Central diabetes insipidus from a patient's perspective: management, psychological co-morbidities, and renaming of the condition: results from an international web-based survey

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Summary

Background Central diabetes insipidus is a rare neuroendocrine condition. Data on treatment-associated side-effects, psychological comorbidities, and incorrect management are scarce. The aim of this study was to investigate patients' perspectives on their disease.

Methods This study used a cross-sectional, web-based, anonymous survey, developed by endocrinologists and patient representatives, to collect the opinions of patients with central diabetes insipidus on management and complications of their disease, psychological comorbidities, degree of knowledge and awareness of the condition among health-care professionals, and renaming the disease to avoid confusion with diabetes mellitus (diabetes).

Findings Between Aug 23, 2021, and Feb 7, 2022, 1034 patients with central diabetes insipidus participated in the survey. 91 (9%) participants were children and adolescents (37 [41%] girls and 54 [59%] boys; median age 10 years [IQR 6–15]) and 943 (91%) were adults (757 [80%] women and 186 [20%] men]; median age 44 years [34–54]). 488 (47%) participants had isolated posterior pituitary dysfunction and 546 (53%) had combined anterior and posterior pituitary dysfunction. Main aetiologies were idiopathic (315 [30%] of 1034 participants) and tumours and cysts (pre-surgical 217 [21%]; post-surgical 254 [25%]). 260 (26%; 95% CI [0·23–0·29]) of 994 patients on desmopressin therapy had hyponatraemia leading to hospitalisation. Patients who routinely omitted or delayed desmopressin to allow intermittent aquaresis had a significantly lower prevalence of hyponatraemia compared with those not aware of this approach (odds ratio 0·55 [95% CI 0·39–0·77]; p=0·0006). Of patients who had to be hospitalised for any medical reason, 71 (13%; 95% CI 0·10–0·16) of 535 patients did not receive desmopressin while in a fasting state (nil by mouth) without intravenous fluid replacement and reported symptoms of dehydration. 660 (64%; 0·61–0·67) participants reported lower quality of life, and 369 (36%; 0·33–0·39) had psychological changes subjectively associated with their central diabetes insipidus. 823 (80%; 0·77–0·82) participants encountered a situation where central diabetes insipidus was confused with diabetes mellitus (diabetes) by health-care professionals. 884 (85%; 0·83–0·88) participants supported renaming the disease; the most favoured alternative names were vasopressin deficiency and arginine vasopressin deficiency.

Interpretation This is the largest survey of patients with central diabetes insipidus, reporting a high prevalence of treatment-associated side-effects, mismanagement during hospitalisation, psychological comorbidities, and a clear support for renaming the disease. Our data are the first to indicate the value of routinely omitting or delaying desmopressin.

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Introduction

Central diabetes insipidus, a rare neuroendocrine condition with a prevalence of one in 25 000 people, is caused by arginine vasopressin deficiency.[1] The condition is characterised by the production of large volumes of unconcentrated urine, which are compensated for by excessive fluid intake.[2] Once diagnosed, desmopressin, a selective vasopressin V2 receptor agonist, is usually prescribed to overcome the symptoms of polyuria, polydipsia, and nocturia.[3]

Data about desmopressin-associated side-effects, insufficient awareness among medical professionals, and the prevalence of incorrect management of central diabetes insipidus are scarce and restricted to small studies or case series. Occasional published case reports show the tragic and fatal consequences of treatment neglect with omission of desmopressin during hospitalisation, which is partly explained by confusion among health-care professionals between central diabetes insipidus and diabetes mellitus

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Research in context

Evidence before this study

Central diabetes insipidus is a rare neuroendocrine condition resulting from arginine vasopressin deficiency. Data about treatment-associated side-effects, psychological comorbidities, and prevalence of incorrect management due to poor awareness among health-care professionals are scarce. We searched PubMed from the inception of the database to March 1, 2022, for articles published in English, using the terms "diabetes insipidus", "desmopressin", "hyponatraemia", "hyponatremia", "hypernatraemia", "hypernatremia" "inpatient management", "safety", "psychological co-morbidities", "oxytocin", and "re-naming". Desmopressin, a vasopressin V2 receptor agonist, is the current standard of care in central diabetes insipidus. If patients are not correctly instructed on the use of desmopressin, even normal fluid intake can result in life-threatening hyponatraemia. Results from a retrospective study in 137 patients with central diabetes insipidus showed a 27% prevalence of mild and a 15% prevalence of profound hyponatraemia. The same study also reported concerningly high rates of hypernatraemia, especially during hospital admissions, most likely because of inappropriate disease management. Because of its rarity, health-care professionals have a poor awareness of central diabetes insipidus and occasionally published case reports highlight the tragic and fatal consequences of treatment neglect during hospitalisation, which is partly explained by confusion with diabetes mellitus (diabetes). These examples have given rise to an increasing interest in the potential need for renaming central diabetes insipidus. Additionally, only a few attempts have been made to evaluate psychological comorbidities and quality of life (QoL), especially in patients with isolated central diabetes insipidus. The scarcity of available data show the difficulties in emotion recognition and the higher levels of depression and anxiety symptoms in patients with central diabetes insipidus compared with healthy controls despite adequate therapy with desmopressin.

Added value of this study

This is the largest survey to date in central diabetes insipidus using a customised questionnaire designed by medical professionals and patients. Our data indicate a high prevalence of desmopressin-induced hyponatraemia leading to hospitalisation. To our knowledge, our results are the first to show the value of routinely omitting or delaying desmopressin (desmopressin escape) to allow intermittent aquaresis. Patients who used this method had a lower prevalence of hyponatremia leading to hospitalisation compared to those not aware of this approach (22% vs 34%). Patients with central diabetes insipidus reported a high prevalence of psychological comorbidities and reduced QoL, this was apparent irrespective of an additional anterior pituitary dysfunction, which challenges the assumption of existing data that concomitant anterior pituitary hormone deficiencies are largely responsible for psychological changes and reduced QoL.

We show that mismanagement during hospitalisation (eg, delay or non-availability of desmopressin) and confusion with diabetes are not an exception but reported by most patients. Renaming the disease to minimise these events was strongly supported by 85% of the patients.

