NEUROLEPTIC MALIGNANT SYNDROME (NMS): A RARE PRESENTATION INDUCED BY AN ANTIEMETIC - CASE REPORT

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SUMMARY
Neuroleptic Malignant Syndrome is one of the life threatening complications of antipsychotic psychotropic medication. We here report a case of a 39 years old male who has had a diagnosis of paranoid schizophrenia since the age of 18. He had been on antipsychotic therapy since then. He was on a combination of antipsychotics. He had mild hyper-salivation for a long time but was not very concerned about it. He requested and was prescribed Hyoscine Hydrobromide 300 mcg BD for hyper-salivation. There was no other medication change. After 5 days of starting Kwells, the patient presented with Neuroleptic Malignant syndrome. One has to watch for NMS while starting Hyoscine Hydrobromide for someone on antipsychotics.

Key words: schizophrenia - antipsychotics - Hyoscine Hydrobromide - Neuroleptic Malignant Syndrome

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CASE REPORT

A 39 year Old, Male, Married man who lives with his wife and children. He is Unemployed and a devout Muslim. He is well known to Mental Health Services with a diagnosis of Paranoid Schizophrenia for the last 17 years. He was diagnosed with Schizophrenia in 1985 (17 years old), and has had several informal admissions. He was admitted to the psychiatric inpatient unit on 17/12/2007 when he presented at the Out Patient Department confused, muddled, suspicious, inappropriate, highly paranoid and talking about “danger” everywhere. He does not drink alcohol or use any illicit drugs.

The differentials considered were:
1. Relapse due to on going stresses, Difficult family situation (Ongoing issues with wife, sexual dysfunction);
2. Side effects of Hyoscine Hydrobromide;
3. Poor compliance with medication;

He had been on following medication for last many years and had been stable:
- Clozapine 100 mg mane, 350 mg nocte;
- Depixol 50 mg im every 2/52;
- Chlorpromazine 50 mg mane, 100 mg nocte;
- Procyclidine 2.5 mg bd.

There had not been any change of antipsychotic medication though Hyoscine Hydrobromide was added 6-7 days before the admission, for hypersalivation.

On the day of admission, the Physical examination was within normal limits except for mild rigidity. Temperature was normal, BP was high: 143/100, PR was a high: 98/min.

Except at the time of admission the BP, PR and Temperature usually remained within normal range for the rest of his admission.

Considering all the possibilities including relapse of the illness, all blood investigations were done. All blood tests including FBC including WBC count, LFT, U & E’s, Glucose were within normal limits except CPK (normal: 0-170) which was 6211 on 17/12/07. ECG was normal.

All antipsychotics were stopped. He deteriorated further with relapse of skin eczema which worsens with his worsening of mental illness. Only Benzodiazepines, either in the form of lorazepam or diazepam were tried. CPK were being done every 3-4 days.

CPK was 560 on 27/12/07 and 432 on 1/1/08. He was started on quetiapine 50 mg at night, CPK rose to 1008 on 08/01/08 and quetiapine was stopped. CPK was 1504 on 11/01/08, all other blood investigations, urine investigations and ECG were normal.

Mental illness and eczema became worse with oedema and ulcers over leg and foot. His case was discussed with the Medics and a possibility of Rhabdomyolysis/DVT was considered. He was transferred to a Medical Unit on 12/01/08. He was transferred back to the psychiatric unit the next day after ruling out any medical problems. On the Psychiatric ward the management was mainly behavioural management and lorazepam to contain the patient.

CPK: 434 on 29/01/08. He was then rechallenged with clozapine, but CPK rose to 868 on 5/2/08 and clozapine was stopped. To try to stabilise while avoiding antipsychotics, Depakote was started, 500mg BD. CPK was 606 on 13/02/08.

Abilify was started on 18/2/08, CPK rose to 1586 on 23/02/08. Aripiprazole was stopped. He continued to deteriorate in mental state to the stage of becoming doubly incontinent. He needed seclusion at times. Antibiotics were started for his skin condition. Depakote was increased to 1 gm BD on 3/3/08, CPK was 1596.

