

Characteristic Features of a Case of Recurrent Neuroleptic Malignant Syndrome

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A 56-year old schizophrenic patient developed three episodes of Neuroleptic Malignant Syndrome (NMS) after age of 50. Patient was under treatment with risperidone and clozapine during the first two episodes respectively. But no antipsychotic was ever used during the 45-month period between 2nd and 3rd lethal episodes of NMS, and the patient was only treated with ECT, and promethazine as needed base. Patient used to show sub syndromal catatonia throughout this period. This might reflect a "trait vulnerability" to NMS which for full expression of the disorder need some sort of "state variable" such as a drug.

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Introduction

Neuroleptic malignant syndrome (NMS) is an uncommon complication of antipsychotic drugs with a mortality rate of about 10%-20%. It usually presents as the combination of core symptoms of hyperthermia and severe muscular rigidity, as well as some other symptoms such as diaphoresis, tachycardia, elevated or labile blood pressure, dysphagia, incontinence, tremor, delirium, lethargy, stupor, coma, mutism, leukocytosis, liver transaminase and Creatine kinase (CK) elevation. According to the recent reports with some second generation antipsychotics, rigidity and hyperthermia may not always be present. Temperature elevation can be mild to severe. The initial progression of the syndrome may be insidious or it may have a rapid onset (1-3).

Case Report

A 56 year old schizophrenic man who

suffered the disorder since age 14 with positive and regressive symptoms developed progressive symptoms of dysphagia, muscular rigidity, and excessive salivation. During early days of the disorder, no fever or changes in complete blood count (CBC) were noted. But during the second week leukocytosis and raised CK became apparent. Sixty mg/day of IV dantrolene started during the first week of the disorder failed to control symptoms and severe bronchorrhea led to right lobar pneumonia. So patient referred to the intensive care unit in there aggressive antibiotic and supportive therapy continued for about 6 weeks. Pneumonia and NMS resolved, but long duration of immobility, feeding via NG-tube, extensive muscle destruction, and of course continued psychotic symptoms led to cachexia and patient died soon after discharge.

The corresponding author first visited the patient about 6 years ago when he was discharged from a private hospital after several years living at there and referred to a caring center for chronic psychotic patients. Regressive symptoms, significant thought disorder, and agitations alleviated with 400 mg/day of clozapine and 4 mg/day of risperidone. But psychotic symptoms worsened after about 4 months. Dosage of risperidone gradually raised

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to 12 mg/day. Excessive salivation emerged and clozapine tapered during a 2-month period. Patient referred to a private hospital soon after symptoms of NMS emerged, and successfully treated with dantrolene and bromocriptine.

Troublesome psychotic symptoms recurred after about 5 months for which olanzapine, 10 mg/day had no effect after 4 months. In the last resort and with an assumption that sialorrhea in the last episode was due to NMS not to clozapine, this drug restarted and olanzapine discontinued. For 4 months his condition was stable with 400 mg/day of clozapine and after that sialorrhea recurred soon after followed by rigidity and dysphagia and with a diagnosis of second episode of NMS patient again transferred to hospital. Treatment with dantrolene and bromocriptine was successful.

Patient remained at hospital for about 45 months. Ward staff absolutely condemned from using any form of antipsychotics even as PRN and he was treated with high doses of benzodiazepines, promethazine (as PRN for disinhibited behavior) and various mood stabilizers such as lithium and sodium valproate, although benzodiazepines and mood stabilizers were discontinued and ECT became the main modality of treatment. During this period patient received 135 ECTs on an average of one session/week. Patient was fairly stable in spite of significant symptoms of thought disorder, disinhibited behavior, and time to time merging regressive symptoms. Rigidity, mild dysphagia, and psychomotor retardation remained as notable extrapyramidal symptoms. An outstanding symptom developed after second episode of NMS was a humpbacked posture maintained by the patient most of the time posing his eyes opposite to his knees. In addition, two episodes of transient NMS-like symptoms including rigidity and dysphasia emerged and resolved spontaneously after less than one week.

Continued disinhibited behavior and changing hospital policy caused patient relocated in another ward after that regressive behavior became insuppressible, ended to the third and lethal episode of NMS after about 2 months.

