THE NEUROLEPTIC MALIGNANT SYNDROME – A PRACTICAL CHALLENGE FOR EVERY PRACTITIONER

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ABSTRACT

The neuroleptic malignant syndrome (NMS) refers to a rare but potentially life-threatening complication of the use of antipsychotic drugs, even with the newer atypical neuroleptics, that can develop with hyperthermia, rigidity and autonomic dysregulation. Even if some risk factors have been described, its actual pathophysiology remains unclear. The diagnosis represents a real challenge for every practitioner, irrespective of the medical speciality where the first presentation occurs. NMS as a whole is far from being elucidated since the manifestations are nonspecific, with atypical variants being more and more frequent and changing the overall NMS picture, the clinical course is so unpredictable, sometimes fatal, and it still represents a therapeutic dilemma which underlies its dim prognosis. This article presents 3 cases that question the classical picture of NMS, trying to broaden our understanding of this largely undefined syndrome.

Key words: neuroleptic malignant syndrome, case, atypical, neurologic

INTRODUCTION

After its first description by Delay and colleagues in the 1960s, several attempts were made to better outline NMS. It is known to occur as a rare, but life-threatening adverse drug reaction triggered by antipsychotic or other medications predominantly in young adult males, otherwise irrespective of age and gender.

The list of risk factors is still to be clarified however, the treatment with a high-potency neuroleptic is the most frequently cited. Several pathogenic hypotheses have been formulated involving the central dopamine-related transmission, the sympatoadrenal, GABA, serotoninergic and/or glutamatergic activity dysregulation.

The classically acute clinical presentation develops with the onset of fever, extrapyramidal signs and symptoms, altered mental status, dysautonomia and, without timely diagnosis and adequate management, life-threatening complications. Atypical presentations, where one or more classical symptoms or signs may be missing, have been more and more frequently recognized, perhaps due to a higher awareness amongst doctors, as a result of a clinical shift in presentation and/or concurrently with the introduction of the newer, atypical neuroleptics. The diagnosis is based on the exclusion of other potentially confounding conditions, on clinical presentation and course together with a special pattern of the laboratory findings suggestive of muscle injury. The classical NMS represented a difficult condition to clinicians, with its acute onset that is mostly dealt with in the emergency room, but the diagnostic and therapeutic challenge increased manyfold with the recognition of these atypical variants.

The NMS treatment consists mainly of the withdrawal of the offending drug and supporting measures including body temperature control, adequate hydration, hydroelectrolytic balance maintenance, venous thromboembolism prophylaxis and, when

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required, cardiorespiratory and hemodynamic support under close monitoring. The optimal pharmacologic treatment of NMS is still under debate but definitely more effective when applied early in the course of this condition. The dopaminergic drugs play the most important role, dopaminergic agonists being most frequently relied upon until now. Other drugs and therapeutic approaches (benzodiazepines, myorelaxants, electroconvulsive therapy, etc.) may be useful in alleviating symptoms and have been used with conflicting results. Secondary prophylaxis is strongly recommended.

The 3 cases presented below raise a few issues that may question our current understanding about the clinical presentation and the treatment of NMS.

The levodopa-based treatment may be administered in combination with carbidopa or benserazide and can be effective as a first-line treatment in NMS, irrespective of the severity of presentation, by addressing most of the NMS features.

