

PONTINE AND EXTRAPONTINE OSMOTIC MYELINOLYSIS AFTER THE SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE (SIADH) ASSOCIATED WITH FLUOXETINE

Case report

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ABSTRACT - Osmotic demyelination syndrome (ODS) may be precipitated by aggressive correction of a hypo or hyper-osmolar states. We describe the case of a 53-year-old woman that was started on fluoxetine 20 mg/day for depression and nine days later was found to have fluoxetine-induced syndrome of inappropriate secretion of antidiuretic hormone. After hyponatremia correction the mental status of the patient gradually improved, but subsequently she had intermittent difficulty in speaking, naming objects, memory deficits and psychomotor slowness. Magnetic resonance revealed bilateral symmetric hyperintense lesions in the basal ganglia, temporal lobe and hippocampal formation compatible with ODS. These symptoms gradually resolved and she was discharged home without any deficits. Two months later, a new image showed lesion in pons and the other lesions had disappeared. Fluoxetine therapy had never been related with a complication like that.

KEY WORDS: central pontine and extrapontine myelinolysis, osmotic demyelination syndrome, hyponatremia, fluoxetine.

Mielinólise osmótica pontina e extrapontina após a síndrome da secreção inapropriada de hormônio antidiurético associada com fluoxetina: relato de caso

RESUMO - A síndrome de desmielinização osmótica (SDO) pode ser precipitada pela correção agressiva de um estado hiper ou hipoosmolar. Nós descrevemos o caso de mulher de 53 anos que havia iniciado o uso de fluoxetina 20 mg/dia para depressão e que nove dias depois foi diagnosticada como tendo síndrome da secreção inapropriada de hormônio antidiurético induzida por fluoxetina. Depois da correção da hiponatremia o estado mental da paciente gradualmente melhorou, mas subsequentemente ela apresentou dificuldade intermitente para fala e para nomear objetos, déficits de memória recente e lentidão psicomotora. Ressonância magnética revelou lesões hiperintensas bilaterais e simétricas na região dos gânglios da base, lobo temporal e hipocampo compatíveis com SDO. Estes sintomas gradualmente se resolveram e a paciente foi de alta sem qualquer déficit. Dois meses mais tarde uma nova imagem cerebral mostrou lesão na ponte e ausência das lesões antigas. Até onde sabemos a terapia com fluoxetina nunca foi relacionada a uma complicação tardia como esta.

PALAVRAS-CHAVE: mielinólise central pontina e extrapontina, síndrome de desmielinização osmótica, hiponatremia, fluoxetina.

Central pontine myelinolysis (CPM) was first described in alcoholic and malnourished patients in 1959¹ and subsequently has been expanded in recent years to include patients with symmetrical extrapontine lesions, notably in the basal ganglia, thalami and midbrain. Recently, with better understanding, these conditions were more appropriately recognized as

part of the osmotic demyelination syndrome (ODS). This disorder it is not exclusively iatrogenic like early thought. Focal symmetric demyelination in the central nervous system may be precipitated by aggressive correction of a hypo or hyper-osmolar states. Patients at risk of ODS should be carefully subjected to osmolar correction to avoid brain injury.

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We describe the case of a woman, presenting with severe hyponatremia and syndrome of inappropriate secretion of antidiuretic hormone (SIADH), strongly associated with the use of fluoxetine. After correction of her sodium abnormality, despite the strict observance of recent therapeutics guidelines, the patient developed pontine and extrapontine osmotic myelionysis. In this paper we try to relate the fluoxetine therapy as the initial cause of the ODS. As we know fluoxetine therapy had never been related with a complication like that.

CASE

A 53-year-old woman was seen in an emergency department for evaluating a chest pain and dyspnea for the past two months. The patient also reported associated forgetfulness, decreasing energy, anhedonia, insomnia, anxiety and irritability for the past four months. No psychotic symptoms were identified. She had no familiar cardiovascular risk. She was been treated for systemic arterial hypertension for the past eight years and last year was on losartan (100 mg/day) plus hydrochlorothiazide (25 mg/d). Acute myocardial infarct was ruled out and renal function

was normal. The serum sodium was 135 mmol/L. The patient was discharged for a cardiologist evaluation and she was started on fluoxetine (20 mg/day).

