



Letter to the Editor

Safety of clozapine in patient with treatment resistant schizophrenia & asymptomatic constitutional macrothrombocytopenia (Harris syndrome)



Dear Editor,

1. Introduction

Serious haematological side effects, like agranulocytosis, neutropenia, thrombocytopenia, eosinophilia, have been associated with clozapine use (Lee et al., 2015; Munro et al., 1999). Despite the low incidence of haematological side effects (Myles et al., 2018), clozapine is reportedly underutilized or avoided fearing haematological and metabolic side effects (Sreeraj et al., 2017). There are individuals with low haematological parameters constitutionally (e.g., Benign ethnic neutropenia (BEN) and Harris platelet syndrome (asymptomatic constitutional macrothrombocytopenia). Current evidence reports no increased risk of severe neutropenia in individuals with BEN during Clozapine treatment (Richardson et al., 2016) and recommendations have been proposed for the same (Manu et al., 2016). Harris platelet syndrome is a clinical entity characterized by mild to severe thrombocytopenia, giant platelet with normal platelet functions without any bleeding manifestations with geographical predilection (seen in people from eastern states of India) (Naina and Harris, 2008; Naina and Harris, 2010). On an extensive literature review, no case reports, guidelines or recommendations were available for individuals with Harris platelet syndrome with concurrent treatment with clozapine. In this report, we describe successful treatment of a patient with schizophrenia with co-morbid Harris platelet syndrome with clozapine.

2. Case description

A 62-year-old married lady, homemaker, from the eastern part of India, had presented with an illness of 30 years duration, insidious in onset, continuous course characterised by unprovoked irritability, delusion of reference, delusion of persecution, 2nd person auditory hallucination, anhedonia, avolition along with cognitive decline leading to significant bio-socio-occupational dysfunction. She attained menopause at the age of 45 years and had been on oral hypoglycaemic treatment for Type 2 diabetes since 20 years. There was no family history of mental illness. Previously, she had been treated with adequate trials of Quetiapine, Olanzapine, Aripiprazole, Lurasidone, Risperidone and Haloperidol. Detailed general physical examination revealed Body mass index (BMI) of 30.2 Kg/m² and on MRI Brain showed diffuse cerebral and cerebellar atrophy. On mental status examination, she appeared to have auditory hallucination (commanding type), delusion of reference and persecution with absent insight. A diagnosis of Schizophrenia (DSM-5) was made and treatment resistant was established as per modified Kane' criteria. Clozapine trial was considered. Pre-clozapine workup revealed low platelet count (45000/ μ l) with low haemoglobin level (for which supplements were

provided). Peripheral smear done baseline revealed microcytic hypochromic anaemia with neutrophilia and thrombocytopenia with giant platelets. Haematologist opinion was sought and on review of her previous medical records, she was found to have chronic thrombocytopenia without bleeding manifestations. A co-morbid diagnosis of ethnic thrombocytopenia (Harris syndrome) was made after ruling out probable differential diagnoses. Clozapine trial was initiated and the dose was gradually increased up to 150 mg with regular monitoring of haematological parameters (especially platelet count) and side effects. Serum clozapine level on stable dose of 150 mg/day was 319 ng/ml. No further decline in the platelet count was noted during the hospital stay with platelet count ranging between 65000–82000/ μ l (Table 1) without bleeding manifestations (with Absolute Neutrophil Count (ANC) above 4000/ μ l). Overall improvement of 30% was noted in the psychotic symptoms (Brief Psychiatric Rating Scale BPRS scale) at 4 weeks and the patient was discharged. In subsequent follow-ups, further improvement in psychopathology was observed with an improvement in platelet counts.

3. Discussion

This report suggests the safety of clozapine in a schizophrenia patient with co-morbid Harris platelet syndrome. Harris platelet syndrome is usually an inherited asymptomatic and under-recognised clinical entity which generally does not require any intervention but inappropriately treated with corticosteroids or splenectomy (Naina and Harris, 2008). It is found to be associated with MYH9 mutation and recognised to be prevalent in as high a 1/3rd of population in certain parts of India (Naina et al., 2002).

