Management of cranial Diabetes Insipidus – clinical outcomes and patient perception of care.

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Abstract

Objective:
There is growing recognition of morbidity and mortality that can occur in patients with cranial diabetes insipidus (CDI) during hospitalisation, due to prescribing errors and dysnatraemia, often related to confusion between CDI and diabetes mellitus amongst non-specialists.

Methods:
Data for each hospitalisation in patients with CDI attending OUH were collected retrospectively. The same cohort were invited to complete a questionnaire by telephone.

Results:
109 patients were included, median age 42 (range 6-80) years. Route of desmopressin was tablet, melt and nasal spray in 74%, 7% and 17% of patients, while two patients used a combination of tablet and nasal spray.

There were 85 admissions to OUH in 38 patients between 2012 and 2021. Daily measurement of serum sodium was performed in 39% of admissions; hyponatraemia and hypernatraemia occurred in 44% and 15% of admissions. Endocrine consultation was sought in 63% of admissions post-2018.

45/78 patients (58%) self-reported ≥1 admission to any hospital since diagnosis. Of these, 53% felt their medical team did not have a good understanding of the management of CDI
during hospital admission. 24% reported delay in administration of desmopressin, while 44% reported confusion between CDI and diabetes mellitus, often leading to unnecessary blood glucose monitoring.

Conclusion:

Dysnatraemia is common in hospitalised patients with CDI. More than half of patients perceived their medical team’s understanding of CDI to be poor when admitted with intercurrent illness. A coordinated approach including early consultation of specialists, frequent serum sodium monitoring, and education of hospital specialists, is needed to address this.
Introduction

Cranial Diabetes Insipidus (CDI) is a rare condition, with a prevalence of <10 per 100,000 (1) and lack of familiarity with the condition may lead to confusion by non-specialists with the much more common diabetes mellitus. Despite the availability of effective treatments for CDI, the diagnosis is associated with excess mortality compared with the general population, as demonstrated in a 2017 meta-analysis (2). A recent large observational study from Switzerland (n=3382 patients with hypopituitarism, n= 807 with CDI) demonstrated that hospitalised patients with hypopituitarism and concomitant CDI have a 3.7 greater odds of in hospital death compared with matched general inpatient controls, while there was no significant increased odds of death in hypopituitary patients without CDI (3).

While the increased mortality seen in hospitalized patients with CDI may be influenced by the prognosis of the underlying cause of CDI, e.g. traumatic brain injury (4), or associated conditions e.g. metabolic and hypothalamic complications of craniopharyngioma (5), there is growing recognition within endocrine physician and patient groups of the morbidity and mortality associated primarily with a delay in administration of desmopressin and resulting dehydration in this patient group, perhaps related to lack of awareness of the critical nature of the condition and it’s treatment. Over half of respondents to a Society for Endocrinology (SfE) survey in 2018 reported concerns regarding management of CDI in the previous two years, with the most common safety concern being the prescription and administration of desmopressin (6). In 2016, Gleeson et al wrote of concerns about the safety of hospitalised patients with CDI, after finding that desmopressin was omitted in 14/17 hospital admissions.
(88%) in a single centre UK audit, due to unavailability of the medication in the majority of cases (7).

In 2018, the SfE published guidance on the inpatient management of CDI (8), prompted by an NHS patient safety alert (9). Key recommendations included that all patients with CDI are identified on admission, and that the endocrine team is alerted and remains aware of them during their hospital stay. Desmopressin should be considered a critical drug and be available to all wards twenty-four hours per day. An alert system for all patients prescribed desmopressin was recommended, to reduce medication errors. This system is in place in our institution. However, despite this guidance, patients with CDI still regularly report concerns about lack of physician and other health professionals’ awareness of the condition, and issues around administration of desmopressin in hospital. We set out to formally assess this in a cohort of patients with CDI attending a tertiary endocrinology centre.

**Aims**

The aims of this study were two-fold; firstly, to assess in-hospital outcomes in hospitalised patients with CDI by review of electronic records from 2012-2021, and secondly, to assess the same patient cohorts’ perceptions of their care via telephone questionnaire.

**Methods**

Patients with CDI were identified from the pituitary clinic database in the adult and paediatric endocrinology departments; those with a recent diagnosis within the past 12 months were excluded. A retrospective review of electronic medical records for all hospital admissions to Oxford University Hospital (OUH) between 2012 and 2021 was performed,
and data collected for prespecified clinical and biochemical parameters. Some outcomes (endocrine consultation, monitoring of fluid balance, prescription of desmopressin) were collected from 2018 onwards, when use of electronic system for documentation of consultations became more widespread in the hospital and following the publication of the SfE guidance (8). Hyponatraemia and hypernatraemia were defined as serum sodium concentration <135mmol/L and >145mmol/L, respectively.

