Quality of life in the patients with central diabetes insipidus assessed by Nagasaki Diabetes Insipidus Questionnaire

Aya Nozaki[1], Takao Ando[1], Satoru Akazawa[1], Tsuyoshi Satoh[2], Ikuko Sagara[1], Ichiro Horie[1], Misa Imaizumi[1], Toshiro Usa[1], Robert T. Yanagisawa[3], and Atsushi Kawakami[1].

[1]Division of Endocrinology and Metabolism, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, Japan

[2]Division of Endocrinology and Metabolism, Isahaya General Hospital, 24-1 Eisho-Higashi, Isahaya, Nagasaki, Japan

[3]Division of Endocrinology, Icahn School of Medicine at Mount Sinai School of Medicine, Box 1055, One Gustave L. Levy Place, New York, New York, USA

Short title: Nagasaki Diabetes Insipidus Questionnaire

Corresponding author: Dr. Takao Ando, Division of Endocrinology and Metabolism, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, Japan, 852-8501

Phone: +81-95-819-7262; **Fax:** +81-95-849-7270; **Email:** takaoando@gmail.com

Abstract

Purpose: Central diabetes insipidus (CDI) is characterized by polyuria and polydipsia due to a deficiency of vasopressin. Currently, the treatment goal for CDI is improvement of quality of life (QOL) by desmopressin (DDAVP) without developing hyponatremia. However, there is no reliable measure for QOL in CDI patients. We evaluate our original questionnaire for QOL, consisting of 12 questions focusing on polyuria, polydipsia, and DDAVP treatment, in CDI patients who underwent a switch from nasal spray to oral disintegrating tablets of DDAVP.

Methods: Twenty-five CDI patients under nasal DDAVP treatment, six with newly developed CDI, and eighteen healthy individuals without known polyuric/polydipsic disorders as control subjects were enrolled. QOL scores were determined by our questionnaire at the enrollment and three months after the start of oral DDAVP treatment and were examined by the Wilcoxon signed-rank test.

Results: Eleven questions detected improvement in QOL. The sum of the QOL scores of the eleven questions increased from 29.2 ±5.6 under nasal to 36.8 ±4.5 under oral DDAVP ($p<0.001$). There were no clinically relevant changes in serum levels of Na. After eliminating two questions about DDAVP treatment, the sum of QOL scores was 15.3 ±6.5 in untreated CDI patients, 24.4 ±5.2 in those with nasal treatment, 28.9 ±4.9 in those with oral DDAVP, and 29.5 ±3.6 in healthy controls. The difference among groups were significant ($p<0.05$ in Steel-Dwass

test) except between patients treated with oral DDAVP and healthy controls.

Conclusions: Our questionnaire can be used to accurately assess QOL in CDI patients.

Keywords: diabetes insipidus, quality of life, questionnaire, desmopressin

Introduction

Central diabetes insipidus (CDI) is characterized by chronic polyuria and polydipsia due to a deficiency of arginine vasopressin (AVP) secretion in the posterior pituitary (1,2). AVP is secreted in response to hyperosmotic and hypovolemic stimuli from the nerve endings of neurons originating in the supraoptic and paraventricular nuclei of the hypothalamus (3,4). The physiological action of AVP is to maintain circulating plasma volume by reabsorbing water from the kidney's collecting ducts and concentrating the urine (5). The most frequent etiologies of CDI are the destruction or degeneration of AVP-secreting neurons by various causes such as hypothalamic pituitary tumors and inflammation (3).

The ultimate treatment for CDI would be to restore the physiological secretion of AVP using stem cell transplantation (6), but currently, a reasonable goal is the improvement and, if possible, normalization of patients' QOL to a similar level to that in individuals without CDI using a synthetic analogue of AVP (desmopressin, DDAVP) without influencing electrolytes or inducing hyponatremia (7).

There are a few formulations of DDAVP available and each has its specific advantages and disadvantages. For example, the anti-diuretic effect of intranasal DDAVP is known to be inconsistent. This disadvantage comes from its unstable bioavailability mainly due to its route of administration. Drug absorption can be influenced not only by patient's skill but also local

factors; for instance, a blocked nose / rhinorrhea and nasal hyperemia are known to decrease and increase absorption of nasally administered DDAVP, respectively (8,9). Polyuria and polydipsia seen in CDI patients under nasal DDAVP treatment vary significantly from day to day (7). An oral tablet of DDAVP has been reported to be well tolerated in adults (10,11) as well as children (12,13), and the switch from intranasal to oral DDAVP from nasal formulation has been shown to improve antidiuretic control (8,9,14). It has been repeatedly described that patients prefer the oral formulation to intranasal DDAVP (8,12,13). The preference for oral DDAVP over nasal formulation would be at least partially associated with preferable characteristics of oral DDAVP including better and consistent absorption, fewer complications, and ease of administration (15). The QOL of CDI patients seems to be easily influenced by the formulations of DDAVP in use other than the dosing and timing schedule of DDAVP.

