Heterogenous patterns of recovery of thirst in adult patients with adipsic diabetes insipidus

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Summary

Background: The natural history of adipsic diabetes insipidus (ADI) is not well described, and reports of recovery of thirst are rare.

Design and Methods: Case histories presentation. ADI was identified by demonstrating absent thirst and arginine vasopressin (AVP) responses to hypertonic saline infusion.

Results: Twelve patients with ADI were identified (craniopharyngioma 5, anterior communicating artery aneurysm (ACOM) repair 4, congenital 1, neurosarcoidosis 1, prolactinoma 1). Three patients died. Six patients had permanent ADI. Three patients had recovery of thirst, with a heterogenous pattern of recovery. In the first case, ADI had developed after clipping of an ACOM aneurysm. Ten years after surgery, he sensed the return of thirst; repeated hypertonic saline infusion showed recovery of thirst and AVP secretion. In the second case, a 41-year-old female with an intrasellar craniopharyngioma developed post-operative ADI with persistent hypernatremia. Two years post-operatively, she complained of thirst, and hypertonic saline infusion showed normalization of thirst but absent AVP responses, confirming recovery of thirst, but with persistent diabetes insipidus (DI). In the second case, a 41-year-old female with an intrasellar craniopharyngioma developed post-operative ADI with persistent hypernatremia. Two years post-operatively, she complained of thirst, and hypertonic saline infusion showed normalization of thirst but absent AVP responses, confirming recovery of thirst, but with persistent diabetes insipidus (DI). In the third case, a 29-year-old Caucasian had craniotomy and radiotherapy for craniopharyngioma and developed ADI post-operatively. Eight years post-op, she presented with thirst, seizures and pNa of 112 mmol/l. Hypertonic saline infusion showed persistent DI but thirst responses typical of compulsive water drinking; she has had recurrent hyponatraemia since then.

Conclusions: We report that 3/12 patients with ADI recovered thirst after longstanding adipsia with heterogenous pattern of recovery. Both the mortality of 25% and the recovery rate of 25% should be considered when planning long-term surveillance.

Introduction

Adipsic diabetes insipidus (ADI) is a rare, potentially life-threatening condition, which is characterized by continuous hypotonic polyuria due to arginine vasopressin (AVP) deficiency and failure to experience the sensation of thirst in response to plasma hyperosmolality.¹ Thirst is usually preserved in hypothalamic diabetes insipidus (DI), as the hypothalamic osmoreceptors remain intact, and compensatory drinking prevents hyperosmolar dehydration, even without treatment.
with desmopressin (DDAVP). However, DI has been reported with absent thirst in a variety of clinical conditions; most frequently following clipping of anterior community artery aneurysm3,4 and craniopharyngioma surgery5,6 but also in association with a wide variety of other conditions including traumatic brain injury, neurosarcoidosis and toluene exposure.7 Patients with ADI are far more likely to develop hypernatremia than the vast majority of patients with DI who retain intact thirst.8 Hypernatremia dehydration complicating ADI is associated with significant morbidity, including development of cardiovascular complications such as hypotension, renal failure and hypovolemic shock,9 and we have previously reported a vulnerability to thrombotic disorders including pulmonary embolus, during episodes of hypernatremia dehydration in patients with ADI.1 In addition, patients with ADI are vulnerable to a wide spectrum of abnormalities, such as sleep apnoea, obesity and seizures, which are associated with wider hypothalamic dysfunction. There is also a significant mortality in patients with adipsic DI7,10 However, recovery from adipsia has also been reported in isolated cases. O’Reilly et al.11 reported recovery of thirst in a patient who developed ADI secondary to neurosarcoidosis, though it was unclear from the paper whether vasopressin secretion also recovered. In addition, recovery from post-surgery adipsia has also been reported in three paediatric patients with craniopharyngioma,12 despite persistence of associated DI.

We report the progress of three adult patients with ADI in whom there was a heterogeneous recovery of thirst. In one, there was recovery of thirst and vasopressin secretion and in the second there was recovery of thirst with persistence of DI. In the final case there was a unique progression from adipsia to compulsive water drinking, with serious consequences including admission with severe symptomatic hyponatraemia, despite persistent absence of vasopressin secretion. In this article, we report for the first time that recovery from adipsic DI is heterogeneous, and that this may have significant management implications.