Implications of all the available evidence

The concerning numbers of mismanagement during hospitalisation and the confusion with diabetes makes it imperative to provide health-care professionals with more information about central diabetes insipidus and its management, and to ensure that desmopressin is recorded as an essential medication that must be available over the full 24 h. Our data point to the importance of desmopressin escape as a cost-free method resulting in lower prevalence of life-threatening hyponatraemia. Educating patients about this approach should be done when initiating desmopressin with reminders when attending clinics. Future studies should investigate whether promotion of desmopressin escape leads to lower risk of hyponatraemia. In view of the prevalent psychological comorbidities and reduced QoL shown in our study, future research is needed to investigate the psychopathological characteristics and possible treatment options in central diabetes insipidus. Renaming of central diabetes insipidus, avoiding the word diabetes, would help ensure that the disease is recognised as requiring specialist life-sustaining therapy, which is distinct from diabetes. Such renaming is being actively considered by members of the international endocrinology societies.

(diabetes).[4] These examples of mismanagement and confusion have given rise to increasing interest in the potential need for renaming central diabetes insipidus to avoid confusion with diabetes.

An enormous amount of research has been devoted to quality of life (QoL) in patients with anterior pituitary dysfunction; however, research covering QoL and psychological comorbidities in patients with central diabetes insipidus is scarce. A few small studies have shown that even if patients were asymptomatic in terms of polyuria and polydipsia, psychological comorbidities occur, with adverse effects on QoL, compared with individuals without diabetes insipidus.[5,6] However, important questions regarding psychopathological characteristics remain unanswered.

To address these issues, we aimed to assess patients perspectives regarding their disease management, psychological comorbidities, knowledge and awareness of the disease among health-care professionals, and renaming central diabetes insipidus.

Methods

Study design and participants

This study used an anonymous, cross-sectional, web-based survey (DImond survey [Assessment of the characteristics of patients with central diabetes insipidus – from the diagnosis to the management of the condition]) done via the website of the Department of Clinical Research, University Hospital Basel, Basel, Switzerland. Patients with central diabetes insipidus were invited to participate in this voluntary 10 min survey. Patients younger than 18 years were defined as children and adolescents; those aged 18 years and older were defined as adults. The questions were developed by a multinational team of endocrinologists from Switzerland, the UK, and Ireland, together with patient representatives from the USA. The survey consisted of eight sections with 35 main questions, and it was implemented as a custom web application supporting smartphones, tablets, and computers. Data were stored in a secured database of the University of Basel, Basel, Switzerland. Participant anonymity was ensured by hosting the application on internal servers, not using any external service providers, or collecting identifying data (eg, IP addresses or user-agent strings). Additionally, only strictly necessary client-side cookies were used. A random token was generated when the user navigated to the first question. This token was valid for a short period, but it lost its validity after submitting the survey, thus allowing users to complete the questionnaire even after the loss of internet connection or with temporary interruptions.

Recruitment was done in three ways using different strategies and contact channels to gain a large sample that reflected the full spectrum of patients with central diabetes insipidus. (1) Physicians involved in this project informed patients with central diabetes insipidus by telephone and directly during routine visits or hospitalisations about this voluntary anonymous survey and shared the link to the homepage. Patients were contacted without any prespecified eligibility criteria. (2) Announcements were shared on websites of the UK Pituitary Foundation (on Oct 28, 2021) and Pituitary Worlds News (on Dec 17, 2021) with a description and direct link to the survey. (3) A description and link to the survey were shared on social media: a post was shared on the Got diabetes insipidus? Facebook group on Oct 20, 2021, and a post was shared on the Twitter account of the Pituitary Society on Dec 13, 2021.

Before the start of the survey, patients or their legal representative were informed about the anonymity of the data collection, and that by consenting to participate, the data would be processed, analysed, and published for research purposes (appendix pp 2–5). The proposal of this survey was submitted to the local ethics committee, Ethical Committee Northwest and Central Switzerland, which confirmed that a research project with anonymous health-related personal data does not fall within the scope of the Swiss Human Research Act and study conduct permission was granted. We used the Checklist for Reporting Results of Internet E-Surveys and the Consensus-Based Checklist for Reporting of Survey Studies for reporting (appendix pp 19–24).

Outcomes

The objectives were to investigate patients' perspectives on management and complications as in-patients and out-patients, psychological comorbidities, degree of knowledge and awareness among health-care professionals, and views for renaming central diabetes insipidus to avoid confusion with diabetes.

Disease management and complications were assessed through questions focused on occurrence and total number of hyponatraemic and hypernatraemic episodes since diagnosis, current and previous types and doses of desmopressin preparations, practice of intentionally delaying and omitting desmopressin dose to reduce the risk of hyponatraemia, occurrence of desmopressin access problems, and episodes of withdrawal from desmopressin treatment while in a fasting state (nil by mouth) during hospitalisation. Occurrence of psychological problems after diagnosis subjectively associated with central diabetes insipidus (depressed mood, sleep disturbance, heightened anxiety, stress management disturbance, change in eating habits, and change in personality), change in QoL subjectively associated with central diabetes insipidus (social activities, recreation, and fun; physical wellbeing; and mental wellbeing), level of QoL, ability to trust others, social interaction, sexual arousal, and anxiety level in general life were assessed with a 10-point scale. Confusion of central diabetes insipidus with diabetes by health-care professionals and level of knowledge of physicians on central diabetes insipidus from a patient's perspective was assessed on a 10-point scale. All of the questions asked in the survey are listed in the appendix (pp 14–18).

