Transsphenoidal surgery for pituitary tumours: frequency and predictors of delayed hyponatraemia and their relationship to early readmission

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Abstract

Objective: A major cause of readmission after transsphenoidal surgery (TSS) is delayed hyponatraemia. The purpose of this study was to identify predictors of hyponatraemia one week post surgery and predictors of 30-day readmissions for hyponatraemia.

Design: A retrospective cohort study including patients who had TSS performed for pituitary lesions.

Method: The risk of readmission for hyponatraemia was assessed in consecutive patients between January 2008 and March 2016. The risk of hyponatraemia one week post surgery was assessed in patients admitted for TSS between July 2011 and March 2016.

Results: Of all included patients, 56/522 (10.7%) were readmitted within 30 days. Hyponatraemia was found in 14/56 (25%) of 30-day readmissions. We did not identify any predictive variable for hyponatraemia on readmission. The number of patients with hyponatraemia on the seventh post-operative day was 26/314 (8.3%). The risk of hyponatraemia one week post surgery was increased by an odds ratio of 2.40 (95% CI: 1.06–5.40) in patients with a tumour abutting the optic chiasm and by an odds ratio of 1.16 (1.04–1.31) per mmol/L decrease in sodium levels on the first post-operative day.

Conclusions: Hyponatraemia occurred in 25% of readmissions; however, we did not identify any predictive variable for readmission with hyponatraemia. One week post surgery, 8.9% had hyponatraemia. Tumours pressing on the optic chiasm as well as a fall in sodium levels on the first post-operative day were associated with an increased risk of hyponatraemia one week post surgery. We suggest that a day 7 serum sodium <130 nmol/L should lead to concern and the provision of patient advice.

Introduction

A common complication of transsphenoidal surgery (TSS) for pituitary adenomas is a disturbance in water and electrolyte balance with hyponatraemia reported as one of the most frequent post-operative complications and reasons for readmission (1, 2, 3). A systematic review, including 2974 patients from 10 case series, found that the frequency of reported delayed hyponatraemia ranged from 3.6% to 19.8% (1). In a large study extracting 1240 cases from the American College of Surgeons NSQIP database, the 30-day readmission rate was 8.9%, and
29.5% of these were due to hyponatraemia (2). However, almost all recent publications on water and electrolyte disturbances after TSS have been retrospective, and only a few prospective studies have been carried out (4, 5, 6). The prospective study by Kristof and coworkers (4) followed 57 consecutive cases daily for fourteen days after TSS and found isolated hyponatraemia in 21%, similar to the 20.6% found in the study by Olson and coworkers (6). Conversely, post-operative diabetes insipidus (DI) was found in 38.5% by Kristof and coworkers (4), compared to 17% by Olson and colleagues (5). Mechanisms underlying water and electrolyte disturbance post TSS include trauma or handling of the neurohypophysis, with the steep increase in antidiuretic hormone (ADH, vasopressin) levels on the first post-operative day (POD) believed to explain the observed hyponatraemia on day 1 (5).

Frequent readmission for hyponatraemia has prompted investigation into predictors of such occurrences: one systematic review concluded that age, gender, tumour size, rate of decline in sodium and Cushing's disease were all potential predictors of delayed hyponatraemia (1). If there are easily identifiable risk factors for developing significant post-TSS hyponatraemia, readmission may be avoidable.

The purpose of the present study was to seek to identify predictors of readmission for hyponatraemia and predictors of hyponatraemia on POD 7 and describe post-TSS sodium abnormalities from a single centre with a standardised protocol.

Methods

Design

This was a retrospective study of all patients admitted for TSS at the John Radcliffe hospital from January 1st 2008 to March 1st 2016. Using electronic patient records, we accessed all available information on blood samples, surgical procedures and endocrine review before and after surgery. The study was registered as an audit with the Oxford University Hospitals Audit Department, and all data were anonymised.

