Neuroleptic Malignant Syndrome without Hyperthermia Induced by Aripiprazole Extended-Release Injection

Ilario C, Sentissi O* and Coste C
Department of Mental Health and Psychiatry, University Hospital of Geneva, Switzerland

Abstract

Neuroleptic malignant syndrome may be considered an idiosyncratic neurological condition with potentially lethal consequences associated with the assumption of all antipsychotics, first described in the early sixties in association with the antipsychotic haloperidol. Recently, several cases of the syndrome have been reported in literature as a complication of typical and atypical antipsychotic drugs. Moreover, a widespread use of antipsychotics in numerous neuropsychiatric disorders has lead to the analysis of the risks and consequences of neuroleptic malignant syndromes. This case report describes the occurrence of a neuroleptic malignant syndrome in a 55-year-old woman with intellectual disability presenting with organic delusional disorder, following administration of aripiprazole extended-release injection. Although cases of neuroleptic malignant syndrome induced by aripiprazole or atypical antipsychotics extended-release have been published in literature, this is the first case report regarding a neuroleptic malignant syndrome induced by aripiprazole extended-release injection.

Keywords: Neuroleptic malignant syndrome (NMS); Aripiprazole extended-release injection; Antipsychotic drugs

Introduction

Neuroleptic Malignant Syndrome (NMS) is a rare, idiosyncratic and unpredictable adverse reaction associated to antipsychotic use with life-threatening [1] consequences. All antipsychotics may be associated with the development of a neuroleptic malignant syndrome, especially the first generation antipsychotics (Table 1). The incidence rate of NMS in subjects treated with antipsychotic drugs is actually approximately 0.02%, compared to a rate of 3% recorded 50 years ago [2]. The syndrome occurs in all age groups (including children), but young adults are more affected [3], and the male/female ratio is 2:1 with a high mortality rate in 10-20% of cases. However, lower mortality rates have recently been observed most probably related to early detection of NMS and improved management [2]. The key risk factors for neuroleptic malignant syndrome are demographic (male gender), environmental (restraint, dehydration) and pharmacological (polypharmacy, oral haloperidol, aripiprazole, long-acting flupentixol), because of their pharmacodynamics mechanism. Concurrent medical conditions are also relevant (delirium, confusion) [4]. Authors reported a correlation between a higher proportion of antipsychotics, the pharmacokinetic properties and the severity of the syndrome [5].

The pathogenesis is still unknown [1], but investigations have revealed involvement of two main mechanisms: an abnormal reaction of skeletal muscle with a central D2 receptor blockade [6] and the removal of tonic inhibition from the sympathetic nervous system, with sympathoadrenal hyperactivity and dysfunction leading to autonomic dysfunction [7]. The clinical features are often heterogeneous in onset, presentation and progression. Most patients develop mental status change with delusion, mutism and catatonia, then muscular lead pipe rigidity with tremor, hyperthermia (above 38°C) and autonomic instability [1,8]. Leukocytosis and Creatine Kinase (CK) elevation are commonly observed. The largest systematic review of literature comparing the characteristics and differences of the neuroleptic malignant syndrome induced by first and second generation antipsychotic has reported a lower incidence and severity of symptoms with second-generation antipsychotics with fewer extrapyramidal symptoms and less rigidity [8].

