Brief report

Second generation antipsychotics causing neuroleptic malignant syndrome

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Abstract

Neuroleptic malignant syndrome (NMS) is a rare yet potentially lethal medical emergency encountered by psychiatrists. NMS is commonly associated with potent first generation antipsychotics, especially haloperidol and fluphenazine. However, there are many case reports of NMS caused by treatment with second generation antipsychotics (SGA). Mortality from NMS caused by SGA may be less and the presentation may also be different. The article discusses two case reports of neuroleptic malignant syndrome caused by SGA both of which have some unusual features.

Key words: Neuroleptic malignant syndrome, first generation antipsychotics, second generation antipsychotics

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Introduction

Neuroleptic malignant syndrome (NMS) was first described in 1960 by Delay and was formally known as 'akinetic hypertonic syndrome' (1). NMS is primarily a diagnosis of exclusion as none of the symptoms of NMS are diagnostic. Table 1 outlines the DSM 5 criteria for diagnosis of NMS. Although, the prevalence of NMS is around 0.4-1.4%, the potential lethal outcome requires high levels of vigilance (2).

Abrupt and profound dopamine D2 receptor blockade by antipsychotics in the nigrostriatal system is postulated to be the reason for clinical manifestations of NMS. Although first generation antipsychotics (FGA) are mostly implicated, second generation antipsychotics (SGA) including newer medications like ziprasidone, aripiprazole, paliperidone, asenapine (3) and intra-muscular risperidone can also cause NMS. Genetic susceptibility and other neurotransmitter abnormalities may increase the risk. High-potency FGA, recent or rapid dose increase, rapid dose reduction, abrupt withdrawal of anticholinergics, psychosis, organic brain disease, alcoholism, Parkinson's disease, hyperthyroidism, psychomotor agitation, mental retardation, dehydration and high ambient temperatures are some of the other predisposing factors.

The four classical symptoms of NMS are fever, rigidity, autonomic disturbances and elevated creatinine phosphokinase (CPK). However, the presentation could be atypical with no fever, rigidity or elevation of CPK and therefore atypical NMS remains a problematic entity (4). According to available reviews the entity of atypical NMS can be diagnosed when there are three of the four cardinal signs of NMS which are fever, rigidity, autonomic disturbances and elevated CPK (5). The atypical presentation can be seen mostly with SGA. Some atypical features observed are: extremely elevated serum sodium, absence of rigidity, normal CPK, generalised tonic-clonic seizures preceding NMS, anterograde amnesia and deficits in learning verbal information (6).

We describe two patients with atypical NMS caused by treatment with SGA.

Case 1

This was a 68-year old female who had schizophrenia for 40 years and a more recent diagnosis of dementia for one year. She was on chlorpromazine 75 mg and was compliant with treatment. She developed suspiciousness and irritability over 10 days with psychotic symptoms. As attempts to increase the dose of chlorpromazine resulted in extra pyramidal side effects (EPSE), she was started on olanzapine 10mg daily. Olanzapine was increased to 20mg daily over 7 days. After 12 days of initiation of olanzapine, the patient developed generalised rigidity and sweating. By the following day the clinical condition worsened, with development of fever spikes, fluctuation of blood pressure, delirium with a white blood cells count of $10.8\times10^3/\mu l$ and a neutrophilia of 82%. Computed tomography (CT) scan of brain, electro encephalogram (EEG) and lumber puncture revealed no abnormality. Blood and urine culture yielded no growth. The CPK levels were 850U/l, 576U/l and 32U/l respectively on day 6, 9 and 14 following development of rigidity and sweating. Lorazepam 4mg three times a day and bromocriptine 7.5 mg a day was commenced on day 6 of illness and she was completely well on day 14.

Case 2

This was a 40-year old female who had schizophrenia for 25 years. She was stable on clozapine 400 mg and amisulpiride 300 mg combination without any changes in doses when she developed NMS. The clozapine had been initiated 13 years previously and the amisulpiride had been added 5 years ago. She presented with an acute dystonic reaction. She had dehydration, fever and generalized rigidity on the first day. Although the acute dystonic reaction responded to intramuscular benztropine, the generalised rigidity persisted. The white blood cell count was $10.26\times10^3/\mu l$, with a neutrophil count of $6.35\times10^3/\mu l$. CPK was 2546U/l on day 2 and 3908U/l by day 4. Chest x ray, blood and urine culture were normal. CT scan of brain, lumbar puncture and EEG did not reveal abnormality. The patient was initiated on lorazepam 4 mg three times a day, which was continued for 7 days. The CPK decreased from 3490U/l on day 6 to 1476U/l on day 8. She was completely well by day 14.

Discussion

Available data suggests that in NMS, abnormalities in mental status and other neurological signs precede systemic signs in more than 80% of cases, as evident by these two case reports (6). Both patients had rigidity while the second patient had an acute dystonic reaction, which is unusual, but which has been described previously in the literature (6).

