

## **Hypernatremic Thirst Deficiency and Memory Disorders Following Hypothalamic Lesions**

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**Summary.** This report describes two patients with a hypodipsic-hypernatremic syndrome and memory disorders associated with hypothalamic lesions. The literature is reviewed. Pathophysiologic mechanisms underlying the syndrome and the therapeutic approach to these patients are discussed.

**Key words:** Hypernatremia – Thirst deficit – Amnesia

### **Introduction**

Hypodipsic hypernatremia is a rare clinical syndrome which has been described following lesions involving the hypothalamic-neurohypophyseal area. The main elements of the syndrome are persistent hypernatremia, not modifiable by increased water intake, decrease or absence of thirst, plasma hyperosmolality and normal renal function.

A study of two patients with a chronic and an acute hypothalamic lesion respectively gave us the opportunity to analyze this clinical picture, with particular reference to the associated memory disorders, to discuss the pathophysiologic mechanisms underlying the syndrome and to offer some useful suggestions on the therapeutic approach to these patients.

### **Case Reports**

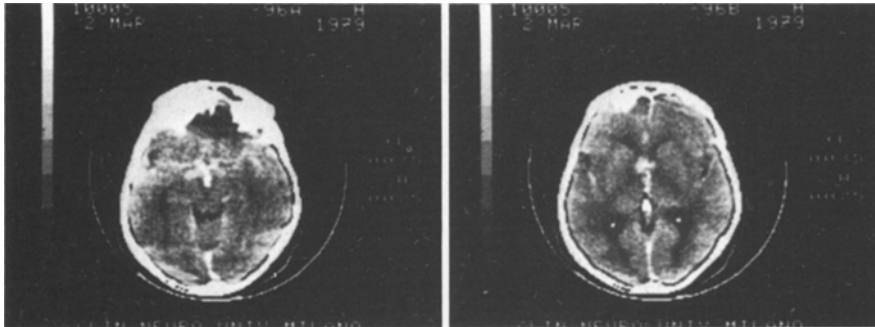
#### *Case 1*

A.G., a 48-year-old woman, was referred to us at the University Hospital in January 1978. On admission she said that her menses had terminated when she was 38, but she had been otherwise healthy until January 1971 when, for approximately 4 months, she complained of intense thirst and polyuria. A diabetes mellitus was suspected, but oral glucose tolerance was within the normal range. The patient recovered spontaneously and no further clinical investigations were performed. Seven years later, when she first came to our attention, she had a 2-year history of dryness of the eyes, mouth and skin and, for the last 6 months, had mild weakness of the lower limbs, decreasing visual acuity and some difficulty in concentration. A year before,

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**Table 1.** Relevant laboratory values in the two patients

	A.G.	G.C.	Normal range
<b>Blood</b>			
– Glucose (fasting)	79	108	50 – 110 mg/100 ml
– Urea	46	50	10 – 50 mg/100 ml
– Creatinine	1.0	1.3	0.6 – 1.2 mg/100 ml
– Sodium	160	174	137 – 142 mEq/l
– Potassium	3.5	3.36	3.5 – 5.0 mEq/l
– Chloride	118	122	98 – 106 mEq/l
– Renin (basal)	6.0	–	0.7 – 1.7 ng/ml · h
– Aldosterone (basal)	5.8	–	7 – 17 ng/100 ml
– pH (arterial)	7.38	–	7.35 – 7.45
– pCO <sub>2</sub> (arterial)	42	–	35 – 45 mm Hg
– HCO <sub>3</sub>	24	–	24 – 26 mEq/l
<b>Urine</b>			
– Specific gravity	1005	1020	1003–1030
– pH	5	5.5	
Plasma osmolality (repeated measures)	from 300 to 330	from 310 to 330	282–292 mOsm/kg H <sub>2</sub> O
Urine osmolality (repeated measures)	from 250 to 350	from 370 to 380	

**Fig. 1.** CT scan of the brain showing a hypothalamic mass occupying the III ventricle and the anterior columns of the fornix

on the grounds of a reduced lacrimal secretion assessed by the Shirmer's test, a diagnosis of "Sjögren's syndrome" had been made. On examination, she showed normal vital signs, with blood pressure 100/70 mm Hg, and heart rate 72/min. A mild proximal weakness of the lower limbs prevented her from standing on a chair without assistance. Visual acuity was 4–5/10 in both eyes (with spectacles) and ophthalmoscopy revealed a bilateral pallor of the disk. Visual field examination showed bitemporal scotomata suggesting a posterior chiasmatal involvement.