Statistical analysis

No formal sample size calculation was made; a target sample size of more than 800 participants (with no allowance for multiplicity) was considered adequate. All statistical analyses used R (version 4.1.2). Discrete variables are expressed as frequencies and continuous variables reported as median and interquartile range. Prevalence estimates are reported with 95% CI, calculated with the Wald Interval method. Data regarding the practice of delaying or omitting desmopressin dose until breakthrough symptoms (increased urinary frequency and strong thirst) occur to allow aquaresis, referred to by some as desmopressin escape or water off-loading, was collected. We refer to this method as desmopressin escape. A univariate logistic regression model was done to describe the association of desmopressin escape performance with the prevalence of hyponatraemia: patients aware of and used desmopressin escape were compared with patients who were aware of but did not follow the

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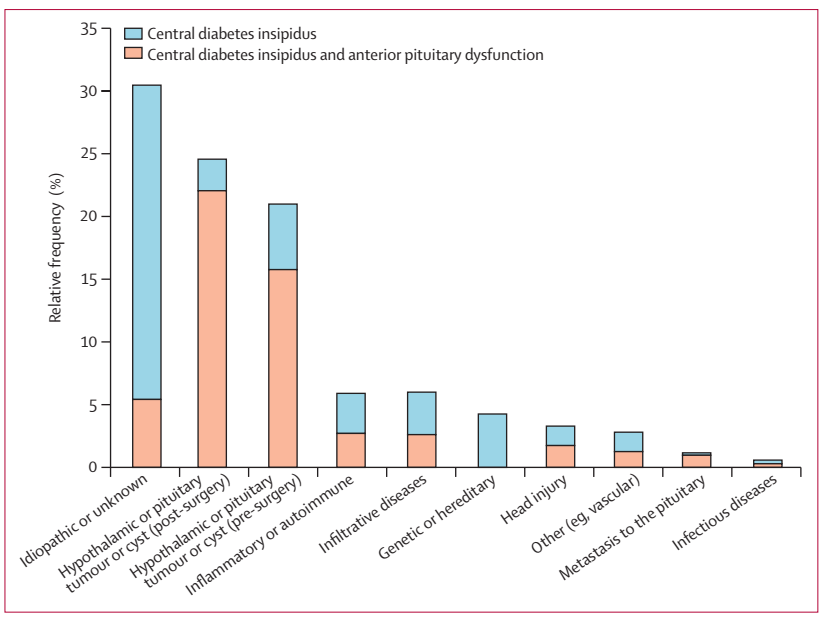

Figure 1: **Causes of central diabetes insipidus**
The proportion of participants with isolated central diabetes insipidus cases and proportion with combined central diabetes insipidus and anterior pituitary dysfunction due to each clinical cause.

approach and with patients who were not aware and did not use the approach. We report odds ratios with 95% CI. Qualitative measures (ie, diagnostic test burden, knowledge about central diabetes insipidus among physicians, and different psychological characteristics) were indicated on a visual analogue scale ranging from 0 (no, none, or minimum) to 10 (extreme or maximum). All analyses are exploratory and were assessed in the entire population, patients with isolated posterior pituitary dysfunction, and patients with combined anterior or posterior pituitary dysfunction separately.

Role the of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 23, 2021, and Feb 7, 2022, 1034 patients with central diabetes insipidus participated in the survey. 91 (9%) participants were children and adolescents (37 [41%] girls and 54 [59%] boys; median age 10 years [IQR 6–15]) and 943 (91%) were adults (757 [80%] women and 186 [20%] men]; median age 44 years [34–54]). 488 (47%) participants had isolated posterior pituitary dysfunction and 546 (53%) had combined anterior and posterior pituitary dysfunction. Median duration of central diabetes insipidus was 9 years (3–19) and the initial symptoms (eg, polyuria, reported by 930 [90%] participants, polydipsia reported by 905 [88%] participants, and nocturia reported by 810 [78%] participants), began a median of 0·3 years (0·1–1·0) before diagnosis. An initial diagnostic provocation test was done in 602 (58%; 95% CI 0·55–0·61) participants (appendix p 6). The causes of central diabetes insipidus are reported in figure 1 and table 1. The number of additional anterior pituitary hormone dysfunctions are reported in figure 2 and the appendix (p 6).

994 (96%) participants were receiving desmopressin therapy (figure 3; appendix p 11). Prevalence of the types of preparation and availability of desmopressin in the local pharmacy are reported in the appendix (pp 6–7). 985 (95%) participants indicated that they saw a medical doctor twice (IQR one to two) a year for reviews and check-ups of their central diabetes insipidus: 857 (83%) saw an endocrinologist, 99 (10%) saw a general practitioner, 16 (2%) saw another specialist (eg, oncologist), and 13 (1%) saw a nephrologist.

Desmopressin escape was used by 667 (67%; 95% CI 0·64–0·70) of 994 participants who received medication. 386 (39%; 0·36–0·42) of 994 participants used this approach daily, 160 (16%; 0·14–0·19) participants used this approach several times a week, and 121 (12%; 0·10–0·14) participants used the approach once a week. 205 (21%; 0·18–0·23) of the 994 participants who were receiving desmopressin were not aware of desmopressin escape; 122 (12%; 0·10–0·14) were aware of desmopressin escape but did not use it.

In the out-patient setting, 230 (22%; 95% CI 0·20–0·25) of 1034 participants reported episodes of hyponatraemia (median two episodes [IQR two to four]), with a similar incidence in adults and children and adolescents (appendix p 7). 211 (21%; 0·22–0·27) of 994 participants seen in an out-patient setting who were receiving desmopressin medication reported episodes of hyponatraemia. Hyponatraemia was reported by 114 (17%; 0·17–0·20) of 667 patients who used desmopressin escape, 65 (32%; 0·26–0·28) of 205 participants who were not aware of desmopressin escape, and 32 (26%; 0·19–0·35) of 122 participants who were aware of desmopressin escape but did not use the method. Patients who used desmopressin escape had a significantly lower prevalence of hyponatraemia compared with those not aware of this method (OR 0·44; 95% CI 0·31–0·64; p<0·0001) and compared with those aware of desmopressin escape but who did not use this method (0·58; 0·37–0·92; p=0·018). There was no association between type of desmopressin preparation and prevalence of hyponatraemia (appendix p 13).