Methods

The diagnosis of ADI is confirmed in our unit by demonstrating subnormal vasopressin and thirst responses to hypertonic saline infusion. After an overnight fast, and having resting recumbent, 5% sodium chloride solution is infused intravenously for 2 h at a rate of 0.05 ml/kg/min. Blood is taken at 30-min intervals for the measurement of plasma sodium, osmolality and vasopressin. Thirst is measured using a visual analog scale.13 At the completion of the infusion, patients were allowed free access to water for 30 min. Thirst measurements are recorded and the volume of water consumed was measured.2 ADI was defined as subnormal thirst responses to hypertonic saline, and water intake less than half of the lower limit of normal in healthy controls (< 500 ml). Normative data were derived from a data bank comprising responses of 40 healthy controls.14

Patients with ADI were identified from the log book of investigations kept in the pituitary investigation unit in the hospital.

All studies had local area ethical approval. All subjects or, where applicable, the next of kin, gave informed written consent.

Results

Twelve patients who were under the care of the unit for the management of ADI were reviewed (craniopharyngioma 5, anterior communicating artery aneurysm (ACOM) aneurysm repair 4, congenital 1, neurosarcoidosis 1, prolactinoma 1). Patients who continued to demonstrate polyuria when off DDAVP, associated with adipsia in the setting of hypernatremia dehydration, were deemed to have continuation of adipsic DI and were not subjected to the discomfort of formal re-investigation. This was justified on the basis of our own published data which shows that hypernatremia is not an issue with outpatient monitoring of DI with intact thirst7; hypernatremia is a de facto recognition of persistence of adipsia.

Six patients had persistent ADI. Three patients had died and have previously been reported.7 Three remaining patients had demonstrated recovery of thirst, verified by formal testing. As the pattern of recovery is different in each case, their case histories are presented.

Case 1

A 51-year-old male was admitted with a subarachnoid haemorrhage and underwent emergency clipping of an ACOM. There was intraoperative aneurysm rupture and he was transferred to ICU post procedure. During Day 1 in ICU, he developed a diuresis of >700 ml/h. His plasma sodium was 148 mmol/l and he was given subcutaneous DDAVP with a reduction in urine volume and increased urine concentration. On the fourth day post procedure he was tolerating oral fluids, but his plasma sodium rose to a peak of 168 mmol/l, with a plasma osmolality of 351 mOsm/kg and urine osmolality of 185 mOsm/kg. Despite being clinically dehydrated, he did not complain of thirst. He was maintained on oral DDAVP 0.2 mg three times a day with strict obligatory fluid intake of 2–3 l per day. Post-operative insulin tolerance testing revealed a partial growth hormone deficiency, but normal cortisol secretion. He had evidence of borderline hypogonadotropic hypogonadism and secondary hypothyroidism. He reported normal energy levels and libido, and did not wish for testosterone therapy. He was placed on levothyroxine therapy.

Two months post-surgery he was admitted electively for a hypertonic saline infusion. His plasma sodium level rose to a peak of 152 mmol/l during the infusion, but there was complete absence of vasopressin response confirming hypothalamic DI. In addition he did not have any sensation of thirst, and consumed a low volume of 480 ml of water during 30 min at the end of the test. He also underwent intravenous infusion of tri-metaphan camsylate, which produced a rapid reversible fall in arterial blood pressure. Following a drop in systolic arterial blood pressure from 120 to 80 mmHg, plasma vasopressin concentrations rose significantly to 204.5 pmol/l. The normal baroregulated AVP secretion confirmed osmoreceptor dysfunction.