In neuroleptic malignant syndrome subsequent to administration of aripiprazole, rigidity and autonomic symptoms are present in all cases reported [9], with a lower frequency of hyperthermia, diaphoresis and tachypnea than in neuroleptic malignant syndromes induced by other second-generation antipsychotics [1]. However, literature reports three cases of neuroleptic malignant syndrome...
syndrome induced by aripiprazole in which pyrexia was absent [10-12]. On average, neuroleptic malignant syndrome develops 14 days following the initial administration of aripiprazole with a mean prescribed dosage of 5 to 30 mg/day [9], in some clinical illustrations, in association with other psychotropic drugs, such as selective serotonin reuptake inhibitors (fluoxetine and escitalopram) [9]. Selective serotonin reuptake inhibitors (SSRIs) may contribute to the development of neuroleptic malignant syndrome with an increase in serotonin which inhibits dopamine release in the ventral tegmentum area and the substantia nigra [13] and thereby may worsen a hypodopaminergic state induced by antipsychotics. NMS has been reported also in association with escitalopram and citalopram, antidepressants that are not known to inhibit the cytochrome P450 system (the Cyt P450 system is not relevant for NMS-development) [13,14]. Twenty-nine cases of neuroleptic malignant syndrome in association with a second-generation antipsychotic and serotonergic antidepressants have been published in literature, but only one case involved oral aripiprazole and escitalopram, with symptoms appearing after one week of treatment [13,15]. The different types and presentations of NMS could be explained by: different risk factors in populations; possible association of NMS with other lethal syndromes; incidence of NMS in patients treated by neuroleptic agents, which is still unclear (from 0.7% to 2.2%) [6].

In our knowledge, this is the first case report concerning a neuroleptic malignant syndrome induced by aripiprazole extended-release injection, medication, which is increasingly being prescribed by clinicians.

**Case Presentation**

Mrs F, a 55-year-old Caucasian single woman presented a medical history of intellectual disability caused by traumatic brain injury at the age of 17, and organic delusional disorder with supposedly related temporal lobe epilepsy. She was monitored in outpatient psychiatric basis and received treatment with quetiapine 300 mg twice daily, lorazepam 1 mg three times daily and amlodipine 5 mg daily. However, the patient experienced an episode of aggressiveness consistent with delusional phenomena and recurrences due to poor treatment compliance. She was admitted to our psychiatric crisis unit for the fourth time in 2016, accompanied by her mother following an acute exacerbation of auto and hetero-aggressiveness and delirious speech. In a patient with organic encephalopathy, using atypical antipsychotics is "off-label", but in this clinical situation of chronic psychosis and behaviour disorder such as aggressiveness, this treatment remains one of the few options available. On admission, Mrs F presented an abrupt change from baseline mental status with severe anxiety and inappropriate affect. On examination, no abnormalities were detected. Urine and blood tests were within normal limits. Following consultation with the patient and her family, we decided to switch to aripiprazole extended-release injection (400 mg), in favour of its adequate safety profile, few metabolic side effects and its powerful/ solid anti-impulsive and antipsychotic effects. Subsequently, we prescribed oral aripiprazole 15 mg/day with a reduction of quetiapine at 300 mg/day for a week, then discontinued. The first injection of aripiprazole extended-release (400 mg) was administered fourteen days after oral administration (Figure 1). No side effects were observed. The level of aripiprazole the day after the injection was at 507 nmol/l (330-1115 nmol/l), and active metabolite (dehydroaripiprazole) at 287 nmol/l. Ten days after the treatment, the level of aripiprazole was at 332 nmol/l and the level of dehydroaripiprazole at 225 nmol/l. Eight day after the injection, the patient experienced mood worsening with feelings of worthlessness and escitalopram 5 mg/day was introduced. Eleven days after the first injection of aripiprazole extended-release, the patient complained of muscular rigidity and intermittent mutism. The examination showed a mild rigidity, slight decrease in deep tendon reflexes with walking abnormalities and asymmetric upper limb tremor. The day after, the patient was transferred to the emergency department with suspected neuroleptic malignant syndrome due to a sudden deterioration of the clinical symptoms (dilated pupils, heavy sweating and diarrhea were absent). The patient was aggressive and presented fluctuating level of conscientiousness, limbs and axial extrapyramidal symptoms (such
as severe rigidity, hypokinesia, dysphagia and asymmetric upper limb
tremor), poverty of speech, intermittent mutism. Mild hyperreflexia,
no dystonia and no posturing. Mrs F’s temperature was 37.5°C, blood
d pressure 155/93 mmHg, pulse 106 beats per minute, respiratory rate
20 per minute (baseline for the subject: 140/80 mmHg, 70 beats per
minute). Laboratory data showed leucocytosis (13,000 cells/mm³),
increased creatine phosphokinase (CK: 8,511 IU/L) and acute renal
failure (serum creatinine: 89 µmol/L; glomerular filtration flow:
63 mL/min/1.73m²), other blood test values, complete metabolic
panel and ionogram levels were all within normal limits. Immediate
electroencephalographic (EEG) examination showed global slow
activity without argument for comitiality or metabolic disorder. The
magnetic resonance imaging showed damage to the left temporal lobe
caused by brain injury (at the age of 17).

