ARCHIVES of NIMH
The Official Journal of National Institute of Mental Health, Dhaka

Case report

A young patient with treatment-resistant schizophrenia: a case study

Md Inamul Islam, Md Kamrul Hassan, Roksana Arshed, AHM Kazi Mostafa Kamal, Golam Ferdous

Abstract

Schizophrenia is considered as one of the major psychiatric illnesses characterized by a tuft of positive, negative and cognitive symptoms. With the introduction of chlorpromazine in the 1950s and subsequently other antipsychotic drugs, the treatment of schizophrenia was revolutionized. However, soon it was seen that some patients had little or no clinical response to treatment with multiple different antipsychotic drugs. Treatment-resistant schizophrenia is a nightmare for not only the suffering patient, but also for the treating physician. A young patient diagnosed with schizophrenia showed no clinical response to three second-generation antipsychotic drugs at optimum doses. With the administration of clozapine, dramatic improvement was seen at standard dose. The patient was successfully treated with no relapse or recurrence. This academic case is presented to create awareness and insight about treatment-resistant schizophrenia cases, so that they can be assessed properly and treated efficiently without unnecessary delay.

Declaration of interest: *None*

Keywords: Treatment-resistant schizophrenia; clozapine; case study

Introduction

Schizophrenia is a serious mental illness that affects a person's thoughts, feelings, and behaviors. Patients suffering from schizophrenia often lose insight, which means they are not in touch with the outside reality. It causes significant disturbances and distress for the individual, their near and dear ones. It hampers the personal, academic, occupational, familial, social and financial aspects of the individual. Effective treatments are available with a good number of antipsychotic drugs. Some patients do not show the expected response with treatment. Treatment-resistant schizophrenia is a severe mental health burden as it prolongs the sufferings of the patient and course of the disease. It affects around 34% of thepatients with diagnosis of schizophrenia.[1] Till today only clozapine has shown its efficacy in treating the resistant cases. We documented this interesting and academic case of a young patient from Rangpur who had treatment-resistant schizophrenia and was successfully treated with clozapine.

Case Report

This 18-year old young male, a student of class XI, was brought to emergency and casualty department with the complaints of violent and aggressive behavior, undue suspiciousness, irrelevant talk, self-muttering, sleep disturbance, and belief of being followed and observed. He was immediately assessed by a psychiatrist and was tranquilized with intra-muscular haloperidol. He was admitted in the psychiatry ward for further assessment and treatment.

Detailed history of the patient was obtained, which showed that he developed the aforementioned symptoms within a short span of 3-4 days. Before the onset of symptoms, he was living an apparently normal life of a young adult. Suddenly he developed some abnormal behaviors like undue suspicion of being harmed by others and claimed that some people were observing him and his entire family. Those unknown persons were plotting to kidnap and kill his family. He confined himself within his home and also insisted his family members not to go outside. He strongly believed that he was under constant video surveillance. He developed irritability which in turn lead to violent and aggressive behavior. He used to remain very restless, moved to and fro within his house. He heard voices and conversations, talking about him and his family

members. Those voices and conversations were derogatory and persecutory in nature. Some of the voices he could recognize as his friends and others as unknown. Later he developed self-muttering as he tried to communicate with those voices.

On mental status examination, he was found aloof, isolated and restless. Constant self-muttering was present. Prominent delusions of persecution and reference were found. He had third-person auditory hallucinations and his insight was impaired. He was diagnosed as a case of schizophrenia. Pharmacotherapy was initiated with oral second-generation antipsychotic, risperidone. Initial dose given was 4mg/day which was increased gradually. After 4 weeks at a dose of 12mg/day, the patient developed extra-pyramidal side effects (EPSE) in the form of tremor and dysphasia. As no improvement was seen, antipsychotic was shifted from risperidone to quetiapine. As per guidelines, the dose of quetiapine was increased gradually to 750mg/day to obtain expected response. As there was no responseafter 3 weeks of treatment withquetiapine, oral olanzapine was prescribed. With the maximum dose of olanzapine (20mg/day), no improvement of psychotic symptoms was gained in another 2 weeks. Patient was still having florid hallucinations and delusions.

