Serotonin syndrome versus neuroleptic malignant syndrome: a case report

Mercedes Fernández[1]
Laura Lago[1]
M. Gema Alonso[2]
Ana Guede[3]
Jose Luis Benavente[1]
Jose M Olivares[1]

[1]Servicio de Psiquiatría. Complejo Hospitalario Universitario de Vigo. Pontevedra. España
[2]Servicio de Neurología. Complejo Hospitalario Universitario de Vigo. Pontevedra. España
[3]Servicio de Urgencias. Complejo Universitario de Vigo. Pontevedra. España

Correspondence:
Dr. J.L. Benavente Martín.
Servicio de Psiquiatría. Hospital Público Álvaro Cunqueiro.
Complejo Hospitalario Universitario de Vigo (CHUVI).
Estrada Clara Campoamor, 341
36212 Vigo. Pontevedra. España.
E-mail: jose.luis.benavente.martin@sergas.es

Dear Editor,

Neuroleptic malignant syndrome (NMS) is a serious complication, generally associated with antipsychotic treatment that usually appears within 24-72 hours after initiation or change in antipsychotic treatment, and usually occurs with drugs that block dopaminergic receptors. However, it may also occur with the withdrawal of anti-parkinsonian drugs[1-7]. Among the diagnostic criteria for NMS, the most accepted are Levenson one´s (Table 1)[3], in which fever, stiffness and creatine phosphokinase (CPK) elevation are considered as main criteria. The presence of factors such as bradipsiquia or some type of organic disorder[1-5] are presumed to occur at the onset of NMS.

On the other hand, Serotonin syndrome (SS) is an adverse reaction related to the administration of drugs that link to the serotoninergic receptors. Those drugs trigger an overactivation of 5-HT 2A and 5-HT 1A postsynaptic central and peripheral serotonergic receptors[8]. It usually appears in the first 24 hours, and although it is usually due to the interaction between serotonergic agents with different mechanisms of action (85%), it can also occur due to an overdose (15%)[9].

Table 1 Levenson Diagnostic Criteria for Neuroleptic Malignant Syndrome and Sternbach for Serotonin Syndrome

Malignant neuroleptic syndrome	Serotonin syndrome
Fever	Changes in mental state
Stiffness	Agitation
Elevation of CPK	Myoclonus
	Hyperreflexia
Tachycardia	Diaphoresis
Abnormal BP	Chills
Tachypnea	Temblor
Altered consciousness	Diarrhea
Diaphoresis	Incoordination
Leukocytosis	Fever

CPK: creatine phosphokinase; BP: blood pressure

The onset of SS is usually faster than NMS, from minutes to hours after drug initiation[8]. Their severity can be very diverse, from lethal forms to lighter ones[10] in which even the diagnosis can be unnoticed[9]. The most characteristic clinical manifestations are alterations in the mental state (delirium, anxiety, hypervigilance and akathisia), autonomic hyperactivity (diarrhea, sweating, tachycardia, hyperthermia and mydriasis), and neuromuscular disorders (tremor, hyperreflexia, myoclonus and stiffness)[11]. According to Sternbach's diagnostic criteria, at least 3 of the 10 criteria (Table 1)[9] must be met. Alterations in the SS analyses are leukocytosis, metabolic acidosis and CPK increase. Other complications or findings may include elevation of creatinine, leukocytosis, disseminated intravascular coagulation, myoglobinuria, fever, cardiac arrhythmias, renal failure, coma, and death[8-10].

In order to determine the differential diagnosis between NMS and SS, the drugs to which the patient has previously been exposed, as well as the most recent dose changes, must be taken into account. However, in clinical practice, it is not uncommon to associate different psychoactive drugs, and to make simultaneous changes in treatments, so sometimes the differential diagnosis between the two can be a challenge.

Clinical case

We present the case of a 57-year-old woman diagnosed with bipolar disorder and mild learning disability. Around the age of 20, she suffered from two maniacs episodes, no further relapses until current one. During the last few years she had been treated with haloperidol (3 mg/d), pimozide (2 mg/d), sertraline (25 mg/d), trazodone (200 mg/d) and lormetazepam (2 mg/d). The only medical history was dyslipidemia, on treatment with simvastatin (10 mg/d).

