Diagnostic and therapeutic challenges in neuroleptic malignant syndrome: a severe medical case

Problematiche sulla diagnosi e sul trattamento della sindrome maligna da neurolettici: un caso clinico severo

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SUMMARY. Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic medical emergency usually associated with the use of dopamine antagonists, commonly typical antipsychotic drugs. However, it has been observed that it can occur with atypical antipsychotics as well. NMS is characterized by altered consciousness, fever, rigidity, autonomic instability and high creatine phosphokinase (CPK) blood levels. Here, we report a case of a 44-year-old female patient with history of a treatment-resistant bipolar disorder. She was admitted to our psychiatric ward for severe psychomotor agitation and treated with a therapy based on typical and atypical antipsychotics. During the course of the hospitalization she developed NMS. In this case, the diagnosis was delayed due to the slow and insidious symptom presentation, therefore requiring a differential diagnosis. Autoimmune NMDA receptor encephalitis, catatonic syndrome and malignant catatonia have been excluded. The patient met all the DSM-5 criteria for NMS: exposure to dopamine-blocking agent, severe muscle rigidity, fever, diaphoresis, dysphagia, altered level of consciousness, mutism, tremors, tachycardia, high or labile blood pressure, leukocytosis, high creatine phosphokinase. Since robust evidence-based protocols are lacking, here we discuss the relevance of this case in order to highlight the hurdles of a prompt diagnosis, clinical management of associated complications and treatment possibilities for such emergency.

KEY WORDS: neuroleptic malignant syndrome, differential diagnosis, severity, treatment.

RIASSUNTO. La sindrome maligna da neurolettici (SMN) è una emergenza medica rara usualmente associata all'uso di antagonisti della dopamina, più comunemente agli antipsicotici tipici. Tuttavia, la SMN può verificarsi anche con l'uso di antipsicotici atipici. È caratterizzata da un'alterazione dello stato di coscienza con febbre, rigidità, instabilità autonomica ed elevazione del valore delle creatinfosfochinasi. Qui riportiamo il caso di una paziente di 44 anni con una storia di disturbo bipolare resistente al trattamento, che è stata ricoverata presso il nostro SPDC per grave agitazione psicomotoria, e trattata con una politerapia che comprendeva antipsicotici tipici e atipici. Nel corso del ricovero ha sviluppato una SMN, la cui diagnosi è stata ritardata a causa della lenta e insidiosa presentazione dei sintomi per cui è stato necessario effettuare un'accurata diagnosi differenziale. Sono state escluse l'encefalite autoimmune anti-recettore NMDAR, la sindrome catatonica e la catatonia maligna. Il quadro soddisfaceva tutti i criteri DSM-5 per la SMN: esposizione ad agenti bloccanti dopaminergici, grave rigidità muscolare, iperpiressia, diaforesi, disfagia, alterazione dello stato di coscienza, mutacismo, tremori, tachicardia, pressione arteriosa elevata o labile, leucocitosi, elevazione delle creatinfosfochinasi. Il caso qui discusso è rilevante per evidenziare le difficoltà di una diagnosi tempestiva, della gestione clinica, delle complicanze associate e delle scelte terapeutiche, a causa della mancanza di un solido protocollo evidence-based per il trattamento di questa emergenza.

PAROLE CHIAVE: sindrome maligna da neurolettici, diagnosi differenziale, severità, trattamento.

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a life-threating condition that most commonly occurs following the administration of antipsychotics or their rapid discontinuation. NMS is more often associated with the use of first generation antipsychotics with high potency[1]. However, a large number of existing studies identified an association of NMS with new generation antipsychotics[2] and also with clozapine are described many cases of NMS commonly after an abrupt discontinuation[3]. Since incidence rates of NMS in broader literature range from 0.01 to 3.2%[4,] it is clear that this syndrome still represents an important cause of mortality and morbidity amongst patients treated with antipsychotics[5]. For this reason, it is mandatory for these cases to be considered with greater attention.

CASE REPORT

C.C. is a 44-year-old female patient suffering from bipolar disorder with psychotic features, diagnosed at the age of 17. In her past medical history, she presented with 5 hospitalizations due to severe mixed episodes with psychomotor agitation, poor pharmacological response and recurrent extrapyramidal side effects (such as rigidity, tremors, akathisia and sialorrhea). These episodes were followed by periods of good psychopathological compensation, but the patient never showed a complete functional remission during time and she was unable to recover a full affective and working autonomy, therefore depending on her family for assistance.

