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What About Neuroleptic Malignant Syndrome In The Atypical Era? An Algerian Experience

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Abstract:
Neuroleptic malignant syndrome (NMS) is a rare but serious complication of neuroleptic treatment, which can be life threatening in 10-20% of cases. It represents a neuropsychiatric diagnostic and therapeutic emergency. Individualized as "akineto-hypertonic syndrome" by Delay and Deniker. Its incidence is currently estimated at between 0.01 and 0.02% of patients receiving antipsychotic treatment of all classes. The sex ratio is two men to one woman. Clinically, NMS manifests as hyperthermia, rigidity and dysautonomia with disturbed consciousness. Biologically, a constant increase in creatine phosphokinase (CPK) is associated with hyper-leukocytosis. The imputability of NMS to conventional neuroleptics (NC) has been widely demonstrated. Nevertheless, cases of NMS following the prescription of atypical antipsychotics (AA) have been reported in the literature. What is our experience of prescribing first and second generation neuroleptics in relation to NMS? In our article, we present three clinical cases of genuine malignant syndrome, illustrating all the diagnostic and therapeutic difficulties, via a brief review of the literature. The first case, of a young 17-year-old patient hospitalized for his 2nd brief psychotic episode, presented with NMS fifteen days after his stay, during a switch between a 1st and 2nd generation neuroleptic (olanzapine). In the second case, a 34-year-old patient with decades of schizophrenia developed NMS ten days after switching to a conventional antipsychotic. Finally, the third patient, aged 53, suffered an NMS after a combination of a long-acting neuroleptic and haloperidol and chlorpromazine in intramuscular injection.

Key Word*: neuroleptic malignant syndrome, classic neuroleptic, atypical neuroleptic.*

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I. Introduction

Neuroleptic malignant syndrome (NMS) is a rare but formidable complication of neuroleptic treatment, sometimes life-threatening in a quarter of cases (10-20%) [1]. Individualized in 1960 from the work of Delay and Deniker as "akineto-hypertonic syndrome", it is a rare nosological entity given the widespread use of neuroleptics [2]. The fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) categorizes neuroleptic malignant syndrome as a movement disorder and other drug-induced adverse effects (APA, 2013) and has proposed a number of diagnostic criteria presented in (Tab 1)[3]. The risk is greatest when neuroleptic treatment is first introduced, regardless of dose. While the relationship between NMS and conventional neuroleptics (NC) is well established, several authors have reported cases of NMS following the prescription of atypical antipsychotics (AA), notably clozapine, olanzapine, quetiapine and amisulpride [4]. According to prospective studies, estimates of its frequency range from 0.02 to 2.4% of people receiving antipsychotics, regardless of dosage and route of administration [5].

The difficulties associated with this issue lie in the delayed diagnosis of atypical cases of NMS, rapid management and the reintroduction or non-reintroduction of antipsychotic treatment, since its severity can be life threatening, as mentioned above.

What is our experience of first and second-generation neuroleptic prescriptions in relation to SMN? In our article, we present three clinical cases of genuine malignant syndrome, illustrating all the diagnostic and therapeutic difficulties, via a brief review of the literature.

II. Patients and observations

1st clinical case:

Adolescent B.N, aged 17, had been hospitalized for a second brief psychotic episode with severe behavioral disturbances. A fortnight after his hospitalization, the young adolescent presented a deterioration in general condition during a Switch between 1st and 2nd generation neuroleptics. The prescribed doses were 40 drops per day of haloperidol and 1 x 10 mg tablet of olanzapine. He was rushed to a medical intensive care unit after the onset of neuropsychiatric symptoms including lockjaw, rigidity, dyskinetic movements, tension lability,

akathisia, tasikinesia, tremors, hypersialorrhea, hypersudation, tachycardia at 147 beats per minute and dyspnea. All of this evolved in a febrile context (40°C), with no obvious infectious focus. Biological tests revealed only a tenfold increase in creatine phosphokinase (CPK): 2146 IU/l. NMS was diagnosed according to DSM-5 criteria (Tab.1). The patient's general condition improved just under symptomatic treatment with fluid and electrolyte rehydration and diazepam after one week, with progressive decrease in CPK. Reintroduction of a 3rd-generation antipsychotic, aripiprazole 10 mg daily, one month after total stabilization of hemodynamic and biological functions.

