A CASE STUDY ON SCHIZOPHRENIA INDUCED MULTIPLE COMORBIDITIES

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ABSTRACT
Schizophrenia is a mental disorder characterized by abnormal social behavior which includes false beliefs, confusion, and auditory hallucination. Antipsychotic drugs therapy increases the risk of developing diabetes mellitus and coronary artery disease (CAD) in schizophrenic patients. Hence, we have planned for a systematic approach toward the management of comorbidities induced in schizophrenic patients. A case study was conducted in a 42-year-old female patient diagnosed with schizophrenia along with Type-2 diabetes mellitus, hypothyroidism, diabetic retinopathy, diabetic nephropathy, systemic hypertension, CAD-acute coronary syndrome recent inferior wall myocardial infarction. The patient was treated with atypical antipsychotics, antplatelets, antianginals, statins, hypoglycemic agents, and other supportive measures. The patient improved symptomatically. The antipsychotic treatment for schizophrenia induces abnormal metabolic syndrome which results in decreased glucose and lipid metabolism that leads to obesity, hyperglycemia, and dyslipidemia associated with cardiovascular risks. Often antipsychotics are combined with benzodiazepines and antiparkinson agents to reduce the risks caused from large doses of antipsychotic medication. However, people receiving first-generation antipsychotics have higher prevalence of developing diabetes mellitus and cardiac risks compared to second-generation antipsychotics. Hence, we conclude that atypical antipsychotic drugs such as amisulpride, aripiprazole, and ziprasidone should be given to schizophrenic patients because these drugs have little effects on abnormal metabolic syndrome when compared to other antipsychotics. There is a need for proper screening of blood glucose level and cardiovascular risks assessment before the administration of antipsychotic medications to schizophrenic patients and also during the course of treatment regularly.

Keywords: Schizophrenia, Diabetes mellitus, Coronary artery disease.

INTRODUCTION
Schizophrenia is a mental disorder characterized by abnormal social behavior and failure to understand the reality which includes false belief, confusion, and auditory hallucination, and lack of social engagement [1,2]. Late adolescence and early adulthood are peak periods for the onset of schizophrenia which is usually later in women than in men [3]. The peak ages for onset are 25 years for males and 27 years for females [1]. Over the years, various studies have been done and have reported that patients with schizophrenia are susceptible to comorbidities. However, little is known about the proper management and treatment of such cases.

CASE REPORT
Schizophrenia patient's diagnosed history
A 42-year-old female patient visited ear, nose, and throat department with chief complaints of a severe headache and otalgia. She was diagnosed with otitis externa in right ear, external auditory canal edema, and perforated eardrum, and advised to keep ichthammol glycerin pack for 3 days. Later she was planned for tympanoplasty.

Fasting blood sugar and postprandial blood sugar test was performed before the surgery and was found with hyperglycemia. Hence, the tympanoplasty was postponed, and under the guidance of diabetologist, the patient was diagnosed with Type-2 diabetes mellitus based on the complete blood glucose profile test performed and also found with the history of insomnia for 8 years and mentally abnormal for 12 years without any medication. Hence, under the guidance of the psychiatrist, the patient was diagnosed with schizophrenia based on the positive and negative syndrome scale for mental illness assessment. Meanwhile, the patient developed with complaints of active ear discharge, pedal edema and under the guidance of endocrinologist, and nephrologist; the patient was diagnosed with hypothyroidism based on hypothyroid stimulating hormone values and also with diabetic retinopathy and diabetic nephropathy based on an appropriate test. During the period of treatment for above complaints, the patient developed with complaints of upper abdominal pain, breathlessness for 4 h, and hence, ultrasound abdomen scan recommended, and its report found with bilateral mild pleural effusion, mild pericardial effusion, and bulky uterus with uterine fibroid. Under the supervision of the cardiologist, the patient was reported with hyper values in lipid profile test expect high-density lipoprotein with hypo values. Electrocardiogram (ECG) was analyzed and reported with sinus tachycardia with Q and T wave inversion in LII, LIII, and arteriovenous fistulae an echocardiogram assessed with left ventricular ejection fraction=40% and coronary angiography was performed and diagnosed with coronary artery disease (CAD) - single vessel disease, evolved inferior wall myocardial infarction, and systemic hypertension.