Throughout the years, the patient has been treated with mood stabilizers (e.g. lithium, valproic acid and carbamazepine), first generation antipsychotics (FGA) (e.g. chlorpromazine, thioridazine, clotiapine and haloperidol), second generation antipsychotics (SGA) (e.g. risperidone and quetiapine) and benzodiazepines (BZD), with a poor success on preventing relapses. In 2005, due to the pharmacoresistance, the patient switched to Leponex (Italian brand-name for clozapine) 200 mg daily, showing a moderate functional improvement and a good psychopathological stability for many years. On December 2017, the patient started to use the generic drug since the brand-name one was no more available in Italy. From there on, the family reported the gradual onset of various and worsening symptoms, ranging from disinhibition, formal thought disorders, somatic delusions, secondary depressive delusions, anxiety and subtotal insomnia. In September 2018, the patient came to our psychiatry unit with a two-month-long history of severe psychomotor agitation, hyperactivity, aggression, oppositional and inappropriate behavior. The first two days in the emergency unit the patient received therapies as needed with: sodium valproate 400 mg + delorazepam 2 mg iv, haloperidol 5 mg + delorazepam 2 mg im, promazine 25 mg im, aripiprazole 9,75 mg im + lorazepam 4 mg im. Upon admission, the following therapy was administered: aripiprazole 9.75 mg im twice daily, and lorazepam 4 mg im three times daily. Aripiprazole injections were then discontinued and switched to 30 mg tablets once daily, has been restored the therapy with clozapine 150 mg daily and added valproic acid 400 mg. iv once daily. In addition, on the first night the patient received chlorpromazine 100 mg *per os.* However, we were unable to check whether the patient was taking clozapine regularly at home, because the family did not share any detail. Due to the persistence of agitation and oppositional symptomatology, beside to severe thought and behavioural disorganization, delusions, auditory allucinations and self-injurious behaviour started at day 2 from hospital admission, the patient was phisically restrained (according to the protocol of Fondazione Policlinico Tor Vergata).

Notwithstanding, during the second day of treatment the patient presented with fever up to 38.1 °C, 37.8 °C during the third day and between 37.2 and 37.7 °C during the following 20 days. Urine culture test, chest x-ray and a pneumology visit were performed in order to exclude infections and they resulted negative. However, she received an antibiotic therapy based on ceftriaxone 2 mg iv, daily.

Staring from the fourth day, together with hyperpyrexia, the patient showed a significant increase in creatine phosphokinase (CPK) blood levels, from 185 up to 1507 IU/L at day 4 and up to 2204 IU/L at day 5. Additionally, the red blood cells count increased up to 14.54 mil/ml, with an elevation of myoglobin and LDH.

During the sixth day, the patient started to experience severe dysphagia, which required the insertion of a nasogastric tube for both feeding and therapy administration. She also presented with other multiple medical conditions, such as pressure lability (ranging from 140/80 up to 178/92), tachycardia (ranging from 98 up to 141 bpm), diaphoresis and seborrhea. Following the sixth day after the admission, the patient began to alternate between agitation, hypoactivity, motor slowing and sedation, she appeared increasingly confused, disorganized, violent outbursts, and the clinical picture was similar to a delirium.

For this reason, on the twelfth day, aripiprazole was discontinued and clozapine was increased up to 175 mg. daily.

On day 15 the patient started to show a high degree of extrapyramidal generalized rigidity, mutism, amimia and tremors. With the appearance of extreme muscle stiffness, a major criterion necessary for the diagnosis of NMS, together with the exposure to a dopaminergic blocker and hyperpyrexia[6], the diagnosis of Neuroleptic Malignant Syndrome has been made. Also, many of the previous symptoms and signs such as the increase blood levels of CPK, leukocytosis, autonomic dysfunctions, dysphagia, delirium, have been traced back to NMS, which in this case has had a slow and insidious evolution. For this reason, clozapine was initially reduced and then discontinued after few days, in the hypothesis that it may have played a role in the clinical evolution. Finally, also valproic acid was discontinued for an elevation of lipase (123 U/L), and the patient received only delorazepam 9 mg. daily.

Further investigations were done in order to rule out other organic disorders, such as anti-NMDA autoimmune encephalitis[7,8], which present with confusional symptoms, catatonia, visual hallucinations[9], and with neurological symptoms like seizures, movement disorders, ataxia, dystonia and the MRI is often positive. However, brain CT scan, brain MRI and cerebrospinal fluid antibody analysis resulted negative. Only EEG showed right centrotemporal theta-beta paroxysmal alterations together with diffuse slowing. For this reason, the patient received levetiracetam 500 mg twice daily.

