

## Association of Diabetes Mellitus and Clozapine : A Case Report

AMRITHA BHAT S, ANTHONY A. DINESH, ASHOK M.V., SUNITHA SIMON KURPAD & GANAPATHI, B.

### ABSTRACT

A case of Paranoid Schizophrenia who developed Type 2 diabetes mellitus while on treatment with clozapine, is described. A brief review of literature is provided. In this case, Clozapine therapy could have caused the diabetes, or accelerated a pre-existing process. This report aims to highlight the importance of monitoring for hyperglycemia, an adverse effect of clozapine, which is being increasingly recognized in recent times.

**Key Words:** Clozapine, diabetes mellitus, schizophrenia

There are increasing reports of use of newer antipsychotics being associated with diabetes mellitus (Dan et al., 2001). We report one such case and provide a brief review of literature.

### CASE

Mr. X, a 25 year old male, with history of type 2 diabetes mellitus (DM) in the mother, presented to us in 1992 with a three month history of delusions of persecution and reference, thought broadcast, and third person auditory hallucinations.

He was diagnosed as having paranoid schizophrenia and given typical neuroleptics. Response to treatment was poor and his symptoms persisted despite receiving ECT. In 1999, he was started on clozapine following a serious suicidal attempt. At the time of initiating clozapine therapy, his weight was 69 kgs, body mass index (BMI) 23.9, and random blood sugar (RBS) 152 mg/dl. In six months, he had improved. Three months after clozapine was started, RBS was 190 mg/dl and he was advised diet control and exercises. However, two months later, RBS was 401 mg/dl and oral hypoglycemics were prescribed. With this, he did well for more than a year.

Four months ago, he had recurrence of psychotic symptoms. Compliance with both clozapine and oral hypoglycemics was questionable. His weight was 80.4 kg, BMI 27.8 and his blood sugars were

elevated (Fasting Blood Sugar-168 mg/dl, Post Prandial Blood Sugar-211 mg/dl).

The doses of clozapine and oral hypoglycemics were titrated. Over two weeks, his psychotic symptoms improved while his blood sugars normalized.

### DISCUSSION

Impaired glucose metabolism was first described in psychotic patients even before the introduction of antipsychotics. The hypotheses put forward to explain this association were: circulating insulin antagonists (Schimmelbusch et al., 1971), maternal zinc deficiency (Andrews, 1992) and an immunological explanation (Holden, 1999). Whether the onset of DM in our patient was before or after the introduction of clozapine is unfortunately not clear, as at the time of his ICU admission for intermediate syndrome secondary to consumption of an organophosphorous compound, his elevated blood sugars were not followed up. It could be that the elevated RBS at that time was considered a transient phenomenon like stress hyperglycemia and the onset of DM was actually after clozapine was started. The other possibil-

ity is that the patient already had early DM, which worsened after use of clozapine. This could have been ascertained had a glycosylated haemoglobin level been done.

Newer antipsychotic medications are associated with occurrence of hyperglycemia, new onset type 2 DM, exacerbation of existing diabetes and diabetic ketoacidosis. Hyperglycemia is more frequently reported with chlorpromazine, clozapine, and is also seen with risperidone and quetiapine.

**TABLE 1: Mechanism of action of impaired glucose metabolism caused by antipsychotics**

1. Interfering with beta cell insulin secretion. Decrease pancreatic beta cell responsiveness to blood sugar levels because of antagonism to 5HT 1 A receptors.
2. Increasing insulin resistance.
  - Increase appetite and calorie intake.
  - Changes in the distribution of body fat.
  - Decreased oxidative metabolism in tissues.
  - Interferes with insulin action cascade.
  - Increased counter regulatory hormones.
  - Increased free fatty acid release from adipose tissues.

There may be a causal relationship between clozapine and the development or worsening of diabetes; onset of hyperglycemia may be rapid and severe (within six months of initiation of therapy) as was seen in our patient. Association is not dose dependent and risk does not end with extended use (Koller et al., 2001). If our patient already had diabetes, then clozapine could have just worsened it.

Recent controlled studies have shown that clozapine and olanzapine have adverse effects on glucose metabolism independent of adiposity (David et al., 2000). The odds of being pre-obese or obese are nine times more in the psychiatrically ill than control subjects (Simon Kurpad et al., 2001). Our patient was normal as shown by the BMI

before he started taking clozapine, but has moved into the pre-obese range after starting clozapine.

All the studies mentioned highlight the role of antipsychotics in the development of diabetes. However, we found no studies on the impact of diabetes on the course and outcome of schizophrenia. This needs further examination.

For patients with known risk factors for diabetes, it is recommended that weight, plasma glucose and lipid levels be monitored quarterly for the first year and annually thereafter. For those without risk factors, it is felt that monitoring the same every year after the age of 45 years is sufficient (Dan et al., 2001).

However, it should be borne in mind that monitoring is to be tailored to the needs of an individual patient. We would recommend more frequent monitoring, especially given the rapid onset/worsening of diabetes in the case under discussion.

Also, treatment options in these patients have to be individualized. The continuation of clozapine requires clinical judgement and informed discussions with

the patient and family members.

## CONCLUSION

Clozapine is perhaps the best option in treatment resistant schizophrenia. Monitoring for agranulocytosis and seizure risk has become a part of clinical practice. In this patient, clozapine was started at a time when its association with DM was not clear. There is now an emerging consensus on the need to monitor for other complications like DM.

Clozapine is often used in very ill patients and such patients may not voluntarily report symptoms of diabetes mellitus like polydipsia. Further polydipsia is not uncommon in chronic schizophrenic patients (Leon et al., 1994). Clinicians need to have a high index of suspicion and recognize diabetes mellitus early in patients on clozapine.

## REFERENCES

Andrews R.C. (1992) Diabetes and schizophre-

nia: genes or zinc deficiency? *Lancet*, 340 (8828), 1160.

Dan WH, John W.N. (2001) Hyperglycemia and antipsychotic medications. *J.Clin. Psychiatry*, 62 (supp 27), 15-26.

David C.H. (2000) Clinical experience with insulin resistance, DKA, Type 2 DM in patients treated with atypical antipsychotic agents. *J.Clin. Psychiatry*, 62(supp 27), 10-14.

Holden R.J, Pakula I.S. (1999) The link between diabetes and schizophrenia: an immunological explanation. *Aust. New Zealand J. Psychiatry*, 33 (2): 286-287.

Koller E, Bruce S, Katherine B, Greg, D. (2001) Clozapine associated diabetes. *Am.J. Med.*, 111, 716-723.

Leon J, Verghese C, Tracy J-I, Josissen R.C, Simpson G.M. (1994) Polydipsia and water intoxication in psychiatric patients: a review of the epidemiological literature. *Biol Psychiatry*; 35 (6), 408-419.

Schimmelbusch W.H, Mueller P.S, Sheps J. (1971) The positive correlation between insulin resistance and duration of hospitalization in untreated Schizophrenia. *Brit. J. Psychiatry*, 118, 429-436.

Simon Kurpad Sunita, Himanshu Tandon, K.Srinivasan (2001) Prevalence of obesity among psychiatrically ill patients. *Ind. J. Psychiatry*, 43(2), 138-146.

\*AMRITHA BHATS, M.B.B.S., Post graduate, ANTHONY A. DINESH, M.B.B.S. Post graduate, ASHOK M.V., M.D., Associate Professor, SUNITHA SIMON KURPAD, MRCPsych DNB Associate Professor, Department of Psychiatry, GANPATHI, B., M.D., D.M., D.N.B., Associate Professor, Department of Medicine, St. John's Medical College, Bangalore.

\* Correspondence