Treating Hyponatremia in an Empty Sella Syndrome Patient Complicated with Possible Myelinolysis

Wen-Chin Lee, MD; Yuan-Fu Cheng, MD; Jin-Bor Chen, MD

Hyponatremia as the presenting manifestation of empty sella syndrome is rare. There is little clinical experience in the management of this problem and its possible therapeutic complications. We herein report on a 44-year-old woman with a past history of massive postpartum hemorrhage who was admitted because of hyponatremia and disturbed consciousness. Initial biochemical data suggested the effects of antidiuretic hormone, but fluid restriction alone offered limited benefit. Later, hormonal levels indicated hypopituitarism. Magnetic resonance imaging and cisternography led to a diagnosis of empty sella. Although glucocorticoid substitution was initiated and the clinical condition initially improved, possible myelinolysis subsequently became a complication. With early recognition and immediate replacement of hypotonic fluid, the patient completely recovered. We report this case to illustrate the fact that glucocorticoid substitution and concurrent fluid restriction can probably lead to myelinolysis in empty sella syndrome patients. We suggest that the serum sodium level should be frequently monitored and that much more attention should be paid to the neurologic signs when substituting glucocorticoids in these patients, even though the increment in the serum sodium level is acceptable. Once possible myelinolysis develops, early recognition is critical, and the immediate replacement of hypotonic fluid is suggested. *(Chang Gung Med J 2002;25:838-43)*

Key words: glucocorticoid substitution, hyponatremia, empty sella, myelinolysis.

Hyponatremia as the presenting manifestation of empty sella syndrome was first reported in 1987.[1] Its clinical presentation resembles that of the syndrome of inappropriate antidiuretic hormone (ADH) secretion, but fluid restriction alone is unable to correct this problem. Sheehan's syndrome (postpartum anterior pituitary necrosis) is often accompanied by empty sella.[2,3] As such, glucocorticoid substitution is the mainstay treatment in this setting. However, there are no practical guidelines for glucocorticoid substitution in these hyponatremic patients. Excessive glucocorticoids given in too short of a period of time may increase the risk of rapid correction of the hyponatremia and resultant neurologic deficits. In addition to the well-known risk factors for myelinolysis, such as alcoholism, liver disease, malnutrition, thiazide therapy, and extreme hyponatremia (< 105 mmol/l),[4] adrenocortical insufficiency may also be a potential risk factor. Herein, we report on an empty sella syndrome patient who received glucocorticoid substitution and concurrent fluid restriction to correct hyponatremia, subsequently developed possible myelinolysis, and ultimately survived with no neurologic sequelae. Causes of the rapid correction of the hyponatremia in this setting are further discussed.

From the Division of Nephrology, Department of Internal Medicine, Chang-Gung Memorial Hospital, Kaohsiung.
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Address for reprints: Dr. Wen-Chin Lee, Division of Nephrology, Department of Internal Medicine, Chang Gung Memorial Hospital, 123, Ta Pei Road, Niaosung 833, Kaohsiung, Taiwan, R.O.C. Tel.: 886-7-7317123 ext. 8306; Fax: 886-7-7322402; E-mail: pooh@anet.net.tw

CASE REPORT

This 44-year-old woman, a housewife, was admitted because of hyponatremia and disturbed consciousness. She had no liver disease and never drank alcohol. She also denied any history of using diuretics. She had a history of postpartum hemorrhage which had occurred 13 years previous. Amenorrhea and failure to lactate developed thereafter. Fatigue and cold intolerance were also found. She neglected these problems and received no treatment. She lived an uneventful life until 1 day prior to this admission when she suffered from vomiting and diarrhea. Drowsiness developed the next day. She was then sent to our hospital for further management.