The severity of NMS is also linked to frequent and often severe intercurrent medical complications. During the hospitalization, C.C. developed 5 systemic infections[10]. On day 20, temperature increased up to 38.8 °C, with blood cultures testing positive for Staphylococcus Hominis and urine cultures for Candida Albicans, treated successfully with gentamicin and fluconazole. On day 35 fever increased again up to 37.5 °C, with urine culture testing positive for Klebsiella Pneumoniae, treated effectively with piperacillin-tazobactam for two days and then switched to ertapenem for 15 days. On day 60 the patient had hyperpyrexia again, with temperature rising up to 39 °C, urine culture positive for Candida Albicans and blood culture positive for Pseudomonas Aeruginosa. Hence, a therapy with fluconazole for 20 days and ciprofloxacin for 4 days was administered. On day 67 blood cultures were positive for Staphylococcus Hominis and urine cultures were positive for Klebsiella Pneumoniae, treated successfully with meropenem and ertapenem for two weeks.

In addition, during the first 60 days the patient had severe electrolyte alterations, such as hypokalemia, with potassium blood levels ranging from 2.5 and 3.4 mEq/L, and hypomagnesemia, with magnesium blood levels ranging from 1.05 and 1.58 mg/dl. However, both electrolytes were restored when needed.

What is described are the possible severe complications that can occur in the course of an SMN, which must be identified and treated promptly. In the first two and half months, no specific therapy was performed for NMS, but enteral and parenteral nutrition, electrolyte imbalances and medical complications were treated over time. The patient underwent pharmacotherapy comprising only levetiracetam and benzodiazepines and, as soon as possible,

started physiotherapy with passive mobilization. After this time the symptoms began to improve gradually. Dysphagia progressively decreased, the nasogastric tube was removed and the patient started oral feeding again. She became more collaborative and communicative with her family. However, due to the persistent extrapyramidal rigidity, the patient received levodopa 200 mg-benserazide 50 mg ¼ of tablet three time daily, with rapid improvement of rigidity.

With the regression of the SMN and the condition of delirium (the patient did not remember what happened in the two previous months, so much that she asked the mother what had happened, and if she had been paralyzed), the basic psychiatric symptoms of mixed bipolar state were again represented with opposition, refusal of the food and therapies, persecutory and poisoning delusions, depressive delusions, nihilistic delusions. Hence, at day 93 clozapine was reintroduced following the guidelines that suggest to wait at least two weeks after the symptoms of NMS have resolved, starting with a low dose and slowly titrating, an initial posology of 25 mg up to 200 mg was administered[4].

In this case the treatment with clozapine proved to be effective, since psychiatric symptoms progressively decreased. At the end of the hospitalization, which lasted over 4 months, there was a modest turning into a phase of hypomania. A switch from levitiracetam to valproate treatment was made, which appeared more suitable for the therapy of maintenance of the current mood disorder, and when motor autonomy improved the patient was discharged.

Multiple differential diagnoses were taken into account, amongst them a form of catatonia was considered as a possible symptom's explanation. DSM-5 criteria for catatonia include the presence of three symptoms among the following: stupor, cataplexy, waxy flexibility, mutism, negativism, mannerisms, stereotypies, psychomotor agitation, grimaces, trend towards fixed posture (voluntary assumption of inappropriate or bizarre postures), echolalia and echopraxia[11]. But the patient during the hospitalization never presented cataplexy or waxy flexibility, posturing, mannerisms, stereotypies, grimaces, echolalia or echopraxia. Malignant catatonia (MC) was also considered as another possible differential diagnosis, in this case the symptoms are similar but considerably more severe respect NMS and they are not correlated with the antipsychotic therapy. Moreover, some forms of catatonia can be considered as part of the same clinical spectrum[12]. However, the progression of MC is significantly worse, mortality hits 70-100% and electroconvulsive therapy (ECT) remains the only treatment for this condition, without this treatment only 1 patient on 5 survive. For these reasons, NMS has to be considered as an antipsychotic-induced, weakened variant of MC[13].

DISCUSSION

The present case report shows a patient who met all the DSM-5 criteria for neuroleptic malignant syndrome[4]. However, the slow and insidious progression of symptoms has significantly delayed a prompt diagnosis. Regarding hyperpyrexia it was initially considered as due to an infectious disease, in the NMS are considered typical a temperature of 38° degrees or more, but other clinical cases are also evaluated without such very high body temperature; moreover, patients with NMS on second generation antipsychotic drugs might show a smaller degree of hyperthermia[14]. Creatine phosphokinase blood levels were also quite confusing as they were originally referred to the ongoing psychomotor agitation. However, altered state of consciousness, generalized rigidity and autonomic dysfunctions concurred to a correct diagnosis. The complexity and severity of the clinical picture is also related to the intercurrent medical complications like sepsis and electrolyte alterations. In this case it was decided to treat the patient only with supportive treatments without any tailored management. On the other hand, some other authors have stressed the importance of a fast and specific treatment for such condition[15]. Moreover, it was difficult to assess which antipsychotic was responsible for the symptoms observed. The patient, in fact, was taking haloperidol 5 mg im (1 time), promazine 50 mg, im (1 time), chlorpromazine 100 mg per os (more time), aripiprazole 7.5 mg im twice daily and then 30 mg per os for 10 days and also clozapine 150-175 mg daily. Moreover, it remains unclear, in our case report, whether, at home, the patient had a partial adherence and-or discontinued clozapine treatment; it has been well described that rapid clozapine discontinuation can causes a vast variety of symptoms including delusions, hallucinations, altered state of consciousness, autonomic dysfunctions and NMS[16].

