Neuroleptic malignant syndrome in a patient with bipolar depression on stable dose of quetiapine

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ABSTRACT

We report a case of a 37-year-old widow with a diagnosis of bipolar I disorder who presented with catatonia and neuroleptic malignant syndrome (NMS) while in the depressive phase of her illness. The neuroleptic malignant syndrome developed in the context of a stable dose of long-acting quetiapine (300mg) for five years. Her depression and catatonic state were hypothesised as the contributing factors for her NMS. Her catatonic symptoms were initially managed with regular benzodiazepines and she was later given electroconvulsive therapy during her admission. Her NMS improved after five days and her catatonic symptoms fully resolved after the second electroconvulsive therapy. The aim of this case report is to highlight the presentation of NMS in a depressed and catatonic patient, despite her long-term stability and a relatively low dose of quetiapine.

Keywords: Neuroleptic Malignant Syndrome, Bipolar Depression, Quetiapine

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a group of symptoms characterised by severe muscle rigidity and elevated temperature in an individual who has been exposed to antipsychotics, in the absence of other possible contributing organic cause. These are normally accompanied by other common symptoms such as autonomic instability, changes in conscious level, leucocytosis and blood evidence of muscle injury such as elevated creatinine kinase level. [1] The understanding of this syndrome has been mostly derived from clinical encounters due to its relatively low incidence (0.01-0.02% among those on antipsychotics). [2] In this case report, we highlight a case of quetiapine-induced NMS in a depressed bipolar patient with catatonia while on a stable dose of quetiapine for five years.

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CASE REPORT

This is a case of 37-year-old female of Malay ethnicity, recently widowed with a 10 year history of bipolar I disorder and three previous manic episodes that required in-patient admission and treatment. Since her most recent admission in 2011, she had been in remission with monotherapy of extended-release quetiapine 300mg for maintenance. Prior to that, she had been treated with risperidone, olanzapine and valproate at different periods but these medications were ceased due to intolerable side effects. She developed of significant tremors while on risperidone and had problematic weight gain with olanzapine and valproate. Since she was on put quetiapine, she has been compliant to this medication and being monitored regularly

during outpatient follow-ups.

Her husband's sudden death from cardiovascular disease precipitated her depression two months prior to presentation. The depressive episode was not associated with any manic or psychotic symptoms. Initially, she was still able to maintain her daily function with some supports from close family members. However, her condition deteriorated two weeks prior to the admission whereby she has been sleeping poorly, with self-neglect, poor nutritional intake, psychomotor retardation and eventually becoming stuporous. During this period, her family continued giving her quetiapine every nights. Subsequently, five days prior to her admission, she developed generalised rigidity. However, there was no associated fever, fitting episode, vomiting or head injury during this period.

On admission to psychiatric ward, she was found to be clinically dehydrated with generalised body rigidity, stupor, blank stare, mutism, negativism and hyperreflexia in both upper and lower limbs with down-going plantar reflex. Her vital signs assessment indicated the presence of fever (temperature: 38-40°C) with a high systemic blood pressure (142-173/80-122mmHg) and fluctuating pulse rate ranging from 97 to 162 beats/min. Electrocardiogram showed sinus tachycardia with no acute ischaemic changes. Blood investigation revealed leucocytosis (18.7 x 10^9/L) with left lateral shift (neutrophil count 15x 10^9/L). There was an increased urea level (13.2mmo/L) with raised creatinine (130umol/L). Other electrolytes and liver function test were within normal limits. Urinalysis noted the presence of protein and blood cell. Creatinine kinase (CK) was elevated (483 U/L) with normal CK-MB (25 U/L). The repeated CK showed an increasing trend which peaked at 2,034 U/L on day two of admission. Urine myoglobin, septic workout, and screening for syphilis, hepatitis and HIV were all negative. Bush-Francis Catatonia Rating Scale (BFCRS) score on presentation was 24, consistent with the presentation of catatonia.

Based on the clinical history and findings, working diagnoses of neuroleptic catatonia with NMS was offered. Her quetiapine medication was discontinued immediately. She was started on regular lorazepam up to 6mg over 24-hour for the management of her catatonic symptoms along with supportive care. She was rehydrated with intravenous fluid with regular paracetamol for her fever.