Table 1: diagnostic criteria for NMS according for dsm-5 [3].

diagnostic criteria for neuroleptic malignant syndrome
Exposure to a dopamine antagonist, or discontinuation of a dopamine agonist, in the last 72 hours before the development of symptoms; - Hyperthermia > 38°C on at least 2 occasions; - Profuse sweating; - Generalized muscular rigidity, described as "lead-pipe-like" in the most severe forms; - altered mental state, characterized by delirium or altered consciousness ranging from stupor to coma; - Elevation of creatine phosphokinases (CPK) to at least 4 times the upper limit of normal; **Autonomic nervous system activation and instability, manifested by** : · Tachycardia (heart rate at least 25% higher than baseline), - Hypersudation, - Elevated blood pressure (systolic or diastolic increased by at least 25% over baseline) or fluctuating blood pressure (change in diastolic ≥ 20 mm Hg or change in systolic ≥ 25 mm Hg in the last 24 hours), - Tachypnea (respiratory rate increased by at least 50% over baseline), - Urinary incontinence and pallor; **Symptoms are not due** to another substance or other neurological or general condition and are not explained by an underlying mental disorder.

2nd clinical case:

Mr. O. K, aged 34, was treated for schizophrenia since the age of 20, with moderate cannabis use. A "sensitivity" to first-generation neuroleptics was noted ten days after his hospitalization: muscular rigidity with tremors, blood pressure lability and profuse sweating appeared with a haloperidol-based treatment: 120 drops three times a day and 100 mg/d of Levomepromazine in the evening. Neuroleptic treatment was then immediately interrupted and diazepam was administered for symptomatic treatment of pre-existing extrapyramidal side effects. Two days later, the clinical picture worsened with the onset of fever at 39.5°C, without any notable infectious focus, with exaggeration of the extrapyramidal syndrome, generalized rigidity, tachypnea at 145 beats per minute and somnolence. The clinical picture was rapidly completed by hyper-sudation and respiratory difficulties due to bronchial congestion. Biological tests revealed hyperleukocytosis at 13.7 k /ul, rhabdomyolysis with CPK elevated to 6963 IU/l and LDH to 985 IU/l, and severe acute renal failure with creatinine clearance at 10 ml / min. Liver function tests were disturbed, with a prothrombin time of 50%. The diagnosis of NMS was based on the Levenson criteria, with 3 major and 6 minor criteria (Tab. 2) [6].

Based on these findings, the patient was admitted to intensive care. Management was based on immediate discontinuation of antipsychotics, hydro-electrolytic hyper-rehydration, and administration of muscle relaxants for rigidity, oxygen therapy and antipyretics. In view of the persistence of NMS, the onset of consciousness disturbances and an increase in CPK (30,000 IU/l), as well as a worsening of rigidity, Bromocriptine was gradually introduced on the 25thday after the onset of NMS, due to the lack of availability of Dandrolème (antidote). This prescription had led to a progressive regression of symptoms after three months from the start of the process, resulting in serious complications such as aphasia lasting several months, multiple pressure sores at support points and coxis, which required care for several months. Unfortunately, the long-term rigidity resulted in permanent motor disability of the lower limbs due to severe tendon retractions in the knees, for which the surgical indication was unsuccessful.

3rd clinical case:

Mr A.A, aged 53, had suffered from schizophrenia since the age of 32. He had been hospitalized on the 9th day of 100 mg fluphenazine decanoate for psychotic decompensation. He had been treated with sedative neuroleptics such as chlorpromazine, and on the 15th day of hospitalization, the patient was put on injectable haloperidol and chlorpromazine in high doses to control the agitated states. Signs of neuroleptic impregnation were noted, and 48 hours later, the patient's condition worsened with the appearance of symptoms suggestive of NMS according to DSM-5 criteria (Tab.1), despite the absence of fever, notably blood pressure lability, tachycardia at 150 beats per minute, extrapyramidal stiffness, trismus, hypersialorrhea, asthenia and profuse sweating. Biological tests revealed elevated CPK levels (1694 IU/l) and an ionic disorder.

