Cerebral Salt-Wasting Syndrome in a Patient With Neuroleptic Malignant Syndrome

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Background: Hyponatremia associated with neuroleptic malignant syndrome has thus far been described as a syndrome of inappropriate secretion of antidiuretic hormone.

Objectives: To ascertain and describe the role of cerebral salt-wasting syndrome as the cause of hyponatremia in a patient with neuroleptic malignant syndrome.

Patient: A psychotic patient being treated with olanzapine presenting with sopor, muscle rigidity, polyuria, tachycardia, pyrexia, and severe hyponatremia.

Methods: Serial serological examinations of plasma tonicity (sodium level and osmolality), brain natriuretic peptide, and antidiuretic hormone were performed, and sodium excretion and urine osmolality were determined from 24-hour urine collection. In addition, markers for rhabdomyolysis were monitored.

Results: The patient shows clear symptoms of cerebral salt-wasting syndrome in association with neuroleptic malignant syndrome, characterized by severe hyponatremia, volume depletion, and elevated brain natriuretic peptide but normal antidiuretic hormone levels. Cerebral salt-wasting syndrome improved under dantrolene sodium treatment and concomitant fluid and sodium replacement.

Conclusion: Hyponatremia in patients with neuroleptic malignant syndrome might more likely reflect cerebral salt-wasting syndrome than a syndrome of inappropriate secretion of antidiuretic hormone as an additional aspect of autonomic dysregulation caused by antidopaminergic drugs.

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HYPONATREMIA frequently develops in patients on neurologic intensive care units, and this important electrolyte imbalance can complicate the course of acute neurologic disorders. Two pathophysiological mechanisms have been suggested to cause noniatrogenic hyponatremia: cerebral salt-wasting syndrome (CSWS) and inappropriate secretion of antidiuretic hormone (ADH).

Cerebral salt-wasting syndrome was first introduced by researchers in 1950 and describes an electrolyte balance disorder that can complicate the course of acute neurologic disorders such as intracerebral hemorrhage, subarachnoid hemorrhage, and meningitis.

Cerebral salt-wasting syndrome must be clearly distinguished from a syndrome of inappropriate secretion of ADH because it is the opposite of dilutional hyponatremia, with increased extracellular fluid caused by inappropriate ADH secretion. In contrast, CSWS is characterized by a volume-depleted state secondary to primary natriuresis with hyponatremia, signs of hypovolemia (reflex tachycardia, postural hypotension, reduced skin turgor, and low central venous pressure), and diuresis (high urine volume, high renal sodium excretion, and normal or high urine osmolality). The underlying pathomechanism of CSWS is not fully understood, but impaired sodium resorption of the proximal nephron has been suggested. Herein, we describe a woman who simultaneously presents with CSWS and a neuroleptic malignant syndrome (NMS), and discuss possible pathophysiological mechanisms these 2 conditions have in common as a consequence of central dopaminergic dysregulation.

REPORT OF A CASE

A 57-year-old woman was originally admitted to a psychiatric hospital because of a psychotic episode 10 days before being transferred to our neurologic intensive care unit. Her psychiatric history had not been un-
usual up to then. She was treated with the atypical neuroleptic drug olanzapine for 10 days and, in addition, with haloperidol decanoate (twice, 10 mg total) 2 days before being transferred. On the day the patient was transferred, she developed consciousness disturbances with sopor and intermittent agitation. Physical examination findings showed tachycardia, reduced turgor of the skin, and pyrexia (body temperature, 40°C). Neurologic examination findings revealed severe rigor of the neck and the limbs. Her central venous pressure was low (2 mm Hg) at admission. Laboratory findings showed severe hyponatremia (sodium level, 108 mEq/L) with low plasma tonicity (235 mosm/kg water) and signs of rhabdomyolysis (creatine kinase level, 6975 U/L; myoglobin level in the urine, 224,000 µg/L [12,790 nmol/L] maximum). To specify the nature of hyponatremia, we determined the serum levels of osmotic regulatory peptides and found enhanced concentrations of brain natriuretic peptide (BNP) but normal levels of ADH (Table). The results of further diagnostic investigation (chest x-ray film and electrocardiography) were normal, and no clinical signs of infection (urinary tract, abdomen, or lung) were observed. The results of cranial computed tomography were also normal, particularly with regard to brain tumor or other space-occupying lesions. The significant clinical findings and laboratory values at admission are summarized in the Table.