CPK on 06/03/08 was 2168, the dosage of Depakote reduced and lithium was added in an attempt to try something to help him. He continued to deteriorate and was assessed under the mental health act on 14/03/08 and was not found to be detainable under the act due to lack of capacity.

We started making arrangements for the last resort, ECT.
Meanwhile the CPK came down, 476 and again a rechallenge with clozapine was considered on 26/03/08. CPK was 90 on 29/03/08, 77 on 4/4/08, 207 on 17/04/08, 127 on 22/04/08.

He became stable, CPK was 164 on 08/05/08 and 166 on 18/06/08 and he was discharged home on 26/06/08 on clozapine.

**Table 1. Timeline of treatment in this case**

<table>
<thead>
<tr>
<th>Dates</th>
<th>CPK</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/12/2007</td>
<td></td>
<td>Hyoscine HBR started for Hypersalivation</td>
</tr>
<tr>
<td>17/12/2007</td>
<td>6211</td>
<td>All antipsychotics stopped</td>
</tr>
<tr>
<td>27/12/2007</td>
<td>560</td>
<td></td>
</tr>
<tr>
<td>01/01/2008</td>
<td>432</td>
<td>Started Quetiapine 50 mg ON</td>
</tr>
<tr>
<td>08/01/2008</td>
<td>1008</td>
<td>Quetiapine stopped</td>
</tr>
<tr>
<td>11/01/2008</td>
<td>1504</td>
<td></td>
</tr>
<tr>
<td>29/01/2008</td>
<td>434</td>
<td>Rechallenged with clozapine</td>
</tr>
<tr>
<td>05/02/2008</td>
<td>868</td>
<td>Clozapine stopped, Depakote(500 mg BD) started</td>
</tr>
<tr>
<td>13/02/2008</td>
<td>606</td>
<td></td>
</tr>
<tr>
<td>18/02/2008</td>
<td></td>
<td>Aripiprazole started 10 mg OM</td>
</tr>
<tr>
<td>23/02/2008</td>
<td>1586</td>
<td>Aripiprazole stopped</td>
</tr>
<tr>
<td>03/03/2008</td>
<td>1596</td>
<td>Depakote increased to 1 GM BD</td>
</tr>
<tr>
<td>06/03/2008</td>
<td>2168</td>
<td>Depakote reduced and Lithium added</td>
</tr>
<tr>
<td>26/03/2008</td>
<td>476</td>
<td>ReChallenged with Clozapine</td>
</tr>
<tr>
<td>29/03/2008</td>
<td>90</td>
<td>Clozapine was continued</td>
</tr>
<tr>
<td>04/04/2008</td>
<td>77</td>
<td>Clozapine was continued</td>
</tr>
<tr>
<td>17/04/2008</td>
<td>207</td>
<td>Clozapine was continued</td>
</tr>
<tr>
<td>22/04/2008</td>
<td>127</td>
<td>Clozapine was continued</td>
</tr>
<tr>
<td>08/05/2008</td>
<td>164</td>
<td>Clozapine was continued</td>
</tr>
<tr>
<td>18/06/2008</td>
<td>166</td>
<td>Discharged on 26/06/2008 on Clozapine, lithium stopped slowly</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Typically, NMS presents with hyperthermia and muscle rigidity initially which may co-occur or be followed by confusion, agitation, irritability, restlessness and at times impaired consciousness. Since there is no universally accepted diagnostic criterion therefore NMS is largely a clinical diagnosis made by exclusion in the contextual setting.

There is prominence of autonomic dysfunction causing sweating, tachycardia and labile blood pressure.

The main causes for NMS are (Benzer 2009):

- **All classes of neuroleptics (dopamine D2-receptor antagonists) are associated with NMS, and dopamine receptor blockade is considered the cause of NMS.**
  - Experimental blockade of dopamine in the striatum can cause rigidity, tremor, and rhabdomyolysis.
  - Blockade of dopamine in the hypothalamus can cause impaired temperature regulation and hyperthermia.
  - This theory does not explain why only some patients develop NMS. It also does not explain why patients rechallenged with neuroleptics do not always redevelop NMS.

