

Neuroleptic Malignant Syndrome Induced by Low Dose Aripiprazole in First Episode Psychosis

Case presentation:

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CASE PRESENTATION

Introduction

Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction that is potentially life threatening, especially if it is not recognized and treated early. NMS develops on exposure to antipsychotic medications. The incidence of NMS has been reported to be 0.02%–2.44%,¹ with the majority of cases occurring in individuals between 18 and 59 years of age.² The underlying mechanism for the development of NMS is unclear; however, it is believed to be related to rapid dopamine (D₂) blockade by antipsychotics. Of patients who develop NMS, 66% have been reported to have onset of NMS symptoms within 2 weeks after starting an antipsychotic medication.³ In some patients, prodromal symptoms may become apparent within hours of initiating antipsychotic medication. The full syndrome develops in approximately 3–5 days.² The classic triad involves the autonomic nervous system, the extrapyramidal system, and cognitive changes. Proposed research criteria for NMS listed in the *Diagnostic and Statistical Manual for Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR) involve severe muscle rigidity and hyperthermia along with two other criteria, including altered mental status, elevated creatine phosphokinase (CPK), elevated white blood cell count, incontinence, diaphoresis, tremor, mutism, tachycardia, labile blood pressure, and dysphagia, that develop in association with treatment with antipsychotic medication.⁴

NMS is seen less frequently with second generation (atypical) antipsychotics than with conventional antipsychotics.⁵ Aripiprazole is a relatively new antipsychotic with a unique mechanism of action involving partial agonism with high affinity at dopamine D₂ and serotonin 5-HT_{1A} receptors as well as antagonism at serotonin 5-HT_{2A} receptors.⁵ It has been shown to be effective in the treatment of schizo-

phrenia and bipolar disorder, with antipsychotic and antimanic properties superior to placebo at dose ranges of 10–30 mg/day.

The case described here involved a patient with first episode psychosis who developed NMS on a low dose of aripiprazole.

Initial Presentation

Ms. M, a 57-year-old Caucasian woman, was involuntarily admitted. She believed that she had won a lottery and people were after her and trying to kill her to get her money. She appeared to be very suspicious and believed her thoughts were being inserted from outside by some “strange” people in order to control her behavior. Her physical and neurological examinations were normal.

Treatment

Ms. M was given aripiprazole 10 mg/day, which was the only medication she was taking. On day 2, she began to complain of stiffness around her neck. She was found to have muscular rigidity and bradykinesia. Since the extrapyramidal symptoms (EPS) improved with benztropine, the aripiprazole was continued. On day 4, Ms. M developed a shuffling gait, resting tremor, masked face, cogwheel rigidity, and drooling. She became mute and was noted to be confused. She also stopped eating and drinking on her own. Her temperature increased to 101.5°F and her white blood cell count was elevated (16,000/mm³). Her blood pressure ranged between 110/75 and 150/100 mmHg, and her pulse was 108. Her creatine kinase (CK) levels were normal. Although

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some improvement was observed when she was treated with 2 mg of lorazepam, she continued to be catatonic and was transferred to a medical unit. No other etiology was found to explain the findings. To rule out an organic cause for late onset psychosis, a magnetic resonance imaging (MRI) scan of the brain was obtained which was within normal limits. The patient did not have any history of substance abuse, and a urine toxicology screen was negative.

Within 10 days of admission to the medical unit, patient made an uneventful recovery in motor function and self-care after the aripiprazole was discontinued and the lorazepam was increased to 3 mg/day. Unfortunately, a residual state of confusion and slight drooling persisted for several weeks.

Discussion

NMS is unlikely to develop in patients taking aripiprazole because this agent acts as a functional dopamine agonist in hypodopaminergic states. The *Physicians' Desk Reference* mentions two "possible" cases of NMS induced by aripiprazole documented in a premarketing clinical database.⁷ Our case differs from other cases of NMS with aripiprazole reported in the literature,⁸⁻¹⁰ in that the patient developed NMS as described in the DSM-IV-TR at low doses of aripiprazole in first episode psychosis. We found only one recently published report of NMS occurring with aripiprazole in an antipsychotic naïve patient.¹¹ It is believed that lower doses of antipsychotic medication decrease the incidence of NMS. However, this question is controversial given the absence of controlled data comparing the incidence of NMS and dosing strategies. Although it is well known that second generation antipsychotics produce lower rates of EPS relative to conventional antipsychotics, it has been proposed that inadequate control of EPS is a risk factor for NMS.¹² In conclusion, our case report suggests that clinicians should be aware of the risk of NMS even with low doses of second generation antipsychotics and should carefully monitor patients especially when EPS develop.

COMMENTARY by Jack M. Gorman, MD

Although the incidence of NMS has decreased since the introduction of the second generation antipsychotics, Evcimen and colleagues present us with another reminder that these newer agents can still cause NMS. Even clozapine, with its relatively low affinity for the D₂ receptor compared with other antipsychotic drugs,

has been reported to cause NMS.^{13,14} The report here of a case of NMS clearly related to aripiprazole is particularly interesting in view of the drug's unusual mechanism of action. Aripiprazole is a partial D₂ receptor agonist, which supposedly only becomes an antagonist when dopamine levels in the striatum become excessive. Nevertheless, even though only a relatively low dose was involved, there can be no question that aripiprazole was the culprit in this patient.

Another somewhat unusual feature of the case described here is a first onset of schizophrenia in a woman of this age (57). Although late onset schizophrenia has certainly been reported, it is fairly rare. This raises the question not only of diagnosis but also of whether some peculiar physiology of this particular patient made her more sensitive to aripiprazole and/or more vulnerable to NMS. Unfortunately, given our relatively poor understanding of most aspects of antipsychotic drug actions in the brain and our only partial understanding of what precisely causes NMS, this idea must remain purely speculative.

In terms of diagnosis, it is worth noting that the patient's CPK was not elevated. Although this is the sign of NMS that most clinicians seem to remember, it is not always found in NMS. Furthermore, because intramuscular injections also increase CPK levels, in many patients it is never clear if elevated CPK is actually related to NMS. Although in the past I have pointed out that physicians order expensive MRI tests too frequently, in this case the appearance of neurological signs in a woman with new onset psychosis at 57 years of age certainly mandates an MRI scan. Fortunately, no intracranial lesions such as a hemorrhage or mass were seen. Finally, although this patient was febrile, that is not always the case with NMS. I remember a patient with NMS who, because he was also on steroids for a collagen-vascular disease concomitant with psychosis, was not able to mount a febrile response.

Catatonia is sometimes mistaken for NMS. Patients with NMS are often so rigid that they appear catatonic. In patients with a relatively short exposure to antipsychotic drugs who appear to be catatonic, an evaluation for NMS is always recommended.

The treatment of NMS includes stopping the offending antipsychotic drug, stopping anticholinergic drugs, judicious use of benzodiazepines, cooling the patient down, and providing respiratory and cardiac support, usually in an ICU. Because it bears some similarity to the serotonin syndrome and malignant hyperthermia, some clinicians also recommend dantrolene as a treatment for NMS. However, there is no firm evidence that

dantrolene is actually helpful¹⁵ and most clinicians do not use this agent to treat NMS, as was the case with the patient reported here.

This case demonstrates two main concepts. First, aripiprazole, like all other antipsychotic drugs, can cause NMS and, second, that immediate diagnosis and excellent treatment usually lead to a good result.

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