Her family reported changes in her condition for a month. The previous month she presented with depression, insomnia and dysphoria. Because of the worsening in her condition, medication was adjusted. Haloperidol dose was increased to 0.7 mg/d, sertraline dose was increased as well to 200 mg/d, and hydroxyzine was added as a new drug at 50 mg/day. All changes were made two weeks before she was admitted to Hospital.

She was referred to the Hospital by her GP following a four days history of deterioration of her mental state. In the initial A&E assessment she was unable to stand up, and although the capacity of comprehension was preserved, she was unable to articulate a word; she also suffered from ex-

treme anxiety, and pointed out constantly to her larynx (it seemed to indicate dysphagia). In physical examination the most remarkable findings were: rigidity in limbs, myoclonies, orolingual movements and brisk patellar reflexes. Body temperature was 38°C, heart rate was 120 bpm; she was tachypneic but oxygen saturation and lung auscultation were normal. Blood pressure was normal as well. In blood analysis, she had a leukocytosis (16.8 x10e9/L) with neutrophilia (85.7%), significant elevation of CPK (1,730 IU/L), hypernatremia (151.0 mEq/L) and mild anemia (11 g/dl), without anomalies in glucose, urea, creatinine and rest of parameters. The chest x-ray and the electrocardiogram were within normal range.

She was admitted to the Neurology ward, where she was diagnosed with NMS.

The previous treatment was discontinued and only diazepam (30 mg/d) was prescribed. Initially during her admission, the temperature increased up to 39ºC, but later showed a rapid and progressive improvement, both in its general state and in the blood analyses. In the investigations conducted during admission, there were no abnormalities in the hemogram and biochemistry (general, liver and renal function), neither in the coagulation study, study of thyroid function, serologies. Neuroimaging tests (CT and MRI) and lumbar puncture were normal as well. The only relevant findings were a raise in the ESR (89 mm/h), hypernatremia (149 mEq/L) and hypokalemia (2.7 mEq/L). Because of those findings, a referral to the Endocrinology service was made. She was diagnosed of SIADH (vasopressin 13.4 pg/mL, (normal range: 0.1-7.6). Relatives reported polydipsia in recent years.

Despite the overall clinical improvement, the mood remained depressed and she still had a mild dysarthria, so after 14 days in the Neurology ward she was transferred to the Psychiatry ward, being diazepam the only medication prescribed. Repeated blood analyses showed changes compared to the previous ones, with a raise in ESR (138 mm/h); normocytic anemia (red blood cells, 2.86 X1012); hemoglobin, 8 g/dL; and low iron, 45 ug/dl (no previous blood iron); the rest of the parameters were within normal range. A referral was made to the Internal Medicine Service, who started treatment with intravenous iron, and with 30 g/d of prednisone with the working diagnosis of polymyalgia rheumatica. In the following days the patient general condition improved. Mood remained stable, neurological symptoms remitted, and blood test were within normal limits.

After 21 days of admission, she was discharged with the diagnosis of neuroleptic malignant syndrome *vs* serotonin syndrome, bipolar disorder, mild learning disability, probable polymyalgia rheumatica, polydipsia for resistance to ADH. At discharge, she was stable on Olanzapine (15 mg/d), Citalopram (30 mg/d), Diazepam 30 (mg/d), Prednisone (30 mg/d), Omeprazole, simvastatin and iron salts.

Three weeks after discharge, new blood tests were performed. ESR showed a marked improvement (28 mm/h), anemia improved as well (hemoglobin, 11.5 g/dL) and a remission of iron deficiency (iron, 88 ug/dl) was noted; the rest of the parameters were normal. The patient remained stable.