Patients investigated personal history
The patient's personal history was investigated to identify the cause and onset of schizophrenia. The patient's birth is by normal vaginal delivery. The patient had normal and regular menses. Patient gestated for the first time at the age of 20 years and the second time at the age of 21 years. Both babies were delivered by lower segment cesarean section due to overweight of about 4 kg, respectively. The firstborn baby lactated for 11 months and the second baby for 1 year. During the age of 34 years, the patient developed with symptoms of insomnia and feeling restlessness, and confusion. During the age of 39–40 years, the patient was developed with auditory hallucination and delusions but left untreated for past 8 years which induce severe ear infection. During the age of 40 years, the patient developed with frequent severe headache and nocturia. At present, at the age of 41 years, the patient developed with pain in the upper limb, radiating to the left scapula.
Patient’s - schizophrenia and comorbidities pathogenesis
The combination of genetic and environmental factors play a key role in the development of schizophrenia [3,4]. Environmental factors associated with the development of schizophrenia include social isolation, drug use, and prenatal stressors. Maternal stress may induce hypermethylation and underexpression of reelin (large extracellular matrix glycoprotein that regulates neuronal migration and positioning in developing brain by controlling cell-cell interaction) [5]. This leads to a reduction in gamma-amino butyric acid receptors and maternal nutritional deficiencies as well as maternal obesity and Reduced metabolic activity in the frontal cortex and serotonin, glutamate through dysfunction of its N-methyl D aspartate receptor are identified as possible risk factors for schizophrenia [1]. Since the positive symptoms of schizophrenia occur at the earlier age but because of lack of knowledge regarding this, the patient was left untreated.

Fig. 1 shows an outline of the pathogenesis of schizophrenia [6].

People with untreated schizophrenia have a higher risk of obesity. Type 2 diabetes mellitus, dyslipidemia and hypertension and contribute to the overall cardiovascular disease risks [7]. However, in this case, the patient with schizophrenia and diabetes mellitus left untreated for an extended period. The pathology of schizophrenia resembles that dysregulation of hypothalamic-pituitary axis and high serum cortisol levels in people with elevated serum cortisol increases gluconeogenesis, insulin resistance, and metabolic syndrome [8]. The prevalence of diabetes and cardiovascular disease is increased 2–3 fold in people with schizophrenia [9]. Since antipsychotic medications may also cause adverse metabolic effects due to non-adherence, it result in irregular glucose and lipid metabolism that may induce obesity, hyperglycemia, and dyslipidemia which associated with cardiovascular risks [10,11]. Due to withdrawal from health care among family members may result in multiple comorbidities. The prevalence of modifiable risk factors is shown in Table 1 [12].

Management given
The patient initially was admitted with chief complaints of a severe headache and otalgia and was diagnosed with external auditory canal edema, otitis externa, and perforated eardrum. The patient was treated with tablet ranitidine 150 mg bid and tablet amoxicillin 250 mg+clavulanic acid 125 mg Q6 h, and ear drop ciprofloxacin 1* bid given for 1 week. The random blood sugar and postprandial blood sugar were assessed before tympanoplasty and diagnosed with Type-2 diabetes mellitus, continued the medication along with tablet metformin 500 mg bid for next 1 week. Meanwhile, the patient was identified with the history of insomnia and mental abnormalities for past 8 years under no medication. Then, she was diagnosed with schizophrenia, treated with atypical antipsychotics - tablet amisulpride 400 mg 0-0-1 for next 2 weeks. Subsequently, she was found with abnormal thyroid stimulating hormone value 13.8, and diagnosed with hypothyroidism, Type-2 diabetic retinopathy, and nephropathy and continued all medication along with thyroid supplement tablet levothyroxine 100 mcg 1-0-0 for next 3 weeks. During the treatment, the patient developed with breathlessness and was discharged with following medications for 1 week. The patient improved symptomatically and was discharged with following prescribed medications (Table 2).

Table 1: Estimated prevalence of modifiable cardiovascular risk factors in people with schizophrenia

| Modifiable risk factor | Prevalence (%) | Relative risk |
|------------------------|----------------|--------------|
| Smoking                | 50–80          | 2–3          |
| Dyslipidemia           | 25–69          | ≤5           |
| Diabetes               | 10–15          | 2–3          |
| Hypertension           | 19–58          | 2–3          |
| Obesity                | 45–55          | 1.5–2        |
| Metabolic syndrome     | 37–63          | 2–3          |