About 16% of cases of NMS develop within 24 hours of initiation of an antipsychotic, while 66% develop within the first week, and virtually all cases manifest within 30 days, with an average of 4-14 days (7). It is unusual for NMS to occur beyond 1 month after initiation of treatment, unless the dose is changed or an additional antipsychotic is administered. The second patient developed NMS after 13 years of clozapine and 5 years of amisulpiride, which is unusual. However NMS can occur years in to therapy, as well as after stopping therapy.

Another unusual finding with the first patient is the low CPK levels, which is considered as a feature of atypical NMS. The offending antipsychotic in the first patient was olanzapine, while clozapine or amisulpiride or both were implicated in the second. Although some studies have found olanzapine-induced NMS to be rare, with a rate of 0.01%, Zarrouf et al. reported 36 such cases in 88 cases of NMS caused by SGA (6); according to this review, six cases were associated with clozapine monotherapy, while 22 cases were associated with combination therapy (4). Considering the above evidence it is likely that the risk of NMS with clozapine increases when clozapine is combined with another antipsychotic. Another observation made by Zarrouf et al, which was also seen in our second patient, is that clozapine can be associated with NMS, even in patients on long-term steadydoses (6). The observation that clozapine associated NMS may have less EPSE and lower CPK levels, was not seen in our patient, similar to the cases reviewed by Zarrouf (6). It is interesting that the second patient developed all the typical features of NMS contrary to the popular belief that SGA, particularly clozapine, cause atypical features.

Out of the factors that have been correlated with NMS, agitation, dehydration, and restraint was present in the first patient (6). The second patient was dehydrated due to the acute dystonic reaction. Both cases occurred at a time where the ambient temperature was unusually high, which has been proposed as a contributory factor (6). It is said that NMS is commoner among females in their early forties, which is reflected in the cases described (6).

Table 1. DSM 5 criteria for diagnosis of NMS

- Exposure to dopamine antagonist, or dopamine agonist withdrawal, within past 72 hours
- Hyperthermia
- Rigidity
- Mental status alteration
- CPK elevation
- Sympathetic nervous system lability, defined as at least 2 of the following:
  - Blood pressure elevation or fluctuation
  - Diaphoresis
  - Urinary incontinence
- Hypermetabolism, defined as heart rate increase and respiratory rate increase
- Negative work-up for infectious, toxic, metabolic, and neurological causes

Clinical signs and symptoms

- Neuromuscular – Tonicity, lead-pipe rigidity, hypersalivation, external eye muscle contraction, hyperextension of the neck, tonic facial spasm, dysphagia, dysarthria, chorea, posture or gait problems
- Autonomic system – Increase in arterial pressure, tachycardia, excessive sweating, urinary and fecal incontinence
- Other features – Delirium, mutism, stupor or coma

Biochemical findings

- Increased – LDH, CPK, AST and ALT, alkaline phosphatase, CSF proteins, serum catecholamines
- Hyperuricemia, hyperphosphatemia, hyperkalemia, myoglobinemia
- Leukocytosis, thrombocytosis
- Proteinuria
- Decreased serum iron and calcium
- Myoglobinuria
- Metabolic acidosis

Table 2. Biochemical findings that may be associated with NMS

- Increased LDH
- Increased creatine kinase (50-100% of cases)
- Increased AST and ALT
- Increased alkaline phosphatase
- Hyperuricemia
- Hyperphosphatemia
- Hyperkalemia
- Myoglobinemia
- Leukocytosis (70-98% of cases)
- Thrombocytosis
- Proteinuria
- Decreased serum iron
- Increased CSF protein
- Hypocalcemia
- Myoglobinuria
- Metabolic acidosis

The two patients were managed in liaison with the medical team. One patient was treated with bromocriptine and lorazepam and the other was treated with lorazepam. Both patients recovered well. The management of NMS includes withdrawal of antipsychotics, treatment with benzodiazepines, particularly lorazepam, and supportive therapy. Bromocriptine, dantrolene, L-dopa and carbamazepine are used without strong evidence. Electro convulsive therapy is thought to be therapeutic for NMS and the associated mental illness. In the second patient, other possible causes such as central nervous system infection were also looked for and excluded, as presentation several years after initiation of antipsychotic is atypical.

Re-challenge with antipsychoticis associated with a risk of recurrence of NMS; according to a previous study, 5 out of 6 patients developed NMS following re-challenge with the same drug that caused the initial episode, whereas 9 out of 10 patients did not develop NMS following re-challenge with a less potent antipsychotic (8). If restarting, it is essential that the anti psychotic be started with very small doses and that titration should be done at a slower pace than usual, together with a close monitoring. Using an antipsychotic structurally unrelated to the offending antipsychotic or a drug with low dopamine affinity such as aripiprazole, quetiapine or clozapine are considered safe.

These case report sillustrate that despite reports of NMS being uncommon with SGA and having atypical presentations, SGA can cause NMS, which can be characterized by typical as well as atypical features.

Declaration of interest

None declared

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