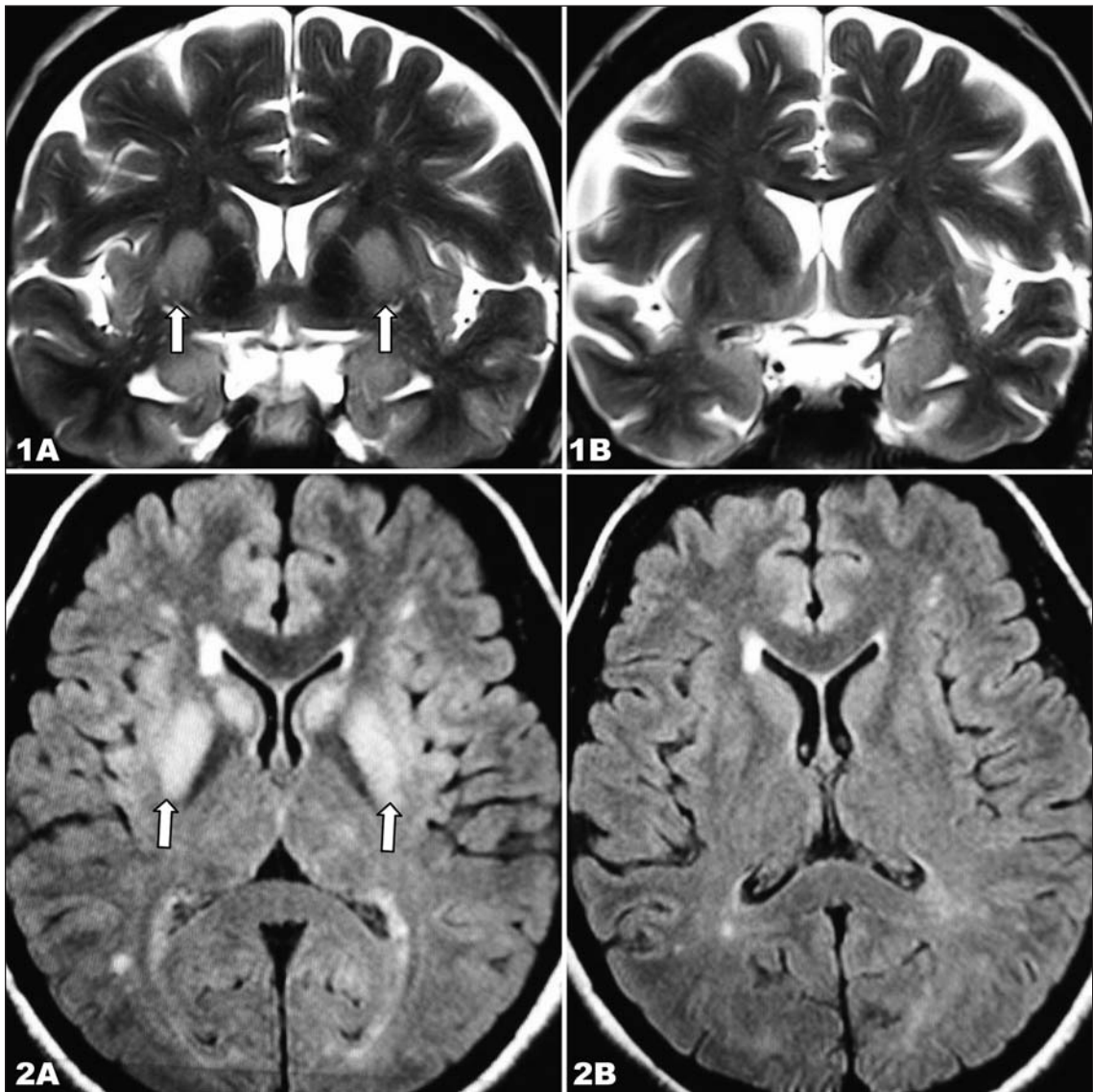
Nine days later, the patient started with weakness and nausea in the morning. At night of the same day she became confused, was unable to stand or feed herself, and had one episode of vomit. Three hours later she became unresponsive and had a generalized seizure, during approximately 1 minute, followed by sleepness. After the attack she was brought to our emergency service. On admission the patient was lethargic, with impaired attention and alertness, but she was normovolemic and without focal motor deficits. Her blood pressure was 210/100 mmHg. She had mild generalized muscle rigidity, Babinski's sign bilaterally and increased deep tendon reflex. The initial serum sodium was 105 mmol/L, the potassium 2.9 mmol/L and the complete laboratory evaluation is show in the Table. She was performed a cranium tomography and cerebrospinal fluid analysis that were normal. Thyroid stimulation hormone (TSH) level was within normal limits. No indications of pneumonia were found on chest X-ray. Abdomen ultrasonography was normal.