Physical examination revealed a chronically ill-looking, moderately nourished female. She weighed 48 kg and was 156 cm tall. Her blood pressure was 120/67 mmHg. Her pulse rate was 60 beats/min, her respiratory rate was 19/min, and her temperature was 36.5°C. She was drowsy, her fluid status was clinically euvolemic, and her conjunctiva appeared anemic. There was scanty axillary and pubic hair. The thyroid gland was not palpable, and no remarkable findings were present in the chest or abdomen. Laboratory data were as follows: hemoglobin 95 g/l, white blood count 8.1 × 10^9/l, platelets 177 × 10^9/l, glucose 5.8 mmol/l, blood urea nitrogen 1.1 mmol/l, serum creatinine 62 μmol/l, sodium 116 mmol/l, potassium 2.6 mmol/l, chloride 85 mmol/l, calcium 2.1 mmol/l, albumin 35 g/l, serum osmolality 231 mmol/kg, urine osmolality 257 mmol/kg, urinary sodium 155 mmol/l, urinary potassium 20 mmol/l, and urinary chloride 140 mmol/l. Urinalysis revealed unremarkable findings. Hypopituitarism was confirmed by a determination of the hormonal levels (Table 1). Severe adrenocortical insufficiency with a low cortisol level was found. Initial brain computed tomography (CT) revealed no evidence of cerebral edema, infarction, hemorrhage, or mass. Magnetic resonance imaging (MRI) showed an equal intensity of both the sella turcica and the cerebrospinal fluid (Fig. 1). Cisternography demonstrated an intrasellar filling of contrast in the pituitary fossa. Thus, a diagnosis of empty sella was made.

She received a normal saline infusion and potassium supplements in the emergency room. The hypokalemia was thus corrected, but the serum sodium level continued to drop. Intravenous fluid supplementation was discontinued on admission. After

Table 1. Hormonal Levels And Test Results

Glucocorticoid function tests	
Cortisol at 08:00	12 nmol/l (248-635)
Corticotropin	2.2 pmol/l (2.0-11.4)
Thyroid function tests	
Thyroid-stimulating hormone	0.71 mIU/l (0.25-4.0)
Free thyroxin	< 1.0 pmol/l (10.2-25.9)
Gonadotropin function tests	
Follicle-stimulating hormone	93 IU/l (20-138)
Luteinizing hormone	0.74 IU/l (15-62)
Estradiol	26 pmol/l (22-374)
Prolactin	70 pmol/l (150-1150)
Growth hormone	< 0.1 μg/l (< 10)

Normal values are indicated in parentheses.

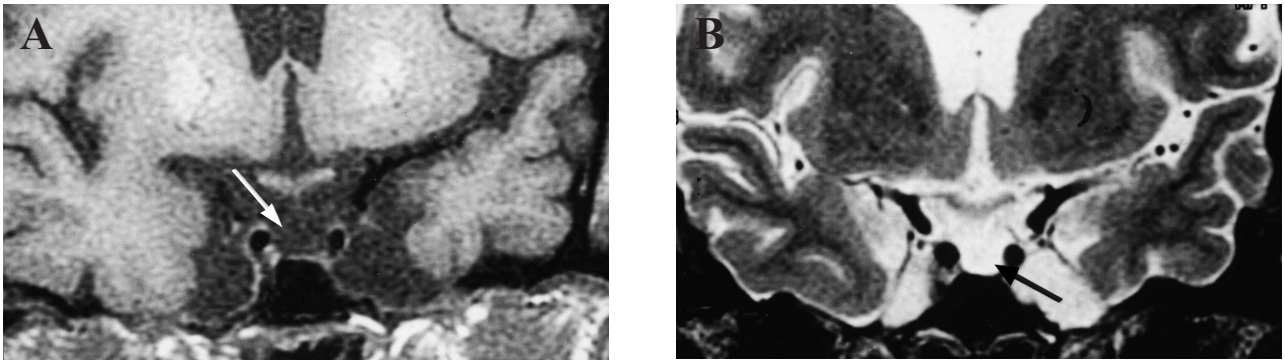

Fig. 1 Magnetic resonance imaging of the brain revealing equal intensity of the sella turcica and the cerebrospinal fluid. (A) T1-weighted image taken in the coronal plane showing hypointensity over the sella region (white arrow). (B) T2-weighted image taken in the coronal plane showing hyperintensity over the sella region (black arrow).