Discussion

First episode of NMS emerged 36 years after developing schizophrenia at age 14 and the second and third episodes at ages 52 and 56 respectively. Patient was under treatment with risperidone and clozapine while he developed the first and second episodes. But during the 45-month period between second and third episodes no antipsychotic was ever used. Mood stabilizers (including lithium) were discontinued months before the third episode and patient was only treated with ECT, benzodiazepines, and promethazine as PRN. Reports about the relationship between promethazine, lithium, prior treatment with ECT and NMS do exist (2,3).

An important feature of the presented case was catatonia-an uncommon clinical syndrome mostly seen in psychotic and mood disorders. It can also occur as idiopathic catatonia or in the context of some medical conditions, as well as by many drugs like antipsychotics. This syndrome can be seen in extreme forms of neuroleptic-induced parkinsonism and NMS (2,4).

The typical presentations of NMS and malignant catatonia cannot be differentiated either clinically or by laboratory tests, suggesting that NMS is a specific type of catatonia (4,5). Malignant catatonia tends to have a prodrome of excitement and agitation prior to the onset of rigidity, while NMS tends to begin with rigidity (2).

Benzodiazepines and ECT have been successful in the treatment of both catatonia and NMS (4). On the other hand, ECT has been associated with catatonia (6). A non-depolarizing muscle relaxant has been associated with NMS after repeated general anesthesia (7), and halogenated inhalational anesthetics, such as halothane, and depolarizing muscle relaxants, such as succinylcholine, may be responsible for Malignant hyperthermia (MH) which can be very similar to NMS (2,4).

There was no evidence for other causes of NMS, such as serotonin syndrome, heat stroke, central nervous system infections, status epilepticus, stroke, brain trauma, neoplasms, acute intermittent porphyria, tetanus, and environmental and psychological factors such

as hot and humid conditions, agitation, dehydration, and exhaustion (2) in this case.

Catatonic features throughout the 45-month period between second and third episode of NMS might reflect a "trait vulnerability" to NMS which for full expression of the disorder need some sort of "state variable" such as a drug (8). A genetic vulnerability has been described in recurrent NMS (2,8). Over representation of the A1 allele of the dopamine D2 receptors gene may contribute to this phenomenon. Familial clusters of NMS support this hypothesis (1). Sub syndromes of catatonia that do not meet the DSM or ICD criteria, and genetic and familial form of catatonia also has been described (4,9). Posturing that developed only after second episode exemplifies similarities between pathophysiologic mechanisms of NMS and catatonia (8).

The transition of baseline symptoms to a full-blown NMS occurred smoothly and during first days of exacerbation of symptoms CBC and CK level was unremarkable. Other reporters also mentioned this phenomenon (10).

References

1. Janicak PG, Beedle. Medication-induced Movement Disorders. In: Sadock BJ, Sadock VA editors. Kaplan and Sadock's Comprehensive text book of Psychiatry. Baltimore: Lippincott Williams and Wilkins; 2009. P. 2996-3003.
2. Tonkonogy J, Sholevar DP. Neuroleptic malignant syndrome. 2010 May 7. Available from: URL:<http://emedicine.medscape.com>
3. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry 2007. 164: 870-6.
4. Taylor MA, Fink M. Catatonia in psychiatric classification: A home of its own. Am J Psychiatry 2003; 160:1233-41.
5. Carroll BT, Graham KT, Thalassinos AJ. A common pathogenesis of the serotonin syndrome, catatonia, and neuroleptic malignant syndrome. J Neuropsychiatry Clin Neurosci 2001; 13: 150.
6. Shams J, Rahmani B, Farzad Asefi F. Developing catatonia after ECT in an schizoaffective patient. Iranian Journal of Psychiatry and Behavioral Sciences. 2010; 4(2): 58-60.
7. Tsuchiya N, Morimura E, Hanafusa T, Shinomura T. Postoperative neuroleptic malignant syndrome that occurred repeatedly in a patient with cerebral palsy. Paediatr Anaesth 2007; 17(3): 281-4.
8. Detting M, Sander T, Weber M, Steinlein O. Mutation analysis of the ryanodine receptor gene isoform 3(RYR3) in recurrent neuroleptic malignant syndrome. J Clin Psychopharmacol 2004; 24(4): 471-3.
9. Stober G. Genetic predisposition and environmental causes in periodic and systematic catatonia. Eur Arch Clin Neurosci 2001; 2(suppl 1): 21-4.
10. Gambassi G, Capurso S, Tarsitani P, Liperoti R, Bernabei R. Fatal neuroleptic malignant syndrome in a previously long-term user of clozapine. Aging Clin Exp Res 2006; 18(3): 266-70.