**CASE REPORT**

**A rare iatrogenic association of syndrome of inappropriate secretion of antidiuretic hormone, neuroleptic malignant syndrome and rhabdomyolysis**

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**Abstract**

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is considered the prevalent cause of hyponatremia in hospitalized patients. Neuroleptic malignant syndrome (NMS) is an idiosyncratic drug reaction showing fever, dysautonomia and rigidity with increased levels of Creatinine-phosphokinase (CPK) dependent on leakage of muscle contents into the circulation and defined as rhabdomyolysis. Although different diagnostic criteria for NMS have been established, it should be recognized that atypical presentations occur, particularly during treatment with atypical antipsychotics. We here present a case report of a psychiatric patient affected by a SIADH complicated with NMS/rhabdomyolysis, induced by second-generation (atypical) antipsychotic drugs in combination with carbamazepine and promazine.

**INTRODUCTION**

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is considered the prevalent cause of hyponatremia in hospitalized patients [1]. Neuroleptic malignant syndrome (NMS) is an idiosyncratic drug reaction showing fever, dysautonomia and rigidity with increased levels of creatinine-phosphokinase (CPK), dependent on leakage of muscle contents into the circulation and defined as rhabdomyolysis [2]. Although different diagnostic criteria for NMS have been established, it should be recognized that atypical presentations can occur, particularly during treatment with atypical antipsychotics [3]. We present a case report of a psychiatric patient affected by a SIADH complicated with NMS/rhabdomyolysis induced by an oral therapy of atypical antipsychotic drugs in combination with carbamazepine and promazine. The patient had a medical history of ten years bipolar disorder and, recently, his psychiatrist increased the promazine dosage.

All antipsychotic drugs are associated with adverse events such as sedation, cardiac arrhythmia, postural hypotension, sexual dysfunction and sudden cardiac death [4]. Moreover, the antipsychotic drugs are involved in all the three potentially life-threatening events, such as syndrome of inappropriate antidiuretic hormone secretion, NMS and rhabdomyolysis. The second-generation antipsychotics were initially assumed to be free from the risk of inducing NMS because of their more favorable pharmacodynamic profile. The post-marketing studies have confirmed that also these drugs possess a reduced, but still present, risk of NMS complication [3, 5].

Anyway, the association between SIADH and NMS is an infrequent finding [6] while the coexistence of three different adverse effects such as SIADH, NMS and rhabdomyolysis is described only in two cases following oral sulpiride or parenteral paliperidone therapy [7, 8].

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We report a very unusual case of the coexistence of SIADH/NMS/rhabdomyolysis following an oral polytherapy in a psychiatric patient.

CASE PRESENTATION

A 56-year-old Caucasian male presented to the Emergency Department of our Hospital with a four days history of altered consciousness level, hyperpyrexia (38.7°C), tachycardia, profound diaphoresis, myalgia and severe muscle weakness. The relatives referred a medical history of type 2 diabetes mellitus (metformin 500 mg three times a day) and bipolar disorder, treated with antipsychotic drugs (paliperidone 3 mg once a day, olanzapine 10 mg once a day), carbamazepine 400 mg twice a day and promazine hydrochloride 90 mg twice a day. He has been under the actual drug therapy for 24 months when, 10 days before the hospital admission, the promazine dose was increased (from 60 to 90 mg twice a day) to achieve a better control of the anxiety. Three months before the hospital admission, routine blood laboratory parameters, including serum transaminases, blood urea nitrogen, creatinine, sodium, potassium, Cr and carbamazepine level, were in the normal range.

At the admission, the relatives denied seizures, polydipsia, nausea, vomiting, diarrhea or a recent use of diuretics while the fever started two days before. The blood pressure was fluctuating between values of 140/80 and 170/95 mmHg with a sinus heart rate fluctuating between 79 and 118 beats/min and a 39.6°C oral temperature upon admission. The chest, heart, abdominal and neurologic exams were normal without nuchal rigidity or meningeal signs. A mild muscle rigidity was present while the patient presented a severe weakness. The findings of normal skin turgor, moist mucous membranes and the absence of orthostatic hypotension, jugular vein engorgement and edema suggested an euvolemic status. The laboratory parameters (Table 1) associated with normal cardiac and endocrine function suggested a diagnosis of SIADH associated to NMS complicated with rhabdomyolysis. The anamnestic history and radiological investigations, such as a total-body computed tomography failed to identify other possible causes of SIADH. A water load test (0.9% NaCl solution 2 l in 24 h) did not modify significantly the serum Na levels (from 121 mEq/l to 123 mEq/l).

Antipsychotic drugs were stopped and a 1.5% hypertonic NaCl solution (containing Na 255 mEq/l), a 1.4% bicarbonate solution (Na 167 mEq/l) and fluid hydration (0.9% saline 4 l/day) were started. The 1.5% NaCl and bicarbonate solutions were continued until the third day obtaining a serum value of 125 mEq/l with the resolution of the fever. Then, SIADH diagnosis was made and tolvaptan therapy (15 mg/day) started, decreasing the hydration regimen to 2.5 l/day. On the fifth day, after three days of tolvaptan therapy, serum Na level was 139 mEq/ml and a normal mental status was restored, then tolvaptan was stopped and the antipsychotic therapy was resumed (paliperidone 3 mg once a day and carbamazepine 100 mg twice a day, lorazepam 2 mg once a day) in consideration of the onset of agitation and irritability. Unfortunately, we could not measure the different drug levels due to the lacking of specific assay kits. On the 7th day, the patient was discharged presenting 141 mEq/l Na, 1388 mg/dl CK and 160 ng/ml myoglobin, scheduling a weekly follow-up. Hyponatremia, NMS and rhabdomyolysis did not relapse at subsequent monthly follow-up, up to 1 year.