Patient cohorts

Readmission for hyponatraemia was assessed using Cohort 1, consisting of patients who had TSS within the given period. A subset of Cohort 1 was included in Cohort 2: from July 2011 it was standard procedure to perform a serum sodium assessment one week post surgery (POD 7), and all patients admitted for TSS after this date were included in Cohort 2. We excluded patients with hyponatraemia pre-surgery, while for patients who had surgery conducted more than once, we only included the most recent admission in both cohorts.

Transsphenoidal surgery procedure

Standard procedure for TSS was a routine biochemical evaluation prior to surgery including renal function, electrolytes and liver function, at a pre-surgery assessment or on the surgical ward. Patients were admitted to the surgical ward the day before or the day of surgery. After TSS, all patients were placed on a 2-L fluid restriction. Apart from patients with DI, patients were encouraged to continue fluid restriction after discharge. All patients were given a daily dose of 20 mg hydrocortisone per day in divided doses until assessment of sodium levels and full pituitary function at 6 weeks post surgery. Patients with Cushing’s disease were initially treated with 20 mg hydrocortisone three times per day.

Outcomes

Readmission was identified in the electronic patient record. The reasons for readmission were recorded allowing more than one cause of readmission, e.g., headache as well as hyponatraemia. Hyponatraemia was defined as serum sodium levels below 130 mmol/L, and hypernatremia was defined as a sodium level >150 mmol/L. Sodium levels assessed at day 6, 7 or 8 were included as sodium levels at POD 7. If sodium was assessed on more than one of these days, the result was prioritised in the following order: POD 7 > POD 6 > POD 8. The presence or absence of tumour in contact with the optic chiasm was based on most recent pre-operative MRI.

Statistics

We used binary logistic regression to identify predictors of readmission and predictors of hyponatraemia one week post surgery, initially in a univariate regression analysis secondarily adjusted for gender and age. It was planned to include all significant predictors in a multivariate regression model using backwards stepwise regression. All analyses were conducted using IBM SPSS, version 23.0. Two-sided P values <0.05 were considered significant.
Results

From January 1, 2008, to March 1, 2016, 569 TSS procedures were performed at the John Radcliffe Hospital in Oxford, UK; for 43 individuals who had more than one TSS procedure performed during this period, only the most recent entry was included in the analysis. Four individuals with hyponatraemia prior to surgery were excluded (none of these required readmission), leaving 522 individuals in Cohort 1. Between July 1, 2011, and March 1, 2016, 332 TSS procedures were performed in 314 individuals constituting Cohort 2, a subset of Cohort 2. None of these individuals in Cohort 2 had hyponatraemia prior to surgery. In Cohort 1, approximately half of the patients were women (262/522 (50.2%)) and the mean age was 52 (s.d. 16) years. The most common type of tumour was a non-functioning pituitary tumour in 198/522 (37.9%), while 204/522 (39.1%) had tumours abutting the optic chiasm. The primary pituitary surgeon (SC) conducted 496/522 (95%) of these procedures. As shown in Table 1, there were no major discrepancies in demographic background or other variables between Cohort 1 and Cohort 2.

Table 1 Baseline characteristics. Data are presented as n (%).