Discussion

A relevant data to establish the differential diagnosis between the NMS and SS is the time elapsed between the change in treatment and the onset of symptoms. While the onset of SS is usually more acute, in the first 24 hours[12], the NMS is highly variable, as it may take from 1week up to 5 weeks[1, 2]. In our case, the treatment was changed around 2 weeks before of the onset of symptoms, which would support the diagnosis of NMS.

Simultaneous prescription of dopamine antagonist drugs and serotonin agonists is common in clinical practice[13], even some drugs, such as quetiapine and risperidone, have effects on both receptors[14]. Patients with NMS and SS manifestations have been described, and symptoms overlap. Due to this, controversy has arisen among authors who believe that an alteration in the balance between both neurotransmitter systems may be the common cause of both[15], and that it may even be the same picture with different manifestations[6, 7]. On the other hand, other authors emphasize the importance of differentiating them, making the point that therapeutic implications are the main reason to look for discrimination, since the treatment is different in each case[13,16].

In our patient, she took a high dose of drugs with serotonergic effect. In the literature, there are more than 10 cases of SS that are attributed to the association of trazodone with other serotonergic drugs. In the case described, in addition to the treatment with trazodone, the dose of sertraline was recently increased, which would support the diagnosis of SS.

With regard to the severity of the condition, the SS can present with a wide range of manifestations, from mild cases that can be unnoticed to other severe or even lethal ones[17]; On the other hand, NMS symptoms are always serious[18]. In this case, although the initial presentation was very striking, the subsequent evolution was very favorable.

The most common manifestations of NMS are severe stiffness and autonomic instability (especially at the onset of the disease), as well as leukocytosis, elevated CPK, and low sideremia. In contrast, myoclonus, hyperreflexia (especially in lower limbs), restlessness, agitation and gastrointestinal

symptoms (nausea, vomiting and diarrhea) lead to the presence of SS[1, 2,9,13]. In the patient the SS symptoms predominated, but the alterations in the blood analyses and the hyperthermia made neurologist think of a NMS. She met 4 of the diagnostic criteria of Levenson's NMS (CPK elevation, tachycardia, tachypnea and leukocytosis), but it could not be considered a NMS according to these, since the 3 majors have to be met, or 2 of the majors and 4 of the minors must be met (Table 1). Neither of them met in our case report. On the other hand, it must be taken into account that in some cases of SS, leukocytosis and elevation of CPK have also been described[16, 19].

Therefore, several factors support the diagnosis of SS, such as the latest changes in treatment, clinical presentation and, above all, that the diagnostic criteria for NMS were not met. The main factor against this diagnosis was the period between changes in treatment and the onset of the disease (2 weeks), which is more typical of NMS. We have not found any publication that relates polymyalgia rheumatica with SNM or SS. On the other hand, the higher predisposition of patients with learning disability to NMS has been described[5, 22].

The role of D2 receptors is modulated by iron, which is part of them. It is known that hyposideremia causes a decrease in the number of D2 receptors and increases their susceptibility to akathisia in patients treated with antipsychotics[20, 21]. It has also been observed that iron deficiency causes changes in the dopaminergic receptors of the striatum in mice and that some of these changes revert once there is an increase of iron in the midbrain[23].

Rosebush and Mazurek found that sideremia was low in 96% of their patients with NMS. In addition the authors suggested that the abrupt decline in sideremia could contribute to the onset of NMS, since in their 6 cases they had a previous sideremia, and a significant decrease was observed at the beginning of the clinical picture (mean sideremia of 85 to 35 ug/dl) [20]. In the case described, no sideremia was requested at the time of admission, but 2 weeks later iron levels were below the normal range.

Sodium elevation in blood serum, as found in the patient on admission, has also been observed in NMS publications caused by various antipsychotics[24–27].

Although there were some manifestations of NMS, the patient was eventually diagnosed with SS. We raise the possibility that the presence of factors such as low sideremia or dehydration may trigger manifestations that are considered diagnostic criteria of NMS. It would be advisable to take these parameters into consideration in future publications to deepen the knowledge of both syndromes.

