Recurrence of neuroleptic malignant syndrome

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Neuroleptic malignant syndrome (NMS) is a rare idiosyncratic reaction associated with the use of neuroleptics that has an incidence of 0.02 to 3% among patients taking these drugs. This is a very serious complication with a mortality rate that reaches 10-20%. It is therefore very important to have high clinical suspicion and use appropriate criteria to objectify this clinical picture early, stopping the medication causing the picture and to avoid the subsequent complications as much as possible that would be responsible for both its mortality and sequels. We present that case of an 81-year old woman who was admitted to the Psychiatric Hospitalization Unit (PHU) for a depressive episode with psychotic symptoms who developed a neuroleptic malignant syndrome (NMS) when Haloperidol was introduced. After its suspension and subsequent clinical recovery, antipsychotic treatment with Risperidone was reintroduced and she suffered a recurrence of NMS. Finally, significant improvement was achieved with several sessions of electroshock therapy (EST).

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Recidiva de un síndrome neuroléptico maligno

El síndrome neuroléptico maligno (SNM) es una reacción idiosincrásica infrecuente asociada al uso de neurolépticos que presenta una incidencia de 0.02 a 3% entre los pacientes tratados con estos fármacos. Se trata de una complicación muy grave con una mortalidad que asciende al 10-20%. Por ello, es de gran importancia mantener una alta sospecha clínica y utilizar unos criterios adecuados para objetivar este cuadro precozmente, suspendiendo la medicación causante del mismo, y evitando así en lo posible las complicaciones posteriores que serán responsables tanto de la mortalidad como de las secuelas. Nuestro caso es una mujer de 81 años que ingresa en la Unidad de hospitalización psiquiátrica (UHP) por un episodio depresivo con síntomas psicóticos y desarrolla un síndrome neuroléptico maligno (SNM) al introducir Haloperidol. Tras su retirada y recuperación clínica posterior se reintroduce tratamiento antipsicótico con Risperidona y sufre una recidiva del SNM. Finalmente, experimenta mejoría con varias sesiones de terapia electroconvulsiva (TEC).

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a medical emergency associated to the use of neuroleptics characterized by altered mental status, rigidity, fever and autonomic dysfunction, with an incidence of 0.02-3%.[1,2] It typically develops during the first week after the neuroleptic is introduced, although it may also appear after years of treatment.

It should be taken into account that not only the antipsychotics may cause NMS but that also antidopaminergic drugs used as antiemetics (Metoclopramide[3]) and the sudden

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Table 1 Risk factors of NMS[11-14]

Related with the drug	Related with somatic condition	Related with psychiatric conditions
- High doses	- Dehydration	- Catatonia
- Rapid increase of the does	- Electrolytic alterations	- Extreme agitation
- Parenteral administration	- Infection	- Alcoholism
- Combination of several neuroleptics	- Traumatism	- Mental retardation
- Association with lithium	- Surgery	- Affective disorders
	- Malnutrition	- Previous treatment with ECT
	- Iron deficiency	
	- Organic brain disorders	

withdrawal of dopaminergic agents used for Parkinson's disease (Levodopa, Bromocriptine) may cause it.[1]

Regarding the neuroleptics involved, although NMS has frequently been associated to the use of "typical" high potency antipsychotics (Haloperidol), this has been described with other low potency antipsychotics and with new "atypical" antipsychotics. Many cases associated to Risperidone,[4-6] Olanzapine,[7,8] Clozapine,[9] Asenapine,[10] Aripiprazole[11] have been published. Although the NMS incidence is similar in both cases, it seems that mortality and risk of recurrence after the antipsychotics are reintroduced are less with the atypical drugs.

Table 1 shows several risk factors associated to NMS.[11-14] NMS has been described in all ages, so that it seems that neither age nor gender are predisposing factors.