There has been an attempt to measure QOL of CDI patients using the Peds QL (16). Peds QL is a measure for acute or chronic health problems in children and adolescents, but is not specialized for a CDI symptom (17). The Adult Hypopituitarism Questionnaire (AHQ) includes four questions about polyuria and polydipsia. The four questions have been shown to detect the difference in QOL between patients with CDI and those without (18,19). However, the AHQ was originally developed to evaluate the QOL of patients with mainly adult growth hormone deficiency (18), and the majority of the questions are not related to CDI symptoms.

Therefore, there has been no reliable measure for QOL in CDI patients.

To overcome this limitation in medical treatment in CDI, we attempted to create a simple questionnaire for QOL focusing on symptoms of CDI. In Japan, DDAVP intranasal spray has been used as the mainstay of CDI treatment unlike many countries where DDAVP oral tablets have been widely used (7,11,15). An oral disintegrating tablet (ODT) of DDAVP was very recently approved and its safety and effectiveness has already been reported in management of CDI in our country (7,8,14). Past studies have shown that oral DDAVP improves the QOL of CDI patients more than nasal DDAVP does (8,12,13). We took advantage of the opportunity of our CDI patients switching from nasal DDAVP to oral DDAVP to evaluate our questionnaire.

Materials and Methods

Participants in the study. (Table 1 and Online Resource 1)

Thirty-one patients with CDI who visited our hospital from May 2013 to May 2014 participated in this study. Twenty-five out of 31 CDI patients had already been treated with DDAVP nasal spray. Of these 25 patients, 21 changed to the treatment with oral disintegrating tablets (ODT) of DDAVP, and 4 patients chose to remain with DDAVP nasal spray. The other 6 of the 31 CDI patients had newly developed CDI and were treated from the beginning with ODT of DDAVP. We also included 18 healthy controls without known polydipsic or polyuric disorders. The study was approved by the local ethical committee, and written informed consent was obtained from an each participant prior to enrollment.

Diagnosis and treatment of CDI.

Patients with newly developed CDI were admitted to our hospital and underwent diagnostic testing, including a hypertonic saline infusion test, to make the diagnosis of CDI. Pituitary MRI was also studied to examine the cause of CDI. After completion of the hormonal and imaging work-up, patients were treated with ODT of DDAVP. Patients who wished to switch from nasal DDAVP to ODT of DDAVP were also admitted. The dose and the timing of the ODT of DDAVP were determined by evaluating the urine volume and interval of each

urination. We advised our patients not to take ODT of DDAVP from 30 min before a meal to 2 hours after the meal. We also advised them to have at least 1 hour when the anti-diuretic effect of DDAVP had worn off to avoid electrolyte abnormalities induced by DDAVP.

Evaluation of the QOL of the CDI patients using our questionnaire (Table 2)

To evaluate the QOL (quality of life) of the CDI patients, we made an original questionnaire based on a preliminary study asking CDI patients several questions regarding liquid intake and urination, and limitations of daily life potentially caused by CDI. Our questionnaire consists of 12 questions, 10 of which are directly related to CDI symptoms. Two questions were about the consistency of the effect of DDAVP and patient's satisfaction with DDAVP. To evaluate the QOL of CDI patients semi-quantitatively, each question had 4 graded answers given scores from 1 to 4; the higher the score, better the QOL. The number ahead of each answer corresponds to the score in the question.

All participants were instructed to indicate the most appropriate answer in the questionnaire at enrollment. Two questions about treatment with DDAVP (Q11 and 12) were not used in healthy controls and the patients who had newly developed CDI. The CDI patients who started ODT were re-evaluated 3 months after ODT treatment.

Data analysis

Among CDI patients who switch from nasal to oral DDAVP, three recent assays of serum levels of Na measured over 6 months under nasal DDAVP were obtained in medical charts. After switching, serum levels of Na were measured monthly for three months. The averages of serum Na under each treatment were compared (paired t test). Frequencies of hyponatremia (<135 mEq/L) were compared by Pearson's chi-squared test.