364 (35%; 95% CI 0·32–0·38) of 1034 participants reported an episode of dysnatraemia leading to hospital admission on at least one occasion. 273 (26%; 0·24–0·29) of 1034 participants (259 [27%; 0·25–0·30] of 943 adults and 14 [15%; 0·08–0·23] of 91 children and adolescents) had a median of two (IQR one to three) hyponatraemia episodes. 260 (26%; 0·23–0·29) of 994 participants under desmopressin treatment reported episodes of hyponatraemia leading to hospitalisation. 145 (22%; 0·18–0·25) of 667 participants who used desmopressin escape, 69 (34%;0·27–0·40) of 205 participants not aware

	Full dataset (n=1034)	Participants with isolated posterior pituitary dysfunction		Participants with anterior and posterior pituitary dysfunction	
		Adults (n=444)	Children and adolescent (n=44)	Adults (n=499)	Children and adolescent (n=47)
Age, years	42 (32–53)	44 (35–53)	7 (5–12)	44 (34–54)	11 (7–15)
Sex					
Female	794 (77%)	368 (83%)	20 (45%)	389 (78%)	17 (36%)
Male	240 (23%)	76 (17%)	24 (55%)	110 (22%)	30 (64%)
Weight, kg	77·1 (63·0–95·0)	77·1 (65·0–93·9)	32 20–43)	82·0 (68·0–98·0)	44·9 (35·0–61·2)
Height, cm	165 (158–173)	167 (160–173)	136 (122–155)	168 (160–174)	141 (114–157)
BMI, kg/m²	27·6 (23·3–32·7)	27·4 (23·4–32·5)	16·8 (12·2–19·2)	29·1 (24·9–33·4)	21·7 (19·0–27·5)
Duration of central diabetes insipidus, years	9·0 (3·0–19·0)	9·0 (3·0–23·0)	3·0 (1·0–5·0)	10·0 (3·0–19·0)	4·0 (2·5–7·0)
Duration of symptoms before diagnosis, years	0·3 (0·1–1·0)	0·5 (0·2–2·0)	0·2 (0·1–0·7)	0·2 (0·1–1·0)	0·1 (0·0–0·3)
Symptoms at the time of diagnosis					
Polyuria*	930 (90%)	412 (93%)	42 (95%)	433 (87%)	43 (91%)
Polydipsia*	905 (88%)	410 (92%)	39 (89%)	420 (84%)	36 (77%)
Nocturia*	810 (78%)	386 (87%)	35 (80%)	365 (73%)	24 (51%)
Cause of central diabetes insipidus					
Idiopathic or unknown	315 (30%)	240 (54%)	19 (43%)	51 (10%)	5 (11%)
Hypothalamic or pituitary tumour or cyst (post-surgery)	254 (25%)	26 (6%)	0	211 (42%)	17 (36%)
Hypothalamic or pituitary tumour or cyst (pre-surgery)	217 (21%)	48 (11%)	6 (14%)	157 (31%)	6 (13%)
Infiltrative disease (eg, sarcoidosis or Langerhans cell histiocytosis)	62 (6%)	25 (6%)	10 (23%)	16 (3%)	11 (23%)
Inflammatory or autoimmune (eg, hypophysitis)	61 (6%)	30 (7%)	3 (7%)	28 (6%)	0
Genetic or hereditary	44 (4%)	40 (9%)	4 (9%)	0	0
Head injury	34 (3%)	16 (4%)	0	17 (3%)	1 (2%)
Other causes (eg, vascular or congenital)	29 (3%)	15 (3%)	1 (2%)	7 (1%)	6 (13%)
Metastasis to the pituitary (eg, lymphoma, breast cancer, or lung cancer)	12 (1%)	1 (<1%)	1 (2%)	10 (2%)	0
Infectious diseases (eg, meningitis, encephalitis, or tuberculosis)	6 (1%)	3 (1%)	0	2 (<1%)†	1 (2%)

Data are median (IQR) and n (%). *Remaining patients could not recall the symptoms (eg, diagnosed in childhood). †This column will not add up to 100% because of rounding.

Table 1: **Baseline characteristics**

of desmopressin escape, and 46 (38%; 0·29–0·46) of 122 participants who were aware of but did not use desmopressin escape had hyponatraemia. Similar to the findings in the out-patient setting, participants who used desmopressin escape had a significantly lower hyponatraemia prevalence leading to hospitalisation compared with those not aware of this method (OR 0·55; 95% CI 0·39–0·77; p=0·0006) and with those aware of but who did not use this method (0·46; 0·31–0·69; p=0·0002; appendix p 137).

150 (15%; 95% CI 0·12–0·17) participants (128 [14%; 0·11–0·16] of 943 adults and 22 [24%; 0·15–0·33] of 91 children and adolescents) had hypernatraemia leading to hospital admission; a median of one episode (IQR one to three) was reported per patient. 59 (6%; 0·04–0·07) patients had episodes of both hyponatraemia and hypernatraemia.

247 (24%; 95% CI 0·21–0·26) participants had problems accessing desmopressin during hospitalisation (eg, for acute illness and elective surgery). Multiple factors could restrict access to medication, the most common reasons were non-availability of desmopressin (139 [56%; 0·50–0·62] participants), other reasons (eg, desmopressin provided only on a scheduled time; 102 [41%; 0·35–0·47] participants), prescription of wrong dose (47 [19%; 0·14–0·24] participants), or complete absence of prescription (32 [13%; 0·09–0·17] participants; appendix p 9).

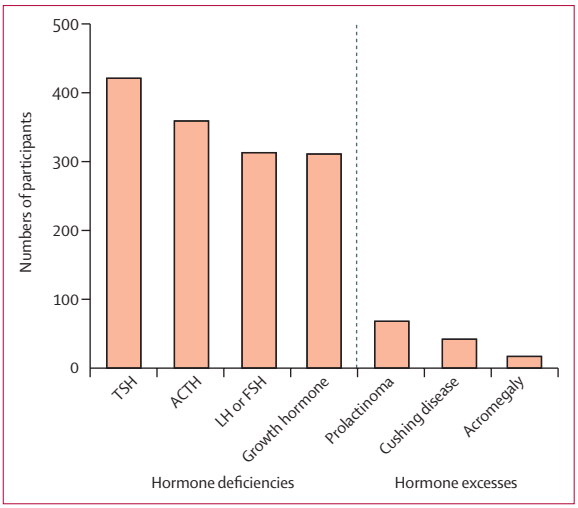

Figure 2: **Anterior pituitary dysfunction**
The numbers of patients with combined central diabetes insipidus and anterior pituitary dysfunction in each category grouped according to the hormones. ACTH=adrenocorticotropic hormone. FSH=follicle-stimulating hormone. LH=luteinising hormone. TSH=thyroid-stimulating hormone.