The patient was transferred to an intensive care unit, where a rehydration regimen with correction of the ionic disorder was recommended. The NMS regressed after 48 hours, with clinical and biological improvement. Two days later, the patient died of cardiac arrest.

Table 2: Diagnostic criteria for NMS according to Levenson [6].

Major signs or symptoms		**Minor signs or symptoms**	
Fever, rigidity, elevated creatine phosphokinase		Tachycardia, tachypnea, profuse sweating, abnormal blood pressure, leukocytosis, altered consciousness	
Criteria Diagnostic original	**3 majors** or **2 majors** + 4 minors	Diagnostic criteria (probable NMS)	**2 majors** + 2 minors or **1major** + 4 minors

III. Discussion

Clinical and biological expression:

First mentioned in 1960 by Delay and Denker following the description of a case on haloperidol [2], neuroleptic malignant syndrome (NMS) is a rare adverse effect associated with the use of antipsychotics and drugs altering dopaminergic neurotransmission, and is life-threatening in 10% to 20% of cases[1]. Data from database studies suggest an incidence rate for NMS of 0.01-0.02% among patients on antipsychotic treatment of all classes [3]. The sex ratio is two men to one woman, with young people more likely than the elderly [7]. Statistically, men under the age of 40 appear to be at greater risk of NMS, but in clinical case 3, this complication occurred after the age of 50. The onset of the syndrome is idiosyncratic[7]. According to published case reports, the majority of cases of neuroleptic malignant syndrome appear in two-thirds of cases within the first two weeks following the introduction of a neuroleptic [5].

This may be due to an increase in the dosage of a current treatment, to combinations, or to a switch between first and second generation neuroleptics [8], as in clinical illustration 1. However, neuroleptic malignant syndrome can occur at any time during treatment. In our three patients, NMS manifested itself between 48 hours and two weeks after the start of antipsychotic treatment. The clinical and biological expression of NMS is associated with unexplained hyperthermia (except in clinical case 3), pallor and rigidity of the skeletal muscles ("lead pipe"), extrapyramidal involvement responsible for akinesia, dyspnoea and swallowing disorders, as well as rhabdomyolysis, and neurovegetative imbalance (or vegetative dysautonomia) with profuse sweating, tachycardia and hypersialorrhea. Disturbances of alertness generally set in within 24 to 48 hours, with thermal ascension, cardiorespiratory and neurological disorders if treatment is not suspended in time. The clinical pictures were typical, especially in the 2nd case. The diagnosis of NMS was made according to the DSM-5 or Levenson criteria [3, 6]. In clinical case 3, however, we note the absence of fever throughout the evolutionary process.

Indeed, incomplete pictures of NMS have been described [9]. In particular, Thase and Shostak [10] reported the observation of a patient presenting with rhabdomyolysis, an elevated blood CK level and extrapyramidal hypertonia without fever. Pope et al [11], in their work, considered hyperthermia to be a major diagnostic criterion for NMS, but 11 of their patients had a temperature below 38°C. Angelopoulos et al [12] reported a case of NMS without fever secondary to the combination of amisulpride and oxcarbazepine. Early warning signs of NMS were noted in our three cases, notably signs of vegetative dysfunction such as hypersudation and arterial instability, which preceded the onset of hyperthermia.

Biological workup will readily show elevated creatine phospho-kinase (CPK) in excess of four times normal, LDH, SGOT and SGPT, and hyperleukocytosis of more than 15,000 white blood cells per liter with polynucleosis.