Patients were informed about the audit by letter, and subsequently contacted by telephone and invited to participate in the questionnaire. Verbal consent was taken, and in paediatric cases the parents were invited to answer on the patients’ behalf. Questions regarding hospitalisations applied to admissions to any hospital since the diagnosis of CDI and for any indication. The project was approved as an OUH NHS Trust Audit (Audit No. 6584).

Data related to patient characteristics are presented as median (interquartile range) and number (percentage). Results were deemed significant for a p-value <0.05. Statistical analysis was performed using GraphPad Prism 8.1.2.

Results

Demographics

109 patients were included, median (IQR) age 42 (24, 60) years. Eleven patients aged <18 years were included, and the age range of the cohort was six to eighty years. Further demographics, aetiology of CDI and route of desmopressin are outlined in table 1.
Hospital admissions

There were 85 hospital admissions in 38 patients over 9 years, table 2. Fifty-five (66%) of admissions were emergency and 29 (34%) were elective; indications for admission are included in table 2.

Inpatient care was supervised by Endocrinology, or Endocrinology consultation was sought, in 19/30 (63%) of all admissions to OUH from May 2018 to May 2021. Daily fluid balance was documented in 14/30 (47%) admissions during this time. Six of 29 (21%) hospital admissions in that time period involved one or more missed doses of desmopressin. Of these, three patients had hyponatraemia and desmopressin was delayed appropriately. A fourth patient refused their prescribed dose because of lack of breakthrough symptoms and a fifth refused because of incorrectly high dose administered earlier in the day; both patients remained eunatraemic. One patient did not have her usual desmospray prescribed on their electronic record; she remained eunatraemic during overnight admission and may have used her own supply. There were two desmopressin prescribing errors noted from May 2018 to June 2021; in one case oral desmopressin was prescribed in milligram (mg) rather than microgram (mcg) leading to a delay in administration while correct prescription was awaited. In the other case mentioned above, the patient was prescribed oral desmopressin at a dose of 300mcg three times daily, rather than 100mcg three times daily. The patient noted this error and refused subsequent doses that day, appropriately. Both patients remained eunatraemic.

Serum sodium was measured daily in 33 (39%) of all hospital admissions to OUH over the nine-year period. In total, 37 admissions (44%) had at least one episode of hyponatraemia,
three had serum sodium measurements <130mmol/L. In 9 admissions (11%) the patient was eunatraemic on admission and developed hyponatraemia in hospital. Thirteen admissions (15%), had at least one episode of hypernatraemia, two had serum sodium measurements ≥150mmol/L. In eight cases (9%) hypernatraemia developed during the hospital admission. Three patients accounted for nine of the 13 admissions complicated by hypernatraemia. One of these patients had CDI in association with a developmental brain abnormality, with cognitive impairment and adipsia, and accounted for the two hospital admissions with serum sodium ≥150mmol/L. They were noted to be unresponsive in one admission, and vomiting in the other two. The other two patients had CDI secondary to germinoma and Langerhans cell histiocytosis, did not have documented adipsia, and in only one of their six admissions was there evidence that they had fasted. There were no documented missed desmopressin doses in any of the cases of acquired hypernatraemia. Seven admissions (8%) were complicated by both hypo- and hypernatraemia.

There were no in-hospital deaths.

**Patient perceptions of hospital care**

Seventy-eight patients (71%) participated in the questionnaire, figure 1. Forty-five patients (58%) reported at least one admission to any hospital since their diagnosis of CDI. Twenty patients (44%) reported at least one episode where a member of the hospital team confused the diagnoses of CDI and diabetes mellitus, leading to unnecessary blood glucose monitoring in many cases. Eleven patients (24%) reported a delay in administration of desmopressin on at least one occasion, leading to thirst and/or polyuria. Amongst paediatric patients, some parents expressed frustration at nocturnal doses of desmopressin being
administered too early in the evening, leading to breakthrough symptoms in the latter half of the night. When asked whether they agreed that their hospital team had a ‘good’ understanding of diabetes insipidus, 18/45 (40%) either agreed or strongly agreed, while 24/45 (54%) either disagreed or strongly disagreed, figure 2. Of those that disagreed or strongly disagreed, 10/24 (42%) felt it adversely affected their management.