535 (52%; 95% CI 0·49–0·55) participants had to avoid eating and drinking for a medical reason during hospitalisations (for any reason) in elective (475 [46%; 0·43–0·49] participants) or emergency (150 [15%; 0·12–0·17] participants) situations. During their hospitalisation, 290 (54%; 0·50–0·58) of 535 participants received no intravenous fluids, of whom 209 (39%; 0·35–0·43) participants used their own desmopressin, desmopressin was given to ten (2%; 0·01–0·03) participants by the medical team, and 71 (13%; 0·10–0·16) participants received no desmopressin—these patients described classical symptoms of dehydration (eg, extreme thirst, dry eyes and mouth, and nausea and shivering).

369 (36%; 95% CI 0·33–0·39; equal proportion of participants with isolated posterior dysfunction and those with combined pituitary dysfunction) had psychological problems or recognised psychological changes associated with their central diabetes insipidus (table 2). 660 (64%; 0·61–0·67 participants; equal proportion of participants with isolated posterior dysfunction and those with combined pituitary dysfunction) reported lower QoL (six [IQR four to seven] out of ten on the visual analogue scale [VAS]). 538 (52%; 0·49–0·55) participants reported effects to social activities, 493 (48%; 0·44–0·51) to recreation and fun, 476 (46%; 0·43–0·49) to physical wellbeing, and 414 (40%; 0·37–0·43) to mental wellbeing. Rates on a VAS regarding anxiety levels in general life, ability to build trust with others, ability in social interaction, and sexual arousal are reported in table 2. The median rates were equal in participants with isolated posterior pituitary dysfunction and those with combined pituitary dysfunction; no major sex and age category specific differences were reported (appendix p 12).

823 (80%; 95% CI 0·77–0·82) participants indicated that health-care professionals had confused their condition with diabetes on at least one occasion. 869 (84%; 0·82–0·86) participants thought that physicians in general (eg, during routine or emergency hospital admissions) have insufficient understanding of central diabetes insipidus and rated the general knowledge of physicians (not involved in the regular treatment of their central diabetes insipidus) as a two (IQR one to four) out of ten on the VAS. 753 (87%; 0·84–0·89) of the 869 participants thought that this poor knowledge affected the management of their condition (eg, repeated blood sugar measurements due to confusion).

884 (85%; 95% CI 0·83–0·88) preferred a renaming of the condition. The most common suggestions were vasopressin deficiency and arginine vasopressin deficiency. The one clear wish from all of the comments was not to use the term diabetes in the name of the disease.

Discussion

The data from our survey, the largest of its kind in patients with central diabetes insipidus, indicate a high prevalence of treatment-associated side-effects leading to hospitalisation—particularly in patients unaware of the desmopressin escape approach—and psychological comorbidities, poor knowledge and awareness of central diabetes insipidus among health-care professionals, and strong support for renaming the condition.

It is often not sufficiently recognised that many patients with rare illnesses, such as central diabetes insipidus, are experts on their conditions. The experiential knowledge that patients acquire after years of treatment is hard-won and unique, and deserves to be considered, both clinically and in research studies. On the basis of this consideration, this survey was developed by a team of expert endocrinologists together with patient representatives using a novel web-based method.

Most commonly, central diabetes insipidus results from acquired disruptions of the hypothalamic–pituitary axis, and less than 10% of the cases are hereditary.[7,8] The spectrum of causes of central diabetes insipidus indicated by our data are consistent with available literature, with hypothalamo–pituitary tumours or cysts the most common cause of central diabetes insipidus (46%); however, there was a large proportion of idiopathic cases (30–50%), especially in isolated central diabetes insipidus.[7–9]

In anterior pituitary dysfunction, gonadotropins and growth hormone are usually more likely to be affected than adrenocorticotropic hormone and thyroid-stimulating hormone. Our data appear to show contradictory results, with thyroid-stimulating hormone as the most common concomitant hormone deficiency and growth hormone as the least common. We speculate that the discrepant high incidence of hypothyroidism might reflect, in part, the high prevalence of primary hypothyroidism in idiopathic central diabetes insipidus,[10] and is probably not distinguished from secondary hypothyroidism by patients.

Additionally, not all adult patients with growth hormone deficiency are tested for or receive growth hormone replacement therapy, and they might be unaware of their deficiency.

Desmopressin is the current standard of care for central diabetes insipidus. Our data show a clear preference for the oral route of desmopressin in those switching the type of preparation. A possible explanation is that alternative nasal preparations show great variability in effectiveness and switching to the oral route has been shown to improve overall control.[11,12] Compared with the results of post-marketing safety data, which indicate a lower risk of hyponatraemia with oral than with nasal desmopressin,[11,12] our data showed a similar prevalence of patient-reported hyponatremia in patients with both preparations. Nonetheless, the use of oral preparations should be preferred, and well designed studies are needed to investigate this advantage. The antidiuretic effect of desmopressin can be affected by several factors, such as solute intake and excretion, and fluctuating bioavailability (eg, by nasal congestion for nasal sprays or concomitant food ingestion for oral route).[13] Despite this, patients often take a fixed dose at scheduled times. If not instructed on use of desmopressin escape, even normal daily fluid intake can result in water retention and development of hyponatraemia in the presence of sustained antidiuresis from rigid dose schedules. In the out-patient setting, a long-term follow-up study revealed a 27% prevalence of mild hyponatraemia and a 15% prevalence of profound hyponatraemia.[14] In our study, patient-reported hyponatraemia was less frequent, suggesting that laboratory-confirmed hyponatraemia might even be higher. Our data also suggest a larger proportion of patients with hyponatraemia leading to hospitalisation. Desmopressin escape, a method to delay or omit desmopressin to allow aquaresis, has long been advised by some physicians to counteract this risk.[15] Our data are the first to show the value of this clinical approach. Patients who were instructed to delay or omit the dose one or more times a week at initiation of desmopressin treatment had a lower prevalence of hyponatraemia. Hyponatraemia is particularly common in the out-patient setting,[14] and in the absence of patient education on hyponatraemia symptoms and desmopressin escape, it can quickly become life-threatening. In our opinion, desmopressin escape should be instructed at every initiation of desmopressin therapy because it is an approach resulting in immediate cost-free health-care improvements (ie, reduced prevalence of life-threatening hyponatraemia and hospitalisation). Future prospective studies should investigate whether this method does lead to lower risk for hyponatraemia. Furthermore, a more careful regimen is needed in paediatric patients, and parents must be educated about hyponatraemia as a result of inappropriate management of desmopressin and fluid intake.[16]