She remained warded in the psychiatric ward with daily review from both neurology and medical teams. Within five days, the patient's vital signs normalised and she started to show some improvement in term of her alertness and motor symptoms. Her CK level reduced further to 482 U/L. Given that she was still in catatonic and depressed state, electroconvulsive therapy (ECT) was commenced on day 8 of admission. The patient showed improvement of her catatonic symptoms after the second dose of ECT treatment. On day 11 of admission her catatonia was fully resolved. Her CK level also normalised to 178 U/L. On day 15 of admission, sodium valproate 400mg BD was started as she was still experiencing some depressive symptoms such as sad mood, hopelessness and anhedonia. After a total of 5 doses of ECT along with medication, her mood symptoms greatly improved hence she was discharged from the hospital on day 21. The quetiapine was not started at the time of discharge in view of the risk of redeveloping NMS.

DISCUSSIONS

Among all second generation antipsychotics, quetiapine is generally less implicated in inducing NMS. Recent systematic reviews and a case-control study comparing different second -generation antipsychotics revealed the relatively low frequency of NMS in quetiapine.

Only 7-12% of NMS cases reported in these studies were linked to quetiapine compared to other second generation antipsychotics. [3, 4]

Quetiapine-induced NMS is clinically featured by the continual occurrence of extrapyramidal symptoms and marked autonomic symptoms, such as diaphoresis, tachycardia, tachypnea, and blood pressure alterations. The prominent autonomic symptoms are postulated to be related to quetiapine's properties of inhibiting noradrenaline reuptake, alpha-adrenergic and histaminergic antagonism, and also to serotonin-related toxicity. [5] This is consistent with our patient in which the rigidity was present up to day 5 of admission. Fluctuation of blood pressure, tachycardia and diaphoresis were also prominent in this case, which led to the high suspicion of NMS when she first presented.

Catatonia, along with physical states that are generally common during its presentation, has been implicated as among relevant risk factors for NMS. This includes dehydration, agitation and physical restraint.[6] Most of these features, which were present in our patient, have contributed to the risk of her developing NMS in this context. Other studies have suggested the role of pre-existing abnormalities of CNS dopamine activity or receptor function and iron deficiency which occur during catatonic state as a relevant contributing factor for NMS. [7, 8] These investigations were not routinely done, hence no relevant findings were available from this to comment.

Another important highlight, in this case, is how the patient developed NMS in the context of stable long-term exposure to quetiapine which the patient had tolerated fairly well. In various studies, NMS is generally found in newly exposed neuroleptics or recent alteration in dose. Addonizio reported that 66% of the cases occurred within two weeks of the initiation or last major modification to dose. [9] Antipsychotic naïve was also found to be a common feature among NMS patients across different second-generation antipsychotics studied. [4] Both of these features were not featured in her case. A review by Trollor et al of 9 case reports in which monotherapy of quetiapine was implicated as the cause of NMS, reported the average days of quetiapine commencement prior to the NMS onset were 21 days with a median of 9 days. [3] This is in contrast to our case, in which the medication has been taken for nearly five years without any problem.

A systematic review on the treatment outcome of 19 cases of NMS induced by quetiapine reported that 30% of cases required intubation and intensive care management. [4] The use of muscle relaxants was more common in 86.7% of cases compared to dopaminergic agents (40%) and anticholinergic (6.7%). 61.5% of cases achieved complete recovery while death was reported in 7.7%. [4] In our case, supportive management was the main approach for the management of her NMS together with stopping quetiapine. Benzodiazepines, lorazepam with an average dose of 3mg per day in divided dose, were the medication of choice as several studies have reported its use to improve symptoms and accelerate recovery of NMS, particularly in milder cases. [10, 11] The ECT was used to treat the co-existing of catatonia, in which the patient showed a good response after the second ECT.

This case report highlights an unexpected occurrence of NMS. Even though NMS is more commonly occur during the initial exposure to antipsychotic such as quetiapine, our case highlights that NMS can occur at any stage during long term treatment if trigger conditions are present. Clinicians should be vigilant and suspect the development of NMS in patients who have been on a stable dose of quetiapine who later present with episodes of depression and catatonia, along with poor

physical health such as poor nutritional status and dehydration. Early detection and treatment can improve patient's outcome.

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