Twenty-four of the 38 patients included in the first part of the study responded to the questionnaire. Of these, ten patients (42%) reported at least one episode where a member of the hospital team confused the diagnoses of CDI and diabetes mellitus. Four patients (17%) reported a delay in administration of desmopressin on at least one occasion. Ten patients (42%) either agreed or strongly agreed with the statement that their hospital team had a ‘good’ understanding of diabetes insipidus, and 12/24 (50%) either disagreed or strongly disagreed.

**Patient perceptions of outpatient care**

Twenty-six patients (33%) reported difficulty getting access to desmopressin when needed in the community. Thirty-two patients (41%) agreed or strongly agreed that their GP had a good understanding of CDI, 30/78 (38%) disagreed or strongly disagreed, while 16/78 (21%) were unsure and commented their GP had no involvement in the management of CDI.

Twenty patients (26%) had switched from one route of desmopressin to another in the past five years. Eighteen patients (23%) recalled at least one episode of hyponatraemia, while thirty patients (38%) routinely delayed or skipped a dose of desmopressin at least once weekly to allow breakthrough aquareesis.
A subset of 31 patients were asked whether they thought it was a good idea to change the name of diabetes insipidus to avoid confusion and improve patient safety; 20 patients (65%) responded Yes. Potential alternate names suggested by patients included *vasopressin deficiency, ADH deficiency, pituitary insipidus and water diabetes*.

**Discussion**

This study is the first to evaluate clinical outcomes in a large cohort of hospitalised patients with CDI, from both an objective viewpoint and the patient perspective. We have demonstrated that dysnatraemia is common in this cohort, often develops in hospital and thus is potentially avoidable. While objective drug prescribing errors were rare, and did not lead to patient harm, more than half of patients felt that the medical team did not have a good understanding of CDI during hospitalisation. Therefore, a clear mismatch between objectively collected data and patient reported outcomes exists and should be considered in further outcome studies of CDI.

We have reported a rate of missed desmopressin dose of 21%. When we reviewed each case, all except one were appropriate clinical decisions made by either the clinician or the patient, and none led to hypernatraemia. This highlights the valuable input of both physicians and patients into the management of CDI, even in hospital. Patients should be empowered to speak up about their CDI in hospital and to carry a Diabetes Insipidus Alert Card (10), and this needs to be promoted in a drive similar to that undertaken for patients with adrenal insufficiency. There were no documented cases of missed desmopressin doses in the eight admissions complicated by acquired hypernatraemia. However, data collection was retrospective so it is possible there may have been a delay from signing off the drug on
the electronic drug chart, to actual drug administration, which may have contributed to the rise in serum sodium in these cases. Indeed, one in four patients self-reported a delay in administration of desmopressin during a previous admission to any hospital, so this is clearly a cause of distress for patients. Desmopressin should be prescribed as a ‘high-alert’ drug, instructing that the dose and timing are reviewed by specialists daily, and careful attention given that the drug is not omitted by mistake. It should be noted on prescriptions and protocols that the timing of dosing can be dynamic, with patients often taking the drug ‘as needed’ in response to breakthrough polyuria rather than waiting for a specific timepoint. Self-administration of the drug should be considered when appropriate, with support from the endocrinology team.

Safe in-hospital management of CDI extends beyond timely desmopressin dosing; close monitoring of fluid balance and serum sodium concentration are also key (8, 11). Daily measurement of serum sodium and documentation of fluid balance were performed in fewer than half of hospital admissions, these are two further benchmarks that require addressing in future quality improvement projects. Daily specialist review of serum sodium and fluid balance should inform reactive changes in desmopressin dosing and water intake, to reduce risk of hypo- and hypernatraemia. This is particularly important in patients with altered level of consciousness and in patients with adipsic CDI who are at particularly high risk of dehydration and hypernatraemia; such patients should be monitored very closely. Insertion of an urinary catheter and hourly urine output monitoring in high-risk patients allows for desmopressin to be administered as soon as breakthrough polyuria occurs, while at the same time avoiding stacking of desmopressin doses and subsequent hyponatraemia if the drug is given on a strict timed basis (12).
The patient questionnaire has highlighted several areas of concern. Most alarming is that over half of patients did not feel that the hospital team had a good understanding of diabetes insipidus during a previous admission, and almost half reported occasions where CDI was confused with diabetes mellitus. This issue of confusion regarding terminology is often discussed within patient groups and online forums, but to the best of our knowledge patient experience has not been formally assessed and published in medical literature prior to now; our findings suggest that there is much work to do in terms of improving awareness of the critical nature of the treatment of this condition within hospitals. There has been discussion within patient and endocrinologist groups regarding a potential change of name to clearly separate the condition from diabetes mellitus, a chronic disease with which there is almost universal familiarity and therefore an understandable propensity to confuse with DI, and indeed two-thirds of patients asked felt this would be a good idea, although the names they suggested were not appropriate as they only pertain to CDI and not DI as a whole.