In this patient, Harris syndrome was incidentally diagnosed during the pre-clozapine evaluation with an apprehension of a possible worsening with clozapine. A close monitoring of platelet count over initial 6 months showed no further decline in platelet counts. Rather, normalisation of counts were noted from 6th week of clozapine initiation. The patient also showed good clinical response to clozapine with stable absolute neutrophil counts. The underlying mechanism for this normalization of platelet count is unclear and role of clozapine in this process needs to be determined. No specific treatment was provided for Harris platelet syndrome.

This case report suggests that underutilization or avoidance of clozapine fearing haematological side effects may be unwarranted, provided a close monitoring. It is of further importance in ethnically prevalent benign conditions like BEN and Harris syndrome to avoid depriving a large section of patients requiring clozapine. Nevertheless, systematic studies are required to further understand the effect and safety of clozapine use in schizophrenia patients with co-morbid blood dyscrasias, which would alleviate the “clozaphobia” in managing this population.

<https://doi.org/10.1016/j.ajp.2019.09.012>

Received 12 August 2019

1876-2018/© 2019 Elsevier B.V. All rights reserved.

Table 1
Platelet count serial assessment.

S. No	Assessment day	Platelet Count (x1000/ul)
1.	1 month before Clozapine initiation	48
2.	Day 1	80
3.	Day 5	65
4.	Day 12	78
5.	Day 19	82
6.	Day 26	74
7.	Day 45	155
8.	Day 60	180
9.	Day 75	110
10.	Day 90	56
11.	Day 120	150
12.	Day 150	180
13.	Day 180	120

Funding Source Declaration

No funding or research grants was received in the course of study, research or assembly of the manuscript titled “SAFETY OF CLOZAPINE IN PATIENT WITH TREATMENT RESISTANT SCHIZOPHRENIA & ASYMPTOMATIC CONSTITUTIONAL MACROTHROMBOCYTOPENIA (HARRIS SYNDROME)”

Declaration of Competing Interest

None.

Acknowledgement

Nil.

References

- Lee, J., Takeuchi, H., Fervaha, G., Powell, V., Bhaloo, A., Bies, R., et al., 2015. The effect of clozapine on hematological indices: a 1-year follow-up study. *J. Clin. Psychopharmacol.* 35 (5) 510–6.
- Munro, J., O'Sullivan, D., Andrews, C., Arana, A., Mortimer, A., Kerwin, R., 1999. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. *Br. J. Psychiatry* 175, 576–580.
- Myles, N., Myles, H., Xia, S., Large, M., Kisely, S., Galletly, C., et al., 2018. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatr. Scand.* 138 (2), 101–109.
- Sreeraj, V.S., Dinakaran, D., Nagendrappa, S., Rao, N.P., Kesavan, M., Varambally, S., et al., 2017. Clozapine: is avoidance of clozapine in diabetes warranted? *Asian J. Psychiatr.* 28, 142–145.
- Richardson, C.M., Davis, E.A., Vyas, G.R., DiPaula, B.A., McMahon, R.P., Kelly, D.L., 2016. Evaluation of the safety of clozapine use in patients with benign neutropenia. *J. Clin. Psychiatry* 77 (11) e1454–e9.
- Manu, P., Sarvaiya, N., Rogozea, L.M., Kane, J.M., 2016. Correll CU. Benign ethnic neutropenia and clozapine use: a systematic review of the evidence and treatment recommendations. *J. Clin. Psychiatry* 77 (7), e909–16.
- Naina, H.V., Harris, S., 2008. Harris platelet syndrome—underdiagnosed and unrecognized. *Arch. Pathol. Lab. Med.* 132 (10), 1546 author reply.
- Naina, H.V., Harris, S., 2010. Platelet and red blood cell indices in Harris platelet syndrome. *Platelets* 21 (4), 303–306.
- Naina, H.V., Nair, S.C., Daniel, D., George, B., Chandy, M., 2002. Asymptomatic constitutional macrothrombocytopenia among West Bengal blood donors. *Am. J. Med.* 112 (9), 742–743.

Harsh Pathak, Dinakaran Damodharan*, Pavithra Jayasankar, Vanteemar S. Sreeraj, Ganesan Venkatasubramanian
Department of Psychiatry, National Institute of Mental Health And NeuroSciences (NIMHANS), Bengaluru, India
E-mail address: dina.nimhans@gmail.com (D. Damodharan).

* Corresponding author.