On Sachdev rating scale for NMS [16], Mrs F’s rating is 16 on
36. When NMS is suspected, a score superior to 8 is in favour of
the diagnosis. On Naranjo Scale, Mrs F’s rating is 9 on 13, a score superior
to 9 is in favour of the diagnosis of adverse drug reaction.

Some drugs, like bromocriptine mesylate (a dopamine agonist),
could be used to treat NMS. However, the supportive and symptomatic
therapy is the most common treatment, because the safety of other
therapies is still unclear. So, the supportive treatment was started.
Oral aripiprazole and escitalopram were discontinued abruptly
(71.4%) and chlorpromazine (11%) in acute complicating
in NMS. Moreover, symptoms are progressive in NMS whereas in
neuroleptic malignant syndrome and serotonin syndrome they develop faster. In some cases an overlap of
both, but muscular rigidity, hypertonia and bradykinesia are specific
to aripiprazole compared to both traditional [17] and atypical
antipsychotic drugs [9].

The atypical clinical presentation of NMS following aripiprazole
administration could be related to its peculiar pharmacodynamic
profile [1]. In fact, aripiprazole possesses a partial agonist activity
at D2 and 5-HT2A receptors, with an affinity 20-fold lower than haloperidol affinity
for D2 [10]. This unique characteristic may be related to the lower
severity rate and duration in contrast to neuroleptic malignant
syndrome induced by other atypical antipsychotics.

Neuroleptic malignant syndrome may be deceptive in
presentation. The most important differential diagnosis is serotonin
syndrome, which can have similitudes in clinical presentation[2].
Hyperthermia, tremor and alteration of mental status can occur in
both, but muscular rigidity, hypertonia and bradykinesia are specific
in NMS. Moreover, symptoms are progressive in NMS whereas in
serotonin syndrome they develop faster. In some cases an overlap of
neuroleptic malignant syndrome and serotonin syndrome may occur
[18].

In this case, the progressive installation of extrapyramidal
symptoms (tremor, hypokinesia and severe rigidity), mutism and
dysphagia associated with CPK elevation and leucocytosis is in favour
of a NMS. However in our case report a typical feature of serotonin

### Table 1: Neuroleptic malignant syndrome induced by aripiprazole.

<table>
<thead>
<tr>
<th>Article</th>
<th>Cases</th>
<th>Indication of aripiprazole treatment</th>
<th>Dosage of aripiprazole</th>
<th>Day to onset</th>
<th>Symptoms</th>
<th>Main findings</th>
<th>Duration of NMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trollor [9]</td>
<td>Nine cases</td>
<td>Psychotic disorder (67%)</td>
<td>Mean 18 mg/day</td>
<td>Range 2-270 days</td>
<td>Rigidly (100%), altered mental status (78%), hyperthermia range 37.1-38.4°C (78%)</td>
<td>Men (67%), age lower than typically seen in NMS, CK&gt;1,000 U/L (50%), white cell count elevated (75%)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Belvederi [1]</td>
<td>Five more cases</td>
<td>Psychotic disorder (71.4%)</td>
<td>Mean 18.9 mg/day</td>
<td>Earlier or on the same day of NMS diagnosis</td>
<td>Rigidly (100%), altered mental status (100%), lower frequency of hyperpyrexia, nausea and vomiting</td>
<td>Rhabdomyolysis associated with a lower peaks of CK</td>
<td>Mean 7.5 days</td>
</tr>
<tr>
<td>Molina [10], Chakraborty [11], Spalding [12]</td>
<td>Three cases without fever</td>
<td>paranoid schizophrenia, childhood-onset schizophrenia, paranoid schizophrenia</td>
<td>15 mg/day, 30 mg/day, 15 mg/day</td>
<td>270 days, 2 days, 3 days</td>
<td>Rigidly, choreoathetoid movements, Rigidity, mutism, catatonia</td>
<td>CK:103 U/L, CK:955 U/L, CK:762 U/L</td>
<td>9 days, 7 days, unknown, more than 4 days</td>
</tr>
<tr>
<td>Our case report</td>
<td>One case</td>
<td>organic delusional disorder</td>
<td>Aripiprazole extended-release 400 mg IM</td>
<td>Eleven days</td>
<td>Muscular rigidity, asymmetric upper limb tremor and akinetic mutism</td>
<td>Leucocytosis CK: 8,511 U/L</td>
<td>60 days</td>
</tr>
</tbody>
</table>