The laboratory values on admission are given in Table 1. An intravenous urogram was normal. Brain CT scan revealed a hypothalamic mass occupying the III ventricle and the anterior columns of the fornix with enlargement of the lateral ventricles (Fig. 1).



**Fig. 2.** Right carotid arteriogram showing an anterior communicating aneurysm

In spite of her high plasma osmolality, the patient denied any subjective sensation of thirst. She was urged to drink, but even after an adequate oral ingestion of water or a vigorous intravenous hydration, plasma sodium never fell below 150 mEq/l. Chlorpropamide 250 mg/day was started and plasma sodium and osmolality rapidly fell to within the normal range. Any attempt to withdraw the drug resulted in a subsequent rise in plasma sodium.

Six months later the patient began complaining of diplopia and severe headache. A ventriculo-atrial shunt was carried out for the relief of intracranial hypertension, but the patient died 3 months after operation. Post mortem examination was not performed.

#### *Case 2*

G.C., a 42-year-old man, was admitted to the Neurologic Clinic of Modena University for subarachnoid bleeding following the rupture of a right anterior communicating artery aneurysm (Fig. 2).

Laboratory investigations, including an ionogram, were normal. After a successful clipping of the aneurysm by the neurosurgeon, the patient was again referred to us. On readmission, he showed severe confusion, mild left hemiparesis and marked dehydration. Confusion subsided in 10 days, but a severe anterograde and retrograde memory defect emerged. A brain CT scan was found to be normal except for many artifacts from the metallic clip on the aneurysm's neck. The results of the laboratory investigations on the 20th day after surgery are shown in Table 1. In spite of his high plasma osmolality, the patient never complained of thirst or even asked for a glass of water. Parenteral administration of free water did not succeed in reducing plasma sodium below 160 mEq/l, while forcing the patient to drink increased polyuria and reduced urine osmolality without obtaining a relevant reduction in plasma hyperosmolality. Clofibrate 2 g/day was, on the contrary, effective in reducing plasma sodium to within the normal range. The drug was discontinued 3 months later without a subsequent rise in plasma osmolality. After 2 years the patient showed a complete recovery except for the subjective complaint of minor memory deficits.

### Biological Investigations

Salt and water metabolism were studied by means of the following clinical tests:

*1. Urinary Concentration After Exogenous ADH Administration.* Urine osmolality, assessed before and 2 h after the intramuscular administration of Pitressin tannate, 6 I.U. in oil, varied from 340 to 700 mOsm/kg H<sub>2</sub>O in patient A.G. and from 375 to 750 mOsm/kg H<sub>2</sub>O in patient G.C. Both patients showed therefore that the ability of their kidneys to concentrate urine after ADH administration was only mildly impaired, probably due to the fact that they were hypokalemic and hypokalemia itself reduces renal concentrating ability.