The hyponatremia was believed to be secondary to fluoxetine-induced SIADH and it was discontinued. Her

Table. Laboratory evaluation during hyponatremia correction.

Exam/day	1 st	2 nd	3 rd	4 th	5 th
Hemoglobin (g/dL)	14.4	14.6	13.5	13.1	
Leucocytes (per mm ³)	14.130	12.140	7.830	6.160	
Band forms (%)	12	10	7	1	
Platelets (per mm ³)	329.000	310.000	282.000	287.000	
INR	1.1				
Glucose (mg/dL)	266	124	114		112
Serum Ca (mg/dL)	8.4	8.2			8.5
Serum Mg (mmol/L)	1.7	2.1	2.4		2.1
Serum Na (mmol/L)	105	114	130	130	138
Serum K (mmol/L)	2.9	3.2	2.9	3.8	3.9
Urinary Na (mmol/L)	70	27			68
Urinary K (mmol/L)	20	15			
Serum osmolality (mOsm/L)	220	261			288
Urinary osmolality (mOsm/L)	400	328			224
Urea (mg/dL)	14	10			8
Creatinin (mg/dL)	0.6	0.7	0.8	0.7	0.7
AST (U/L)	29				
ALT (U/L)	30				
Total bilirubin (mg/dL)	1.0				
pH	7.49				
pCO ₂	33				
HCO ₃	25				
pO ₂	74				
TSH	0.59				

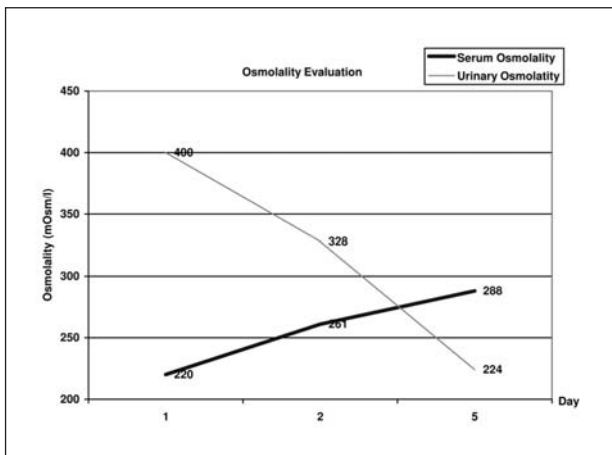
INR, international normalized ratio; TSH, thyroid stimulation hormone; AST, aspartate aminotransferase; ALT, alanine aminotransferase.



Column A: sixth day after hyponatremia correction.