### Discussion

We report a case of a patient with neuroleptic malignant syndrome induced by Aripiprazole Extended-Release Injection. We carried out an exhaustive literature review and we found eighteen case reports with similar characteristics following administration of aripiprazole [9-12] (Table 1), not related to an “off-label” use.

In this clinical situation, rigidity and autonomic characteristics were observed, in line with all cases of neuroleptic malignant syndrome caused by aripiprazole reported. These symptoms are more common compared to cases of patients using clozapine, olanzapine and quetiapine [9]. Furthermore, other extrapyramidal signs detected in our patient such as tremor and hypokinesia, are predominantly related to aripiprazole compared to both traditional [17] and atypical antipsychotic drugs [9].

Some drugs, like bromocriptine mesylate (a dopamine agonist), could be used to treat NMS. However, the supportive and symptomatic therapy is the most common treatment, because the safety of other therapies is still unclear. So, the supportive treatment was started. Oral aripiprazole and escitalopram were discontinued abruptly (the most important intervention), lorazepam 0.5 mg 4 times a day was administered with nursing care, close clinical and paracrilinal monitoring. The patient overall showed slow but progressive improvement in motor and cognitive functions. However, during the two months of treatment in a somatic unit, she developed a number of complications: acute renal failure due to rhabdomyolysis for which a intravenous hydration has been helpful; acute urinary retention that required the instalment of a probe; acute aspiration pneumonia due to swallowing impairment, treated with clindamycin (injection 600 mg 1x/8h, 1800 mg daily). The patient recovered gradually and benefit from progressive administration of clozapine, before returning to our unit. After four months of inpatient care, Mrs F finally went back home.
syndrome, hyperreflexia, was present on diagnosis, most likely related to the use of therapeutic doses of escitalopram.

Neuroleptic malignant syndrome is a life-threatening neurologic emergency, and the risk of a recurrent episode after restarting on neuroleptic agents is relatively high but difficult to quantify. An apparent decrease in severity is, however, suggested by the lower mortality rate reported in the last decade [10]. This may relate to early detection of neuroleptic malignant syndrome as well as to improvements in management of the condition or lower severity with atypical antipsychotics [6]. Subsequent to neuroleptic malignant syndrome, over 30% of patients develop major complications during the first weeks, together with potential persistent long-term sequelae [19]. Considering the impact of genetic polymorphisms on the elimination of aripiprazole, a genotype / phenotype test of CYP2D6 may also be proposed. Allelic variants altering CYP2D6-mediated metabolism may be associated with an increased risk of NMS [13].

Case reports of neuroleptic malignant syndrome induced by aripiprazole or by second-generation antipsychotics extended-release have been published in literature, but we report herein the first case of a neuroleptic malignant syndrome induced by a different formulation of aripiprazole, the extended-release injection never been described in the literature. In conclusion, this original case report may be considered important contribution for clinicians in their daily practice in order to appropriately investigate and address to the serious side effects of extended-release injection of aripiprazole, causing a more prolonged course of NMS. The atypical clinical presentation of NMS following aripiprazole administration could be related to its peculiar pharmacodynamic profile, which represents a modern and innovative therapeutic tool in the treatment of major psychiatric disorders [20]. However, this case report cannot give information on incidences or prevalence and further research is required to increase our knowledge of the consequences and efficacy of treatments and to better understand neuroleptic malignant syndrome, especially in the extended release formulation.

Acknowledgments

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References