- Risk factors for developing NMS include the following:
  - Increased ambient temperature;
  - Dehydration;
  - Patient agitation or catatonia;
  - Rapid initiation or dose escalation of neuroleptic;
  - Withdrawal of anti-Parkinson medication;
  - Use of high-potency agents and depot intramuscular preparations;
  - History of organic brain syndrome or affective disorder;
  - History of NMS.

One of the causes of NMS is Concomitant use of predisposing drugs (eg, lithium, anticholinergic agents)

It may also cause among other presentations opisthotonus, seizures, oculogyric crises and trismus.

It may present as Atypical NMS when there is no muscle rigidity or hyperthermia at the onset. Hyperthermia and muscle rigidity may develop over time or not at all (Picard 2008)

The term NMS was used by Delay for the first time in 1960 when he observed it in patients who were being treated with high-potency antipsychotics (Delay 1960).

Incidence of NMS is suggested to be 0.01–0.02% (Stubner 2004) (4). Mortality is about 4%, probably as a result of earlier diagnosis and better supportive care (Caroff 1993, Shalev 1989, Jahan 1992). The incidence is almost double in males compared to female counterparts.

The most accepted hypothesis behind the occurrence of NMS is probably sudden and profound central dopaminergic blockade mainly D2 and young men are more likely to be affected than women (Balzan 1998).

The most important part of the treatment is cessation of...
the offending drug. The recovery time after cessation of the causative drug is usually seven to 10 days (Caroff 1998) or longer if the offending drug is a depot medication.

There are certain guidelines which if followed can minimise the risk of NMS on restarting an antipsychotic. It is recommended that we should wait for at least two weeks before restarting drugs (or may be longer if any residual symptoms are present), try to use the lowest potency drug possible (If possible avoid depot injections), try to use a drug with low dopamine receptor affinity (e.g. quetiapine or clozapine), start low (and go slow) and increase under proper supervision and appropriate monitoring, avoid concomitant use of lithium (Marino 2006, Rosebush 1989).

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision (DSM-IV), the NMS should be considered only if the patient develops severe muscle rigidity and elevated temperature while receiving a neuroleptic drug and displays two or more of the following signs and symptoms: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and laboratory evidence of muscle injury (American Psychiatric Association 1994).

It can happen even in long term stable patients on antipsychotics even if there has not been any change in the psychotropic medication, Hyoscine was added in this case 6-7 days before the NMS developed. Hence, if there is any change in the presentation at any time, especially after addition of any medication for side effects, due consideration must be given to NMS if the patient is on any antipsychotic. NMS may have different presentation:

a. Mainly/only physical symptoms;
b. Mainly/only mental symptoms, Confusion may worsen the Paranoia and other schizophrenic symptoms;
c. Mainly/only blood abnormalities;
d. a combination of 2 or all of the above.

In this case there were no physical symptoms of NMS such as rigidity, high temperature, autonomic instability, (though symptoms of deteriorating psychosis were present as he could not be given any antipsychotic), and mainly symptoms like altered mental state/ confusion/ muddleness (which might also be contributed by relapse of the illness) were present. The only blood sign was a CPK rise in the beginning and on introduction of any antipsychotic including clozapine.

Early recognition of NMS is essential. Though considered a medical emergency, it can be managed at psychiatric hospitals depending upon the clinical features e.g in the above mentioned case where the only sign was a rise in CPK and no other physical symptoms. The essential part of the management is continuous monitoring of Vitals/blood tests and try keep looking for other signs and symptoms which may indicate a deteriorating NMS.

Once in the “NMS Phase”, in which muscle injury is signified by a raise in CPK (a blood sign), any antipsychotic may cause worsening of signs/symptoms. Once this “NMS Phase” is settled (Duration is different in different patients, e.g. in this case it took 6 months to settle), the same antipsychotic on which it (CPK) showed a deterioration whilst being in the “NMS phase” may become the treatment of choice once that “NMS phase” wears off.

REFERENCES


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