G-CSF mediated neutrophil augmentation in a unique case of comorbid idiopathic Parkinson’s disease and treatment-resistant schizophrenia on clozapine

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Abstract: Treatment of psychosis in Parkinson’s disease (PD) is challenging; pharmacological options are limited, with clozapine considered most effective. The risk of agranulocytosis restricts the use of clozapine, but, where this occurs, cautious re-challenge with granulocyte stimulating factor can be successful. We present a unique case of a patient who developed early-onset PD on a background of antecedent treatment-resistant schizophrenia, who had been treated effectively with clozapine for over 15 years with no adverse events. However, during a hospital admission intended to optimise her Parkinsonian medications, she developed persistent neutropenia necessitating clozapine discontinuation. Numerous attempts to re-challenge with clozapine failed until augmentation with lithium and G-CSF was trialled. Two doses of G-CSF led to a sustained increase in the neutrophil count, allowing the continuation of clozapine therapy in the 1 year of follow up. This illustrates the potential for G-CSF to be used to facilitate clozapine use in a patient population not described previously. Neutrophil augmentation allowed the sustained continuation of this effective therapy, treating her psychotic symptoms without detriment to her movement disorder. We suggest that G-CSF might be considered as a treatment option in other cases where clozapine-associated neutropenia obstructs its use.

Keywords: agranulocytosis, clozapine, G-CSF, Parkinson’s, schizophrenia

Received: 9 June 2020; revised manuscript accepted: 10 August 2020.

Introduction
Parkinson’s disease (PD) is a progressive neurodegenerative disorder, severely affecting the lives of patients and their families. Neuropsychiatric symptoms are non-motor symptoms commonly occurring in its natural history, even at the early stages of disease onset. Their presentation is varied, but most commonly includes depression, anxiety, apathy, fatigue, and psychotic symptoms, all of which may occur independently but frequently overlap. Depending on the definition used, psychotic symptoms may affect up to 50% of treated PD patients and typically manifest as visual hallucinations, illusions, passage hallucinations, and a feeling of presence beside or behind the patient. Auditory hallucinations can occur in the context of visual hallucinations, as can delusions. Although psychosis in PD is associated most commonly with dopaminergic medications aimed at treating the motor symptoms, it can also be the complex outcome of several disease-related factors. However, in rare cases, the psychosis in PD can be associated with a primary psychotic illness such as schizophrenia. In a few case reports, co-existing idiopathic PD and schizophrenia has been confirmed post-mortem, although in vivo motor symptoms were often misattributed to side effects from neuroleptics, while in fact it may have been the combined effect of the former with the underlying PD. Nevertheless, this co-morbidity...
remains uncommon; the hypodopaminergic transmission inherent to PD is unlikely to coexist with the hyperdopaminergic transmission in the mesolimbic pathway that is hypothesized to mediate the positive symptoms of schizophrenia.\textsuperscript{10,11} Furthermore, the typical psychotic symptoms seen in PD often differ from the classic symptoms in schizophrenia, with a greater representation of visual hallucinations and retained insight.\textsuperscript{12} It has been suggested that psychotic symptoms in PD arise due to a disruption in dopaminergic pathways leading to supersensitivity of striatal dopaminergic neurons, which causes imbalance in serotonin, acetylcholine and dopamine.\textsuperscript{13} Other studies have suggested a common pathway between PD and psychosis development as illustrated by schizotypal traits often present in PD.\textsuperscript{14}

Pharmacological management of psychosis in PD with antipsychotics is complicated by their inhibitory effect on dopamine, which affects motor function, and hence they are used only when other options have failed. Double-blind placebo-controlled trials have evaluated the impact of a number of atypical antipsychotics in treating psychotic symptoms. Olanzapine use is not advised in PD; double-blind controlled trials have consistently shown it to be both ineffective in treating psychosis in PD while also causing a deterioration in motor function.\textsuperscript{12,15–17} In contrast, quetiapine has minimal effect on motor symptoms and is often used unlicensed in many European countries despite limited efficacy.\textsuperscript{18}