He was followed up regularly in the outpatient setting. Ten years post initial presentation; he described the sensation of thirst and was voluntarily drinking 1–2 l per day. He was admitted electively for hypertonic saline infusion. Results are shown in Figure 1. His thirst rating increased exponentially during the test and he consumed 600 ml of water in the 30 min after the test, indicating significant recovery of osmoregulated thirst, almost to within the normal reference range, as defined by our own normative data.14 In addition, he had recovery of osmoregulated vasopressin secretion. Subsequently his regular oral DDAVP was discontinued. His plasma sodium level remains stable and he has not required hospital admission for hypo/ hypernatremia. This patient therefore has almost complete recovery of osmoregulated thirst and complete recovery of osmoregulated vasopressin secretion.
Case 2

A 41-year-old Caucasian female presented with a 3-month history of headache, weight gain and irregular menses. At the time of presentation there was no evidence of polyuria or polydipsia, and plasma sodium was 138 mmol/l (135–145 mmol/l). Cerebral imaging revealed a 2 cm ring enhancing lesion in the pituitary fossa and the presence of a left para arachnoid aneurysm, which was subsequently coiled under radiological guidance. Baseline endocrine evaluation showed undetectable gonadotropins, FSH <1 IU/l (1–7 IU/l), LH < 0.6 (2–14 IU/l), but was otherwise normal. Craniotomy and debulking were performed without any intraoperative complications, and histopathology confirmed the excision of a craniopharyngioma.

On Day 2 post-operation her urine output increased to 200–400 ml/h. Her plasma sodium rose to 158 mmol/l. She was given DDAVP 0.5 mg subcutaneously with abolition of polyuria and on Day 4 post-operation she had a plasma sodium level of 140 mmol/l, with stable fluid balance. On her seventh post-operative day, her plasma sodium rose from 147 mmol/l at 7 am to 172 mmol/l at 7 pm. Her urine osmolality was 272 mOsm/Kg and her plasma osmolality was 367 mOsm/Kg; despite the persistent pronounced hypernatremia, she was not thirsty and her oral intake remained suboptimal. After regular DDAVP and intravenous dextrose infusion, her plasma sodium fell to 151 mmol/l over 48 h. The clinical diagnosis of ADI was made. Post-operatively, glucagon testing revealed panhypopituitarism (GH peak <0.5 mg/ml, peak cortisol 61 nmol), and baseline line thyroid function (TSH 0.4 mIU/l with low FT4) revealed secondary hypothyroidism. She was placed on oral hydrocortisone 10 mg twice per day, oral levothyroxine 125 mcg per day, oestrogen replacement and recombinant human growth hormone. Once stable, formal hypertonic saline infusion confirmed the diagnosis of complete DI, with absent thirst responses (Figure 2). She needed titration of DDAVP for symptomatic control with a final dose of 0.2 mg bd.

Two years post-operatively, she reported the return of sensations of thirst, and was spontaneously drinking 2.5 l of water per day. She was admitted electively for hypertonic saline infusion for further assessment. Repeat testing showed persistent deficiency of AVP but a return of thirst responses, with appropriate water drinking after the infusion. Case 2 therefore describes almost complete recovery of thirst but persistent AVP deficiency.

Case 3

A 29-year-old Caucasian female was admitted for craniotomy for craniopharyngioma in 2000. She underwent extensive surgery with a complicated post-operative period, which included subdural hematoma and cerebral shunt insertion. As a result of this, she developed permanent speech abnormalities and mobility reduction, which required extensive rehabilitation. She was noticed to have DI with adipsia post-operatively, denying any thirst sensation at plasma sodium concentration of 159 mmol/l. She also developed chronic hypopituitarism requiring replacement for ACTH, GH, gonadotrophin and TSH deficiency. The diagnosis of adipsic DI was confirmed during hypertonic saline infusion (Figure 3) and she was discharged on DDAVP 0.2 mg every 6 h and was told to drink at least 2 l of water daily in view of her adipsia. Months after surgery she received stereotactic radiotherapy for the remnant tumour. During the first 2 years after surgery she was recurrently admitted with hypernatraemic dehydration and she required frequent ambulatory review for the complex management of her ADI. Frequent self-reported symptoms were malaise and adipsia concomitantly with plasma sodium between 152–159 mmol/l. Over the next 5 years she remained stable on DDAVP 0.2 mg every 8 h with normal plasma sodium in subsequent evaluations and treatment with mandatory fluid oral intake following a sliding scale of fluids.