The change of the QOL score from nasal to oral DDAVP was first evaluated using the sign test. When the result was significant ($p<0.05$), we re-assessed data using the Wilcoxon signed-rank test. After eliminating the questions that did not detect a significant change in QOL of CDI patients, we added the scores of the remaining questions and studied the difference in the sum of the scores under nasal spray treatment and ODT treatment (Wilcoxon signed-rank test).

We also studied the difference of QOL among patients who newly developed CDI, CDI patients who were under nasal spray, CDI patients under ODT of DDAVP, and healthy controls. To this end, total QOL scores were obtained after eliminating 3 questions, two about DDAVP treatment (Questions 11 and 12) and one that did not detect QOL change (Question 9), and compared the results using the Steel-Dwass test.

To test the reliability of our questionnaire, internal consistency and reproducibility

were examined. With regard to internal consistency, the homogeneity of the question items was evaluated using Cronbach's α coefficient. The data analyzed were those obtained upon the enrollment of 21 patients with CDI who switched from nasal to oral DDAVP. A coefficient of 0.7 or higher is preferred for a questionnaire to be internally consistent. For reproducibility, the two sets of answers from the patients whose clinical conditions were stable were examined using the Spearman's rank correlation coefficient, which was obtained by two examinations of CDI patients with our questionnaire at the two consecutive hospital visits without changing the dose or schedule regardless of which form of DDAVP they were using (n=14). A coefficient of 0.7 or higher was considered evidence of acceptable test–retest reliability.

In order to explore latent variables, factor analysis was performed using the likelihood method with an oblique rotation to explore factor loading. Data from CDI patients under nasal DDAVP upon enrollment were analyzed (n=25). Correlations among each question were examined unless questions showed high correlation (<0.9). The homogeneity of variances was tested by Bartlett's test. Factor loading >0.4 was considered significant.

In order to study whether the sum of the QOL scores can predict improvement in QOL when changing from nasal to oral DDAVP, we performed receiver operation characteristic analysis.

Statistical analysis was performed using JMP pro 10 (SAS Institute Japan, Inc.).

P<0.05 was considered significant. All data are expressed as means ±SDs, or is otherwise indicated.

Results

Among 25 patients with CDI who were being treated with DDAVP nasal spray, 21 patients switched to ODT of DDAVP (Online Resource 1).

We first evaluated the changes in serum levels of Na and the frequency of hyponatremia in these 21 patients before and after switching from nasal to oral DDAVP. The averages of serum Na were 139.2 ±2.8 mEq/L under nasal DDAVP and 140.4 ±2.3 mEq/L under oral DDAVP ($p<0.01$). The frequency of hyponatremia, defined as serum Na <135 mEq/L, was 21.1% for nasal spray and 13.3% for oral DDAVP ($p=0.26$). Although the difference in the serum levels of Na was statistically significant, there was no clinically relevant influence of serum Na in CDI patients who switched from nasal to oral DDAVP.

We next evaluated changes in the QOL using the questionnaire (Table 2) before and 3 months after patients started treatment of ODT of DDAVP. Using this questionnaire, QOL of CDI patients can be examined easily and quickly, within a few minutes. We compared the scores of each question to identify any change in QOL in these patients. Significant improvement in QOL was seen in 11 out of 12 questions after changing from nasal to oral DDAVP ($p<0.05$ in

sign test and Wilcoxon signed-rank test). Q9 did not detect changes in QOL (Table 3). The sum of QOL scores of 11 questions excluding Q9 was compared before and after switching from nasal DDAVP to oral DDAVP. There was a significant improvement in the sum of QOL scores (Table 3). These results indicated that QOL improved when nasal DDAVP was switched from a nasal to an oral formulation.

We found that the sum of the QOL score excluding Q9 was 34.0 ±6.1 in the four CDI patients who chose to continue nasal DDAVP treatment, and was not significantly different from that obtained from nasal DDAVP treatment in the 21 CDI patients who switched their treatment ($p=0.21$ in Kruskal-Wallis test).

Among the 6 patients with newly developed CDI, there were improvements in QOL scores for each question; however, the difference was not statistically significant (data not shown). To compare the total QOL, the sum of QOL scores of 9 out of 12 questions was analyzed. We excluded Q9 for not detecting QOL improvement upon changing from nasal spray to ODT of DDAVP, and also excluded Q11 and Q12, which untreated CDI patients and healthy controls did not answer. There was a robust increase in total QOL scores from 15.3 ±6.5 to 25.3 ±5.8 when patients with newly developed CDI started treatment of ODT of DDAVP ($n=6$, $p=0.047$ in Wilcoxon signed-rank test).