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (n=522)</th>
<th>Cohort 2 (n=314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.)</td>
<td>52.0 (16.5)</td>
<td>53.1 (16.7)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>262 (50.2)</td>
<td>161 (51.3)</td>
</tr>
<tr>
<td>Surgeon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary surgeon</td>
<td>496 (95.0)</td>
<td>304 (96.8)</td>
</tr>
<tr>
<td>Trainee surgeon</td>
<td>26 (5.0)</td>
<td>10 (3.2)</td>
</tr>
<tr>
<td>Tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroadenoma</td>
<td>200 (38.3)</td>
<td>129 (41.1)</td>
</tr>
<tr>
<td>Paracellar</td>
<td>77 (14.8)</td>
<td>33 (10.5)</td>
</tr>
<tr>
<td>Chiasma pressure</td>
<td>204 (39.1)</td>
<td>119 (37.9)</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-functioning</td>
<td>198 (37.9)</td>
<td>128 (40.8)</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>78 (14.9)</td>
<td>39 (12.4)</td>
</tr>
<tr>
<td>Cushing’s disease</td>
<td>41 (7.9)</td>
<td>23 (4.4)</td>
</tr>
<tr>
<td>Craniohypophyngioma</td>
<td>32 (6.1)</td>
<td>20 (6.4)</td>
</tr>
<tr>
<td>Rathke cleft cyst</td>
<td>28 (5.4)</td>
<td>19 (6.1)</td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>21 (4.0)</td>
<td>14 (4.5)</td>
</tr>
<tr>
<td>Meningioma</td>
<td>12 (2.3)</td>
<td>10 (3.2)</td>
</tr>
<tr>
<td>Other</td>
<td>112 (21.5)</td>
<td>61 (19.4)</td>
</tr>
<tr>
<td>Previous pituitary surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>73 (14.0)</td>
<td>49 (15.6)</td>
</tr>
</tbody>
</table>

Readmission with hyponatraemia

After TSS, 58/522 (11.1%) patients were readmitted within 30 days from the surgical procedure, with hyponatraemia responsible for 14/58 (24.1%) of readmissions (Table 2). Other causes are shown in Table 2. As shown in Fig. 1, readmissions with hyponatraemia were centred between days 7 and 10 and no one was readmitted after day 10 with hyponatraemia. The mean serum sodium level at readmission was 122 mmol/L (s.d. 5.7). None of our explanatory variables was associated with readmission (Table 3).

As described previously, routine assessment of serum sodium level at day 7 post-op was introduced as a standard protocol from July 2011. In the period prior to July 2011, 5/208 (2.4%) patients were readmitted with hyponatraemia compared to 9/314 (2.7%) patients readmitted from the period between July 2011 and March 2016 ($P=0.75$). A similar proportion was seen in the small number of craniopharyngiomas (data not shown).

Hyponatraemia 1 week post surgery

To assess the number of patients with hyponatraemia one week after surgery, we used Cohort 2, consisting of 314 patients.
individuals. The number of patients with hyponatraemia at POD 1, POD2 and POD 7 was 4/314 (1.3%), 2/314 (0.6%) and 26/314 (8.3%). As illustrated in Fig. 2, patients who developed hyponatraemia at POD 7 had similar sodium levels pre-operatively, but significantly lower levels at POD 1 and POD 2 and borderline different sodium levels 6 weeks post surgery. Furthermore, the serum osmolality appears to follow the same pattern as sodium levels in the two groups (Fig. 2).

The odds ratio for hyponatraemia was 2.40 (95% CI: 1.06–5.40) in patients with a tumour abutting the optic chiasm. Also, each decrease in sodium levels from pre-surgery to the first POD, the risk of hyponatraemia increased on day 7 by 16%.

In the current study, the frequency of readmission within 30 days was 11%, and hyponatraemia was responsible for readmission in 14 of 58 cases, accounting for 24% of readmissions. In the survey of 1200 TSS procedures in the US, they found that 8.5% were readmitted (2), whereas Bohl and coworkers found that 8.9% were readmitted within 30 days (3). In the US Study,

### Discussion

None of the variables included in this study predicted readmission for hyponatraemia, although a tumour pressing on the chiasm was associated with a 2- to 3-fold increase in the risk of hyponatraemia on day 7. Also, for each mmol/L decrease in sodium levels from pre-surgery to the first POD, the risk of hyponatraemia increased on day 7 by 16%.