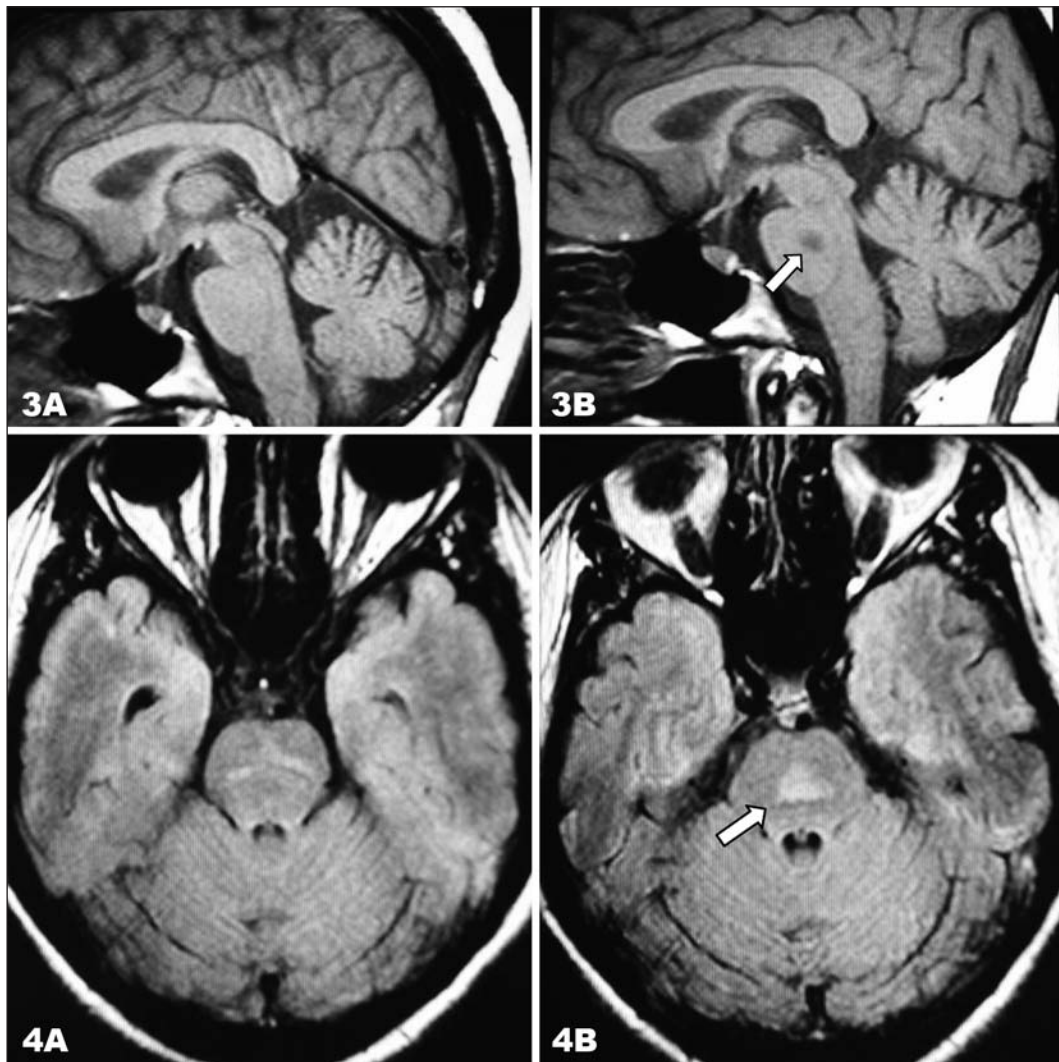
Column B: two months later.

Fig 1. (A) Coronal T2-weighted image and Fig 2. (A) Axial FLAIR image shows bilateral symmetric hyperintense lesions in the basal ganglia (Observation: the arrows are showing the lesions.). Two months later the lesions had disappeared 1 (B) and 2 (B).



Graph. Urinary and serum osmolality evaluation during the hyponatremia correction.

systolic blood pressure was controlled with oral nifedipine. Fluids were restricted to 1000 mL/day and because the severity of symptoms hypertonic saline solution was given plus 80 mg of intravenous furosemide. The hypokalemia was also corrected with 200 mmol K⁺/day. With improvement of her hyponatremia, the patient became more alert, generalized muscle rigidity, Babinski's sign and increased deep tendon reflex disappeared, but her condition subsequently worsened. She had intermittent difficulty in speaking, naming objects, memory deficits and psychomotor slowness. Magnetic resonance images (MRI) revealed bilateral symmetric hyperintense lesions in the basal ganglia (Figs 1A and 2A). The serum Na⁺ continued to return to normal over the next few days. The patient's speech cleared and her mentation returned to the premonitory level in five days, paralleling the resolution of her hyponatremia (Graph). The fluid restriction was discontinued with-



Column A: sixth day after hyponatremia correction Column B: two months later

Fig 3. (B) Sagittal T1-weighted image showing hypointense lesion in the pons and Fig 4 (B) axial FLAIR image shows an increased signal in the same region (the arrows are showing the lesions). Note the lesions absence two months early in 3 (A) and 4 (A) images.

out recurrence of hyponatremia. After few days she was discharged home without any deficits. At 2-months follow-up she continued without any symptoms. Another MRI revealed resolution of the basal ganglia lesions (Figs 3A and 4A) and a new image in the pons (Figs 3B and 4B) compatible with pontine myelinolysis.

DISCUSSION

Hyponatremia is the most common electrolyte abnormality observed in a general hospital population and it should be especially considered in patients taking a selective serotonin re-uptake inhibitor^{2,3}. First described in 1959 by Adams et al.¹ as central pontine myelinolysis and now more appropriately described as osmotic demyelination syndrome, this condition is

characterized by regions of demyelination throughout the brain most notably when hyponatremia had been corrected rapidly.