In all three clinical cases, classical neuroleptics were clearly implicated in the onset of NMS, but the hypothesis of atypical neuroleptics or their combination cannot be formally ruled out. Nevertheless, in our clinical cases, a number of risk factors have been identified:

- Associations between:
- A classic antipsychotic and a toxic intake in clinical case n°2,
- A classic antipsychotic and an atypical antipsychotic in clinical case n°1,
- A classic antipsychotic and a long-acting neuroleptic in clinical case n°3
- Administration of high doses of neuroleptics in an elderly patient in clinical case 3, which probably led to multivisceral failure and death.

Etiopathogenic context:

The pathophysiology of neuroleptic malignant syndrome remains controversial [3, 13]. Nevertheless, there are several theories aimed at explaining the pathophysiological mechanisms leading to neuroleptic malignant

syndrome [14-15]. We will mention the two basic pathophysiological theories of NMS. The first is peripheral, and relates to the effect of calcium release in the sarcoplasmic reticulum of striated muscle cells, resulting in permanent muscle contraction and increased body temperature. This is exactly what happened in clinical case 2, with its severe motor complications. The second theory is a central one: the central anti-dopaminergic activity of neuroleptics stimulates the cholinergic system, inducing an extrapyramidal syndrome of rigidity and tremor.

The hyperthermia of neuroleptic malignant syndrome appears to be the result of three associated elements:
- Increased thermogenesis, mainly through muscular contracture;
- Impaired thermoregulation;
- Reduced thermolysis, which is linked to several defective mechanisms, including cutaneous vasoconstriction responsible for the frequently described pallor.

The differential diagnosis of NMS is essentially made with serotonin syndrome, and with infectious and toxic causes of central nervous system damage [15]. Progress is closely linked to the speed with which the diagnosis is made [16].

In terms of management:

As the average recovery time after discontinuation of treatment is 7-10 days, due to the half-life of these drugs, most people recover within a week, and almost all within 30 days [3]. In our patients, this dysfunction necessitated suspension of the neuroleptic in question, and symptomatic treatment was sufficient to reverse the SMN in case n°1 after one week. In case n°2, on the other hand, resolution took 3 months. In fact, with specific therapies introduced early, such as bromocriptine, this would have been shorter, and we might have avoided the serious complications, namely renal failure due to prolonged rhabdomyolysis in a patient in multi-visceral failure: respiratory distress, liver failure, associated with DIC. Indeed, all these complications have been described in case studies in the literature [3, 10, 16].

As for case n°3, the question remains unanswered as to the cause of death: Was death due to a complication of NMS? A malformation or heart disease? Alternatively, any other cryptogenetic cause?

The reintroduction of neuroleptics was deferred until the NMS was completely cured, while using low-activity neuroleptics and avoiding delayed forms. Indeed, patients with a history of malignant syndrome are at greater risk of relapse, with a recurrence rate of 30% [1, 2, 7]. Studies have shown that the average time to recovery from NMS is 26 days for delayed neuroleptics and 13 days for other neuroleptics [7]. In our case, treatment was resumed after six weeks for the first case and one year for the second, given the state of somatic deterioration and the temporary disappearance of psychiatric symptoms.

Treatment was prescribed at half dose, with a change of molecule in line with recommendations [15]. Both patients were closely monitored clinically and biologically, in particular with regular CPK measurements for the first three months, and in the event of early symptoms such as altered consciousness and generalized rigidity when treatment was resumed.

Conflicts of interest

The authors declare no conflicts of interest.

IV. Conclusion

In our experience, no cases of NMS due to Atypics have been reported in the number of validated studies. The cases encountered are more or less induced by classical neuroleptics with pre-existing risk factors, but the likelihood of an atypical neuroleptic being incriminated cannot be ruled out, especially as many cases of acute dyskinesia syndrome induced by atypical neuroleptics have been recorded, which should prompt caution.

The seriousness of the complications induced by neuroleptics makes them a therapeutic class, which must be handled with great caution, weighing up the risks and benefits of each prescription, especially as the pathophysiology of this syndrome remains virtually unknown. The classic recommendations for preventing NMS remain valid, in particular caution with regard to drug combinations (especially neuroleptics) likely to induce such a complication.

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