Clozapine is an atypical antipsychotic licensed in the United Kingdom (UK) for treatment of psychosis in PD. Its unique receptor profile as a 5-HT2A and D4 receptor antagonist with weak D2 blocking properties allows for effective control of psychotic symptoms without worsening motor function.\textsuperscript{18} Its use is, however, limited by the risk of inducing neutropenia and agranulocytosis so requires strict monitoring. Neutropenia is defined as an absolute neutrophil count less than $1.5 \times 10^9$/l and agranulocytosis less than $0.5 \times 10^9$/l. Life-threatening agranulocytosis occurs in 0.68% of patients within the first year, decreasing by a factor of 10 thereafter.\textsuperscript{19,20} Approved clozapine monitoring systems, where they exist, limit relevant risk. Dose adjustments and/or cessation following a significant drop in neutrophil count may be recommended, yet adjunct pharmacological options aiming to boost neutrophil counts may also be explored when clinically relevant.

A small number of reports have been published dealing with the acute or long-term management of agranulocytosis during clozapine therapy. In particular, granulocyte colony stimulating factor (G-CSF) has been used with good effect to treat clozapine-induced agranulocytosis in schizophrenia.\textsuperscript{21} However, to our knowledge, there is a single prior case report which describes the use of G-CSF for clozapine induced agranulocytosis in PD, clozapine being used in this context to treat the psychosis and tremor secondary to PD.\textsuperscript{22}

We present a second case where use of G-CSF allowed maintenance of clozapine therapy in PD, and the first case to trial this approach in a patient with comorbid schizophrenia and PD.

**Case report**

We present a middle-aged female with comorbid early onset PD on a background of treatment-resistant paranoid schizophrenia. She was diagnosed with paranoid schizophrenia in her early twenties, characterised by severe self-neglect, isolation, paranoid ideation, and thought disorder. She was initially commenced on risperidone but, due to extrapyramidal side effects, this was discontinued after a year. Multiple other oral agents, including olanzapine and trifluoperazine, were trialled before she was initiated on flupentixol decanoate depot due to partial response and non-adherence. She eventually suffered a relapse of her psychosis, and clozapine was commenced. For 15 years, her mental state remained stable on clozapine 500mg and citalopram 40mg daily, with no adverse events. In her early thirties, she developed early onset idiopathic PD, confirmed with dopamine active transporter (DaT) imaging and antipsychotic medication withdrawal and she was prescribed Stalevo (levodopa/carbidopa/entacapone).

In June 2019, she was admitted to general hospital due to a deterioration in her PD, characterised by reduced oral intake and decompensated swallowing secondary to poor compliance with medication. Physical examination revealed profound rigidity, bilateral resting tremor, hypomimia and slow speech, with mental state examination noting paranoid ideation and command auditory hallucinations to self-harm. A drop in neutrophil count to $1.28 \times 10^9$/l resulted in clozapine being withheld for 48h. Rechallenge with clozapine led to another drop in neutrophils from $2.88 \times 10^9$/l to $1.26 \times 10^9$/l. Clozapine was stopped following haematology advice and quetiapine was commenced.
A deterioration in swallowing precipitated a switch to a rotigotine patch for 48 h before enteral co-careldopa could be resumed, and quetiapine was increased to 100 mg twice daily in early July the same year. However, her parkinsonism worsened and quetiapine was discontinued. While her rigidity consequently improved, her mental state deteriorated, with delusional beliefs and auditory hallucinations becoming apparent. This was further complicated by the acquisition of hospital-acquired infection, likely chest related due to an aspiration event, which required antibiotic treatment. A percutaneous endoscopic gastrostomy (PEG) was fitted for administration of nutrition and medications. Clozapine retitration began at the end of July with daily full blood count monitoring. This precipitated another drop in neutrophil count to $0.67 \times 10^9/l$, requiring clozapine cessation with a detrimental effect on her mental state. Following multidisciplinary team discussion, clozapine was restarted at an initial dose of 25 mg daily alongside lithium carbonate 200 mg daily. Clozapine was increased progressively to a total dose of 125 mg daily with a positive impact on psychotic symptoms. However, further drops in neutrophil counts led to a reduction in clozapine dose, which was eventually stopped again when levels fell to $1.24 \times 10^9/l$. Figure 1 charts this fluctuation in neutrophil levels chronologically.