ETIOPATHOGENIC MECHANISMS

The mechanism by which NMS develops is unknown, but several theories have been described.[15] One of these states that there is an alteration in the central dopamine neuroregulation, this alteration being responsible for the hyperthermia and autonomic dysfunction at the level of the hypothalamus, and for the rigidity and tremor, at the level of the nigrostriatal pathway. On the other hand, dopamine does not totally explain the clinical picture, so that it is considered that other neurotransmitters, such as gamma-aminobutyric acid, acethylcholine[16] and serotonin, are involved.[8]

Another theory has proposed the existence of a primary alteration in the striated skeletal muscle, and that the neuroleptics produce a direct toxic effect on it.[15]

In addition, genetic studies have described a genetic predisposition to develop this syndrome.[17] Certain polymorphisms of the dopamine 2 receptor gene could be involved. Thus, in those that have allele A1, the density of this receptor is reduced in the striatum and caudate nuclei, this being associated to a decrease in the dopaminergic activity.

A neuroimmunological hypothesis has recently been proposed[18] in relation to an acute phase response in which several cytokines and proteins responsible for the symptoms and biochemical alterations of the syndrome are involved.

CASE PRESENTATION

We present the case of an 81-year old woman, married, and without children, who was admitted to the Psychiatric Hospitalization Unit (PHU) due to severe depressive episode with psychotic symptoms. As psychiatric backgrounds, she had a first depressive episode at 63 years and another severe depressive episode at 73 years of age with psychotic symptoms that required admission. Due to lack of improvement with psychopharmacological treatment, she required electroconvulsive therapy (ECT), with favorable response. As somatic backgrounds, hypertension, cavernous hemangioma of the liver and bilateral gonarthrosis stand out. Her treatment consisted in venlafaxine, lorazepam, indapamide and pantoprazole.

While being studied within the Neurology Consultation due to a possible incipient cognitive deterioration, she was referred to the Emergency Service due to behavioral disorder and psychotic symptoms. She was finally admitted to the PHU on an emergency basis.

Prior to admission, her mood state deteriorated and alterations in thinking content consistent with delusional ideations of poverty and being poisoned appeared, this being why she refused food and pharmacological treatment. On admission, she was conscious, temporally and spatially oriented, irritable, tachypsychic, with speech focused on the ideations of poisoning, accompanied by great anxiety,

psychomotor restlessness, anhedonia and feelings of hopelessness.

Treatment was initiated with Haloperidol until reaching a maximum dose of 4 mg/day added to her usual antidepressant medication. At the end of 4 days, she began with decreased awareness, 38.6º fever, sweating, significant rigidity in upper limps, dysphagia and increase in creatinine kinase (1267 U/L) with minimum leukocytosis (fulfilling all the NMS diagnostic criteria proposed by the new Consensus of international experts,[19] which are shown in Table 2). Therefore, psychopharmacological treatment was discontinued and fluid therapy, analgesia and oxygen therapy were initiated. At 15 days, after improvement and apparent remission of the picture, antidepressant and neuroleptic treatment with Risperidone was initiated gradually with dose escalation until reaching 2.5 mg/day due to persistence of the depressive picture. After 10 days, and after receiving intravenous metoclopramide due to a picture of vomiting, she suffered a recurrence of NMS, and was transferred to the Internal Medicine Department. All treatment was suspended again. After resolution of different subsequent complications (bilateral pneumonia, acute coronary syndrome, atrial fibrillation, splenic infarction, bacteriema due to MARSA), 8 sessions of ECT were applied, obtaining a very favorable response and remission of the clinical depression and thinking alterations. Thus, hospital discharge was agreed on.

Table 3 shows some of the clinical and analytic data that orients the diagnosis.