CONCLUSIONS

The present case highlights the severity and complexity of NMS which, despite the reduction in its incidence, remains a condition difficult to manage, and mortality is more recently estimated between 10 and 20 percent[15]. The difficulty of a timely diagnosis especially when symptoms appear insidiously or could be referred to internal medicine disorders, and the difficulty of making therapeutic choices without precise guidelines, are critical points to focus on. Moreover the difficulty in managing these cases is related not only to NMS, but also to the underlying medical complications and in the severe cases to prolonged hospitalization. Ultimately, the correct association between the responsible drug and the symptoms can represents a further challenge to the comprehensive understanding of the case.

Overall, considering that these clinical cases have become less frequent due to newly treatment strategies, this may make more difficult to promptly identify the non-rare case that still arise. Therefore, our clinical case seems very useful to underline the importance of being updated over the complexity of such cases and have the clinicians promptly ready to consider also more unusual clinical scenarios with diagnostic and therapeutic challenges related to NMS that still exist in the clinical practice.

Conflict of interests: the authors have no conflict of interests to declare.

REFERENCES

1. Eelco FM Wijdicks. Neuroleptic malignant syndrome. 2017. Available from: https://bit.ly/3bwhxJD
2. Chandran GJ, Mikler JR, Keegan DL. Neuroleptic malignant syndrome: case report and discussion. CMAJ 2003; 169: 439-42.
3. Karagianis JL, Phillips LC, Hogan KP, LeDrew KK. Clozapine-associated neuroleptic malignant syndrome: two new cases and a review of the literature. Ann Pharmacother 1999; 33: 623-30.

4. Simon LV, Callahan AL. Neuroleptic malignant syndrome. 2018. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019. Available from: https://bit.ly/3bxQ3mX
5. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry 2007; 164: 870-6.
6. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA (USA): American Psychiatric Association, 2013.
7. Dutra LA, Abrantes F, Toso FF, Pedroso JL, Barsottini OGP, Hoftberger R. Autoimmune encephalitis: a review of diagnosis and treatment. Arq Neuropsiquiatr 2018; 76: 41-9.
8. Lazar-Molnar E, Tebo AE. Autoimmune NMDA receptor encephalitis. Clin Chim Acta 2015; 438: 90-7.
9. Najjar S, Steiner J, Najjar A, Bechter K. A clinical approach to new-onset psychosis associated with immune dysregulation: the concept of autoimmune psychosis. J Neuroinflammation 2018; 15: 40.
10. Bilanakis N, Peritogiannis V, Kalampokis G. Infections as complications of neuroleptic malignant syndrome. World J Biol Psychiatry 2009; 10: 973-6.
11. Luchini F, Bartolommei N, Benvenuti A, Mauri M, Lattanzi L. Catatonia from the first descriptions to DSM-5. J Psychopathol 2015; 21: 145-51.
12. Luchini F, Lattanzi L, Bartolommei N, et al. Catatonia e sindrome maligna da neurolettici: condizioni cliniche diverse di uno stesso spettro? Descrizione di tre casi. Riv Psichiatr 2012; 47: 178-85.
13. Mann SC, Caroff SN, Fricchione GL, Cabrina Campbell E, Greenstein RA. Malignant Catatonia. In: Frucht SJ, Fahn S. Movement disorder emergencies diagnosis and treatment. Humana Press, 2015.
14. Sarkar S, Gupta N. Drug information update. Atypical antipsychotics and neuroleptic malignant syndrome: nuances and pragmatics of the association. BJPsych Bull 2017; 41: 211-6.
15. Tse L, Barr AM, Scarapicchia V, Vila-Rodriguez F. Neuroleptic malignant syndrome: a review from a clinically oriented perspective. Curr Neuropharmacol 2015; 13: 395-406.
16. Cheng M, Gu H, Zheng L, Wang H, Zhong Z, Wen S. Neuroleptic malignant syndrome and subsequent clozapine-withdrawal effects in a patient with refractory schizophrenia. Neuropsychiatr Dis Treat 2016; 12: 695-7.