Hyponatremia causes generalized encephalopathy with manifestations that include malaise, nausea, headache, lethargy, confusion, seizures, coma, and death. Focal neurologic signs are rare. The severity of symptoms depends on the degree and rate of development of hyponatremia. A rapid decrease in sodium levels may lead to coma and seizures, but if hyponatremia develops slowly, patients are much less symptomatic⁴. The risk factors for development of ODS after correction of chronic hyponatremia include hypokalemia, malnutrition, chronic alcoholism⁵, hypoxia⁶, burn injury, surgical removal of pituitary

tumor and those who have undergone orthotopic liver transplant⁷.

The typically histopathologic features include symmetric demyelination of the pons. The characteristics are a triangular to "bat-wing" lesion that spreads centrifugally from the median raphe and is located in the dorsal basis pontis with relative sparing of tegmentum, corticospinal and corticobulbar tracts except in the most severe cases. CPM and extrapontine myelinolysis (EPM) may occur alone or in conjunction⁸.

The cause and pathogenesis of CPM/EPM are not known. One proposed mechanism of demyelination has involved osmotic shifts with harmful metabolic consequences to oligodendrocytes. Another proposed mechanism of demyelination attributes changes to vasogenic edema developing from osmotic opening of the endothelial blood-brain barrier. Vascular endothelial injury due to rapid osmotic change and subsequent demyelination was also involved in the patho-etiology of EPM⁹. In this patient, extrapontine abnormalities resolved in 2 months, suggesting reversible immediate causes, but surprisingly another tardier lesion appears in the pons.

The clinical presentation of CPM typically includes progressive lethargy, quadriparesis, dysarthria, ophthalmoplegia, dysphasia, ataxia, and reflex changes that usually occurs 2-7 days after treatment for the underlying disease or electrolyte disturbance has been initiated. Akinesia, ataxia, catatonia, choreoathetosis, cogwheel rigidity, disorientation, dysarthria, dystonia, extrapyramidal symptoms, emotional lability, gait disturbance, movement disorders, mutism, myoclonus, myokymia, parkinsonism, rigidity, and tremor have all been described in patients with EPM alone¹⁰. The Babinski's sign, encountered in this particular case, could be found in 21% of patients with ODS and increased deep tendon reflex in 36%¹¹, but they were found before correction of the hyponatremia, therefore, should not be attributed to EPM. However, her intermittent difficulty in speaking, naming objects, memory deficits and psychomotor slowness certainly were. She did not present any symptom of the CPM spite the MRI lesion.

Demyelination in pontine or extrapontine locations does not appear exclusively in adult or alcoholic patients with hyponatremia¹² but may occur when the serum sodium level is normal^{13,14} or elevated^{15,16}. The osmotic demyelination syndrome may occur even when the serum sodium abnormality is corrected within limits considered "safe"^{17,18}. This patient re-

ported present typical lesions in MRI compatible with EPM/CPM besides carefully correction of hyponatremia. It is clear that rapid correction of hyponatremia is not the only factor involved.

Riggs et al.¹⁹ suggest that osmotic stress and oligodendrocyte topography rather than rapid correction of hyponatremia may be the key to the development of osmotic myelinolysis. Lateral pontine and extrapontine myelinolysis can be associated with hypernatremia and hyperosmolality²⁰. Experimental data shown that high and sustained levels of hypernatremia could induce brain myelinolysis in rats²¹. In both hypo and hypernatremic states, the significant event may be an increase in serum sodium or serum osmolality with sufficient rapidity and magnitude. Osmotic myelinolysis may not be exclusively an iatrogenic disorder (resulting from aggressive correction of chronic hyponatremia) but may result from other rapid changes in serum osmolality.

The distribution of cerebral demyelinating lesions in patients with hyponatremic encephalopathy could be compatible with hypoxic damage⁶. It appears that ischemic hypoxia severely impairs the brain's adaptive mechanisms during hyponatremia by reducing cerebral oxygen availability. It may be an important comorbid factor in the morbidity associated with hyponatremic encephalopathy²². Bilateral basal ganglia lesions such as these may be seen in association with hypoxia, but in this case, no respiratory disturbance, cardiac arrest, or hypotension had occurred. Hypoxic brain damage was unlikely.