Table 2 Diagnostic criteria of NMS: consensus of experts panel[19]

	1	2
Exposure to dopamine antagonist or dopamine agonist withdrawal within past 72 h	+	+
Hyperthermia (>38 º C on at least 2 occasions)	+	-
Rigidity	+	+
Mental status alteration (reduced of fluctuating level of consciousness)	+	+
Creatinine kinase elevation (at least 4 times the upper limit of normal)	+	-
Sympathetic nervous system lability, defined as at least 2 of the following Blood pressure elevation (systolic or diastolic ≥ 25% above baseline) Blood pressure fluctuation (≥ 25 mm Hg systolic change within 24 h) Diaphoresis Urinary incontinence	+	+
Hypermetabolism defined as heart rate increase (≥ 25% above baseline) AND respiratory rate increase (≥ 50% above baseline)	+	+
Negative work-up for infections, toxic, metabolic or neurologic causes	+	+

1 Criteria fulfilled in the first episode of NMS
2 Criteria fulfilled in the second episode of NMS

DISCUSSION

The NMS is a very serious complication with very elevated mortality (10-20%). Thus, faced with the least clinical suspicion of it, the causing medication should be immediately suspended along with other serotoninergic, anticholinergic or lithium drugs. A series of support measures are also necessary to maintain adequate hydration and nutrition, to control temperature, and to correct any hydroelectrolytic alteration and offer ventilation support. The use of pharmacological treatment is complementary and sufficient scientific evidence does not exist to recommend its use initially, so that it should be reserved for those cases that do not favorably respond to the withdrawal of the neuroleptic drug.[20]

Regarding use of EST, it is indicated as first line of treatment when acute catatonia cannot be ruled out or catatonic characteristics predominate, when there is residual catatonia or posterior psychosis and when there is psychotic or catatonic depression. It is also useful in serious cases of NMS that do not respond to medical treatment during the first week.[21,22]

It must be taken into account that not only antipsychotic drugs are responsible for NMS. It may also be caused by other dopamine blockers used as antiemetics. Therefore, in the case of vomiting, the use of Metoclopramide must be avoided, using an alternative that does not involve the dopaminergic pathway, as for example, Ondasetrón.

Most of the cases are resolved during the first two weeks after the drug is suspended. Once the picture has been resolved, it is very likely that the base symptoms may persist and due to the high likelihood of recurrence of the syndrome, a series of precautions must be taken when reintroducing a neuroleptic drug. In the first place, we should wait at least 15 days after the episode is resolved. It is preferable to use a low potency atypical antipsychotic drug, gradually escalating the dose. The symptoms should be strictly controlled, with seriated controls of the CPK. In spite of the precautions taken, a recurrence of 30% recurrence has been described.[6]

Although many cases of NMS with different atypical antipsychotics have been described, it appears that the risk of recurrence is less when these are used. Clozapine is probably the antipsychotic drug having the least risk of

Table 3 Clinical and analytic data

	26/03/12 (1st NMS episode)	19/04/12 (NMS Recurrence)	12/05/12 (Episode of bronchoaspiration caused pneumonia)
CPK[1]	1267 U/L	107 U/L	95 U/L
Leukocytes[2]	10,550	11,700	16,900
Cogwheel rigidity	+	+	-
Decreased level of awareness	+	+	-

[1] Normal values: 20-180 U/L
[2] Normal values: 4000-10000

development of NMS due to its psychodynamic profile, lower affinity for D2 and high affinity for D4 receptors, although there are no conclusive studies. Risperidone, an antipsychotic belonging to the family of butyrophenones, is an antagonist having high affinity for the type 2 serotonin receptors (5HT2) and dose-dependent blockers of type 2 dopaminergic receptors (D2). However, in spite of the low incidence of extrapyramidal effects at low doses, we should keep in mind that it can also cause a relapse of the NMS.

To conclude, and in order to obtain an early diagnosis and avoid medical-legal problems, we recommend:

To keep in mind the elevated percentage of recurrences of NMS (30%), as is stated in the literature. And in accordance with this case, it should be remembered that even though the risk is less, recurrence may also occur after reintroducing a new generation antipsychotic drug. It must also be kept in mind that this risk exists even in elderly persons.

To assume the diagnostic criteria of the new international experts Consensus that has been obtained through the Delphi method and that has recently been published.[19]

With this analysis, based on the case, we aimed to contribute to the prevention of one of the most frequent serious medical - legal complications faced by the Spanish psychiatrists and to avoid mortality in this type of patient.

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