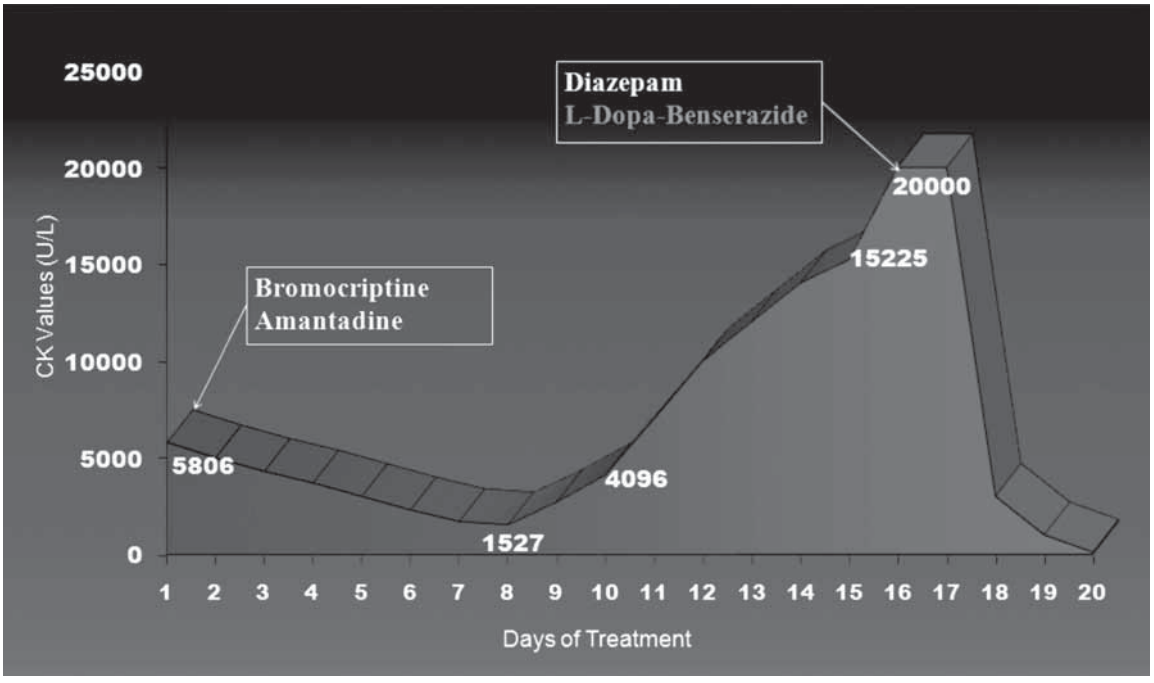
CASE 1

The first case presents a female patient, 51 years of age, diagnosed with paranoid schizophrenia for which she had received previously Risperidone and Ziprasidone. She suffered an acute onset of fever (39°C), catatonia, verbal and food negativism, restlessness and trismus. Her clinical condition was accompanied by a significant, progressive rise in the serum level of creatine kinase (CK) that could not be accounted for by any other concomitant condition. A diagnosis of NMS was made and treatment was started with Bromocriptine (maximum dose 20 mg/day) and Amantadine (maximum dose 200 mg/day) which led to a temporary slight improvement then evolved unfavourable as the patient became bedridden and with the occurence of stupor, persisting fever, increasing serum CK levels to more 20.000 U/L and acute renal failure (creatinine 1.5 then 2.6 and 4.5 mg/dL). The treatment was then changed to Diazepam (i.m.; maximum dose 40 mg/day, 9 days) and L-Dopa-Benserazide (dispersible formulation, p.o.; maximum dose 250 mg L-Dopa/day, 14 days). The treatment change was followed by progressive remission of fever, discoloration of urine and improvement of trismus and hypertonia, which allowed for feeding and mobilization. The patient was transferred for hemodialysis and, under continued NMS treatment, she evolved favourably and recovered completely within the next 2 weeks.

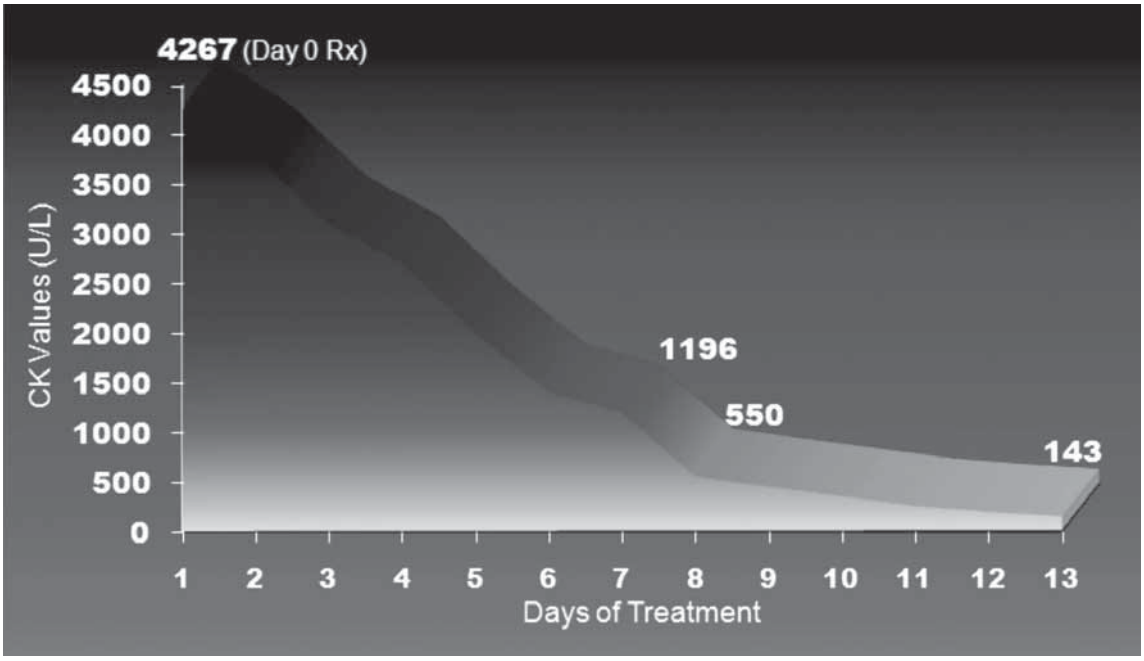
Issue: this case, together with other NMS cases treated in a similar fashion, proved in favor of the hypothesis that L-Dopa formulations (including combinations) should be considered as first-line NMS treatment, irrespective of the severity at presentation. The dispersible formulations, when available, seem to fit better the goals and increase the administration ease of the treatment in this difficult to treat group of patients.

