

Neuroleptic Malignant Syndrome and Serotonin Syndrome

APM Resident Education Curriculum

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Historical Background

- Syndrome malin des neuroleptiques
 - Rapidly progressive neurovegetative state
 - Observed during early clinical trials of haloperidol
 - 1960
- Neuroleptic Malignant Syndrome
 - First appeared in English literature in 1967
 - Belated recognition in the U.S.

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Delay in 1960 observed this syndrome of a rapidly progressive neurovegetative state that preceded cardio-vascular collapse and death during the early clinical trials of haloperidol and coined the term syndrome malin des neuroleptiques.

Prior to the 1960s, clinical descriptions resembling NMS associated with phenothiazines were not formally diagnosed as NMS.

Caroff in 1980 published the first review of the sixty cases reported in the world literature. He estimated that NMS occurs in as many as 1% of neuroleptic treated patients and may have a mortality rate of 20%.

Reference

Caroff SN. The neuroleptic malignant syndrome. J Clin Psychiatry. 1980 41(3):79-83.

Incidence

- Typical antipsychotics
 - Best estimate 0.1-0.2% (Caroff and Mann, 1996)
 - Wide variance in estimates 0.1-3.0%
- Atypical antipsychotics
 - It remains unclear whether atypical antipsychotics are less likely to cause NMS compared to typical antipsychotics (Troller, et al., 2009)

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This estimate is produced by pooling the results of studies reporting the occurrence of NMS among large numbers of patients treated with antipsychotics at a particular center.

The wide variance is thought secondary to variance in diagnostic criteria, survey techniques and clinical settings.

NMS can result from treatment with atypical antipsychotics, and that it often presents with the classic features and course of illness reported previously in associated with typical antipsychotics. Only 30%, however, met the strict criteria for NMS in a case review by Carloff and Mann in 2000 the rest presented with an incomplete picture

Reference

Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North AM 1993; 77(1):185-202.

Trollor JN, Chen X, Sachdev PS. Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. CNS Drugs. 2009;23(6):477-92.

Sachdev P, Kruk J, Kneebone M, et al. Clozapine-induced neuroleptic malignant syndrome: review and report of new cases. J Clin Psychopharmacol. 1995 Oct;15(5):365-71.

Pathogenesis

- Central dopamine hypoactivity

Evidence

- All antipsychotics implicated share dopamine receptor antagonism
- Withdrawal of dopamine agonists or “freezing” episodes in Parkinson’s disease have induced NMS-like states
- Dopamine agonists appear beneficial in treatment
- Disruption of dopamine tracts produce NMS-like states
- A case report utilizing SPECT revealed almost complete D2 receptor blockade in a patient with NMS
- Reduction in CSF homovanillic acid (HVA) in NMS
 - Reduction persisted after recovery

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These cases imply that NMS-like syndromes occur when a rapid decrease in dopaminergic activity occurs.

This decrement may be caused by the blockade of dopamine receptors, decrease in dopamine stores, or the elimination of a dopaminergic agent.

NMS may represent the final common pathway of a rapid and significant impairment of dopaminergic function in the striatum and hypothalamus.

Pathogenesis

- Central dopamine hypoactivity (continued)

Theory (Strawn et al, 2007, Fricchione 1985)

- Patients susceptible to developing NMS may have a baseline central hypodopaminergia
 - Trait vulnerability
- The hypodopaminergic state is further stressed with pharmacologic or stress-induced reductions in dopamine activity
 - State vulnerability

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Fricchione GL. Neuroleptic catatonia and its relationship to psychogenic catatonia. *Biol Psychiatry*. 1985 Mar;20(3):304-13.

Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. *Am J Psychiatry*. 2007 Jun;164(6):870-6.

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