Our data also show that a large number of patients were unable to source desmopressin during hospitalisation when they were in a fasting state and without intravenous fluid replacement. Many of these patients reported symptoms of dehydration. Previously, Behan and colleagues[14] reported concerningly high rates of hypernatraemia, particularly in in-hospital settings, probably as a result of inappropriate management. However, once admitted with hyponatraemia, physicians intuitively tend to discontinue desmopressin treatment.[17] This can lead to rapid overcorrection of serum sodium and result in severe neurological injury, if not appropriately monitored.[17] These findings suggest that the in-hospital management of patients should be led, or at least accompanied by, a specialist because patients with central diabetes insipidus are known to be highly vulnerable to rapid volume depletion in the context of severe illness if not adequately managed.[4,18] Concern about mismanagement and delay of appropriate treatment led to a recent call for a campaign to increase awareness and education of medical personnel, and the request to include desmopressin as a high-alert medication with 24 h access in hospitals.[19] Consequently, the Society for Endocrinology UK published a clinical guidance covering the in-hospital management of patients with central diabetes insipidus.[20]

Our data indicate a high prevalence of psychological comorbidities in patients with central diabetes insipidus, particularly heightened anxiety, depressed mood, sleeping difficulties, and low sexual drives, consistent with previously published studies.[6,21,22] The patients also reported a reduced QoL, despite reduction of polyuria with desmopressin therapy. Impaired QoL and psychological changes in patients with anterior pituitary dysfunction are well recognised, and replacement therapy improves symptoms.[23,24] By contrast, few attempts have been made to evaluate psychological comorbidities in isolated central diabetes insipidus. The available data suggest that reduced

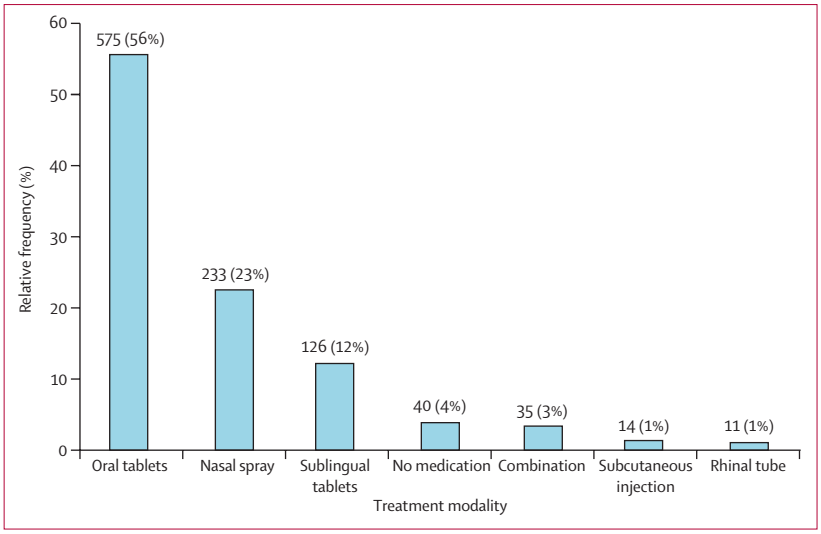

Figure 3: **Type of desmopressin preparation**
Bar plots represent the proportion of each desmopressin preparation. Data are absolute numbers and relative frequencies (%).

	Full dataset (n=1034)	Participants with isolated posterior pituitary dysfunction (n=488)	Participants with anterior and posterior pituitary dysfunction (n=546)
Psychological problems or changes since diagnosis	369 (36%; [33–39])	173 (35%; [31–40])	196 (36%; [32–40])
Heightened anxiety	258 (25%; [22–28])	115 (24%; [20–27])	143 (26%; [23–30])
Sleep disturbance	263 (25%; [23–28])	113 (23%; [19–27])	150 (27%; [24–31])
Depressed mood	239 (23%; [21–26])	99 (20%; [17–24])	140 (26%; [22–29])
Stress management disturbance	181 (18%; [15–20])	86 (18%; [14–21])	95 (17%; [14–21])
Change in eating habits	168 (16%; [14–18])	82 (17%; [13–20])	86 (16%; [13–19])
Change in personality	124 (12%; [10–14])	51 (10%; [8–13])	73 (13%; [11–16])
Documented psychological condition after the diagnosis	111 (11%; [9–13])	41 (8%; [6–11])	70 (13%; [10–16])
Reduced quality of life after the diagnosis	660 (64%; [61–67])	308 (63%; [59–67])	352 (64%; [60–68])
Social activities	538 (52%; [49–55])	249 (51%; [47–55])	289 (53%; [49–57])
Recreation and fun	493 (48%; [44–51])	234 (48%; [44–52])	259 (47%; [43–52])
Physical wellbeing	476 (46%; [43–49])	218 (45%; [40–49])	258 (47%; [43–51])
Mental wellbeing	414 (40%; [37–43])	192 (39%; [35–44])	222 (41%; [37–45])
Subjective rates on a visual analogue scale, median [IQR]			
QoL*†	6 (4–7)	6 (4–8)	6 (4–7)
Ability to trust*†	7 (4–8)	7 (4–8)	7 (4–8)
Social interaction*†	7 (5–8)	7 (6–8)	7 (4–8)
Sexual arousal*†‡	3 (2–7)	4 (2–8)	3 (1–6)
Anxiety level in general life*§	6 (3–8)	6 (3–8)	6 (3–7)

Data presented in median [IQR] and n (%; [95%-CI]). QoL=quality of life. *Rated on a visual analogue scale from 0 (minimum, no, or none) to 10 (maximum or extreme). †Low score on this parameter reflects more adversely affected. ‡Answered by 819 patients. §High score on this parameter reflects more adversely affected.

