

A CASE STUDY ON SCHIZOPHRENIA INDUCED MULTIPLE COMORBIDITIES**JAGADEESAN M*, KIRAN KUMAR R, JUSTIN JACOB ABRAHAM**

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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 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, antiplatelets, 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.© 2018 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2018.v11i6.23979>**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-aminobutyric 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 treated with tablet ranitidine 150 mg bid and tablet amoxicillin 250 mg+clavulanic acid 125 mg Q8 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 ultrasound scan was recommended and reported with mild pericardial effusion, and acute coronary syndrome (ACS). Consequently, coronary angiography performed and the patient diagnosed with CAD - single vessel disease, elevated myocardial infarction. The patient was treated with tablet clopidogrel+aspirin 150 mg (antiplatelet+thrombolytic) 0-1-0, tablet rosuvastatin 40 mg (antihyperlipidemic) 0-0-1, tablet furosemide+spironolactone 40 mg (diuretics) ½-½-0, tablet nicorandil 5 mg (antianginals) ½-0-½, tablet losartan 25 mg (antihypertensive) 1-0-0, carvedilol - 3.125 mg (antihypertensive) 1-0-1, tablet trimetazidine 35 mg (antianginals) 1-0-1, and continued along with previously mentioned medications for 1 week. The patient improved symptomatically and was discharged with following prescribed medications (Table 2).

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

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	40mg	½-½-0
Tablet	Nicorandil	5mg	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	Becosules		1-0-0
Ear drops	Ciprofloxacin	2 drops	1-0-1
Tablet	Metformin	500 mg	1-0-1
Tablet	Vildagliptin	50 mg	1-0-1
Tablet	Levothyroxine	100 mcg	1-0-0
Tablet	Spironolactone	25 mg	0-1-0

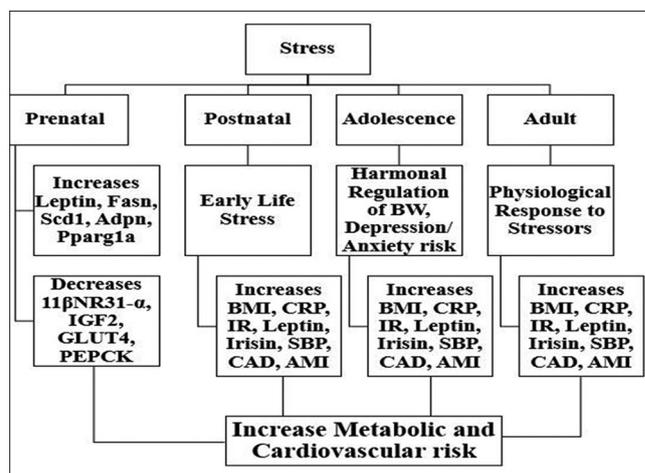


Fig. 1: Pathogenesis of schizophrenia-inducing adverse metabolic syndrome

level combined with measurement of glycated hemoglobin (HbA1c) both before and after administration of antipsychotic agents and medications include 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 antiplatelets such as heparin, clopidogrel for myocardial infarction, and antianginals such as isosorbide 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 sugar 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.

REFERENCES

- Ruth AH, Porth C. Porth Pathophysiology: Concepts of Altered Health States. 8th ed. Philadelphia, PA: Wolters Kluwer; 2008. p. 1367-9.
- Walker R, Whittlesea C. Clinical Pharmacy and Therapeutics. 5th ed. New York: Churchill Livingstone; 2012. p. 479.
- Van Os J, Kapur S. Schizophrenia. *Lancet* 2009;374:635-45.
- Picchioni MM, Murray RM. Schizophrenia. *BMJ* 2007;335:91-5.
- Negrón-Oyarzo I, Lara-Vásquez A, Palacios-García I, Fuentealba P, Aboitiz F. Schizophrenia and reelin: A model based on prenatal stress to study epigenetics, brain development and behavior. *Biol Res* 2016;49:16.
- Massmann GA, Zhang J, Seong WJ, Kim M, Figueroa JP. Sex-dependent effects of antenatal glucocorticoids on insulin sensitivity in adult sheep: Role of the adipose tissue renin angiotensin system. *Am J Physiol Regul Integr Comp Physiol* 2017;312:R1029-38.
- Barnett AH, Mackin P, Chaudhry I, Farooqi A, Gadsby R, Heald A, et al. Minimising metabolic and cardiovascular risk in schizophrenia: Diabetes, obesity and dyslipidaemia. *J Psychopharmacol* 2007;21:357-73.
- Brenner K, Liu A, Laplante DP, Lupien S, Pruessner JC, Ciampi A, et al. Cortisol response to a psychosocial stressor in schizophrenia: Blunted, delayed, or normal? *Psychoneuroendocrinology* 2009;34:859-68.
- Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry* 2010;196:116-21.
- Newcomer JW. Antipsychotic medications: Metabolic and cardiovascular risk. *J Clin Psychiatry* 2007;68 Suppl 4:8-13.
- Nirojini PS, Bollu M, Nadendla RR. Prevalence of medication non-adherence among the psychiatric patients—results from a survey conducted in a tertiary care hospital. *Int J Pharm Pharm Sci* 2014;6:461-3.
- De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Möller HJ, et al. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European psychiatric association (EPA), supported by the European association for the study of diabetes (EASD) and the European society of cardiology (ESC). *Eur Psychiatry* 2009;24:412-24.
- Rang HP, Ritter JM, Flower RJ, Henderson G. Rang and Dales Pharmacology. 7th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2007. p. 553-4.
- Holt RI, Peveler RC. Obesity, serious mental illness and antipsychotic drugs. *Diabetes Obes Metab* 2009;11:665-79.
- Holt RI. Cardiovascular disease and diabetes in people with severe mental illness: Causes, consequences and pragmatic management. *South Afr J Diabetes Vasc Dis* 2012;9:107-11.
- Vishnupriya R, Ezhilramya J, Meenakshi B. Metformin in the prevention of metabolic syndrome associated with initiation of atypical antipsychotic therapy in adolescents and young adults - A randomized, open labelled, single centered study. *Int J Pharm Pharm Sci* 2016;8:200-6.
- Hanssens L, De Hert M, Kalnicka D, van Winkel R, Wampers M, Van Eyck D, et al. Pharmacological treatment of severe dyslipidaemia in patients with schizophrenia. *Int Clin Psychopharmacol* 2007;22:43-9.