DISCUSSION

The investigated patient presented a medical history, clinical symptoms and laboratory values consistent with SIADH diagnosis, complicated by rhabdomyolysis and symptoms of an unregulated sympathetic nervous system hyperactivity suggesting a NMS presenting only a mild muscular rigidity. NMS is a diagnosis of exclusion and differential diagnosis relies on four major criteria: hyperthermia, rigidity, autonomic disturbances and mental status changes. Usually, DSM 5 criteria exclude a ‘classic’ NMS in the absence of severe muscular rigidity. Anyway, other classifications, such as Adityanjee & Adernibighe criteria, take into consideration ‘atypical’ forms of NMS where extrapyramidal signs are not strictly necessary. Moreover, also the traditional Levenson’s criteria stated that the association of two major criteria (present in our patient) such as fever >38.0°C and increased serum CK levels with at least four minor criteria (altered consciousness level, dysautonomia, tachypnea and labile arterial pressure) suggests NMS diagnosis, also if a frank muscular rigidity was not present [9]. The second-generation antipsychotic drugs such as paliperidone and olanzapine, despite reducing the overall incidence of the syndrome, could induce atypical NMS forms, sometimes difficult to diagnose [5].

In our case study, the promazine dosage was increased but this drug could explain the onset of NMS while SIADH is not typically described as one of its side effects. Moreover, a potential role of the chronic carbamazepine therapy in the SIADH onset is possible. Our patient showed on hospital admission the level of Na serum at its nadir while PK level was steadily

| Table 1: Laboratory parameters on different days |
|-----------------------------------------------|
| r. r.  | sNa  | uNa  | P. Osm | U.A  | Cr.  | BUN | sCPK/myoglobin | U. Osm | FENa | FEUA |
| DAYS   | mEq/l| mEq/l| mOsm/kg| mg/dl| 0.5–0.9 mg/dl | 10–50 mg/dl | 250–500/20–80 mg/dl | 50–1200 mgOsm/kg | 0.1–0.5% | 5–12% |
| 1      | 121  | 1.2  | 43     |      |      |      |      |      |      |      |
| 2      | 123  | 7.8  | 65     | 35.327/- |      |      |      |      |      |      |
| 3      | 125  | 4.0  | 39     | 41.558/- | 352  | 0.54     |      |      |      |      |
| 4      | 129  | 33/21/1701 |      |      |      |      |      |      |      |      |
| 5      | 139  |      |      |      |      |      |      |      |      |      |
| 6      | 145  | 15 567/518 |      |      |      |      |      |      |      |      |
| 7      | 141  | 3.4  | 24     | 1388/160 |      |      |      |      |      |      |
| 14     | 144  | 3.2  | 28     | 445/50 |      |      |      |      |      |      |

Gray row: SIADH diagnosis was made and tolvaptan therapy was started.

r.r.: reference range, sNa: serum sodium, uNa: urine sodium, P. Osm: plasma osmolality, U.A.: serum uric acid, Cr.: serum creatinine, BUN: blood urea nitrogen, sCPK: serum creatine phosphokinase, U. Osm.: urine osmolality, FENa: sodium fraction excretion, FEUA: uric acid fraction excretion.
increasing, suggesting that SIADH was antecedent to rhabdomyolysis/NMS appearance. Thus, severe hyponatremia could represent the trigger event of both rhabdomyolysis and NMS [9, 10]. The mechanism of muscle fibers myolysis in SIADH is dependent on cell swelling and/or the imbalance of cellular Na/K pumps increasing the intracellular calcium levels with lysis of the cells [11]. Anyway it is impossible to identify the role of a single drug in this complex clinical picture. Probably, promazine triggered the toxicity of the therapy inducing first and foremost NMS and SIADH while the severe hyponatremia was responsible of the intense rhabdomyolysis. At present, the relationship between SIADH and NMS is unknown. Common neuroanatomical areas, such as the basal ganglia, the cerebral cortex and the hypothalamic region are usually involved in both NMS and demyelinating lesions dependent on overcorrection of hyponatremia [12]. Normally, the monoamine transporters are involved in the Na/Cl-dependent reuptake of the catecholamine to regulate the extracellular monoamine concentrations. Thus, the imbalance of sodium, could determine an altered norepinephrine/dopamine ratio in these cerebral areas increasing the NMS risk in SIADH [13]. Furthermore, acute kidney failure is a harmful complication of rhabdomyolysis, complicating 30% of the cases but not found in our patient. The fluid hydration and urinary alkalinisation are indicated as the mainstay of therapy to preserve the kidney function and the intense water diuresis induced by tolvaptan could have a preserving role of the glomerular filtration. A further point of discussion is that SIADH has to be considered a challenging diagnosis when rhabdomyolysis is concomitant, since the increased levels of blood urea nitrogen, creatinine and uric acid could be misleading. In our case, the criteria of SIADH diagnosis were met only on the third day.

In conclusion, our case report gives evidence against the multiple psychiatric therapies not according to accepted medical standards and the false sense of safety of the oral vs. parenteral therapy. The physicians need to be aware of rare but life-threatening harmful side effects such as SIADH, NMS and rhabdomyolysis, also using the second-generation antipsychotic drugs, mainly in combination with other central nervous system drugs.

CONFLICT OF INTEREST STATEMENT

None declared.

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