Table 2: **Psychological comorbidities**

QoL is partly explained by fluctuations in desmopressin efficacy, leading to changes in symptom control, or by concomitant pituitary hormone deficiencies.[5,25,26] Our data show that the reduction in QoL is equally common in patients with isolated central diabetes insipidus and those with combined pituitary dysfunction, which challenges the assumption that concomitant pituitary hormone deficiencies are largely responsible.

Oxytocin, the second neuropeptide released from the posterior pituitary, is known to mediate neuropsychiatric effects, including antidepressant, anxiolytic, and socioemotional functioning properties, suggesting a potential role for oxytocin deficiency in the increased psychopathology. This is supported by the results of the study by Aulinas and colleagues.[6] Of note, one study reported that a single dose of intranasal oxytocin improved emotion recognition in ten patients with craniopharyngioma and concomitant central diabetes insipidus.[27] Conversely, in neuropsychiatric conditions, intranasal oxytocin has shown inconclusive results.[27] Future studies to investigate whether oxytocin deficiency occurs in central diabetes insipidus and whether treatment improves psychological symptoms would be of interest.

According to NHS England and the National Reporting and Learning System, 471 adverse incidents were reported from 2009 to 2015 involving desmopressin treatment.[4] Of these, prescription of the incorrect dose (n=56) and dose omission (n=76), were the most common errors.[4] Four of these dose omissions resulted in death due to severe dehydration.[4,28] Consequently, the NHS sent an alert to all doctors informing them of the risk of omitting this life-sustaining medication.[4] In line with this and in agreement with a study by Dilrukshi and colleagues,[29] 24% of hospitalised patients in our survey reported problems accessing desmopressin during routine or emergency hospitalisations, most commonly due to non-availability. Owing to its rarity, central diabetes insipidus is often neglected by health-care professionals, and increased awareness of this disease is urgently needed. Additionally, central diabetes insipidus is often confused with diabetes. Patients in our survey indicated high rates of confusion with diabetes and insufficient understanding of central diabetes insipidus among health-care professionals. Together, confusion and poor knowledge about central diabetes insipidus, can significantly increase the risk of mismanagement during hospitalisation, as indicated in this survey. Future survey studies could explore the knowledge of health-care professionals on central diabetes insipidus and confirm the validity of the patient's perspective. Renaming of central diabetes insipidus and avoiding the word diabetes could help health-care professionals understand that central diabetes insipidus requires specialist life-sustaining therapy, which is distinct from diabetes. Several patient representative associations and foundations strongly support this approach. Most of the participants in our study suggest arginine vasopressin deficiency or vasopressin deficiency as alternative disease names; participants highlighted the need to not use diabetes in the name of the disease. For the nephrogenic form, arginine vasopressin resistance or vasopressin resistance could be suggested.[30] A working group was set up in 2022 by the main endocrinology societies worldwide (European Society of Endocrinology, Society for Endocrinology [UK], Endocrine Society, Endocrine Society of Australia, Brazilian Society of Endocrinology, Japanese Endocrine Society, Pituitary Society, European Society for Paediatric Endocrinology, American Society of Nephrology) to discuss and propose alternative names for central diabetes insipidus.

The main limitation of our study is that, due to the survey design, we cannot make causal inferences. We have no control group from the general population or patients with isolated anterior pituitary dysfunction for comparison and no standardised longitudinal assessment of outcomes for patients with and without central diabetes insipidus. Because our intent was not to assess causal effects, we did not use causal inference methods or adjust for confounding, and no weighting was done. Although a substantial amount of data shows higher psychological comorbidities in patients with anterior

pituitary dysfunction compared with the general population, psychological burden could be associated with the underlying disease. Because our data indicate lower QoL and psychological comorbidities are similar in patients with isolated posterior pituitary dysfunction and combined anterior pituitary dysfunction, it is reasonable to interpret our results as showing a higher psychological burden for patients with central diabetes insipidus than for members of the general population. The second main limitation is that due to the anonymous survey design, we have no empirical information on the representativeness of our very large sample. Our approach allowed us to include a very large sample and we assume that it reflects the views of patients, but we cannot rule out that selection bias affected our findings; however, we used a broad recruitment strategy, through social media, online dissemination, and personal contacts, and all actively recruited patients were contacted without any prespecified eligibility criteria. In our survey, 77% of the participants were females and the effect of sex on psychological outcomes is unclear; however, sex-stratification showed no major differences in our results. Third, also due to anonymity, response rates or differences according to each health-care system could not be analysed. Finally, the reliability of self-reported data, especially for unawareness of hyponatraemia not leading to hospitalisation, makes interpreting potential anterior pituitary dysfunction, such as hypothyroidism and growth hormone deficiency, difficult; the absence of information about other comorbidities should be considered as a limitation. However, the outcomes of our survey are substantial, objective events which patients most likely remember very well, limiting the potential effect of recall bias. In summary, our data underline the need to provide health-care professionals with more information about central diabetes insipidus and its management, and to better educate patients about the strategy of desmopressin escape. More research is needed on the prevalence of psychological comorbidities and possible treatment options in central diabetes insipidus. Furthermore, the renaming of central diabetes insipidus is being actively considered by members of the international endocrinology societies.

Contributors

CA designed the questionnaire; contributed to data collection, analysis, and interpretation; did the literature search; and wrote the manuscript. All authors modified and refined the questionnaire. MC-C edited the questionnaire, contributed to data analysis and data interpretation, edited the manuscript, and supervised all steps of the study. LGH contributed to the data interpretation and edited the manuscript. All other co-authors contributed to data collection, contributed to data interpretation, and revised the manuscript. All authors had access to all the data and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

We can share deidentified, individual participant-level data that underlie the results reported in this Article and related documents, including the study protocol and the statistical analysis plan. Data will be available with the publication of the manuscript and issued after receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent to the corresponding author. The steering committee of this study will discuss all requests and decide, based on the scientific rigor of the proposal, whether data sharing is appropriate. All applicants are asked to sign a data access agreement.