CASE 2

The second case presents a male patient, 33 years of age, treated previously with Haloperidol



CASE 1



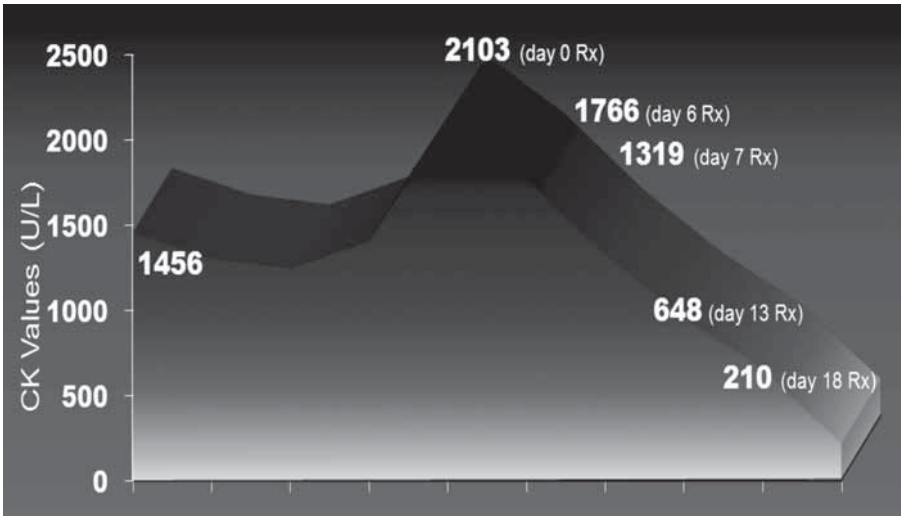
CASE 2

and Chlorpromazine for psychomotor agitation during alcohol withdrawal. The patient developed fever (38,6°C), trismus, unintelilgible communication, hallucinations, hypersalivation and refused feeding. Based on his impressively increasing serum CK levels and after carefully considering other potential causes for his condition, NMS was diagnosed and treatment was started with Diazepam (5 days i.v., with a maximum dose of 40 mg/day, and another 5 days p.o.) and L-Dopa-Carbidopa (maximum dose 500 mg L-Dopa/day, 8 days and tapper over 7 more days). The fever remitted from the second day of treatment, with progressive improvement in communication, feeding and ambulation. This favourable change happened as the serum CK level significantly and progressively decreased after the introduction of treatment.

Issue: this case suggests that NMS signs and symptoms can develop in patients with alcohol withdrawal, with no other apparent confounding condition, treated with neuroleptics for psychomotor agitation, thus complicating its diagnosis and the clinical outcome. It also raises an alarm sign concerning heavy alcohol consumption and alcohol withdrawal that could represent risk factors for NMS. The treatment with L-Dopa proved equally effective in these patients, confirming recent data.

CASE 3

The third case presents a male patient, 32 years of age, diagnosed with schizophrenia. He had been treated previously with Haloperidol and Risperidone. In the last weeks, he had experienced febrile



CASE 3

peaks and developed reduced communication, isolation and behavioural oddities. During the last days before diagnosis he developed persistant fever and generalized extrapyramidal rigidity. Looking at the patient's recent history, an unexplained isolated increased serum CK level was retrospectively found (more than 2 months before), but with a higher level in the day of presentation (day 0). Since other causes for his condition and high CK level could not be found, a diagnosis of NMS was made and treatment was started with L-Dopa-Benserazide (maximum dose 750 mg L-Dopa/day). The fever remitted from the 3rd day of treatment, accompanied by a progressive improvement in communication, behaviour and mobility. The significant decrease of the CK level paralleled closely the evolution of the clinical status. The treatment lasted for 20 days, including the tapper performed with the L-Dopa dosage after the normalization of the serum CK level and the remission of signs and symptoms.

Issue: this case suggests a more protracted course of NMS for this patient, mimicking intercurrent illnesses and/or fluctuations in his psychiatric status, before a NMS diagnosis was made on the occasion of what may have looked like an acutization of his condition.

CONCLUSIONS

NMS is a heterogeneous condition that most of the time develops acutely, as a medical emergency, and can lead to potentially life-threatening complications. The fact that it represents a relatively rare condition makes it difficult to study it in order to more exactly outline its clinical features and contributes to the lack of double-blind or placebo-controlled clinical trials which impacts on the selection of the optimal management approach. The present article tries to exemplify some of the recent challenges, diagnostic and therapies, raised by the occurence of atypical variants under various clinical situations in the recent years. The diversity of presentations doesn't only depend on new risk factors and comorbidities but also on the onset type (possibly also protracted) and presentation signs and symptoms. L-Dopa containing drugs have proved to be an effective and safe approach, a first-line pharmacologic treatment, confirming the pivotal role of the dopamine-related mechanisms in NMS.

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