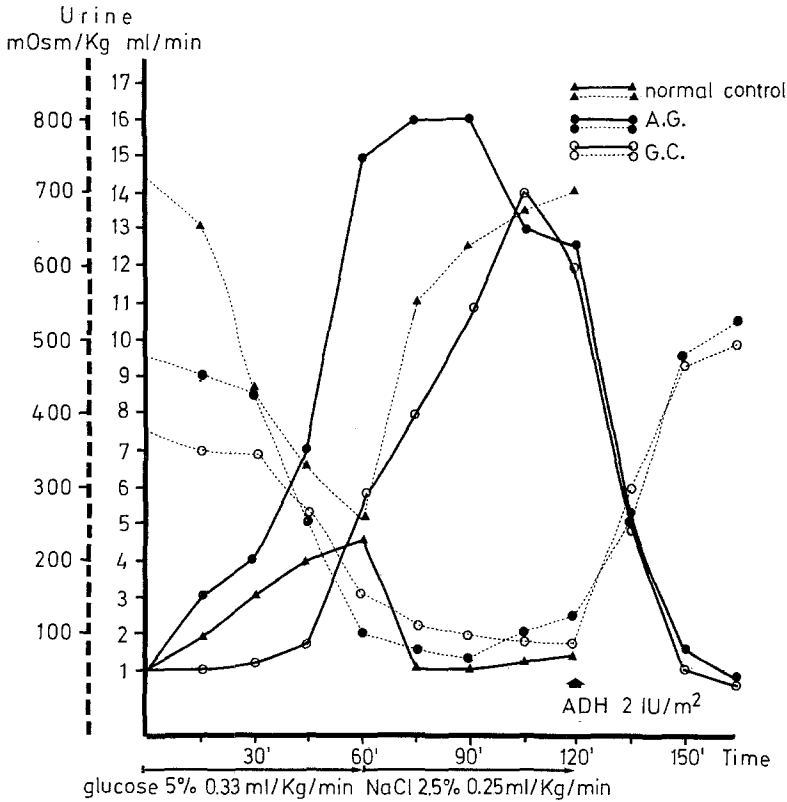
*2. Hyckey-Hare Test.* The test was performed after an overnight fast and rest. A solution of 5% glucose in water was given intravenously at 0.33 ml/kg body weight/min for the period of 1 h, followed by NaCl 2.5% at 0.25 ml/kg body weight/min. Since after 30 min of hypertonic infusion free water clearance was not reduced, ADH was given IM at the dose of 2 I.U./m<sup>2</sup>. Figure 3 compared the findings of the two patients with those of control subjects and shows that osmotic stimuli had almost no influence on urine osmolality and free water clearance.

*3. Tilt Test.* After an overnight dehydration, normal saline was infused at the rate of 5 ml/min, for a period of 80 to 120 min while the patient was in the recumbent position. Following determination of a stable water diuresis during recumbency, the patient was asked to stand for 90 min and then returned to the recumbent position until stable water diuresis resumed. Then the procedure was repeated except that 60 ml of 50% alcohol were given orally before changing to the upright position. Urine was collected from an indwelling bladder catheter at 20 min intervals and at the same time blood samples were taken. Figure 4 shows the performance of A.G. on this test. Orthostasis caused a decrease of free water clearance and an increase of urine osmolality similar to that observed in normal subjects. The effect was mediated by ADH release, since alcohol, which blocks the secretion of ADH, prevented orthostatic antidiuresis as in normals.

### Neuropsychological Investigations

Seven tests were administered on two successive sessions, 7 months apart, in order to evaluate short-term and long-term memory. The following two tests were used to evaluate short-term memory:

*1. Digits Forward.* This well known test of immediate verbal memory was administered and scored following the rules set up by De Renzi and Nichelli [19].



**Fig. 3.** Hickey-Hare test. The plots show free water clearance (*solid line*) and urine osmolality (*dotted line*) in response to hypertonic saline infusion. In the two patients hypertonic infusion did not result in an increase of urine osmolality as in normal subjects. Rather urine flow increased with saline infusion. Water diuresis, still in progress at 120 min, was terminated by exogenous ADH