Post hoc, we assessed the risk of readmission for patients with hyponatraemia at POD 7 in Cohort 2. Of the 26 patients identified with hyponatraemia at POD 7, 8 of the patients were admitted. As shown in Supplementary Table 1 (see section on supplementary data given at the end of this article), neither sodium levels nor any of the other variables explained why these specific patients were readmitted. In addition, we also examined predictors for sodium levels below 135 mmol/L at POD 7, and as illustrated in Supplementary Table 2, the risk of hyponatraemia using this definition was increased in patients with a tumour abutting the chiasm as well as in patients having received desmopressin.

### Hypernatraemia

As shown in Supplementary Fig. 1, the highest frequency of hypernatraemia was found on the first day after surgery, with 5/314 (1.6%) showing a serum sodium level above 150 mmol/L.

### Figure 2

Mean sodium levels and mean plasma osmolality after transsphenoidal surgery stratified by normal sodium (n=288) or low sodium (n=26) levels at the 7th post-operative day (POD). A full colour version of this figure is available at http://dx.doi.org/10.1530/EJE-17-0879.
hyponatraemia accounted for 29.5% of all readmissions compared to 55% in the study by Bohl and coworkers. (2,3). Thus, overall, 30-day readmission after TSS is around 8–11%, and hyponatraemia is present in 24% to 55% of these readmissions. In line with previous studies (7,8), we were not able to identify specific characteristics associated with an increased risk of readmission. As reviewed by Bohl and coworkers (9), most suggested risk factors fail to be reproduced in other studies, and thus, solid risk factors predicting readmission for hyponatraemia remain to be identified. Five of the 14 readmitted patients were reported to have symptoms such as headache, seizure and vomiting, suggesting that readmission for hyponatraemia is a combination of sodium levels, symptoms and other yet unidentified factors.

On the 7th POD, 8.3% of patients had hyponatraemia (plasma sodium <130mmol/L). Of studies continuously assessing sodium levels up till 10 days after the operation, Hensen and coworkers (10) reported that 8.4% of patients at some point had sodium levels below 132 mmol/L, while Olsen et al. (6) found that 23% of patients operated for ACTH-producing adenomas developed sodium levels below 135 and 7.7% below declined to levels below 125mmol/L. The same group later replicated these data in a larger study finding that 23% developed sodium levels below 135 mmol/L and 7.6% below 125 mmol/L (5). In line with our own findings, Hussain and coworkers (11) found that 7.6% had sodium levels below 130 mmol/L at POD 7, whereas others report that 23% had sodium levels below 134 mmol/L at POD 7 (12). In congruence with the current study, Hensen and coworkers reported an initial sodium nadir on POD 1 affecting 2.7% of patients, providing the s-curve of sodium levels with a nadir on POD1 and POD7 after transsphenoidal surgery. Interestingly, we found that patients with hyponatraemia had not recovered their sodium levels even after 6 weeks, suggesting a long recovery period. Overall, our data show that patients with hyponatraemia after TSS exhibit a characteristic pattern with two nadirs, with a frequency of hyponatraemia at POD 1 likely to be 1–2% at POD 1 and 7–8% on POD 7, with persistent hyponatraemia up to 6 weeks after surgery. Analysing readmissions among those with hyponatraemia at POD 7 did not suggest that sodium levels could predict readmission.

In the current study, we identified two factors associated with hyponatraemia on POD7: a pituitary tumour pressing on the chiasm as well as a reduction in sodium levels on POD1. One previous study found that large tumours predicted hyponatraemia (13), whereas the predictive value of a rapid decline in sodium levels on POD1 has not been confirmed in larger studies. In support of the association between tumour size and risk of hyponatraemia, we found a near-significant association between macroadenomas and the risk of sodium levels below 135 mmol/L in a post hoc analysis, which may suggest a power problem in the current study. The association between the anatomical position of the tumour and the risk of hyponatraemia has not been investigated in other studies, but one could speculate that a close association of the tumour to the chiasm would cause a higher risk of pressure/damage to the stalk during surgery compared to tumours with a more caudal position. The hypothesised stalk damage might result in a reduced ability to secrete vasopressin, as observed as early as 1 day in a sub-group of patients. This neuronal damage might explain the association between early (POD 1) and late (POD 7) hyponatraemia and the late (POD 42) return to pre-surgery levels.