Demyelination appears on CT as an area of decreased attenuation in the central pons or in extrapontine locations, although CT may underestimate the true extent of disease. The yield of MRI in determining both the number and extent of lesions in the osmotic demyelination syndrome is significantly better. Acute demyelinating lesions are symmetric and hypointense on T1 weighted images; during the subacute stage they become hyperintense on T2 weighted images probably because of the presence of endothelial injury-induced microhemorrhages. Lesions on MRI may appear days to weeks after the onset of symptoms and may resolve completely over a period of months¹⁰. Like in this case imaging studies performed early during the illness may be unremarkable, but still a diagnosis of central pontine myelinolysis should be suspected and a repeat imaging study might be required in 10-14 days to establish the diagnosis²³. Clinical and MRI findings in the pons may be correlated during the early phase of the

disease. However, patients either improve clinically before the lesion regresses on MRI or they improve clinically independently of MRI findings²⁴.

Despite improved recognition of the classic lesions of CPM/EPM by modern neuroradiological techniques, the absence of autopsy confirmation in most recent reports raises questions about diagnostic accuracy. Over-reliance on the use of neuroimaging to assign a histologically defined diagnosis may explain why recent reports of clinical outcome differ from classic descriptions¹⁰. In fact, some reports shown that autopsied patients with "classic" CPM both clinically and upon neuroimaging had other histopathologies such as hemorrhagic necrosis or ischemic rarefaction of the central pons²⁵. Thereafter, differential diagnosis with infarct, metastasis, glioma, multiple sclerosis, encephalitis, and radiation or chemotherapy should be made.

The first step in the treatment of ODS is prevent neurological injury identifying which patients are at risk of the osmotic demyelination syndrome. The risk of ODS appears to be greatest when the rate of correction is greater than 10-15 mmol/L/day. In symptomatic acute hyponatremia, the initial rate of correction can be 1-2 mmol/L/h for several hours if on any day of treatment the total daily correction is not more than 8 mmol/L/day²⁶.

Both normal and hypertonic saline are hypertonic to the patient's serum osmolality in this setting. Because normal saline for volume expansion may cause ODS when the serum Na⁺ rises, half normal saline may be used to minimize the rate of rise in serum Na⁺. There is some evidence in animals and in man that hypokalemia, when associated with a hyponatremic state, could predispose a patient to the development of demyelination during correction of hyponatremia²⁷. Consequently, normalizing the hypokalemia either before, or at least concomitant with, the serum Na⁺ correction will be a prudent and logical approach.

With the assumption that undefined myelinotoxic compounds are contributing to the demyelinating process in CPM/EPM, once symptoms have occurred, treatment and decreased morbidity could be possible with plasmapheresis. Others have reported complete recoveries after steroid administration¹⁰. Early dexametasone treatment can prevent the blood-brain barrier disruption that is caused by the rapid correction of hyponatremia and its associative demyelinating changes and suggest that dexametasone might be effective in preventing CPM, but these are experimental data²⁸.

Complete recovery is now possible, so CPM and EPM are no longer the devastating neurological ill-

nesses they were when first described. According to the previous literature the prognosis for CPM and EPM were considered to be poor. However, milder courses and survival without substantial neurological deficit have been reported in recent years. Retrospectively evaluation of 44 patients with CPM shows that the outcome does not depend on the severity of neurological deficits during the acute phase of the condition or on concomitant internal diseases, including the degree of hyponatremia. Of the 34 patients for whom follow-up data were available, 32 survived. Of these 11 completely recovered, 11 had some deficits but were independent, and 10 were dependent²⁴. Earlier recognition of patients at risk of ODS, combined with a better understanding of the pathophysiology of electrolyte disturbances in diverse medical conditions, has allowed for more precise fluid and electrolyte management and better clinical outcomes.

It has been observed that ODS may occur despite strict observance of the published therapeutic guidelines, like in this case described here. Variation in individual susceptibility to myelinolysis makes it difficult to determine a proper rate of correction. Therefore, a completely safe rate of correction probably cannot be defined. Nevertheless, it seems reasonable that the rate of correction should be as low as possible, especially if the chronic hyponatremia is accompanied by other risk factors for ODS.

Finally, as we know, this is the first report associating SIADH and hyponatremia due to fluoxetine having a tardier complication like ODS. SIADH is an important, under recognized and serious complication of the selective serotonin reuptake inhibitors. Patients should have their serum sodium concentration monitored, especially in the early stages of treatment.

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