With no response after administration of three antipsychotic drugs at optimum doses for adequate time period, the diagnosis was labeled as “Treatment-resistant schizophrenia”. Oral clozapine was considered as the next medication according to treatment guidelines for resistant schizophrenia. Initial dose given was 12.5mg on first day, 25mg in divided doses on the following day and then gradually doses were increased.After 16 days of clozapine treatment at 300mg/day in divided doses improvementwas observed. Hearing of voices, suspiciousness and self-muttering started to reduce. In the following 5 weeks, psychotic symptoms subsided completely. No hallucination or delusion was present. Patient was observed with the same dose (300mg/day) for the next two weeks before discharge. During that time the patient was completely stable. At present the patient is continuing medication and is on regular follow up. No relapse of any symptoms has been noted yet.

Discussion

Schizophrenia is a severe and chronic psychiatric disorder characterized by disturbances in thought, perception and behavior. It involves a range of cognitive, behavioral and emotional symptoms. There is no simple physical or laboratory investigation available for schizophrenia and diagnosis involves the recognition of a constellation of symptoms negatively impacting personal, social or occupational functioning.

The median lifetime prevalence of schizophrenia is approximately 4.0 per 1000 population.The features of the disorder typically emerge between mid-teens and mid-thirties, with peak age of onset of first psychotic episode in the early to mid-twenties for males and late twenties for females.[2] Gradual changes in thinking, mood and social functioning often begin before the first episode of psychosis, usually starting in mid-adolescence. Schizophrenia can be seen in younger children, but it is usually rare before adolescence.

The DSM-5 outlines the criteria to make a diagnosis of schizophrenia. The key criteria are presence of two or more of the symptoms 1. delusions 2. hallucinations 3. disorganized speech (e.g. frequent derailment or incoherence) 4. grossly disorganized or catatonic behavior 5. negative symptoms (i.e., diminished emotional expression or avolition) for at least a one-month (or longer) period of time and at least one of them must be 1, 2 or 3.

Treatment-resistant schizophrenia is defined as the persistence of symptoms despite ≥2 trials of antipsychotic medications at adequate dose and duration with documented adherence.[3,4] It occurs in up to 34% of patients with schizophrenia.[1,5,7] Although persistent symptoms may be negative or cognitive,[3] persistence of positive symptoms is generally one of the defining features of treatment-resistance.[8] Epidemiological data have revealed that male gender,[9,11] early age of onset of symptoms,[12,14] positive family history of schizophrenia,[15,16] obstetric complications,[17] lack of mood symptoms,[18] severe and prolonged premorbid manifestations,[10,16,19,20] longer period of untreated psychosis,[21,22] prominent negative and cognitive symptoms,[23,24] presence of neurological soft signs, abnormal involuntary movements[25] and low level of

social functioning[26] are associated with treatment resistance.

Many of the adverse effects of clozapine are dose dependent and associated with the speed of titration. These tend to be more common and severe at the beginning of treatment. Very rarely, even standard maintenance doses could prove fatal in clozapine-naïve subjects.[27] For minimizing the problems, it is important to start at a very low dose and increase slowly. Table 1 shows the dose titration schedule of clozapine used in the management of the patient.