4 days of water restriction, the sodium concentration rose to 121 mmol/l, and her consciousness became clearer. Unfortunately, her blood pressure dropped to 90/60 mmHg the next day. Hydrocortisone (100 mg) was given intravenously at 8-h intervals because an adrenal crisis was suspected. Three days later, although her blood pressure had returned to normal values, mutism and spastic quadriparesis developed and progressed to a "locked-in" state. The brain CT at that time revealed no evidence of infarction, hemorrhage, or mass. The sodium concentration was elevated to 142 mmol/l. Because myelinolysis was suspected, hypotonic fluid was given immediately. The glucocorticoid was also tapered-down to 20 mg/day prednisolone. Three days later, the neurologic deficit had gradually improved. Although the MRI, which was performed 6 days after the onset of the neurologic deficit, revealed no evidence of myelinolysis, complete recovery was reached after 5 days of hypotonic fluid supplementation. The serum sodium concentration remained at 136 mmol/l (Fig. 2).

After hormonal substitution of 50 mg cortisone acetate in 2 divided doses and 0.1 mg/day L-thyroxin, the hyponatremia no longer recurred.

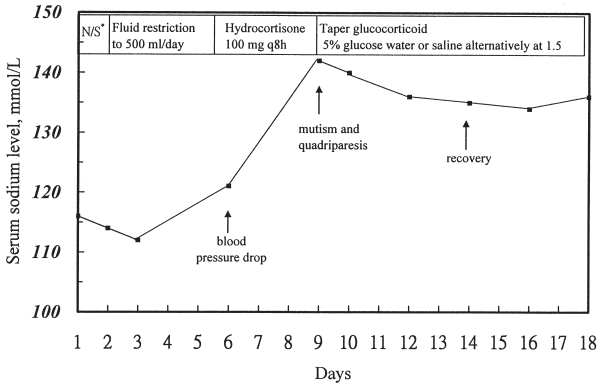

Fig. 2 Clinical course of this patient. The horizontal bars at the top of the diagram indicate the treatment given to the patient. *N/S means normal saline.

DISCUSSION

An empty sella turcica is defined as a sella, which is completely or partly filled with cerebrospinal fluid.[5] When seen after surgery, irradiation, or medical treatment of the pituitary gland, it is considered secondary, but otherwise it is primary. Sheehan's syndrome is often accompanied with an empty sella. Fleckman et al.[2] and Bakiri et al.[3] reported that an empty sella was shown by CT in 12 of 13 patients and 39 of 54 patients with Sheehan's syndrome, respectively. Sheehan's syndrome in this case was responsible for the secondary empty sella syndrome. Both primary and secondary empty sella syndrome can cause hyponatremia, which results from hypopituitarism.

Hyponatremia can be the presenting manifestation of Sheehan's syndrome. It can be chronic or appear in the early post-partum period.[6] ADH is known to play a role in the pathogenic mechanism.[7] However, the cause of ADH secretion in hyponatremia associated with hypopituitarism is related to adrenocortical insufficiency.[8] The glucocorticoid deficit is not an osmotic but a physiological stimulus for ADH secretion.[7,9] Glucocorticoids have been shown to reverse the impaired water diuresis of this disorder by increasing the renal excretion of solute-free water. Ahmed et al. suggested that glucocorticoids promote normal water diuresis by inhibiting the secretion of ADH from the neurohypophysis.[10] Thus, glucocorticoid substitution has been the mainstay treatment of hyponatremia associated with hypopituitarism. In reviewing the literature, we found that the dosage of this hormone substitution has varied (Table 2),[1,6,7,11] ranging from 25 mg/day cortisone to 640 mg/30 hours hydrocortisone. In our case, however, 100 mg hydrocortisone was given intravenously at 8-h intervals due to fear of an adrenal crisis. Unfortunately, neurologic deficits ensued, and myelinolysis was highly suspected.

Myelinolysis was first described as a pathologic entity. However, a reliable diagnosis before death is now possible on the basis of the clinical syndrome and setting. Typical features are disorders of the upper motor neurons, spastic quadriparesis and pseudobulbar palsy, and mental disorders ranging from mild confusion to coma.[12] Brain imaging is the most useful diagnostic test, and an MRI is more sensitive. Nevertheless, myelinolytic lesions may not be apparent on scans during the first 2 weeks of illness. Thus, a diagnosis of myelinolysis should not be ruled out simply because brain imaging during the first 2 weeks of the illness shows no lesions.[12,13] Because therapeutic complications developed and the brain