We considered NMS as one diagnosis because autonomic dysfunction, muscle rigidity, and muscle injury are linked to neuroleptic drug treatment. Cerebral salt-wasting syndrome was considered to be a coexisting diagnosis because hyponatremia is combined with a volume-depleted state. As a consequence of the 2 diagnoses, the patient received dantrolene sodium, 2.5 mg/kg body weight as a loading dose and 20 mg/24 h as continuous perfusion. In addition, the patient’s body temperature was lowered using a cool touch. To prevent renal failure, she received potassium-sodium hydrogen citrate to alkalinate the urine and fluid and sodium to enhance diuresis. Furosemide was not required for forced diuresis because of the CSWS-associated natriuresis. Neuroleptic medication was discontinued. During treatment, the patient’s body temperature decreased to physiological values within 24 hours. Sodium levels increased up to 121 mEq/L within the same period, and were nearly equilibrated within 4 days. Consciousness and elevated muscle tonicity improved with deceleration within 3 days. Renal failure could be prevented. The course of plasma sodium, plasma osmolality, and rhabdomyolysis variables is depicted in Figure 1 and Figure 2. The patient was transferred back to the psychiatric hospital after 5 days because of ongoing delusions.

**COMMENT**

Our patient presented at admission with severe NMS. Stringent clinical criteria of NMS are defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (more information available at: http://www.psych.org/).1 Mean criteria are muscle rigidity and elevated body temperature associated with an antipsychotic medication. These criteria must be accompanied by 2 or more additional symptoms, such as consciousness disturbances, autonomic dysregulation (tachycardia, hypertension, diaphoresis, and incontinence), evidence of muscle injury, or elevated leukocyte level. Our patient fulfilled both mean criteria and presented with nearly all of the additional symptoms, including severe muscle injury (rhabdomyolysis). Neuroleptic malignant syndrome is mainly caused by typical neuroleptic agents (eg, butyrophenone and phenothiazine); less frequently, atypical antipsychotic agents can cause NMS as well.4 Neuroleptic malignant syndrome typically develops within the first 2 weeks of treatment with neuroleptic drugs; however, it may develop at any time during the therapy.3 Hence, the NMS in our patient may have been caused predominantly by the atypical antipsychotic agent olanzapine, which she had received for 10 days. Furthermore, the condition may have been exacerbated by haloperidol, which had been administered twice within 24 hours before onset; this could not be ruled out. Treating NMS in our patient with supportive care and dantrolene was effective. She recovered rapidly and completely.

Second, our patient had severe hyponatremia. On evaluation of the nature of the hyponatremia, we found

### Table. Clinical and Laboratory Findings of CSWS at Admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Value</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature, °C*</td>
<td>40.0</td>
<td>36.5-37.5</td>
</tr>
<tr>
<td>Blood pressure (MAP), mm Hg†</td>
<td>89</td>
<td>&lt;115</td>
</tr>
<tr>
<td>Heart rate/min (resting pulse)†</td>
<td>100</td>
<td>50-80</td>
</tr>
<tr>
<td>Water excretion, mL/24 h (no threshold)</td>
<td>6600</td>
<td>NA</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>2</td>
<td>2-10</td>
</tr>
<tr>
<td>Plasma sodium level, mEq/L</td>
<td>108</td>
<td>135-145</td>
</tr>
<tr>
<td>Serum osmolality, mosm/kg water</td>
<td>239</td>
<td>281-297</td>
</tr>
<tr>
<td>Serum uric acid level, mg/dL</td>
<td>7</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Brain natriuretic peptide level, ng/L‡</td>
<td>982</td>
<td>&lt;334</td>
</tr>
<tr>
<td>Antiuretic hormone level, pg/mL†</td>
<td>457</td>
<td></td>
</tr>
<tr>
<td>Leukocyte count, ×10³/µL</td>
<td>14.56</td>
<td>4-10</td>
</tr>
<tr>
<td>C-reactive protein level, mg/L</td>
<td>15.02</td>
<td>6600</td>
</tr>
<tr>
<td>At admission</td>
<td>6.7</td>
<td>&lt;5</td>
</tr>
<tr>
<td>At admission</td>
<td>64.7</td>
<td>115</td>
</tr>
</tbody>
</table>