The patient was eventually discharged from general hospital in October on clozapine 50 mg twice daily, lithium carbonate 300 mg twice daily and G-CSF as required. She was scheduled for weekly clozapine blood tests and community mental health team follow up. Since discharge, she has not required any further doses of G-CSF and neutrophil counts have remained stable.

**Discussion**

Clinicians are faced with a significant challenge when attempting to treat psychotic symptoms in PD. Whilst quetiapine has been a popular choice due to its lower side effect profile, clozapine has until recently remained the only antipsychotic with robust evidence for treating psychotic symptoms in PD without exacerbating motor symptoms.23,24
It has been further shown to be superior to other antipsychotics in controlling psychotic symptoms. However, more recently, pimvanserin has emerged as an effective treatment option for PD psychosis without motor function deterioration.

Clozapine therapy is limited by its potential to induce life-threatening agranulocytosis, requiring frequent blood monitoring, although relevant guidelines tend to differ between countries. This is more common within the first 3 months of initiating therapy, in white men aged between 40 and 59 and certain HLA haplotypes. However, our case demonstrates the potential for agranulocytosis to occur many years after first commencing clozapine, highlighting the importance of continued blood monitoring. Interestingly, the only other case to use G-CSF to treat clozapine-induced agranulocytosis in a patient with PD also described a similar delayed neutropenia. While the rate of agranulocytosis does not appear to be increased in PD patients treated with clozapine, further research is needed to explore a potential time-related effect.

Although the mechanism of clozapine-induced agranulocytosis is unclear, evidence suggests that this may be immune-mediated rather than toxic. Myeloid precursors and mature neutrophils may be affected, although given severe neutropenia is not dose-dependent, a direct toxic effect is unlikely. Major histocompatibility complex antigens and heat shock protein variants are believed to be directly involved in determining individual response.

Current practice dictates immediate withdrawal of clozapine with the development of neutropenia, which presents limited alternative treatment options. Lithium has been shown to be effective as an adjunct treatment, augmenting short- and long-term neutrophil counts. Haematology specialist input may be required when considering further options, such as the use of G-CSF. This molecule endogenously stimulates bone marrow production and release of granulocytes and stem cells, and can be produced synthetically for exogenous use where neutrophil counts are low.

Clozapine-induced agranulocytosis has an absolute prevalence of approximately 1–2% and there is no current evidence to suggest that idiopathic PD or PD psychosis are independent risk factors for clozapine-induced neutropenia and agranulocytosis. Although a prospective study is yet to occur, there are a number of reports in the literature of patients who received G-CSF to support clozapine rechallenge after an episode of neutropenia or agranulocytosis. A systematic review found that 75% of patients receiving adjunct G-CSF therapy for agranulocytosis were able to continue clozapine therapy for a minimum of 10 months.

In this case report, neutrophil counts initially dropped to a threshold requiring cessation of clozapine following an unexplained jump in neutrophil levels in the preceding days, during which the patient was clinically well. The only known clinical correlate at this time was insertion of a nasogastric tube. Whether this represents an acute inflammatory response that triggered an immune-mediated reaction resulting in clozapine-induced neutropenia, remains unclear. Subsequent dips in neutrophils occurred proximally thereafter, including following an episode of hospital-acquired infection and sepsis. One could speculate that an immune mediated reaction may therefore have occurred in the context of a pro-inflammatory milieu. Lithium alone was insufficient to maintain neutrophil counts in the patient, but two doses of G-CSF allowed the continuation of clozapine therapy without subsequent neutropenia or further G-CSF requirement in 1 year of follow up.

In summary, we report the case of a patient with comorbid idiopathic PD and schizophrenia, who developed a neutropenia 15 years after being treated with clozapine without adverse event. The delay in this case highlights the importance of continual blood monitoring, while the effective use of adjunct lithium and G-CSF illustrates that clozapine therapy can be maintained despite these issues. Neutrophil augmentation allowed sustained continuation of clozapine, treating psychotic symptoms without detriment to the movement disorder. Given the efficacy of clozapine in managing psychosis in PD, G-CSF presents a valuable option for patients who develop life-threatening agranulocytosis in the context of clozapine use.

Conflict of interest statement
The authors declare that there is no conflict of interest.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.
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