Table 2. Clinical Features of Patients with Hypopituitarism-induced Hyponatremia

Case	Authors Year	Initial serum sodium level (mmol/l)	Cortisol level (nmol/l)	Glucocorticoid replacement	Neurologic deficit
1	Okuno et al. 1987	116	61	cortisone 25 mg/day	none
2	Oelkers et al. 1989	111	61	hydrocortisone 100 mg qd	none
3	Oelkers et al. 1989	112	158	hydrocortisone 70 mg qd	none
4	Oelkers et al. 1989	118	132	hydrocortisone 15 mg bid	none
5	Oelkers et al. 1989	115	102	hydrocortisone 15 mg bid	none
6	Oelkers et al. 1989	117	260	hydrocortisone 40 mg qd	none
7	Putterman et al. 1991	111	33	hydrocortisone 640 mg in the first 30 hours	none
8	Boulanger et al. 1999	118	< 28	hydrocortisone 30 mg qd	none
9	Present case	116	12	hydrocortisone 100 mg q8h for 3 days	possible myelinolysis

CT showed no evidence of infarction, hemorrhage, or mass in our patient, myelinolysis was first considered.

Myelinolysis is associated with a rapid rate of hyponatremia correction, rather than with the absolute sodium concentration. Chronically hyponatremic patients do not necessarily develop myelinolysis, which can even occur with hypernatremia.[12] Two possible factors in our case may have contributed to the rapid rate of correction. First, fluid restriction resulted in a negative water balance. Second, a large dose of glucocorticoid substitution as a life-saving measure for the adrenal crisis may have greatly promoted normal water diuresis. In addition, the half-life of ADH is only 15-20 min. Hence, the effect of ADH suppression by glucocorticoids may appear in a short period of time, and result in rapid correction of the hyponatremia. Lower doses of hydrocortisone are usually effective in the correction of hyponatremia resulting from hypopituitarism.[1,6,7] However, when a patient presents with an adrenal crisis and hyponatremia, high-dose hydrocortisone is life-saving. Furthermore, as shown in Table 2, case 7 received an even larger dose of glucocorticoid in a short period of time, and developed no neurologic deficit. Cases 1 and 8 both received glucocorticoid substitution and concurrent fluid restriction and suffered no neurologic deficit, either. Since there are so few reported cases, we cannot infer from Table 2 that cortisol level, initial serum sodium level, or the dosage of glucocorticoids can predict the occurrence of this therapeutic complication. Further study is needed to reveal the factors which affect the rapidity of the correction of hyponatremia with glucocorticoid substitution.

Myelinolysis can occur even if the increment change in the serum sodium level is deemed acceptable.[12,14,15] Thus, even though data from clinical and animal studies indicate a low incidence of myelinolysis if the increase in serum sodium is 12 mmol/l or less in 24 hours, it may be impossible to define a level of correction that is always completely free of risk.[12] Furthermore, considering the short half-life of ADH, clinicians should frequently monitor the serum sodium level, especially during the first few hours of glucocorticoid substitution in hypopituitarism-associated hyponatremic patients.

The outcome of patients with myelinolysis varies, ranging from complete recovery to death.[12] There is also no specific treatment for myelinolysis. Preliminary data from animal studies suggest that re-lowering the serum sodium in the initial hours and days after rapid correction may be beneficial.[16] In our case, we immediately used hypotonic fluid, and the patient gradually achieved complete recovery. More data are needed before re-lowering plasma sodium can be recommended. It should be considered only in patients for which the condition has been corrected too rapidly, and who have developed early neurologic symptoms compatible with possible myelinolysis.

In conclusion, glucocorticoid substitution is the mainstay treatment of hyponatremia associated with hypopituitarism, but the treatment may possibly precipitate myelinolysis. In addition to the well-known risk factors for myelinolysis, such as alcoholism, liver disease, malnutrition, thiazide therapy, and extreme hyponatremia,[2] adrenocortical insufficiency

may also be a potential risk. As practical guidelines for glucocorticoid substitution in cases such as this cannot yet be proposed, clinicians should frequently monitor the serum sodium level and neurologic signs when correcting hyponatremia with glucocorticoids, even though the incremental change in the serum sodium level is acceptable. Once possible myelinolysis develops, early recognition is critical, and immediate replacement with hypotonic fluid is suggested.

