

**CASE REPORT**

## Allergic Cutaneous and Visceral Angioedema Secondary to Clozapine: A Case Report

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### ABSTRAK

*Laporan ini menerangkan kejadian tindak balas ubat clozapine yang jarang berlaku, iaitu alahan kutaneus dan angioedema visera, pada seorang pesakit skizofrenia yang tidak menunjukkan kesan terhadap rawatan ubat-ubatan yang biasa. Kami melaporkan seorang pesakit skizofrenia rintang-rawatan yang mengalami masalah alahan pada kulit dan sistem gastro-usus sejourus beliau menerima rawatan ubat clozapine. Beliau kemudiannya dirawat dengan kombinasi beberapa ubat-ubatan, namun masih mengalami gejala-gejala residual. Manifestasi alahan kepada ubat clozapine and strategi perawatan dibincangkan di dalam laporan kes ini. Terdapat keperluan yang mendesak bagi penghasilan ubat psikotropik yang setanding clozapine untuk merawat pesakit, memandangkan masalah alahan ubat seperti laporan kes ini.*

*Kata kunci: alahan, angioedema, clozapine, skizofrenia*

### ABSTRACT

This report stresses on the occurrence of a rare adverse reaction to clozapine, i.e. allergic cutaneous and visceral angioedema, in a patient with treatment resistant schizophrenia (TRS). We report the case of a schizophrenic patient who was resistant to treatment and developed an allergic reaction involving her skin and gastro-intestinal system upon the commencement of clozapine. She was then treated with a combination pharmacotherapy which left some residual symptoms. The manifestation of allergic reactions to clozapine and its management strategies are discussed in the paper. There is a pressing need to develop a new psychotropic which is on par with clozapine.

Keywords: allergy, angioedema, clozapine, schizophrenia

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## INTRODUCTION

Clozapine was once withdrawn from the market in 1978 due to its life-threatening adverse reaction (Wahlbeck et al. 2000). However, it was reintroduced back in 1990 for individuals with schizophrenia who were resistant to typical neuroleptics (Warnez & Alessi-Severini 2014). Generally, clozapine is proven to be superior to other anti-psychotics (Leucht et al. 2009) and its role is also found in other psychiatric disorders, possibly mania (Ng et al. 2013). Clozapine is well accepted and tolerated in most individuals (Leucht et al. 2013), except few adverse reactions which limits its use (McIlwain et al. 2011; Warnez & Alessi-Severini 2014). To date, clozapine is the only drug licensed for for the treatment of treatment-resistant schizophrenia (TRS) (Kane & Corell 2016).

Angioedema, a systemic allergic reaction to clozapine has not been reported widely. We aim to report a case of allergic angioedema involving skin and gastrointestinal system secondary to clozapine in an individual with treatment resistant schizophrenia (TRS). We highlight the need to develop an alternative drug which is as effective as clozapine in treating this group of patients.

## CASE REPORT

SF, a 22-year-old lady who was diagnosed with schizophrenia 3 yrs earlier, was hospitalized in February 2014 due to relapse of her illness with symptoms of auditory hallucination, persecutory delusion, insomnia,

irritability and aggression, despite being on antipsychotic treatment. Since the onset of her illness, she had never achieved full symptom remission despite being treated with adequate dosage and duration of a few anti-psychotics. She had frequent relapses with aggression as the main presenting symptom which typically required hospitalization. Her first medication was the oral risperidone up to 4mg daily. Due to persisting symptoms and possibility of non-adherence to medication, intramuscular (IM) depot flupenthixol 20 mg was subsequently introduced monthly at first and later fortnightly as symptom control was still not adequate with monthly injection. She who was not known to have any drug allergy in the past.

The diagnosis was revised to treatment-resistant schizophrenia and clozapine was initiated. Her symptoms improved significantly and she was discharged following her parent's request with a dose of 50 mg twice daily. She developed urticaria in the next few days which waxed and waned, and it was not reported to the attending doctor on her subsequent follow up. Clozapine dose was further increased another 25 mg during this visit. She developed mild fever without other symptoms of infections. She visited a general practitioner and she was given tablet paracetamol. Subsequently, she developed periorbital oedema, generalized itchy rashes, loss of appetite, abdominal pain, vomiting and lethargy. She had no respiratory failure. She was admitted to the medical ward. Eosinophilia (10.6%) was detected 3 days after hospitalization. She was

diagnosed with angioedema secondary to clozapine. Her family members objected to the suggestion for a skin prick test for clozapine to confirm the diagnosis. She was successfully treated with regular intravenous hydrocortisone and oral loratadine. She was discharged medically after 3 days.