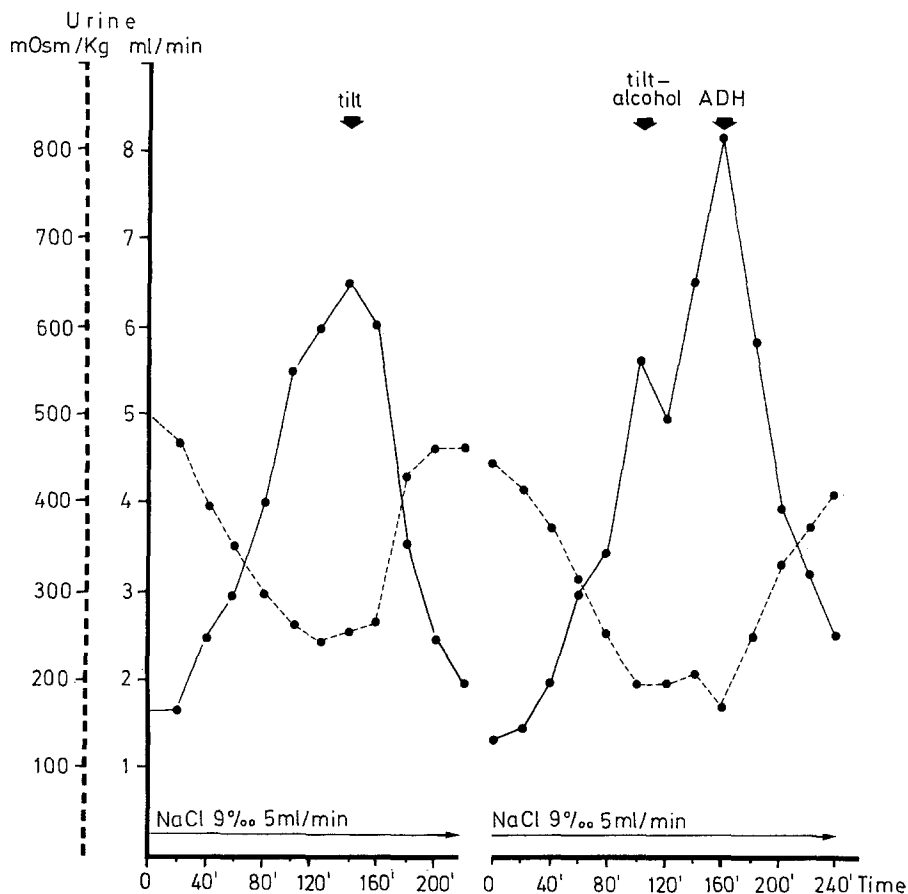
2. *Corsi's Test.* It represents the spatial analogue of Digits Forward. It consists of 9 cubes arranged on a board. The examiner taps the cubes in strings of increasing length and the subject must tap the same sequence immediately afterwards, thus providing a measure of his spatial span [16, 19, 45].

Long-term memory was assessed using 5 tests, 3 involving verbal memory and 2 spatial memory:

1. *Babcock's Story.* A short story was read to the patient and an immediate recall was required and scored. The story was presented again immediately afterwards and delayed recall was asked after a 10-min period filled with other activities [17].

2. *List Learning.* A list of 10 words was read to the patient, who was requested to repeat them in any order he wished. The same procedure was repeated until the criterion of two successive correct recalls was reached [17].

3. *Paired Associate Learning.* A series of 10 paired associate words, 5 semantically related and 5 unrelated, was read to the subject and he was required to recall the associate on the presentation of the first member of the pair. The same procedure was repeated three times [17].



**Fig. 4.** Tilt test (patient A.G.). After establishing a water diuresis with an intravenous infusion of normal saline during recumbency, tilting to upright position for 90 min resulted in urinary concentration (*dotted line*) and fall of water diuresis (*solid line*). When tilting was repeated after administration of ethyl alcohol orally (*right half of the panel*) urine concentration was not observed. Water diuresis was terminated by exogenous ADH

**4. Supraspan Spatial Learning.** The spatial span was first determined by means of the Corsi's test, then the subject was required to learn a sequence two cubes longer than his spatial span. The score was the number of trials to criterion [16].

**5. Visual Maze Learning.** The apparatus was that used by De Renzi et al. [18] and consisted of a matrix of  $10 \times 10$  boltheads arranged on a board. The patient had to learn a path by trial and error, proceeding with a stylus from bolthead to bolthead, the only restriction being not to move diagonally and not to come back towards the bottom. If a wrong bolthead was tapped, this produced a loud unpleasant noise. Practice was continued until the criterion of three successive error-free runs was attained.

Performance Wechsler Scale was also administered to both patients in order to evaluate their general intellectual abilities. Table 2 shows the Performance IQ of the two patients and the scores on the memory test battery, compared with those obtained by normal controls in previous studies [16-19].