We also compared QOL scores among patients with newly developed CDI, CDI

patients under nasal DDAVP treatment, CDI patients under oral DDAVP treatment, and healthy controls (Table 4). We observed an increase in the QOL scores for all the questions, and some of these increased showed a statistically significant difference. We found there was no statistical difference in the QOL scores of any questions between CDI patients under oral DDAVP and healthy controls. The total QOL was the sum of QOL scores of 9 out of 12 questions for each group excluding Q9, Q11 and Q12. There was a treatment-dependent increase in the QOL scores (Table 4 and Figure 1) among patients with CDI. It should also be noted that there was no significant difference in the total QOL scores between CDI patients under oral DDAVP and healthy controls.

Having shown that our questionnaire was able to detect changes in QOL in CDI patients, we examined the reliability and consistency of our questionnaire. Internal consistency was studied using data obtained upon the enrollment of 21 patients with CDI who switched from nasal to oral DDAVP. Cronbach's α coefficient ranged from 0.77 to 0.83 for each question (Online Resource 2), indicating acceptable internal consistency ($\alpha>0.7$). Regarding reproducibility, Spearman's rank correlation coefficients were acceptable and >0.7 except for Q7 and Q9 when CDI patients were examined with our questionnaire at two consecutive hospital visits without changing the dose or schedule of DDAVP (N=14) (Online Resource 2).

We performed factor analysis to identify latent factors in patients' response to our

questionnaire. By analyzing the data from CDI patients under nasal DDAVP (N=25), we were able to identify two factors. Since factor 1 was strongly associated with Q6-8, we interpreted factor 1 as concern about polyuric symptoms out of home. Factor 1 was also significantly associated with satisfaction with the CDI treatment (Q12). Factor 2 was associated with Q1-4, and we interpreted it as concern about polydipsic symptoms (Table 5). Factor 2 was not associated with Q12.

We noticed that some CDI patients under treatment with DDAVP nasal spray had comparable QOL scores to healthy controls (Figure 1). Since CDI patients are recommended to introduce oral DDAVP during admission in our country, we examined whether there is a cut-off for QOL improvement when a patient switched from nasal DDAVP to oral DDAVP using receiver operating characteristic curve analysis. The sum of QOL scores from 11 questions excluding Q9 was used to this end. We determined 37 points as the cut-off for not expecting improvement in QOL≥3 points (sensitivity 50% and specificity 99.94%). Similarly, 36 points was the cut-off for ≥4 points improvement (sensitivity 43%, specificity 99.93%) (Online Resource 3).

We also noticed that a few patients under treatment with oral DDAVP have low QOL scores. We looked at their medical charts and found that some were still under optimization of doing and/or scheduling when their QOL scores were evaluated. We found one showed

improvement of QOL score after optimization.

We finally studied whether the clinical parameters of CDI patients under nasal DDAVP treatment (N=21) may have influenced the dosing of oral DDAVP or the QOL score. We found that the dose of nasal DDAVP was significantly larger in patients with longer disease duration of CDI (>10 years) than those with less than 10 years (9.2 ±3.8 vs. 5.6 ±2.4 ug/day, p=0.029 in unpaired t test). However, we were not able to find a difference in the dose of oral DDAVP between patients with >10 years' disease duration and those with less (126.7 ±36.1 vs 105.0 ±27.1 ug/day, p=0.152 in unpaired t test). We were not able to identify any correlation between the disease duration and the total QOL scores before or after change of DDAVP formulas. Similarly, we were not able to detect any correlation of age or sex with the total QOL score obtained before or after change of DDAVP formulations. There was no correlation between the total QOL scores obtained when CDI patients were treated with nasal DDAVP and those obtained when they were with ODT of DDAVP (data not shown).

Discussion

We have created and validated an original self-administered questionnaire, called the Nagasaki Diabetes Insipidus Questionnaire (NADIQ), to evaluate the QOL of CDI patients. We were able to examine the QOL of such patients for the first time using our questionnaire. Using NADIQ, we found a wide distribution of QOL in CDI patients treated with nasal DDAVP. We showed that there was a significant improvement in QOL when nasal DDAVP was switched to the newly approved oral formulation. Similarly, there was a marked increase in QOL when patients with newly developed CDI were treated with ODT of DDAVP. We have also shown that oral DDAVP treatment gave CDI patients a QOL similar to that in healthy controls. We also identified two latent variables influencing the results of our questionnaire.

