Central Dopaminergic and Noradrenergic Receptor Blockade in a Patient With Neuroleptic Malignant Syndrome

Marc Ansseau, M.D., Ph.D., Charles F. Reynolds III, M.D., David J. Kupfer, M.D., Pierre-François Poncelet, M.D., Georges Franck, M.D., Ph.D., Albert E. Dresse, M.D., Ph.D., and Michel Reznik, M.D., Ph.D.

During treatment with clomipramine and haloperidol, a 54-year-old depressed woman exhibited a typical neuroleptic malignant syndrome (NMS). Among results of biologic tests performed at least 2 weeks after discontinuation of all psychotropic treatment, the absence of normal growth hormone response after both apomorphine and clonidine challenge tests and increased levels of cerebrospinal fluid homovanillic acid and urinary 3-methoxy-4-hydroxyphenylglycol suggest that NMS may be related to central dopaminergic and possible α-noradrenergic receptor blockade.
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First described by Delay and Deniker,[1] the neuroleptic malignant syndrome (NMS) is "the most serious but also the rarest and least known of the complications of neuroleptic chemotherapy." The symptoms include hyperthermia, muscular rigidity, altered consciousness, and autonomic dysfunction (tachycardia, labile blood pressure, and profuse diaphoresis). NMS has been reported in connection with most neuroleptics, but haloperidol and depot fluphenazine are most commonly implicated.[2] It may develop within hours of initial drug exposure or after months of drug use, and it occurs at therapeutic rather than toxic dosage. The exact incidence of NMS is unknown (Delay and Deniker suggested a rate of 0.5% in neuroleptic-treated patients), but an overall mortality rate of 20% has been reported, increasing to 38% with depot neuroleptics.[2]

Although the pathogenesis of NMS remains unknown, recent reports of its development after withdrawal of dopaminergic drugs[3] and of successful treatment with dopaminergic agonists[4,5] suggest that its features can be explained by dopamine-receptor blockade in the basal ganglia and hypothalamus.

We evaluated these putative neurotransmitter disturbances in a patient with NMS by means of cerebrospinal fluid and urine measurements of neurotransmitter metabolites and specific neuroendocrine challenge tests.

CASE REPORT

Ms. A, a 54-year-old woman, was hospitalized in the psychiatric department of a general hospital for major depressive disorder with melancholia according to DSM-III criteria. Her depression had been unresponsive to both amitriptyline and imipramine. Her medical, psychiatric, and family histories were remarkable only for a first depressive episode at age 24 years, which was treated successfully with ECT. Her initial physical examination, ECG, chest x-ray, EEG, and standard laboratory tests were normal. Treatment with clomipramine 25 to 100 mg/day intravenously and haloperidol 2 to 6 mg/day orally was instituted, and some clinical improvement was noted after 15 days. After 4 weeks of therapy, while Ms. A was receiving oral clomipramine 150 mg and haloperidol 6 mg, hyperthermia (38.6°C), mutism, and generalized extrapyramidal rigidity developed. Two days later, while the clinical picture was worsening (temperature, 39.2°C; lead pipe rigidity), NMS was diagnosed and therapy with all psychotropic medications was stopped. However, her condition did not improve during the following 12 days—temperature ranged from 38.4°C to 40.4°C and trophic skin disturbances appeared. Seventeen days after the onset of these symptoms, Ms. A was transferred to the Biological Psychiatry and Psychopharmacology Unit of the University Hospital of Liège for further evaluation.

During this hospitalization of 9 days, complete blood count showed normochromic anemia (hemoglobin, 10.6 g/dl), a normal leukocyte count, and a sedimentation rate of 59 mm in 1 hour. Blood chemistries (including hepatic and thyroid indices) were normal, as was creatine phosphokinase (30 mIU; normal range, 0–100 mIU). Electroencephalography showed diffuse nonspecific slowing, without focal or epileptogenic features, and computed tomographic scan was normal. The lumbar puncture fluid was clear and sterile, and of normal pressure. Cerebrospinal fluid glucose and protein levels (including electrophoresis) were in the normal range. Monoamine metabolites were measured by gas chromatography and compared with normal values from our laboratory: urinary 3-methoxy-4-hydroxyphenylglycol (MHPG), known to reflect central noradrenergic metabolism, was increased to 1430 ng/24 hours (normal, 297–1215); cerebrospinal fluid 5-hydroxyindoleacetic acid, a metabolite of serotonin, was within normal limits—31 ng/ml (normal, 19–63); and cerebrospinal fluid homovanillic acid, a metabolite of dopamine, was increased to 59.2 ng/ml (normal, 30–56).