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Treatment of Delayed Post-Hypoxic Leukoencephalopathy as a complication of carbon monoxide poisoning with risperidone and hyperbaric oxygen therapy

Jeff Huarcaya-Victoria[1]
Angela Podestá-Ampuero[1]
Mario Ledesma-Gastañadui[1]
Carmen Reinoso-Santa Cruz[1]

[1] Department of Psychiatry, Hospital Nacional Guillermo Almenara Irigoyen. Lima, Perú

Correspondence:
Jeff Huarcaya-Victoria
Departamento de Psiquiatría
Hospital Nacional Guillermo Almenara Irigoyen
Av. Grau 800 – La Victoria
Tel: +513242983 / +513242980
E-mail: jeff.huarcaya@unmsm.edu.pe

Dear Editor,

Carbon monoxide (CO) poisoning is considered as a public health problem because it can be responsible for more than half of all mortal poisonings reported in several countries[1]. Unfortunately, for patients and physicians, the symptoms of CO poisoning are non-specific: headache (58.5%), transient loss of consciousness level (40.9%), sinus tachycardia (25.9%), nausea/vomiting (25%), asthenia (20.1%), dizziness (20.1%), palpitations (18.4%), among others[2]. Within the chronic symptoms, we can find several neuropsychiatric sequels: cognitive impairment, motor disorders, chronic delusions, etc[3]. Among these, delayed post-hypoxic leukoencephalopathy is rare and unrecognized, and it is characterized by a neuropsychiatric relapse (delayed neuropsychiatric syndrome, DNS) after a period of stability or clinical improvement after an episode of hypoxia, mostly associated with CO poisoning[4].

In order to review the literature of delayed post-hypoxic leukoencephalopathy as a complication of CO poisoning, we present the case of a 37-year-old woman who developed psychotic, catatonic and cognitive impairment after CO poisoning.

Case report

This is a 37-year-old woman from Huancayo, currently residing in Lima and with second-grade elementary schooling. She does not have a personal somatic or psychiatric background. One out of seven siblings, we determined as a family psychiatric background a brother with depressive disorder, who committed suicide about 18 years ago. The functioning level of the patient before the disease was appropriate in relation to her cultural beliefs, showing good work performance.

By the end of October 2016, the patient suffered unintentional poisoning with CO. She was exposed for about five hours while cooking with coal. Her husband found her in the kitchen, unconscious. She was taken to the Emergency Department of a general hospital, remaining confused and disoriented for about six hours. Her diagnosis was acute CO poisoning and after oxygen therapy treatment, she regained her level of consciousness and wakefulness before 24 hours. The patient did not show any psychiatric or neurological alterations at discharge.

After four weeks of the accident, her husband noticed that at times the patient felt disoriented, showed subtle memory failures, began to refer to ideas of jealousy and to show an irritable mood and tendency to social isolation. After a week, he noticed a psychomotor slowness, showing progressive difficulty to walk and to eat; generalized stiffness; delusions of infestation and jealousy. As days went by, all these symptoms were getting worse, so the patient was taken to the Emergency Department of our hospital. Initially, the neurological examination was undertaken, which evidenced the presence of frontal release signs (grasping, palmomental and rooting reflexes), walking problems and pain during passive and active motion of the right upper limb. Blood biochemical analysis showed no significant alterations. A brain computed tomography (CT) was undertaken, where no structural lesions were evident. Because of the psychotic, disorganized and catatonic behavior, the patient was hospitalized in the General Psychiatry Service.

During mental examination we found a patient awake, partially oriented in person and disoriented in time and

space, no awareness of mental disorder, delusions of persecution, reference, jealousy, somatic and infestation, formal thought disorders: tangential, with lack of logic and distractibility, alogia, poor language, increased latency question-answers, visual and cenesthetic hallucinations (parasites), emotional blunting: unmodified facial expression, poor gesticulation, cognitive impairment, anterograde amnesia. Catatonic signs: stupor, stiffness, ceres flexibilitas, negativism (so she had a nasogastric tube placed to ensure food intake).

The Clinical Global Impression Scale (CGI) was 6; The Bush-Francis Scale for catatonia was 41; The Global Assessment of Functioning Scale (GAF) was 25.