Table 1: Dose titration schedule for clozapine

Day	Morning dose (mg)	Evening dose (mg)
1	-	12.5
2	12.5	12.5
3	25	25
4	25	25
5	25	50
6	25	50
7	50	50
8	50	75
9	75	75
10	75	100
15	150	150
20	200	200
28	200	250

Conclusions

Clozapine is a unique antipsychotic medication as it is the only evidence-based treatment for treatment-resistant schizophrenia[28,30] with 60–70% of those treated showing a response.[31] Although its unique efficacy is well recognized, clozapine is still under-prescribed in most part of the world. A good number of studies clearly show that many a time it is only used after a long delay of several years.[32] The reasons for this may be the fear of side effects, and the inconvenience of therapeutic blood monitoring. This means that many patients who could get benefit from clozapine early in the course of illness are not prescribed in due time.[33,34] This causes lengthening of suffering of patients and it worsens the future prognosis. Moreover, patients with treatment-resistant schizophrenia are often treated with non-evidence based, highly toxic, high-dose antipsychotics and polypharmacy.[32] When clozapine is prescribed, it renders a significant transformation of the disease, improving psychotic symptoms and overall functioning of the patient within a short span of time.

Md Inamul Islam, Graded Specialist in Psychiatry, Combined Military Hospital (CMH), Rangpur, Bangladesh; **Md Kamrul Hassan,** Classified Specialist in Psychiatry, CMH, Dhaka, Bangladesh; **Roksana Arshed,** Dental Surgeon, North Military Medical Complex, Jahra, Kuwait; **AHM Kazi Mostafa Kamal,** Classified Specialist in Psychiatry, CMH, Dhaka, Bangladesh; **Golam Ferdous,** Commandant, CMH, Rangpur, Bangladesh.

Correspondence: Md Inamul Islam, Graded Specialist in Psychiatry, Department of Psychiatry, Combined Military Hospital (CMH), Rangpur, Bangladesh.
Email: inam.irad@gmail.com

How to cite this article: Islam MI, Hassan MK, Arshed R, Kamal AHMKM, Ferdous G. A young patient with treatment-resistant schizophrenia: a case study. *Arch NIMH* 2020; 3(1): 35-8.

Received: 31 July 2020, revised 23 August 2020, accepted 01 Sep 2020

References

1. Meltzer HY. Treatment-resistant schizophrenia– the role of clozapine. *Curr Med Res Opin* 1997; 14(1):1–20.
2. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med* 2005; 2: e141.
3. Howes OD, McCutcheon R, Agid O, Bartolomeis AD, Beveren NJMV, Birnbaum ML, et al. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group consensus guidelines on diagnosis and terminology. *Am J Psychiatry* 2017; 174: 216–29.
4. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 2004; 161(2): 1–56.
5. Demjaha A, Lappin JM, Stahl D, Patel MX, MacCabe JH, Howes OD, et al. Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors. *Psychol Med* 2017; 57: 1981–9.
6. Lally J, Ajnakina O, Forti MD, Trotta A, Demjaha A, Kolliakou A, et al. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychol Med* 2016; 46: 3231–40.
7. Meltzer HY, Rabinowitz J, Lee MA, Cola PA, Ranjan R, Findling RL, et al. Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. *Am J Psychiatry* 1997; 154: 475–82.
8. Farooq S, Agid O, Foussias G, Remington G. Using treatment response to subtype schizophrenia: proposal for a new paradigm in classification. *Schizophr Bull* 2013; 39: 1169–72.
9. Lieberman J, Jody D, Geisler S, Alvir J, Loebel A, Szymanski S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. *Arch Gen Psychiatry* 1993; 50: 369–76.
10. Robinson DG, Woerner MG, Alvir JM, Geisler S, Koreen A, Sheitman B, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 1999; 156: 544–9.

