve Conduction Study and MRI. her blood glucose levels showed poorly controlled diabetes (HbA1C – 9.5%, FBS – 278mg/dl, PPBS – 234mg/dl) in spite of taking OHAs. Her initial treatment plan included omission of all antipsychotics and reduction in dose of glimepiride to 4mg. This led to a drastic fall in the blood glucose levels. Her CBG levels were between 100mg/dl- 150 mg/dl. Soon after this, the dose of metformin was reduced to 1000mg, vildagliptin was omitted and a SGLT-2 inhibitor was added. This caused gradual improvement in her symptoms and subsequently the blood sugar levels and blood pressure were also within acceptable limits.

Discussion: Diabetes and hyperglycaemic emergencies are linked to APDs. There may be several processes that mediate this. In insulin-sensitive cells such muscle cells, hepatocytes, and adipocytes, APDs can block the insulin signalling pathway, resulting in insulin resistance. When choosing a course of treatment, one must consider this elevated risk.

Conclusion: Patients receiving multiple antipsychotics therapy are more likely to experience negative metabolic alterations. This case findings also highlight the importance of glycemic control in patients with acute or subacute onset movement disorders, irrespective of their past glycemic status.

Keywords: Multiple Antipsychotics Therapy, insulin resistance, T2DM patient, extrapyramidal symptoms, hyperglycemia

INTRODUCTION

Antipsychotic drugs (APDs) are frequently administered to treat different types of mental disorders [1]. These medications are frequently taken for a lifetime because mental problems are chronic diseases. APDs, however, have the potential to have major glucometabolic adverse effects, such as type 2 diabetes and hyperglycaemic emergencies, which can lead to non-compliance with medication [2]. There is currently no method to effectively combat these negative effects. Understanding the causes of APD-induced diabetes could aid with its prevention and treatment, which will enhance the APDs' therapeutic results. Insulin-induced IRS-1 tyrosine phosphorylation, PI3K, and Akt activity

have been demonstrated to be reduced in skeletal muscles of type 2 diabetes patients [3]. Obese type 2 diabetes affects Akt2 phosphorylation in adipose tissue [4]. As a result, abnormalities in the insulin pathway in insulin target cells may play a key role in the development of diabetes. It has been demonstrated that APDs block Akt activity, leading to insulin resistance in muscle cells [5]. Increasing weight gain, BMI, and intra-abdominal adiposity have all been linked to APD-induced insulin resistance and diabetes, particularly in individuals receiving prolonged APD medication [6]. This study aimed to describe a T2DM patient with extrapyramidal symptoms and hyperglycemia who was also on several antipsychotic therapies and to determine whether omission of all antipsychotics along with modification of antidiabetic therapy led to better glycemic control.

CASE REPORT

A 55yrs old, Hindu female, resident of West Bengal, housewife, presented to the ER with complaints of having abnormal to and fro movements in both hands for 2 days. She also complained of abnormal movements in her lips which increased on the day of admission. She had a history of taking anti-psychotic medications for many years which include amisulpride, risperidone and clozapine. She is a known case of hypertension, Type II diabetes mellitus and hypothyroidism. She had however denied the use of alcohol, tobacco or illicit substances.

On examination, she showed no signs of pallor, icterus, clubbing, cyanosis or edema. Central nervous system examination revealed a GCS of 15 and neurological examinations including motor and sensory responses were unremarkable. However, the patient showed tremor in both hands as well as in the right corner of her lips. Examination of other systems were normal. Initial laboratory investigations revealed mild anaemia and leucocytosis (Hb- 9.8g/dl, TLC-13800). Her LFT reports and electrolytes within normal limits. The kidney function tests as well as CPK levels were found to be normal. She was also tested negative for the infection profile. However, her blood glucose levels showed poorly controlled diabetes (HbA1C – 9.5%, FBS – 278mg/dl, PPBS – 234mg/dl) in spite of taking OHAs which included a combination of glimepiride (6mg) and metformin (2000mg) along with vildagliptin (100mg). This derangement in blood glucose levels could be related to insulin resistance which can be cause by the prolonged use of polypills. Her blood pressure was slightly raised (150/90 mmHg).