Table 2: Prescribed medication

| Dosage form | Drug name                | Dose  | Frequency |
|-------------|--------------------------|-------|-----------|
| Tablet      | Clopidogrel+aspirin      | 150 mg| 0-1-0     |
| Tablet      | Rosuvastatin            | 40 mg | 0-0-1     |
| Tablet      | Carvedilol              | 3.125 mg| 1-0-1    |
| Tablet      | Furosemide              | 40 mg | ½-½-0     |
| Tablet      | Nicorandil              | 5 mg  | ½-0-½     |
| Tablet      | Losartan                | 25 mg | 1-0-0     |
| Tablet      | Trimetazidine           | 35 mg | 1-0-1     |
| Tablet      | Amisulpride             | 400 mg| 0-0-1     |
| Tablet      | Pantoprazole            | 40 mg | 1-0-1     |
| Capsule     | Becosulizes             |       | 0-0-0     |
| Ear drops   | Ciprofloxacin           | 2 drops| 1-0-1    |
| Tablet      | Metformin               | 500 mg| 1-0-1     |
| Tablet      | Vildagliptin            | 50 mg | 1-0-1     |
| Tablet      | Levetirhalnone          | 100 mcg| 1-0-0    |
| Tablet      | Spironolactone          | 25 mg | 0-1-0     |

Fig. 1: Pathogenesis of schizophrenia-inducing adverse metabolic syndrome

DISCUSSION
Treatment for schizophrenia
The management of schizophrenia includes both psychosocial interventions and psychotropic medication. Both typical and atypical antipsychotic drugs address the positive symptoms of schizophrenia whereas negative symptoms of schizophrenia responses more favorably to atypical antipsychotics [13]. Often antipsychotics are combined with benzodiazepines and antiparkinson agents during the actual phase of treatment to reduce the risks caused by large doses of antipsychotic medications [1]. Hence, in this case, the patient with positive symptoms should be treated with atypical antipsychotic drugs such as amisulpride, aripiprazole, and ziprasidone because these drugs have little effect on weight gain [14].

Treatment for schizophrenia with diabetes mellitus
The management for diabetes in schizophrenic patients according to standard treatment guidelines includes the proper screening of glucose
level combined with measurement of glycated hemoglobin (HbA1c) both before and after administration of antipsychotic agents and medications includes oral hypoglycemic agents like metformin which shows significant effects on controlling the diabetes mellitus along with coadministration of atypical antipsychotic medications [15,16]. If the blood glucose level is higher than 450 mg/dl, then insulin therapy is recommended. The additional management includes dietary modification, increased physical activities, and weight loss reduces the incidence of Type-2 diabetes. Hence, in this case, the patient with high HbA1c, high blood sugar level should be treated with metformin and vildagliptin which is significant in the management of Type-2 diabetes mellitus.

Treatment for schizophrenia with cardiovascular risks and diabetes mellitus
Since hypertension and dyslipidemia pave the way for all cardiovascular risks, the management of hypertension and dyslipidemia in the schizophrenic patient must approach systematically. Cardiovascular risk assessment should include detailed medical history with the physical examination including weight, blood pressure, lipid profile test, blood sugar profile, and ECG [12]. The blood pressure value ranging from 120/80 mmHg to 140/90 mmHg is recommended. If it exceeds; then diuretics, angiotensin converting enzyme inhibitor, beta blocker, vasodilators, angiotensin receptor antagonist, calcium channel blockers, and alpha blockers should be given accordingly to the patient’s condition. In this patient, sodium nitroprusside, a vasodilator and carvedilol are significant in the treatment of hypertension in Schizophrenic patients, should be given.

Dyslipidemia inducing comorbid cardiac risks includes CAD, angina, myocardial infarction, and ACS. No cardiovascular disease outcome trials with statins have explicitly performed in people with schizophrenia, but these drugs are effective in lowering total and low-density lipoprotein cholesterol [17]. So for this patient, statins like rosuvastatin are recommended for ACS because its efficacy is better in schizophrenic patients. Initially, the patient should treat with antplatelets such as heparin, clopidogrel for myocardial infarction, and antianginals such as tisorbide dinitrate, nitroglycerin for angina pectoris, and for dilating the blood vessels.

CONCLUSION
The increased risk factors for developing diabetes mellitus and Cardiovascular disease in a patient with schizophrenia necessitates a significant approach toward the screening of adverse metabolic syndrome and managing them. The ignorance toward the health care of people with schizophrenia makes them more susceptible to comorbidities. Hence, this case stands as an exemplary condition indicating schizophrenic patients are prone to comorbidities such as diabetes mellitus, CAD, and other related cardiac risk factors. Thus, there is a need for proper monitoring of blood level and cardiac functions before the administration of antipsychotics to schizophrenic patients and also during the course of treatment.

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AUTHORS CONTRIBUTIONS
Dr. Jagadeesan M - contributed in choosing the topic, guided throughout the progress of case study and cross-checked the case study on completion. Kiran Kumar R - contributed in collecting the pieces of information regarding patient for case study and accounts for case study writing. Justin Jacob Abraham - contributed in collecting the pieces of information regarding comorbidities pathogenesis for case study and accounts for case study writing.

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