Clonidine and apomorphine challenge tests were performed as follows: growth hormone (GH) was assayed every 20 minutes from 40 minutes before until 120 minutes after the injection of either clonidine 0.15 mg i.v. (diluted in saline to obtain 10 ml administered over 10 minutes) or apomorphine 0.5 mg s.c. (diluted in saline to obtain 0.5 ml). The clonidine test, which assesses central α-noradrenergic receptor sensitivity, did not elicit a normal GH response (basal, 0.5 ng/ml; peak, 1.5; normal peak, > 5), nor did the apomorphine test, which assesses central dopaminergic receptor sensitivity (basal, 1.7 ng/ml; peak, 2.8; normal peak, > 5). Ms. A's clinical condition improved somewhat (her mean daily temperature decreased from 39.3°C to 38.4°C and responsivity increased).

After return to her original hospital, however, Ms. A's condition worsened again and, despite strong supportive treatment, she died 19 days later (45 days after the onset of symptoms). No specific pharmacotherapy for the NMS was tried because no evidence for a possible benefit from specific agents had been published up to that time (1981).[2] Autopsy showed a left

From the Université of Liège Medical School (Drs. Ansseau, Poncelet, Franck, Dresse, and Reznik) and the University of Pittsburgh School of Medicine (Drs. Reynolds and Kupfer).

Reprint requests to: Marc Ansseau, M.D., Ph.D., Biological Psychiatry and Psychopharmacology Unit, Centre Hospitalier Universitaire (B 33), B-4000 Liège Sart Tilman, Belgium.

pneumothorax with atelectasis but no other visceral abnormalities. No gross abnormalities of meninges, cerebral hemispheres, or brainstem were present. Microscopic examination (with a battery of special stains) of multiple sections of the cerebral hemispheres, including basal ganglia, hypothalamus, cerebellum, brainstem, and spinal cord, was unremarkable aside from slight edema and nonspecific meningeal inflammatory reaction.

DISCUSSION

The condition of our patient during haloperidol and clomipramine therapy was suggestive of NMS. A possible etiopathogenetic or facilitative role for tricyclic antidepressants, and particularly clomipramine, has been suggested in the French literature; this may possibly reflect its more frequent use in Europe rather than significant interference at the pharmacologic (and especially dopaminergic) level. An atypical feature in our patient was the absence of leukocytosis and serum creatine phosphokinase elevation. An increase in this enzyme is generally attributed to protracted muscle rigidity, which in association with decreased sweating (an anticholinergic side effect of neuroleptics) may explain the hyperthermia. Normal creatine phosphokinase in this patient, and the persistent temperature elevation, suggests less pronounced rigidity and central dysfunction in thermoregulation.

Two etiologic mechanisms for NMS have been recently suggested. First, clinical similarities between NMS and anesthetic-induced malignant hyperthermia (a pharmacogenetic disorder affecting skeletal muscle that leads to rigidity, hyperthermia, shock, and death after exposure to certain inhalational anesthetics or depolarizing muscle relaxants) suggest that they may have the same origin: an abrupt loss of control of intracellular ionized calcium in the presence of triggering agents.[6] Moreover, dantrolene, the recommended treatment for malignant hyperthermia, has been used successfully in some cases of NMS.[7] Most evidence published to date, however, favors a second mechanism: central dopaminergic blockade. Thus, NMS develops most predictably after treatment with neuroleptics, which share the common characteristic of being potent dopaminergic antagonists. NMS develops especially in association with the most potent dopaminergic antagonists among the neuroleptics (haloperidol and fluphenazine). In addition, NMS has been reported after treatment with dopamine-depleting drugs (tetrabenazine and α-methyltyrosine)[8] and after discontinuation of therapy with large doses of antiparkinsonian (dopaminergic) drugs.[3] Furthermore, central dopaminergic hypoactivity could explain the two major clinical features of NMS: severe extrapyramidal symptoms (at the level of striatal dopaminergic neurons) and hyperthermia (at the hypothalamic level). In support of this concept, intracerebrally injected dopamine has been noted to lower body temperature in animals, an effect mimicked by intraventricular or systemic administration of L-dopa or dopaminergic agonists but prevented by neuroleptics.[9] Finally, recent case reports of dramatic improvement after treatment with dopaminergic agents, such as bromocriptine[5] and amantadine,[4] are consistent with the hypothesis that dopaminergic hypoactivity is involved in the pathogenesis of NMS.

To our knowledge, our case report is the first *in vivo* clinical demonstration of such dopaminergic hypoactivity, as evidenced both by diminished GH response to apomorphine and by increased cerebrospinal fluid homovanillic acid (possibly related to enhanced feedback). The possibility of noradrenergic hypoactivity is also suggested by diminished GH response to clonidine and by increased urinary MHPG (even though the clonidine test is less reproducible than the apomorphine test in eliciting GH response). In fact, neuroleptics are potent α-noradrenergic receptor blockers, and noradrenergic pathways (via α-adrenoreceptors) are involved in decreasing body temperature.[10] Thus, this case report suggests the hypothesis that NMS may be associated with hypothalamic and striatal blockade of dopaminergic and possibly α-noradrenergic receptors and may therefore provide a rationale for the use of combination dopaminergic- and noradrenergic-receptor agonists for the treatment of NMS.

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