Due to the psychotic and catatonic symptoms, 30 mg/day aripiprazole and 30 mg/day diazepam was initiated. Since there was no improvement in the psychotic and catatonic symptoms after three weeks of treatment, it was decided to extend the neuroimaging studies with a brain Magnetic Resonance Imaging (MRI), in which extensive demyelination areas were found in the periventricular and bilateral frontoparietal white matter in probable relation to delayed ischemic encephalopathy (Figure 1). She underwent biochemistry, culture and serology of cerebrospinal fluid, which were found within the normal limits. The following was proposed as a diagnosis: Delayed Post-Hypoxic Leukoencephalopathy as a complication of CO poisoning. The hyperbaric oxygen (HBO) treatment began empirically with a total of 20 sessions, 29 feet for one hour, 2.2 atmospheres absolute (ATA). After two weeks, the catatonic symptoms improved partially, however, the psychotic symptoms persisted, so it was decided to discontinue previous medication, and 6 mg/day risperidone and 10 mg/day diazepam were prescribed. One week after her admission (ninth day of HBT therapy), the patient began to accept food orally, so the nasogastric tube was removed; after two days, she began to walk with help, presenting some instability; the reappraisal of the Bush-Francis Scale for catatonia was 3. Furthermore, the psychotic symptoms were easing, until the patient recognized that the ideas expressed on admission were false; likewise, we notice a better-organized thought, greater orientation and good affective resonance; however, the Screen for Cognitive Impairment in Psychiatry (SCIP) evidenced a severe cognitive impairment. Due to the improvement, regarding symptoms evidenced by the health staff and confirmed by the relatives, she was discharged from the hospital. The patient is currently in the rehabilitation program of our hospital as well as under the control of the General Psychiatry Service in an outpatient facility.

Discussion

Clinically we will find in the DNS a myriad of signs and symptoms, summarized in Table 1. The sudden appearance of apathy, amnesia, disorientation, mutism and loss of sphincter control may happen from 2 to 4 weeks after CO poisoning. If we consider the presence of strange behavior, delusions or depressive mood, we can arrive at a misdiagnosis of schizophrenia, depression or hysterical dissociation. In our patient, catatonic symptoms were important. Quinn *et al.*[5] reported in 2014 the case of a 56-year-old female patient who developed catatonia after suffering from cerebral hypoxia. Until that time, they found 9 cases in the medical