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References

1 Di Iorgi N, Napoli F, Allegri AE, et al. Diabetes insipidus—diagnosis and management. *Horm Res Paediatr* 2012; **77:** 69–84.
2 Robertson GL. Diabetes insipidus. *Endocrinol Metab Clin North Am* 1995; **24:** 549–72.
3 Oiso Y, Robertson GL, Nørgaard JP, Juul KV. Clinical review: treatment of neurohypophyseal diabetes insipidus. *J Clin Endocrinol Metab* 2013; **98:** 3958–67.
4 NHS England. 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 (accessed July 4, 2022).
5 Nozaki A, Ando T, Akazawa S, et al. Quality of life in the patients with central diabetes insipidus assessed by Nagasaki diabetes insipidus questionnaire. *Endocrine* 2016; **51:** 140–47.
6 Aulinas A, Plessow F, Asanza E, et al. Low plasma oxytocin levels and increased psychopathology in hypopituitary men with diabetes insipidus. *J Clin Endocrinol Metab* 2019; **104:** 3181–91.
7 Maghnie M, Cosi G, Genovese E, et al. Central diabetes insipidus in children and young adults. *N Engl J Med* 2000; **343:** 998–1007.
8 Wang LC, Cohen ME, Duffner PK. Etiologies of central diabetes insipidus in children. *Pediatr Neurol* 1994; **11:** 273–77.
9 Blotner H. Primary or idiopathic diabetes insipidus: a system disease. *Metabolism* 1958; **7:** 191–200.
10 Hannon MJ, Orr C, Moran C, et al. Anterior hypopituitarism is rare and autoimmune disease is common in adults with idiopathic central diabetes insipidus. *Clin Endocrinol (Oxf)* 2012; **76:** 725–28.
11 Robson WL, Leung AK, Norgaard JP. The comparative safety of oral versus intranasal desmopressin for the treatment of children with nocturnal enuresis. *J Urol* 2007; **178:** 24–30.
12 Arima H, Oiso Y, Juul KV, Nørgaard JP. Efficacy and safety of desmopressin orally disintegrating tablet in patients with central diabetes insipidus: results of a multicenter open-label dose-titration study. *Endocr J* 2013; **60:** 1085–94.
13 Richardson DW, Robinson AG. Desmopressin. *Ann Intern Med* 1985; **103:** 228–39.
14 Behan LA, Sherlock M, Moyles P, et al. Abnormal plasma sodium concentrations in patients treated with desmopressin for cranial diabetes insipidus: results of a long-term retrospective study. *Eur J Endocrinol* 2015; **172:** 243–50.
15 Melmed S, Koenig R. Rosen C J, Auchus R, Goldfine A. Williams textbook of endocrinology. 14th edn. Philadelphia, PA: Elsevier, 2019.
16 Teare H, Argente J, Dattani M, et al. Challenges and improvement needs in the care of patients with central diabetes insipidus. *Orphanet J Rare Dis* 2022; **17:** 58.
17 Achinger SG, Arieff AI, Kalantar-Zadeh K, Ayus JC. Desmopressin acetate (DDAVP)-associated hyponatremia and brain damage: a case series. *Nephrol Dial Transplant* 2014; **29:** 2310–15.
18 Ebrahimi F, Kutz A, Wagner U, et al. Excess mortality among hospitalized patients with hypopituitarism-a population-based, matched-cohort study. *J Clin Endocrinol Metab* 2020; **105:** dgaa517.
19 Gleeson H, Bonfield A, Hackett E, Crasto W. Concerns about the safety of patients with diabetes insipidus admitted to hospital. *Clin Endocrinol* 2016; **84:** 950–51.

20 Baldeweg SE, Ball S, Brooke A, et al. Society for endocrinology clinical guidance: Inpatient management of cranial diabetes insipidus. *Endocr Connect* 2018; **7:** G8–11.

21 Gebert D, Auer MK, Stieg MR, et al. De-masking oxytocin-deficiency in craniopharyngioma and assessing its link with affective function. *Psychoneuroendocrinology* 2018; **88:** 61–69.

22 Eisenberg Y, Murad S, Casagrande A, et al. Oxytocin alterations and neurocognitive domains in patients with hypopituitarism. *Pituitary* 2019; **22:** 105–12.

23 Koltowska-Häggström M, Mattsson AF, Monson JP, et al. Does long-term GH replacement therapy in hypopituitary adults with GH deficiency normalise quality of life? *Eur J Endocrinol* 2006; **155:** 109–19.

24 Crespo I, Valassi E, Santos A, Webb SM. Health-related quality of life in pituitary diseases. *Endocrinol Metab Clin North Am* 2015; **44:** 161–70.

25 Ishii H, Shimatsu A, Okimura Y, et al. Development and validation of a new questionnaire assessing quality of life in adults with hypopituitarism: adult hypopituitarism questionnaire (AHQ). *PLoS One* 2012; **7:** e44304.

26 Richards GE, Thomsett MJ, Boston BA, DiMeglio LA, Shulman DI, Draznin M. Natural history of idiopathic diabetes insipidus. *J Pediatr* 2011; **159:** 566–70.

27 Hoffmann A, Özyurt J, Lohle K, Reichel J, Thiel CM, Müller HL. First experiences with neuropsychological effects of oxytocin administration in childhood-onset craniopharyngioma. *Endocrine* 2017; **56:** 175–85.

28 Prentice M. Time for change: renaming diabetes insipidus to improve patient safety. *Clin Endocrinol* 2018; **88:** 625–26.

29 Dilrukshi M, Vickars M, May C, et al. Management of cranial diabetes insipidus – clinical outcomes and patient perception of care. *Euro J Endocrinol* 2022; **187:** 487–93.

30 Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. *Nat Rev Nephrol* 2015; **11:** 576–88.