In 2008, she developed a progressive unbearable thirst sensation and was admitted to her local hospital on two occasions with seizures in the presence of dilutional hyponatraemia; on
one occasion plasma sodium on admission was 112 mmol/l and a concomitant urine osmolality of 847 mOsm/kg. In addition, other clinical abnormalities, with a potential hypothalamic origin, including a very strong urge to eat sweet meals, with progressive weight gain and sleep disturbances, began to manifest. She declined formal sleep studies. A new magnetic resonance imaging (MRI) showed a nodular rim enhancing mass in the suprasellar cistern, measuring $13 \times 10 \times 12$ mm (anteroposterior × transverse × craniocaudal) extending along the hypothalamus and floor and right lateral aspect of the third ventricle. Hypertonic saline infusion showed persistent complete vasopressin deficiency but exaggerated thirst responses and failure to suppress thirst despite excess water intake in 30 min after the infusion, a classical combination of responses typical of compulsive water drinking. She complained of intense thirst and a self-reported drinking above 6 l of water throughout the day with failure to suppress thirst despite plasma hyposmolality. Withdrawal of DDAVP leads to unacceptable polyuria due to DI. She continues to suffer intense thirst, with episodic dilutional hyponatraemia. This final case shows persistent DI, but the unique progression of adipsia to clinically significant compulsive water drinking.

Discussion

In this article, we report our follow-up of our cohort of patients with adipsic DI. For a rare disorder such as ADI, a cohort of 12 patients reflects considerable clinical experience. The three deaths emphasize the high mortality in this group, as reported in other studies, but the recovery of thirst in three patients also emphasizes that the progression of the disease is heterogeneous. In the three patients with ADI in whom there was recovery of adipsia, re-establishment of thirst occurred distant from the time of development of the ADI; adipsia could not therefore simply have been a manifestation of cognitive dysfunction in the immediate period following neurosurgery. Recovery of thirst has been rarely reported in patients with ADI. The Newcastle group reported three paediatric craniopharyngioma patients who had complete recovery of thirst with continued DI in the first 9 months after surgery for the tumour. The authors suggested that the early adipsia was due to osmoreceptor contusion, which resolved with time. This is a reasonable suggestion, particularly given that the paediatric brain is better able than that of an adult to recover from neurological insults. We have also seen craniopharyngioma patients who have transient adipsia in the immediate post-operative period, which resolved as cognitive function improved. In these patients we interpret the attenuation of thirst as a reflection of post-operative cognitive decline, though osmoreceptor contusion is a potential alternative explanation. However the interval of time between development of ADI and recovery of thirst in the three patients in this article indicates that a mechanism other than reversal of osmoreceptor contusion is responsible.

Patient 2 gives a history similar to that presented in the paediatric case reports from Newcastle; recovery of thirst but persistence of DI in a patient following surgery for craniopharyngioma. Our patient differed from the three paediatric patients, however, by the delayed nature of her recovery from adipsia. The suggested explanation for the reversal of adipsia in the paediatric series—recovery from surgical contusion—is unlikely to be responsible for the regeneration of thirst perception in our patient however. Neural regeneration is more likely.

Our other two patients present patterns of recovery from ADI which have never previously been reported. Patient 1 recovered both thirst and vasopressin secretion, a scenario not previously described in the literature. This patient had ADI following surgical management of an ACOM, a clinical scenario which has been well described to cause adipsia with DI. It is speculated that, as the blood supply to the anterior hypothalamus, which is the anatomical site of the osmoreceptors, is derived from small perforating branches of the anterior communicating artery, clipping of an aneurysm here can infarct this
area, thus producing ADI. If this is the mechanism, one presumes that neural regeneration in the post-infarct period led to a gradual restoration of normal osmoreceptor function, with a return of both thirst appreciation and vasopressin secretion in this patient. To our knowledge, this has never been reported in ADI following clipping of an anterior communicating aneurysm.