The need for improved awareness of CDI is not limited to the hospital environment, but extends to general practitioners (GPs) and community pharmacists. Twenty percent of patients specifically commented that their GP was not involved in the care of their CDI, but one in three had difficulty sourcing desmopressin from their community pharmacy when needed. In the NHS, patients with CDI are typically reviewed in tertiary care, but prescriptions for long-term medications including desmopressin are provided for by the GP. In this context, it is crucial that we specifically request, at each communication, that
patients have prescriptions for desmopressin issued in advance of need, and that they are never left without the medication.

The main strength of our study is the design that includes both objective outcomes and patient reported outcomes in the same patient cohort; this is the first study to do so and highlights the deficits when objective data alone are collected. We set out to determine outcomes in this patient cohort in a ‘real-world’ setting, without specific intervention that might influence results. No specific protocol was in place for biochemical or clinical monitoring of patients with CDI during the study period so as not to influence the results, and one was not instigated for the purpose of the study. Data collection was retrospective, and confined to 2018 onwards for some variables such as documentation of fluid balance; this is a study limitation particularly when trying to determine the cause of acquired hypo- and hypernatraemia in hospital. We did not limit the questionnaire to only those patients with OUH hospital admissions, to allow for greater numbers. However, when we analysed responses to the questionnaire in the subgroup of those admitted to OUH, they were similar.

While our numbers are large, and follow-up nine years, this is a single-centre study and this is another limitation. In recent months however, a multinational team of endocrinologists, with patient representation, have developed an extended patient survey administered online, termed the DImond survey, which includes a range of topics including patient experience, treatment regimens, and the psychological impact of the diagnosis. It is hoped that these data will inform future interventions in an effort to improve patient outcomes,
and crucially, patient experience, at all parts of the patient journey with CDI, and the results are awaited.

**Conclusion**

Dysnatraemia is common in patients with CDI, and is often acquired in hospital, emphasising the vulnerability of this patient cohort when hospitalised and the need for early expert input in every hospital admission. While objective data collection is important to ensure standards and guidelines are adhered to, it may not fully capture patient experience of their care and therefore future studies of CDI outcomes should strive to include patient experience as an outcome measure. Our patient questionnaire has shown that there is much work to do in terms of improving awareness of this condition within hospitals and in the community. A coordinated patient-centred approach is needed in an effort to reduce adverse events and improve patient experience; with emphasis on (1) early consultation of specialists in hospital with regular review of desmopressin dosing and timing, (2) daily fluid balance and serum sodium monitoring, (3) avoidance of excessive intravenous fluids and desmopressin to avoid iatrogenic hyponatraemia, (4) self-administration of desmopressin if appropriate, and (5) education of health care professionals about the condition.
Figure titles:
Figure 1: Patient recruitment for questionnaire

Figure 2: Patient responses to comment “I feel like the medical team had a good understanding of my diabetes insipidus during my hospital admissions”

Table titles:

Table 1: Demographics

Table 2: Hospital admissions

Declaration of interest:

The authors have no conflicts of interest to declare.