In our questionnaire, only Q9 did not detect improvement in QOL in CDI patients who switched from nasal to oral DDAVP. This was not due to its inconsistency, but could have been due to its instability. We consider that the inability of Q9 at detecting QOL change was most likely due to the subtle difference in the QOL score. Q9 could have shown improvement in QOL if the answers to Q9 were more appropriate. It could be also possible that a larger urine volume per void may reduce the urinary frequency in patients with inadequately controlled CDI.

We also showed that our questionnaire was able to stratify QOL in patients with CDI depending on the treatment status of CDI; with the lowest QOL for untreated patients, the

highest QOL for those with oral DDAVP treatment, and in-between, for those with nasal DDAVP. The findings were anticipated because the anti-diuretic effect of the intranasal DDAVP is known to be inconsistent (7-9) and also because the oral tablets of DDAVP have been shown to allow better, more consistent absorption (15). This study pointed out two latent variables, namely concern of polyuria out of home and concern of polydipsia, which worry CDI patients under nasal DDAVP in their daily life. We showed that concern about polyuria out of home, but not concern about polydipsia, were associated with their satisfaction with the treatment. Urinary frequency including nocturia was not strongly related to satisfaction with the medical treatment in CDI patients. This finding was unexpected since nocturia is well-recognized to impair QOL (20). In contrast, concern about polyuria out of home might not have received enough attention from physicians. We showed that switching from nasal to oral DDAVP was associated with improvements in QOL scores including Q6-8 related to concern about polyuria out of home. Thus, apparent preference for oral DDAVP over nasal DDAVP (8,12,13) and in Q12 in this study came from not only the consistent pharmacological properties of oral DDAVP (15) but also the relief of concerns about polyuria out of home. Taken together, the NADIQ seemed to uncover some of the problems annoying CDI patients in their daily life.

CDI patients under oral DDAVP seem to have a comparable QOL to that of healthy controls. This could have been due to our questionnaire being not sensitive enough to detect the

QOL impairment still present in patients with CDI under ODT of DDAVP. Some CDI patients mentioned that it was troublesome to avoid food for certain period of time before and after taking ODT of DDAVP to have it work as expected. This would be the apparent disadvantage of ODT of DDAVP. Although such a direction is not present in nasal DDAVP, none of our patients wished to return to nasal DDAVP.

We found that the nasal DDAVP treatment seemed to be satisfactory for some patients with CDI, and also found that our questionnaire was useful to predict whether there would be a benefit for a given CDI patient to switch from nasal DDAVP to ODT of DDAVP. Since it would be safe to introduce ODT of DDAVP during admission, the cut-off would be meaningful for a patient who is considering a switch from nasal DDAVP to ODT of DDAVP to avoid unnecessary admission. In addition, it would be possible to consult specifically with patients with low QOL scores based on the results of our questionnaire, and also possible to improve his/her scores, and most likely their QOL, by adjusting the dose and/or timing of DDAVP. We thus believe our questionnaire will be a useful tool in managing patients with CDI.

There are several limitations of this study which should be noted. The study had a small sample size. Patients requiring anterior pituitary hormone replacement therapy were included, and there is a possibility that these hormone treatments might have influenced the score of the QOL questionnaire. Our questionnaire would not be used on CDI patients without a

sense of thirst. It is also not certain if our questionnaire can be used to differentiate CDI from primary polydipsia. It may be necessary to improve and/or modify our questionnaire to better examine QOL of CDI patients. Since the questionnaire was written in Japanese, we are not certain if a translation would produce the same results. It is also not certain whether the concern about polyuria out of home would be associated with satisfaction with medical treatment in CDI patients in other countries. This might be, at least, a reflection of cultural background.

In conclusion, we have successfully created and validated the questionnaire, NADIQ, as a new measure for QOL in CDI patients. This study uncovered that CDI patients' concern about polyuria out of home was associated with the satisfaction with treatment of CDI. NADIQ appears to be a useful tool to manage CDI patients in evaluating the medical treatment and providing clues to improve communication with CDI patients and improve their treatment.

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Figure Legends.

Fig. 1. Comparison among groups of total QOL assessed by our questionnaire.

Total QOL score (excl.Q9, Q11, Q12) among patients with newly developed untreated CDI, CDI patients with nasal DDAVP, CDI patients with ODT of DDAVP, and healthy controls were compared by Steel-Dwass test. * and ** indicates $p<0.05$ and $p<0.01$, respectively.