It must be noted that, in agreement with the general trend of their disease, A.G. scored better in the first than in the second session while the opposite was true for G.C. Both patients

**Table 2.** Reformances of the two patients on a memory test battery

	A. G.		G. C.		Controls
	15. 3.79	4. 10. 79	22. 3.79	15. 10. 79	
<b>Short-Term Memory</b>					
1. Digit forward	6.0	6.0	5.5	6.0	> 4
2. Corsi's test	4.5	4.5	6.0	5.0	> 4
<b>Long-Term Memory</b>					
1. Babcock's story	15.92	6.98	– 0.39	12.67	>15.76 <sup>a</sup>
2. List learning	7.22	4.3	2.76	7.98	> 6.58 <sup>a</sup>
3. Paired associate learning	5.04	5.06	–	7.65	> 8.73 <sup>a</sup>
4. Supraspan sequence learning	9.0	24	>50	28	<12.80 <sup>a</sup>
5. Visual-maze learning:					
trials	13	25	>50	8	13.41 <sup>b</sup>
errors	39	168	227	9	37.5 <sup>b</sup>
I.Q. Performance (WAIS)		80	105		

<sup>a</sup> Cut-off values (adjusted for age and years of schooling [17])

<sup>b</sup> Mean scores of control subjects, adjusted for age and years of schooling [16, 18]

showed a clear cut dissociation between short-term and long-term memory, the former being within the normal range, the latter severely impaired both on verbal and visuo-spatial tasks. This dissociation ruled out the possibility of amnesia being an artifact due merely to defective attention. At the same time the fairly good scores of both patients on the Performance test battery of the WAIS, also ruled out a more general intellectual deficiency. Retrograde amnesia was examined by questions concerning their personal life and outstanding political events. Both patients showed a severe retrograde amnesia, which extended as far as 10 years prior to the onset of illness. Confabulations were observed to fill gaps in retrograde and in anterograde verbal memory and therefore the overall clinical picture closely resembled Korsakoff's syndrome.

## Discussion

Hypernatremia following intracranial disorders is mostly due to simple dehydration, a condition whose many possible causes have been repeatedly listed by authors, who have questioned the existence of a true neurogenic hypernatremia [1, 38, 67].

There are however also cases of hypodipsia and hypernatremia secondary to anterior hypothalamic damage which cannot be explained in terms of simple dehydration, since intravenous fluid administration fails to correct it [6, 33]. The terms "essential" [63], "neurogenic" [64], and "central" [44] hypernatremia have been used to describe them. The following criteria must be met to include a patient in this category [33]: (1) absence of a gross volume deficit; (2) evidence that the antidiuretic hormone can be secreted; (3) evidence that the renal tubules can respond to the antidiuretic hormone.

Both patients met these requirements and although direct evidence of an anterior hypothalamic lesion was only available for patient A.G., the involvement of the same area can also be suspected for patient G.C. on the basis of the fact that the anterior communicating artery and the anterior cerebral artery are known to supply this region [37].

Essential hyponatremia has been repeatedly reported following surgical procedures on anterior communicating artery aneurysms [26, 50, 55], arteriovenous fistulas [27]; craniopharyngiomas [5, 15, 34, 36, 42, 53] and pituitary adenomas [12, 41] and has been related to the bilateral ligation of the anterior cerebral artery performed in the course of surgical intervention [15, 26, 41, 50, 55]. In addition, the same syndrome has been found associated with a variety of hypothalamic lesions including histiocytosis [6, 21, 39, 62], pinealoma [13, 23, 33, 35, 59, 66], glioma [5, 64] and metastasis [36].

The presence of central neurons controlling the ADH release by the posterior pituitary in response to changes in osmolality of extracellular fluid was first suggested by Verney in 1947 [60]. The supraoptic nucleus was first favoured as the primary site of osmoreception [31, 32], but subsequently also the nucleus circularis, dorsomedial to the supraoptic nucleus [28], the lateral preoptic area [9, 43, 49, 61] and the tissue surrounding the anterior wall of the third ventricle [2, 3, 4] have been considered probable sites of the central osmosensitive receptors for thirst mediating the antidiuretic reflex. Baroreceptor mediated stimuli have also been long known to be effective in including ADH release [52]. Neurophysiological studies using electrical monitoring of hypothalamic cells have shown that the same cells in the supraoptic and paraventricular nuclei may increase discharge rate and presumably ADH release in response to either osmotic or non-osmotic (baroreceptor mediated) stimuli [30]. In patient A.G. the two control mechanisms for ADH release have been found to be dissociated, in that she showed complete loss of osmotic control of ADH release, although retaining a normal response to baroreceptor stimuli. Such a dissociation has been reported by De Rubertis et al. [20] and by Halter et al. [27]. Taken together, the experimental and the clinical evidence, favor a model of ADH release which involves two separate inputs (osmotic and volume stimuli) into the same population of hypothalamic neurons specialized for ADH release.