A Nerve Conduction Study and MRI of spine was performed soon after admission which did not show much abnormality. Following admission, her glucose levels were checked 4 times a day (7am, 12noon, 7pm, 1am) which revealed subsequently high sugar levels ranging between 250mg/dl- 400mg/dl. Her initial treatment plan included omission of all antipsychotics and reduction in dose of glimepiride to 4mg. This led to a drastic fall in the blood glucose levels. Her CBG levels were between 100mg/dl- 150 mg/dl. Soon after this, the dose of metformin was reduced to 1000mg, vildagliptin was omitted and a SGLT-2 inhibitor was added. This caused gradual improvement in her symptoms and subsequently the blood sugar levels and blood pressure were also within acceptable limits.

DISCUSSION

Multiple processes could be at play in APD-induced hyperglycemia. Firstly, in the target cells, such as muscle cells, hepatocytes, and adipocytes, APDs can block the insulin signalling pathway, resulting in insulin resistance. Secondly, High amounts of free fatty acids (FFA) and inflammation brought on by APD-induced obesity may also lead to insulin resistance. Thirdly, APDs have the potential to directly harm beta cells, which can result in cell death and malfunction. Based on these processes, an integrated strategy may be required to battle

the diverse effects of APDs on several pathways in order to effectively avoid APD-induced diabetes. In present case the subjects were hyperglycemic may be due to consumption of multiple antipsychotic drugs. In a recent research of 307 patients with psychotic disorders, it was discovered that olanzapine, with a mean treatment length of 7.6 years, caused type 2 diabetes (17%), obesity (48%), dyslipidaemia (35%) and hypertension (32%), while other APDs also had similar side effects [7]. Additionally, the European First-Episode Schizophrenia Trial (EUFEST) found no appreciable variations in these APDs despite a 20–30% incidence rate of hyperglycemia following a year of treatment with olanzapine, quetiapine, and ziprasidone [8]. Atypical antipsychotics (AAPs) encourage insulin resistance and obesity. According to research, AAPs have been found to have an affinity for the dopamine receptors' binding sites as well as those for serotonin, 2,3,6, muscarinic, adrenergic, and histamine. Olanzapine and Clozapine, AAPs with notable associations with obesity and insulin resistance, have at least two orders of magnitude higher binding affinities for muscarinic receptors than other AAPs. This demonstrates how these receptors are involved in the pathogenesis of insulin resistance and obesity [9].

Due to their excellent clinical efficacy, second generation antipsychotics are the cornerstone of the treatment of schizophrenia [10]. Antipsychotic use, however, might have a number of negative side effects. There's a chance that these are neurological negative effects. In present case, subject experiencing with abnormal sensing in different part of the body may be due to negative neurological side effects which disappear with the withdrawn of the concern drugs.

Antipsychotics may cause secondary Parkinsonism by disrupting the DA-Ach balance in the basal ganglia due to D2 receptor blockage. Additionally, Rabbit Syndrome, marked by perioral tremors, may result. Tardive Dyskinesia, which is marked by uncontrollable oro-buccal-lingual dyskinesia, is another neurological adverse effect [11]. It has been suggested that the striatal nerve cells produce newer DA receptors that are supersensitive to even lower amounts of DA in order to combat a long-term DA receptor blockade caused by a neuroleptic [12]. When dopamine levels rise, cholinergic activity declines, which leads to a reduction in GABA release. The increase in involuntary motor activity is brought on by this.

Improved glycemic control, lower HbA1c levels, and use of anti-diabetic medication have all been linked to a lower risk of cognitive and neuromotor dysfunction, according to numerous research. However, there aren't many clinical research that have looked at how SGLT2I and DPP4I affect diabetic patients' cognitive dysfunction. In present case, DPP4i was replaced with SGLT2i mainly because of two reasons. Firstly, compared to DPP4I users, SGLT2I users had a decreased risk of Alzheimer's disease, Parkinson's disease, and new-onset dementia [13]. Secondly, All-cause mortality, cerebrovascular mortality, and cardiovascular mortality were all at a decreased risk for SGLT2I users [14].

CONCLUSION

Patients receiving multiple antipsychotics therapy are more likely to experience negative metabolic alterations. This case findings also highlight the importance of glycemic control in patients with acute or subacute onset movement disorders, irrespective of their past glycemic status.

Declaration by Authors

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