The third patient also presents a unique pattern of recovery of thirst, which has never been reported. She developed unequivocal evidence of ADI, but unlike Patient 2 she not only recovered thirst appreciation, she went on to develop unquenchable thirst. This manifested as high thirst ratings during osmotic stimulation of the osmoreceptors with hypertonic saline infusion, coupled with failure to suppress thirst non-osmotically during the process of drinking, despite drinking more than the usual amount taken in by patients with DI. This is a set of abnormalities which is pathognomonic to patients with compulsive water drinking and highly diagnostically specific for this condition. This presents a very difficult scenario to manage safely. The main challenge with ADI is to limit free water excretion with DDAVP and to maintain a fluid intake balanced to urine output plus 500–1000 ml, according to weight and climate. Despite this, hypernatraemia occurs commonly in ADI in ambulatory care. The combination of DI with compulsive water drinking presents particular vulnerability to dilutional hyponatraemia, due to unregulated fluid intake against a background of DDAVP-mediated restriction of free water clearance. Withholding DDAVP to allow an aquaresis to occur is problematic as patients develop excessive urine output which is socially unacceptable and interferes with sleep, and energy levels. Our patient developed repeated hyponatraemia, which precipitated hospital admission twice, and hyponatraemic seizures once, due to her inability to regulate her fluid intake and the antiaqurethic effect of DDAVP. Without change in the dose of DDAVP, the sudden development of thirst with recurrent hyponatraemia was out of context with previous behaviour and biochemistry; the development of hyponatraemia is crucially dependent on water intake rather than DDAVP dose, so the key issue, confirmed by osmotic challenge, was the new development of polydipsia. We have clinically reduced admissions in this patient with hyponatraemia with advice about delayed

Figure 3. Thirst (A) and plasma vasopressin (B) responses to increased plasma osmolality during hypertonic saline infusion in Patient 3. The shaded area represents the range of responses from a locally derived reference range obtained from 40 healthy controls. Vol.: Volume of water consumed during the 30 min phase after hypertonic saline infusion. Pituitary MRI (left image, 2001): post-operative pituitary MRI showing residual craniopharyngioma. Pituitary MRI (right images, 2008): progression of the nodular rim enhancing mass in the suprasellar cistern, measuring 13 × 10 × 12 mm (anteroposterior × transverse × craniocaudal) and extending along the hypothalamus and floor and right lateral aspect of the third ventricle.
DDAVP once or twice a week until she has voided urine four times. This allows an aquaresis which rids her of excess body water, but on the days in between we have measured plasma sodium concentrations as low as 125 mmol/l.

The mechanism of the development of excessive thirst in this patient is not clear. We have previously reported compulsive water drinking in a patient with craniopharyngioma who also had DI, but that patient had developed excess thirst against the setting of an expanding tumour. Our patient had been treated with craniotomy and radiotherapy; however, serial imaging with MRI showed a nodular rim enhancing mass in the suprasellar cistern, measuring 13 × 10 × 12 mm (anteroposterior × transverse × craniocaudal) extending along the hypothalamus and floor and right lateral aspect of the third ventricle. It is possible that hypothalamic irritation from this mass could be the explanation for the new hypothalamic abnormalities from which this patient suffered. The patient has had stable MRI appearances and is not enthusiastic for further surgical intervention. Irritative lesions such as neurosarcoidosis have been associated with the development of excess thirst and the hypothalamic intrusion of the tumour offers the only logical explanation for her symptoms. On the other hand, the commonest cause of compulsive water drinking is associated psychiatric disease. Our patient had needed neuropsychological evaluation for longstanding difficulties in coping since her first surgery, and although these issues predated the development of polydipsia for many years, a psychological component, however unlikely, cannot be ignored. The co-presentation with abnormal appetite and disturbed sleep, are however, suggestive of hypothalamic involvement.

The assessment of changes in thirst in patients with ADI in the outpatient setting is challenging. It is our practice to ask specifically for any changes in thirst since last visit when the patients attended the clinic. Any improvement in reported thirst is cross checked with plasma sodium concentration and if the latter is low, we progress to repeat osmotic stimulation. As this is a rare condition, it is really about careful clinical history and awareness that recovery from ADI can occur.

In summary, the natural history of ADI is varied. Mortality in this and other series is high, but a proportion of patients do recover thirst, usually with persistence of DI. However, our article shows that even in those patients who recover thirst, there is a spectrum of recovery, from reappearance of thirst alone, recovery of thirst and vasopressin secretion through to conversion of adipsia to polydipsia.

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**References**