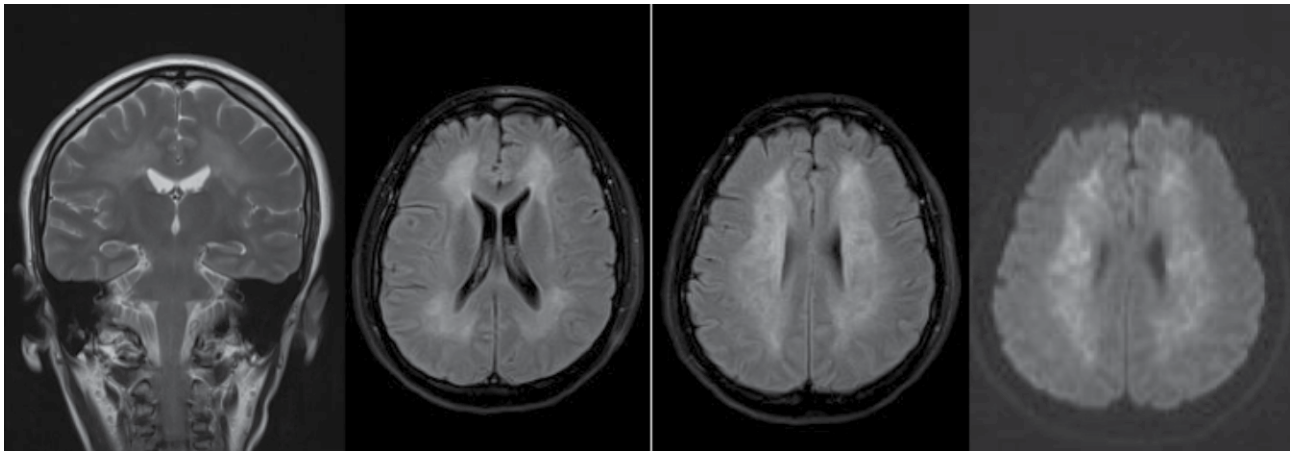

Figure 1 — *MRI of the patient. It was found alteration of the signal that compromised the bilateral parietal periventricular white matter, which shows increase of its signal intensity in FLAIR and T2 with restriction to diffusion. No changes were found after administration of the contrast material*

Table 1 Delayed neuropsychiatric signs and symptoms due to CO poisoning

Neurological (n=65)[16]	Psiquiátricos (n=86)[14]
Masked face (100%)	Apathy (100%)
Glabella sign (92.3%)	Disorientation (100%)
Grasp reflex (89.2%)	Amnesia (100%)
Urinary and/or fecal incontinence (87.8%)	Hypokinesia (95%)
Increased muscle tone (83.3%)	Mutism (95%)
Short-step gait (83.3%)	Irritability, distractibility (91%)
Retropulsion (73.4%)	Apraxia (76%)
Mutism (32.3%)	Bizarre behaviors – silly smiles or frowning (70%)
Tremor (7.7%)	Manneristic behavior (41%)
Intention tremor (7.7%)	Irrational confabulatory talking (30%)
Increased deep tendon reflexes (7.7%)	Insomnia (19%)
Flaccid paresis (3.1%)	Depressed mood (15%)
Weakness (3.1%)	Delusions (12%)
Speech disturbance (1.5%)	Echolalia (2%)
Ankle clonus (1.5%)	Elated mood (2%)

literature in which the DSM-5 criteria for catatonia were met in patients with delayed post-hypoxic leukoencephalopathy, where 2 of them were related to the history of CO poisoning.

Alterations in neuroimaging are varied and nonspecific. Brain MRI may show a relatively symmetrical and confluent compromise of the periventricular white matter and the semioval center, and less frequently compromise of the U-fibres, respecting also the brainstem, cerebellum and gray matter. This damage shows a high signal in the T2/FLAIR sequences and, typically, there is no evidence of mass effects or contrast uptake[6, 7].

The treatment and prevention of DNS due to CO poisoning is not well defined. There is limited evidence of the efficacy of HBO treatment; the supportive and symptomatic treatment is recommended[8,9]. To the best of our knowledge, this is the first case report of a satisfactory treatment with risperidone in the context of psychosis and catatonia due to delayed post-hypoxic leukoencephalopathy. There are case reports that mention the effectiveness of some medications for symptomatic treatment: magnesium sulfate[10], amphetamines[11], amantadine[12], and ziprasidone[13]. The patient improved a week after starting risperidone. However, despite this improvement, other possibilities must be considered: a) the natural evolution of several of these patients is towards a clinical recovery, being this slow and progressive over several months, with discharge usual after one month of hospitalization[14]; b) there is anecdotal evidence of improvement after the use of HBO treatment once the DNS was established[9,15]. Therefore, we cannot make inferences about the possible therapeutic usefulness of risperidone or HBO treatment from this particular case. Our patient's catatonic symptoms improved with non-aggressive measures, and we agree with the opinion of other authors[5], who find that treatment with HBO treatment, antipsychotics, benzodiazepines, among others, must be set up before electroconvulsive therapy (ECT), since there is a lack of evidence to support this treatment approach[5].

In conclusion, to the best of our knowledge, this is the first reported case of successful treatment with risperidone in the context of psychosis and catatonia due to ischemic posthypoxic leukoencephalopathy. There is anecdotal evidence of improvement in these patients with the use of HBO treatment. The case presented points to the importance of a multidisciplinary approach to CO intoxication and its aftermath. The progression of psychiatric disorders in these patients remains poorly understood. Emergency and neurology physicians should be aware of the need for intensive psychiatric intervention and follow-up of these patients.

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