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References

1. Juul KV, Schroeder M, Rittig S, et al. National Surveillance of Central Diabetes Insipidus (CDI) in Denmark: results from 5 years registration of 9309 prescriptions of desmopressin to 1285 CDI patients. The Journal of clinical endocrinology and metabolism. 2014;99(6):2181-7.
2. Jasim S, Alahdab F, Ahmed AT, et al. Mortality in adults with hypopituitarism: a systematic review and meta-analysis. Endocrine. 2017;56(1):33-42.
3. Ebrahimi F, Kutz A, Wagner U, et al. Excess Mortality Among Hospitalized Patients With Hypopituitarism-A Population-Based, Matched-Cohort Study. The Journal of clinical endocrinology and metabolism. 2020;105(11).
4. Hannon MJ, Crowley RK, Behan LA, et al. Acute glucocorticoid deficiency and diabetes insipidus are common after acute traumatic brain injury and predict mortality. The Journal of clinical endocrinology and metabolism. 2013;98(8):3229-37.
5. Thompson CJ, Costello RW, Crowley RK. Management of hypothalamic disease in patients with craniopharyngioma. Clinical endocrinology. 2019;90(4):506-16.
6. Gohil S, Reddy N, Levy M. Cranial Diabetes Insipidus – A survey of patient safety concerns in secondary care. British Endocrine Society Endocrine Abstracts (2018) 59 P0662018.
7. Gleeson H, Bonfield A, Hackett E, et al. Concerns about the safety of patients with diabetes insipidus admitted to hospital. Clinical endocrinology. 2016;84(6):950-1.
8. Baldeweg SE, Ball S, Brooke A, et al. SOCIETY FOR ENDOCRINOLOGY CLINICAL GUIDANCE: Inpatient management of cranial diabetes insipidus. Endocr Connect. 2018;7(7):G8-G11.
9. England Patient Safety Alert NHS. Risk of severe harm or death when desmopressin is omitted or delayed in patients with cranial diabetes insipidus. 2016. https://www.england.nhs.uk/patientsafety/wp-content/uploads/sites/32/2016/02/psa-desmopressin-080216.pdf.
10. [Available from: https://www.pituitary.org.uk/information/publications/essential-free-publications/diabetes-insipidus-awareness-card/).
11. Christ-Crain M, Hoorn EJ, Sherlock M, et al. ENDOCRINOLOGY IN THE TIME OF COVID-19-2021 UPDATES: The management of diabetes insipidus and hyponatraemia. European journal of endocrinology. 2021;185(4):G35-g42.
12. Cuesta M, Hannon MJ, Thompson CJ. Adipsic diabetes insipidus in adult patients. Pituitary. 2017;20(3):372-80.
Table 1: Demographics

| Characteristics                          | Values                  |
|------------------------------------------|-------------------------|
| Number of patients                       | 109                     |
| Female                                   | 59 (54%)                |
| Age (y)                                  | 42 (24,60)              |
| Paediatric (<18 years)                   | 11 (10%)                |
| Duration of CDI (y)                      | 11 (5,20)               |
| Length of follow-up (y)                  | 8 (4,10)                |
| Aetiology of CDI                         |                         |
| Hypothalamic-pituitary (HP) tumour       | 50 (46%)                |
| Following surgery to HP region           | 20 (18%)                |
| Infiltrative disorders                   | 17 (16%)                |
| Idiopathic                               | 11 (10%)                |
| Congenital                               | 4 (4%)                  |
| Traumatic                                | 2                       |
| Other                                    | 7                       |
| Route of desmopressin                    |                         |
| Oral, tablets                            | 81 (74%)                |
| Oral, melts                              | 8 (7%)                  |
| Nasal spray                              | 18 (17%)                |
| Oral and nasal spray                     | 2                       |
| Co-existing ACTH deficiency              | 72 (66%)                |
Table 2: Hospital admissions

| Parameters                                      | Values          |
|------------------------------------------------|-----------------|
| Number of hospital admissions                  | 85              |
| Number of patients                             | 38              |
| Number of admissions to OUH per patient        | 1 (1.3)         |
| Number of patients with one or more admissions |                 |
| 1 admission                                    | 22              |
| 2 admissions                                   | 6               |
| 3 admissions                                   | 3               |
| 4 admissions                                   | 1               |
| 5 admissions                                   | 1               |
| 6 admissions                                   | 3               |
| 7 admissions                                   | 1               |
| 8 admissions                                   | 1               |
| Length of stay                                 | 3 (2.5) days    |
| Admitting specialty                            |                 |
| Medical (including Endocrinology)              | 47 (55%)        |
| Neurosurgical                                  | 26 (31%)        |
| Other surgical                                 | 8 (9%)          |
| Obstetrics/Gynaecology                         | 4 (5%)          |
| Emergency admission                            | 56 (66%)        |
| Elective admission                             | 29 (34%)        |
| Indication for emergency admission*            |                 |
| Infection                                      | 18 (32%)        |
| Confusion/falls/decreased functioning          | 12 (21%)        |
| Abnormal serum sodium                          | 8 (14%)         |
| Headache                                       | 5 (9%)          |
| Seizure                                        | 3 (5%)          |
| Adrenal crisis                                 | 2 (3%)          |
| Other                                          | 10 (18%)        |
| Indication for elective admission              |                 |
| Elective neurosurgery                          | 16 (55%)        |
| Elective surgery (non-neurosurgery)            | 6 (21%)         |
| Chemotherapy                                   | 4 (14%)         |
| Obstetric                                      | 3 (10%)         |

* more than one indication in some cases
Patients with CDI identified
n=110

Information letters sent, followed by phone call
n=109

1 patient declined to participate in questionnaire and requested for their information not to be included in study

Responses
n=78

2 patients declined to participate in questionnaire
2 patients were unable to participate due to memory or communication difficulties
27 patients – unable to contact by phone