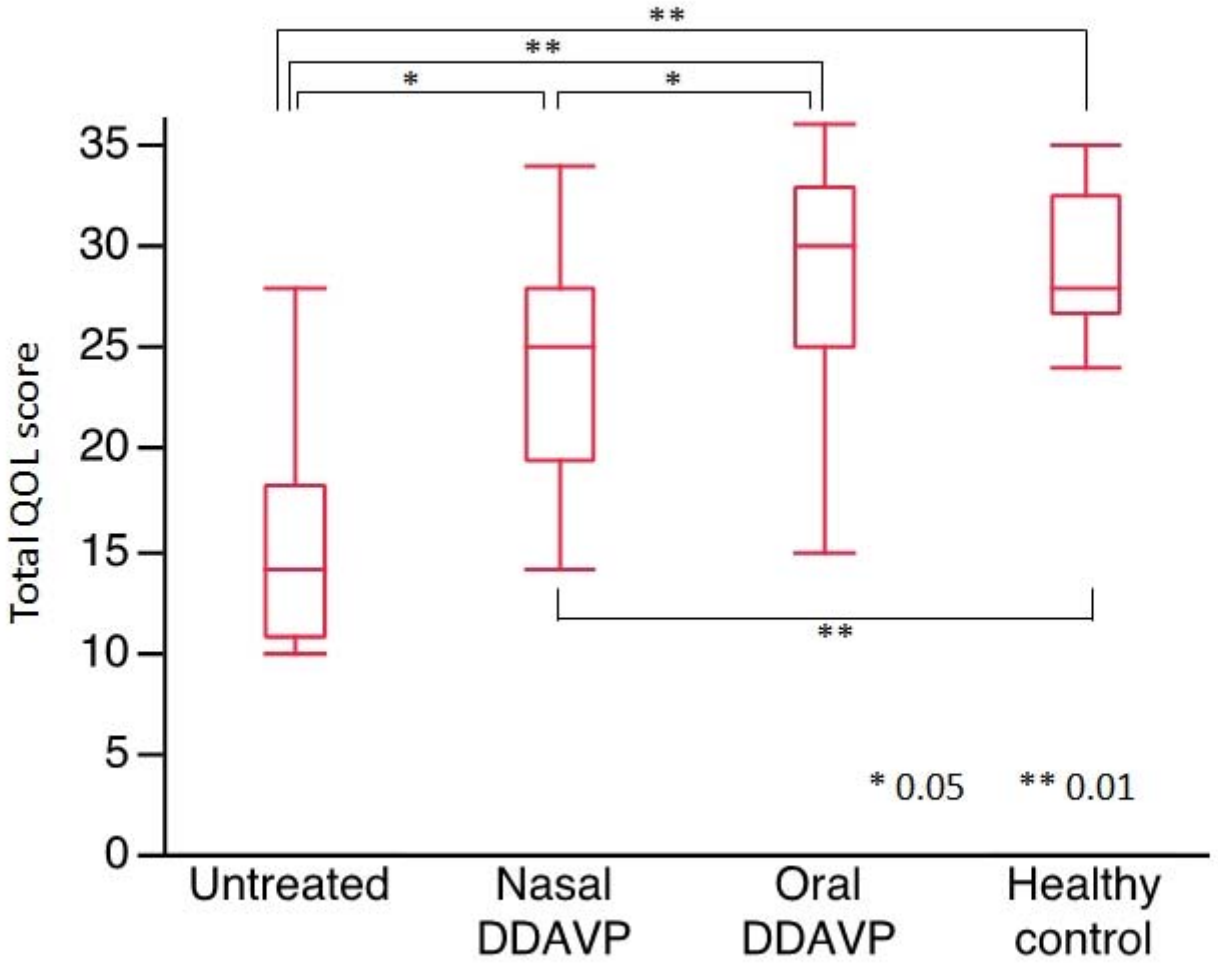

Figure 1. Nozaki et al.

Table 1: Clinical characteristics of the participants.

	Patients with central diabetes insipidus		
	[a]Under nasal treatment	Newly-developed	Control
N	25	6	18
Age (y)	51 ±15.6	61.7 ±19.8	35.4 ±7.8
Females (%)	12 (48.0)	3 (50.0)	6 (33.3)
Disease duration (y)	16 ±13.9	13.5 ±21.5	[b]NA
Etiology			
Familial	0	2 (33.3)	[b]NA
Idiopathic	7(28.0)	1 (16.7)	[b]NA
Secondary			
Brain tumor	6(24.0)	1 (16.7)	[b]NA
Autoimmune	5(20.0)	2 (33.3)	[b]NA
Granulomatous disease	2(8.0)	0	[b]NA
Head trauma and Post-ope	5(20.0)	0	[b]NA
Dose of DDAVP(ug/day)	7.9 ±6.6	[b]NA	[b]NA

[a] under nasal spray of DDAVP. [b] not available.