The control of drinking behavior and of its subjective counterpart (thirst sensation) concurs with the ADH release system to ensure homeostatic control of the water content of the body, so that the two processes are often difficult to disentangle. In the rat, a small bilateral periventricular lesion involving the most medial portions of the medial preoptic and anterior hypothalamic nuclei causes severe adipsia without either aphagia or antidiuresis [7, 11]. This effect cannot be ascribed to the destruction of passage fibers but rather of hypothalamic nerve cell bodies [25]. Several extrahypothalamic regions of the brain have also been shown to either stimulate or inhibit ADH secretion and drinking behavior. They include the amygdala, the anterior thalamic nuclei, the septum, the hippocampus, the periaqueductal gray and the midbrain reticular formation [14, 24, 29, 65]. The widespread inhibitory cerebral influence on ADH neurosecretory cells may explain the excessive ADH secretion found in association with intracranial lesions located outside hypothalamic centers.



In patient A.G. a 4-month period of polydipsia and polyuria preceded by 7 years the second phase of hypodipsia and hypernatremia. To the best of our knowledge the same evolution of thirst disturbances has been reported in only two previous patients [6, 23]. One of them, investigated during the first polydipsic phase, showed no evidence of defective ADH secretion [23]. This suggests that the polydipsic phase was due either to the excitation of the same neurons which would become defective in the hypodipsic phase [23] or to damage to the neural structures normally inhibiting the hypothalamic thirst center.

Memory disturbances have occasionally been reported in association with hypodipsia and hypernatremia following hypothalamic lesions [34] and this is probably due to the proximity of the anterior hypothalamus to structures critical for memory mechanisms. It might also be that amnesia is more frequent in this condition than so far reported and that it has sometimes been overlooked. Both our patients were examined by means of tests that had been standardized on large samples of brain damaged and normal subjects, and for which cut-off scores distinguishing normal from defective performances were available. There was substantial evidence of a long-term memory defect comparable to that reported in patients with mammillary and thalamic damage, i.e. Korsakoff's patients. The impairment was particularly severe in patient G.C., who underwent anterior communicating artery ligation. Norlén and Olivecrona [48] first described two patients who developed Korsakoff's syndrome after operation on aneurysms of the anterior communicating artery and this was confirmed in cases where the surgical procedures were uneventful [40, 57]. In an attempt to identify the area critically involved in the production of such a severe and long lasting memory defect, Taren [58] emphasized the role of the paraolfactory area of Broca and of the anterior perforated space. In support of this notion, he adduced the connection linking these regions, through the fornix, with the hippocampus, whose central role in human memory has long been known [51].

The question of the therapeutic approach to the water balance deficit of these patients is still unsettled. Some of them have in fact a mild deficit of ADH secretion [36, 54], which would justify the administration of the hormone in order to reduce urinary water losses. Since, however, a precise adjustment of fluid intake is virtually impossible in the absence of thirst, sudden episodes of water intoxication can follow ADH treatment. It is worth emphasizing that it is not the endogenous ADH secretion that is defective in these patients, but rather the fact that hormone release is no longer controlled by the hypothalamic osmosensitive area but only by the less sensitive plasma volume mediated system. As a consequence patients show wide variations in plasma sodium, which can only be worsened by administering exogenous ADH. Better results in reducing these swings have been obtained with the so-called pro-adiuretic drugs [10, 20, 42, 47, 54]. In our patients both chlorpropamide and clofibrate appeared to be effective in normalizing serum sodium concentrations. The mechanisms by which these drugs affect the osmotic thirst system remains to be clarified. There is evidence that chlorpropamide not only enhances the effect of ADH in the distal nephron [8, 46], but also stimulates the release of ADH [22, 46] and some authors have proposed that ADH itself can play a role in the activation of thirst [56]. Other authors [10, 47] maintain that this drug amplifies cell responses to their specific stimuli by

means of an intracellular effect on the adenylyl cyclase system. In the case of the hypodipsia-hypernatremia syndrome chlorpropamide would act at the level of the hypothalamic osmosensitive cells amplifying their message for the ADH neurosecretory cells.

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