REFERENCES

1. Okuno S, Inaba M, Nishizawa Y, Miki T, Inoue Y, Morii H. A case of hyponatremia in panhypopituitarism caused by the primary empty sella syndrome. Endocrinol Japoni 1987;34:299-307.
2. Fleckman AM, Schubart UK, Danziger A, Fleischer N. Empty sella of normal size in Sheehan's syndrome. Am J Med 1983;75:585-91.
3. Bakiri F, Bendib SE, Maoui R, Bendib A, Benmiloud M. The sella turcica in Sheehan's syndrome: Computerized tomographic study in 54 patients. J Endocrinol Invest 1991;14:193-6.
4. Gross P. Treatment of severe hyponatremia. Kidney Int 2001;60:2417-27.
5. Bjerre P. The empty sella. A reappraisal of etiology and pathogenesis. Acta Neurol Scand Suppl 1990;130:1-25.
6. Boulanger E, Pagniez D, Roueff S, Binaut R, Valat AS, Provost N, Leroy R, Codaccioni X, Dequiedt P. Sheehan syndrome presenting as early post-partum hyponatraemia. Nephrol Dial Transplant 1999;14:2714-5.
7. Oelkers W. Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. N Engl J Med 1989;321:492-6.
8. Wakui H, Nishinari T, Nishimura S, Endo Y, Nakamoto Y, Miura AB. Inappropriate secretion of antidiuretic hormone in isolated adrenocorticotropin deficiency. Am J Med Sci 1991;301:319-21.
9. Gross PA, Ketteler M, Hausmann C, Ritz E. The charted and uncharted waters of hyponatremia. Kidney Int Suppl 1987;21:S67-75.
10. Ahmed ABJ, George BC, Gonzalez-Auvert C, Dingman JF. Increased plasma arginine vasopressin in clinical adrenocortical insufficiency and its inhibition by glucocorticoids. J Clin Invest 1967;46:111-23.
11. Putterman C, Almog Y, Caraco Y, Gross DJ, Ben-Chetrit E. Inappropriate secretion of antidiuretic hormone in Sheehan's syndrome: a rare cause of postpartum hyponatremia. Am J of Obstet Gynecol 1991;165:1330-3.
12. Laureno R, Karp BI. Myelinolysis after correction of hyponatremia. Ann Intern Med 1997;126:57-62.
13. Martin PJ, Young CA. Central pontine myelinolysis: clinical and MRI correlates. Postgrad Med J 1995;71:430-2.
14. Leens C, Mukendi R, Foret F, Hacourt A, Devuyst O, Colin IM. Central and extrapontine myelinolysis in a patient in spite of a careful correction of hyponatremia. Clin Nephrol 2001;55:248-53.
15. Pirzada NA, Ali II. Central pontine myelinolysis. Mayo Clin Proc 2001;76:559-62.
16. Soupart A, Penninckx R, Crenier L, Stenuit A, Perier O, Decaux G.. Prevention of brain demyelination in rats after excessive correction of chronic hyponatremia by serum sodium lowering. Kidney Int 1994;45:193-200.

治療空鞍症候群合併低血鈉症併發疑似髓鞘溶解症

李文欽　鄭元富　陳靖博

空鞍症候群用低血鈉來表現在臨床上並不常見。我們報告一位44歲女性病患，過去曾有產後大出血的病史，因低血鈉症合併意識不清而住院。一開始對病人採取的限水措施效果很有限，稍後荷爾蒙檢驗數值顯示腦下垂體功能低下，而且核磁共振攝影與腦池攝影檢查證實了空鞍症候群的診斷。雖然投予醣皮質類固醇補充，病人臨床症狀也逐漸改善，稍後病人卻產生疑似髓鞘溶解的合併症。由於及早發現並及時補充低張溶液，病人得以完全復原。我們報告這個病例，是要提醒臨床醫師對於這樣的病人，在採取限水措施的情況下，補充醣皮質類固醇有可能併發髓鞘溶解症。因此，我們建議: 對於這樣的病人在補充醣皮質類固醇時，即使血清鈉的增加值仍在所謂的可接受範圍，也要更嚴密地監測血清鈉值與神經學症狀。一旦出現疑似髓鞘溶解的合併症，及早補充低張溶液是可行的做法。(長庚醫誌 2002;25:838-43)

關鍵字：補充醣皮質類固醇，低血鈉症，空鞍症候群，髓鞘溶解症。

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