Table 2: The questionnaire for QOL in patients with central diabetes insipidus (NADIQ: Nagasaki Diabetes Insipidus Questionnaire).

This questionnaire will help us better understand your diabetes insipidus. Please circle the answer that best describes your condition during the PAST MONTH. In this questionnaire, your spontaneous answers are more important.

Q1. I take something to drink with me when going out:
1. Most of the time
2. A lot of the time
3. From time to time
4. Not at all

Q2. I worry if I don't have something to drink on me:
1. Very definitely and quite badly
2. Yes, but not too badly
3. A little, but it doesn't worry me
4. Not at all

Q3. At each meal, I drink:
1. More than 6 cups
2. 4–5 cups
3. 2–3 cups
4. One cup or less

Q4. Not related to meals, I drink:
1. More than 15 cups
2. 10–14 cups
3. 5–9 cups
4. 4 cups or less

Q5. I wake up at night and drink:
1. Most of the time
2. A lot of the time
3. From time to time
4. Not at all

Q6. I am concerned about bathrooms when going out:
1. Very definitely and quite badly
2. Yes, but not too badly
3. A little, but it doesn't worry me
4. Not at all

Q7. I don't want to go out because of my polyuria:
1. Most of the time
2. A lot of the time
3. From time to time
4. Not at all

Q8. I am concerned about polyuria when during transit:
1. Very definitely and quite badly
2. Yes, but not too badly
3. A little, but it doesn't worry me
4. Not at all

Q9. I urinate in the daytime:
1. More than 15 times
2. 10–14 times
3. 5–9 times
4. 4 times or less

Q10. I wake up to urinate at night:
1. More than 3 times
2. 2 times
3. 1 time
4. None

Q11. Desmopressin runs out of its effect earlier than usual:
1. Most of the time
2. A lot of the time
3. From time to time
4. Not at all

Q12. Are you satisfied with current treatment of diabetes insipidus?
1. Not at all
2. A little
3. Yes, but not too much
4. Very definite

The number ahead of each answer corresponds the score in the question to evaluate QOL of CDI patients semi-quantitatively; the higher the score, the better the QOL. Two questions about treatment with DDAVP (Q11 and 12) were not used in the healthy controls and patients with newly developed CDI.

Table 3: QOL score of the each question before and 3 months after patients started treatment of oral disintegrating tablet of DDAVP.

	Score		Difference	
Question	[a]Nasal	[b]Oral	[c]p	[d]p
Q1	2.3 ±1.2	3.1 ±1.0	0.0193	0.0122
Q2	2.2 ±0.9	3.1 ±0.8	0.0017	0.0010
Q3	3.1 ±0.8	3.6 ±0.5	0.0107	0.0088
Q4	2.7 ±1.2	3.3 ±0.9	0.0112	0.0056
Q5	2.9 ±0.9	3.8 ±0.5	0.0005	0.0004
Q6	2.1 ±0.9	2.8 ±0.8	0.0021	0.0012
Q7	3.1 ±0.9	3.6 ±0.5	0.0193	0.0166
Q8	2.0 ±0.9	2.9 ±1.0	0.0001	0.0001
Q9	2.8 ±0.6	2.9 ±0.7	0.2266	[e]ND
Q10	3.2 ±0.7	3.8 ±0.4	0.0020	0.0020
Q11	2.7 ±0.7	3.5 ±0.5	0.0001	0.0001
Q12	2.9 ±0.6	3.4 ±0.6	0.0195	0.0137
[f]Total	29.2 ±5.6	36.8 ±4.5	[e]ND	<0.0001

Data shown are mean ±SD.

[a] and [b] indicate nasal spray and oral disintegrating tablets of DDAVP, respectively.

[c] and [d] indicate the difference analyzed by sign test and Wilcoxon's signed-rank test, respectively.

[e] indicates not done.

[f] indicates the total QOL score obtained by adding the scores of all questions other than Q9.

Table 4: Comparison of QOL scores among patients with newly developed CDI, CDI patients under nasal DDAVP, CDI patients with oral DDAVP, and healthy controls.