*Measured with a bladder sensor.
†Values were determined using commercial immunoassays for laboratory diagnostics according to the manufacturers’ guidelines. For brain natriuretic peptide, an electrochemiluminescence assay was used (Roche, Mannheim, Germany), measured with an analyzer (Elecys 2010; Roche). For antidiuretic hormone, a radioimmunoassay was used (Bühlmann Laboratory, Basel, Switzerland).
that she was volume depleted, showing low plasma tonicity, low central venous pressure, tachycardia, and polyuria caused by enhanced sodium excretion. This is clearly CSWS, not a syndrome of inappropriate secretion of ADH or any other pathological condition. Noticeably, our patient also developed marked hypouricemia (Table), which is thought to be caused by the persistent abnormal urate transport described in CSWS.

The pathomechanisms of NMS and CSWS are not fully understood, but both seem to reflect dysregulation of higher-order centers of autonomic function. Two main pathomechanisms have been suggested for CSWS: decreased sympathetic input to the kidney and inappropriate levels of circulating natriuretic peptides. Natriuretic peptides enhance natriuresis by increasing the glomerular filtration rate and blocking sodium reabsorption in the inner medullary collecting duct. This leads to a volume-depleted state, as was also demonstrated in our patient. Among the natriuretic peptides, BNP seems to be a more likely candidate for mediating renal salt wasting. Consistent with that, we could show enhanced levels of BNP compared with normal ADH levels (Table). A cardiac origin of BNP in our patient could be excluded by an inconspicuous medical history, a normal chest x-ray film (no signs of left- or right-sided cardiac insufficiency), normal electrocardiographic results, and the absence of any clinical signs of cardiac failure. Interestingly and proving normal cardiac function, BNP levels declined under fluid and sodium replacement therapy (Table). At the same time, the patient’s clinical condition improved.

The effect of circulating natriuretic peptides at the nephron is well documented, whereas their intrinsic function within the central nervous system and peripheral autonomic nervous system is less well understood. A noticeable finding is that extracardiac sources of BNP are closely connected with the sympathoadrenal system. Thus, its brain-derived expression is mainly localized in the hypothalamus and its extracardiac peripheral source is the adrenal medulla. Under certain conditions, there might be a link between CSWS and NMS because sympathoadrenal hyperactivity is a central event in NMS. Antidopaminergic drugs might also cause hypothalamic osmoregulation similar to or as a part of sympathoadrenal dysregulation in NMS. This hypothesis is supported by preclinical evidence showing that centrally acting natriuretic peptides require the integrity of central dopaminergic system function to mediate natriuresis. Haloperidol, for example, can increase the level of central natriuretic peptides and induce natriuresis. We are aware of the speculative nature of our argument, but other causes for CSWS in our patient could be ruled out. There is no evidence for brain pathological features other than neuroleptic drug-induced dopaminergic dysregulation. An infection or a brain tumor could be excluded. There is also no evidence for systemic inflammation caused by an extracerebral infection. We interpret the observed in-
crease in C-reactive protein and in leukocytes (Table) as a systemic inflammatory response reaction because there was no evidence for an infectious focus. Accordingly, the systemic inflammatory response reaction improved without the need for antibiotics.

It is difficult to distinguish whether the observed improvement in hyponatremia is only because of the liquid and sodium replacement and discontinuation of neuroleptic agents or whether it is also supported by the treatment with dantrolene. Dantrolene was originally introduced to treat malignant hyperthermia, but is also effective in treating NMS. It interacts with the ryanodine receptor in skeletal muscle and, thus, slows down calcium efflux from the sarcoplasmic reticulum and, as a consequence, slows down muscle activity-induced fever. Even if ryanodine receptors are also expressed in the brain and are involved in central calcium signaling and neuroprotection, no data are available indicating that dantrolene has a specific central effect in NMS, especially with regard to the dopaminergic system.

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REFERENCES