Then clozapine was withheld and she was started on Tablet Haloperidol. Subsequently she was tried on quetiapine 800 mg daily with combination of haloperidol 5 mg daily and IM flupenthixol 40 mg 3 weekly. Haloperidol was switched later to tablet risperidone and titrated up to 4 mg daily. She reported residual symptoms all the times despite optimization with augmentation and compliance was assured.

## DISCUSSION

Clozapine is the only drug licensed for the treatment of TRS (O'Brien 2004). Despite 30-50% significant clinical response to clozapine for patients with TRS (Chakos et al. 2001), the efficacy of clozapine is limited by certain life-threatening adverse effects, e.g. hypersensitivity, which impose challenges in the management in these group of patients. There are reports on allergic asthmatic reactions (Stoppe et al. 1992), allergic vasculitis (Penaskovic et al. 2005), angioneurotic edema (Mishra et al. 2007) and a case of late-onset angioedema (Tatar et al. 2014) secondary to clozapine.

The understanding of immunological mechanism of allergic reactions to clozapine is based on the hapten hypothesis which involves the

hypersensitivity to the autologous protein from the chemically reactive metabolites of the drug (Park et al. 2001). This is a type I hypersensitivity reaction which is mediated by Ig E antibodies (Lamer et al. 2010). The reaction can be systemic or local. The local reactions can be manifested by cutaneous swelling, nasal or conjunctival discharge, bronchial asthma and gastroenteritis. The systemic reaction can present with anaphylaxis and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome (Warrington & Silviu-Dan 2011). In this case, she developed recurrent episodes of angioedema involving the swelling of skin and possibly mucosal of gastrointestinal system (as there was no objective investigation e.g. colonoscopy, biopsy, done to her).

Sensitization to clozapine is required before a series of reactions to take place. Following sensitization, the initial response will occur within seconds and subsequently subsides within an hour, while a late phase takes 8 to 12 hrs to develop (Murphy et al. 2008). The patient had developed transient urticaria following clozapine administration in ward. However, the presentation was subtle and went unreported. She had an exacerbation of allergic symptoms after clozapine dose was increased a week later.

Both phases involve powerful primary and secondary mediators which are responsible in the production of the clinical symptoms. The IL-1 $\beta$ , TNF- $\alpha$  and GM-CSF regulate the activation, maturation and migration of professional antigen presenting cells (APC), e.g. epidermal Langerhan's cells,

and mast cells. The activated APCs and helper T cells in turn produce cytokines, e.g. IL-12 and IL-4 to regulate the activation, proliferation and differentiation of drug hapten specific T-lymphocytes, which the latter elicit an inflammatory reaction. Histamine and leukotrienes released from mast cells play important roles in Ig E mediated hypersensitivity reaction. The late recruitment of eosinophils which directly activate mast cells and sustain the immunological reaction (Park et al. 2000).

Rechallenge of clozapine has been reported in the case of clozapine-induced leucopenia (Dunk et al. 2006; Stanulovic et al. 2013). However, there is no literature which discussed rechallenging clozapine in the case of allergic reaction. The general principle of management of drug allergy is to withhold the offending medication (Frew 2011). Only when there is definite medical need for the particular medication, there is a strategy of induction desensitization or graded challenge (Castells 2006). The strategy of induction desensitization is discussed in hypersensitivity to antibiotics (Gruchalla 1998) and aspirin (Wong et al. 2000) but was never discussed in case of clozapine.

Among other strategies in clozapine intolerant schizophrenic patients, there is combination or augmentation of various psychotropics and electroconvulsive therapy (Porcelli et al. 2012). There are reports on high-dose aripiprazole (Tripathi et al. 2015) and high-dose quetiapine (Chandrappa & Ho 2012) in cases of TRS intolerant of clozapine. In this case, she was

subsequently maintained on high-dose quetiapine which controlled her illness but few psychotic symptoms still remained.

Allergy to clozapine in TRS renders psychiatrist no equivalent choice in subsequent management. There is a dire need for new development of pharmacological agent which has similar efficacy to clozapine.