11. Szymanski S, Lieberman JA, Alvir JM, Mayerhoff D, Loebel A, Geisler S, et al. Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. *Am J Psychiatry* 1995; 152: 698–703.
12. Meltzer HY, Rabinowitz J, Lee MA, Cola PA, Ranjan R, Findling RL, et al. Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. *Am J Psychiatry* 1997; 154: 475–82.
13. Lieberman JA, Safferman AZ, Pollack S, Szymanski S, Johns C, Howard A, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. *Am J Psychiatry* 1994; 151: 1744–52.
14. Lieberman JA, Kane JM, Safferman AZ, Pollack S, Howard A, Szymanski S, et al. Predictors of response to clozapine. *J Clin Psychiatry* 1994; 55: 126–8.
15. Malaspina D, Goetz RR, Yale S, Berman A, Friedman JH, Tremeau F, et al. Relation of familial schizophrenia to negative symptoms but not to the deficit syndrome. *Am J Psychiatry* 2000; 157: 994–1003.
16. Bartko G, Frecska E, Horvath S, Zador G, Arato M. Predicting neuroleptic response from a combination of multilevel variables in acute schizophrenic patients. *Acta Psychiatr Scand* 1990; 82: 408–12.
17. Alvir JM, Woerner MG, Gunduz H, Degreef G, Lieberman JA. Obstetric complications predict treatment response in first-episode schizophrenia. *Psychol Med* 1999; 29: 621–27.
18. Lieberman JA, Alvir JM, Koreen A, Geisler S, Chakos M, Sheitman B, et al. Psychobiologic correlates of treatment response in schizophrenia. *Neuropsychopharmacology* 1996; 14: 13–21.
19. Wieselgren IM, Lindstrom LH. A prospective 1-5year outcome study in first-admitted and readmitted schizophrenic patients; relationship to heredity, premorbid adjustment, duration of disease and education level at index admission and neuroleptic treatment. *Acta Psychiatr Scand* 1996; 93: 9–19.
20. Bailer J, Brauer W, Rey ER. Premorbid adjustment as predictor of outcome in schizophrenia: results of a prospective study. *Acta Psychiatr Scand* 1996; 93: 368–77.
21. Lieberman JA, Alvir JM, Woerner M, Degreef G, Bilder RM, Ashtari M, et al. Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. *Schizophr Bull* 1992; 18: 351–71.
22. Edwards J, Maude D, McGorry PD, Harrigan SM, Cocks JT. Prolonged recovery in first-episode psychosis. *Br J Psychiatry Suppl* 1998; 172: 107–16.
23. Kinon BJ, Kane JM, Chakos M, Munne R. Possible predictors of neuroleptic-resistant schizophrenic relapse: influence of negative symptoms and acute extrapyramidal side effects. *Psychopharmacol Bull* 1993; 29: 365–9.
24. Kolakowska T, Williams AO, Jambor K, Ardern M. Schizophrenia with good and poor outcome. III. Neurological “soft” signs, cognitive impairment and their clinical significance. *Br J Psychiatry* 1985; 146: 348–57.
25. Schulz SC, Conley RR, Kahn EM. Nonresponders to neuroleptics: a distinct subtype. In: Tamminga CA, ed. *Schizoprenia Scientific Progress* Oxford,UK: Oxford University Press. 1989: 341–50.
26. Wiersma D, Wanderling J, Dragomirecka E, Ganev K, Harrison G, an der Heiden W, et al. Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European centres. *Psychol Med* 2000; 30: 1155–67.
27. Stanworth D, Hunt NC, Flanagan RJ. Clozapine - a dangerous drug in a clozapine-naïve subject. *Forensic SciInt* 2011; 214: c23-5
28. *Psychosis and Schizophrenia in Adults: Treatment and Management* (Clinical Guideline 178) London: Royal College of Psychiatrists, 2014.
29. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry* 2001; 158(4): 518–26.
30. Wahlbeck K, Cheine M, Essali A, Adams C. Evidence of clozapine’s effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. *Am J Psychiatry* 1999; 156(7): 990–9.
31. Meltzer HY. Treatment of the neuroleptic-nonresponsive schizophrenic patient. *Schizophr Bull* 1992; 18(3): 515–42.
32. Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br J Psychiatry* 2012; 201(6): 481–5.
33. Hayes RD, Downs J, Chang CK, Jackson RG, Shetty H, Broadbent M, et al. The effect of clozapine on premature mortality: an assessment of clinical monitoring and other potential confounders. *Schizophr Bull* 2015; 41(3): 644–55.
34. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, et al. 11-Year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009; 374(9690): 620–7.