Question	Score				p					
	[a]UT (6)	[b]N (25)	[c]O (27)	[d]HC (18)	[a]UT vs. [b]N	[a]UT vs. [c]O	[a]UT vs. [d]HC	[b]N vs. [c]O	[b]N vs. [d]HC	[c]O vs. [d]HC
Q1	1.5 ±1.2	2.4 ±1.3	3.1 ±1.0	2.7 ± 1.3	0.4435	0.0739	0.2390	0.2656	0.8981	0.8023
Q2	1.5 ±1.2	2.4 ±1.0	3.0 ± 0.8	2.9 ± 0.9	0.1787	**0.0389**	0.0688	0.1487	0.3833	0.9947
Q3	2.3 ±1.2	3.2 ±0.8	3.6 ± 0.5	3.2 ± 0.7	0.3064	0.0538	0.3056	0.3133	0.9999	0.3925
Q4	1.5 ±0.8	2.8 ±1.1	3.1 ± 0.9	3.2 ± 0.8	0.0670	**0.0118**	**0.0117**	0.7844	0.7401	0.9988
Q5	1.5 ±0.5	2.9 ±0.8	3.7 ± 0.5	3.6 ± 0.5	**0.0060**	**0.0002**	**0.0008**	**0.0007**	**0.0150**	0.8587
Q6	1.3 ±0.8	2.2 ±0.9	2.7 ± 0.8	3.1 ± 0.9	0.2291	**0.0193**	**0.0196**	0.1865	**0.0193**	0.3956
Q7	3.0 ±0.9	3.2 ±0.8	3.4 ± 0.7	3.9 ± 0.3	0.9574	0.5818	**0.0285**	0.6863	**0.0121**	0.0520
Q8	1.5 ±0.8	2.1 ±0.9	2.8 ± 1.0	3.3 ± 0.9	0.4984	0.0506	**0.0109**	0.0646	**0.0010**	0.1966

Q9	1.8 ±1.0	2.8 ±0.6	2.9 ± 0.6	3.2 ± 0.5	0.0932	0.0518	**0.0181**	0.9492	0.2277	0.4662
Q10	1.2 ±0.4	3.2 ±0.6	3.6 ± 0.8	3.6 ±0.6	**0.0006**	**0.0004**	**0.0008**	0.0937	0.1436	0.9998
Q11	[e]ND	2.7 ±0.7	3.3 ± 0.7	[e]ND	[e]ND	[e]ND	[e]ND	**0.0012**	[e]ND	[e]ND
Q12	[e]ND	2.9 ±0.7	3.4 ± 0.6	[e]ND	[e]ND	[e]ND	[e]ND	**0.0082**	[e]ND	[e]ND
[f]Total	15.3 ± 6.5	24.4 ±5.2	28.9 ± 4.9	29.5 ± 3.6	**0.0370**	**0.0059**	**0.0137**	**0.0140**	**0.0085**	0.9996

[a,b,c] and [d] indicate patients with untreated CDI (=newly developed CDI), CDI patients under nasal DDAVP treatment, CDI patients under oral DDAVP treatment, and healthy controls, respectively. Numbers in the brackets indicate the number of the individuals studied. [e] indicates not done. [f] indicates the total QOL score obtained by adding the score of all questions other than Q9, Q11, and Q12.

Statistical difference was determined by Steel-Dwass in Q1 to Q10 and Wilcoxon/Kruskal-Wallis in Q11 and Q12. $P<0.05$ is shown bold.

Table 5: Factor analysis of our questionnaire.

Question	Loading factor 1	2
Q1: I take something to drink with me when going out…	0.26	**0.79**
Q2: I worry if I don't have something to drink on me…	**0.40**	**0.73**
Q3: At each meal, I drink….	0.01	**0.53**
Q4: Not related to meals, I drink…	0.05	**0.61**
Q5: I wake up at night and drink…	0.14	-0.10
Q6: I am concerned about bathrooms when going out…	**0.77**	0.26
Q7: I don't want to go out because of my polyuria…	**0.72**	0.04
Q8: I am concerned about polyuria when during transit…	**0.89**	0.12
Q9: I urinate in the daytime…	0.38	**0.49**
Q10: I wake up to urinate at night…	0.23	-0.34
Q11: Desmopressin runs out of its effect earlier than usual…	0.17	0.06
Q12: Are you satisfied with current treatment of diabetes insipidus?	**0.59**	-0.01

Data from CDI patients under nasal DDAVP were analyzed (n=25). The start of each question is provided for ease of understanding. Correlations among questions were <0.9. Maximum likelihood method with oblique factor rotation was used to explore factor loading. Factor loading >0.4 is considered significant and shown in bold. P<0.0001 in Bartlett's test indicates homogeneity of variances. We determined that Q2 was under influence of factor 2 since the factor loading was larger in factor 2 than in factor 1.