## REFERENCES

- Castells, M. 2006. Desensitization for drug allergy. *Curr Opin Allergy Clin Immunol* 6(6): 476-81.
- Chakos, M., Lieberman, J., Hoffman, E., Bradford, D., Sheitman, B. 2001. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry* 158(4): 518-26.
- Chandrappa, P., Ho, L. 2012. Case reports of patients with treatment-resistant schizophrenia and related psychotic disorders intolerant to clozapine responding to high doses of quetiapine. *Ther Adv Psychopharmacol* 2(5): 207-9.
- Dunk, L.R., Annan, L.J., Andrews, C.D. 2006. Rechallenge with clozapine following leucopenia or neutropenia during previous therapy. *Br J Psychiatry* 188: 255-63.
- Frew, A. 2011. General principles of investigating and managing drug allergy. *Br J Clin Pharmacol* 71(5): 642-6.
- Gruchalla, R.S. 1998. Acute drug desensitization. *Clin Exp Allergy* 28 Suppl 4: 63-4.
- Kane, J.M., Corell, C., U. 2016. The Role of Clozapine in Treatment-Resistant Schizophrenia. *JAMA Psychiatry* 73(3): 187-8.
- Lamer, V., Lipozencic, J., Turcic, P. 2010. Adverse cutaneous reactions to psychopharmaceuticals. *Acta Dermatovenerol Croat* 18(1): 56-67.
- Leucht, S., Cipriani, A., Spinelli, L., Mavridis, D., Orey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R., Kissling, W., Stapf, M.P., Lässig, B., Salanti, G., Davis, J.M. 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 382(9896): 951-62.
- Leucht, S., Corves, C., Arbter, D., Engel, R.R., Li, C., Davis, J.M. 2009. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 373(9657): 31-41.

- McIlwain, M.E., Harrison, J., Wheeler, A.J., Russell, B.R. 2011. Pharmacotherapy for treatment-resistant schizophrenia. *Neuropsychiatr Dis Treat* 7: 135-49.
- Mishra, B., Sahoo, S., Sarkar, S., Akhtar, S. 2007. Clozapine-induced angioneurotic edema. *Gen Hosp Psychiatry* 29(1): 78-80.
- Murphy, K., Travers P., Walport, M. 2008. Chapter 13: Allergy and Hypersensitivity. In Janeway's Immunobiology. 7th edition. New York: Garland Science; 555-97.
- Ng, Y.P., Kassim, S.M., Maniam, T. 2013. Treatment-Emergent Hypomania or Bipolar Disorder? A Case Report. *ASEAN Journal of Psychiatry* 14(2): 157-60.
- O'Brien, A. 2004. Starting clozapine in the community: a UK perspective. *CNS Drugs* 18(13): 845-52.
- Park, B.K., Kitteringham, N.R., Powell, H., Pirmohamed, M. 2000. Advances in molecular toxicology-towards understanding idiosyncratic drug toxicity. *Toxicology* 153(1-3): 39-60.
- Park, B.K., Naisbitt, D.J., Gordon, S.F., Kitteringham, N.R., Pirmohamed, M. 2001. Metabolic activation in drug allergies. *Toxicology* 158(1-2): 11-23.
- Penaskovic, K.M., Annamraju, S., Kraus, J.E. 2005. Clozapine-induced allergic vasculitis. *Am J Psychiatry* 162(8): 1543.
- Porcelli, S., Balzarro, B., Serretti, A. 2012. Clozapine resistance: augmentation strategies. *Eur Neuropsychopharmacol* 22(3): 165-82.
- Stanulovic, V., Venegoni, M., Edwards, B. 2013. Intentional rechallenge: does the benefit outweigh the risk? *Drug Saf* 36(3): 155-61.
- Stoppe, G., Muller, P., Fuchs, T., Ruther, E. 1992. Life-threatening allergic reaction to clozapine. *Br J Psychiatry* 161: 259-61.
- Tatar, Z.B., Oflaz, S., Baran, B. 2014. A case of late-onset angioedema associated with clozapine and redevelopment of angioedema with olanzapine. *J Clin Psychopharmacol* 34(4): 523-5.
- Tripathi, P., Goyal, P., Kumar, D., Prakash, O. 2015. High doses of aripiprazole therapy for a patient with treatment-resistant schizophrenia responsive to, but intolerant of, clozapine. *Aust N Z J Psychiatry* 49(2): 185.
- Wahlbeck, K., Cheine, M., Essali, M.A. 2000. Clozapine versus typical neuroleptic medication for schizophrenia. *Cochrane Database Syst Rev* (2): CD000059.
- Warnez, S., Alessi-Severini, S. 2014. Clozapine: a review of clinical practice guidelines and prescribing trends. *BMC Psychiatry* 14: 102.
- Warrington, R., Silviu-Dan, F. 2011. Drug allergy. *Allergy Asthma Clin Immunol* 7 Suppl 1: S10.
- Wong, J.T., Nagy, C.S., Krinzman, S.J., Maclean, J.A., Bloch, K.J. 2000. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. *J Allergy Clin Immunol* 105(5): 997-1001.

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