A number of predictors for delayed hyponatraemia have been proposed: female gender (10,12), Cushing’s...
disease (10), body mass index (11) and age (13); however, replication of these predictors is inconsistent or lacking. Despite the number of studies, solid predictors for the development of delayed hyponatraemia after transsphenoidal surgery remain elusive.

The most common response to transsphenoidal surgery is DI, which is observed in approximately 40% of patients; total hypophysectomy in animals and humans leads to immediately low vasopressin levels followed by a phase of vasopressin release from degenerating magnocellular neurons and then followed by low vasopressin levels. This would explain the triphasic response with initial polyuria followed by a period of hyponatraemia ending with sustained polyuria. However, in one study of 1541 patients, 34% of patients developed DI but only 1.1% of patients followed the triphasic pattern (10). The authors proposed a similar hypothesis as presented above, with a secretional arrest of vasopressin due to damage to the magnocellular osmoregulatory system followed by degeneration and vasopressin release around POD 7 and subsequent return to normal water and electrolyte adjustment around POD 14. This certainly would account for a number of the observed findings. Most authors thus consider the observed hyponatraemia at POD 7 to be a result of inappropriate vasopressin release, and it is therefore surprising that the two studies having assessed vasopressin levels after TSS both found that vasopressin levels at POD 6–9 did not differ between patients with hyponatraemia and normonnaemia, but the accuracy of vasopressin assays is far from perfect and their sensitivity generally poor (4, 5). Vasopressin is technically challenging to measure and the above findings of vasopressin levels could be biased in one or the other direction (14). In line with the current study, Kristoff and coworkers (4) found that patients with hyponatraemia at POD 7 had low plasma osmolality suggesting an inappropriate secretion of vasopressin in this patient group, i.e. SIADH, compared to patients with normal sodium levels at POD 7. Other natriuretic agents could explain the natriuresis but ADH/vasopressin is currently the most likely agent to cause increased plasma osmolality.

There are a number of limitations to this study: firstly, this is a retrospective study using electronic patient records from clinical settings not designed with this study in mind. Secondly, despite a rather large cohort, the number of events is few, providing estimates with large confidence intervals and adding to the risk of type 2 errors. While the assessment of sodium levels after TSS appears relatively simple, differences in study procedures such as timing of measurements, handling of hyponatraemia and selection of risk variables makes comparison of studies particularly challenging. Also, the current patient population were subjected to a 2-L fluid restriction, which may have reduced the number of patients with hyponatraemia, thereby limiting the external validity of our results to centres with a similar practice.

Several major issues remain, including understanding the pathophysiology of hyponatraemia, identifying risk factors for hyponatraemia/readmission, and clinical guidelines to prevent symptomatic hyponatraemia. Further studies introducing new biomarkers such as copeptin and natriuretic peptides may provide novel insight into the pathophysiology of water and electrolyte disturbances after TSS. Future identification of risk factors for hyponatraemia/readmission should include assessment of patients’ co-morbidities and symptoms, preferably in multi-centre studies. In this study, patients in the last part of the inclusion period were systematically assessed at POD 7 with the aim of identifying patients with hyponatraemia and to provide instructions and care to prevent readmission. Readmission for hyponatraemia can, to some extent, be predicted by the POD 7 serum sodium, and we believe it would be wise to use this level to consider the risk of readmission. In a study by Bohl and coworkers (9), they tested a strategy to prevent readmissions from hyponatraemia: sodium assessment was conducted between PODs 5 and 8, and patients were treated according to a pre-specified strategy, e.g. water restriction. This strategy identified more patients with hyponatraemia, but they were unable to prevent readmissions due to hyponatraemia. This is comparable to the current study: comparing the risk of readmissions from hyponatraemia before and after the introduction of standard sodium assessment in July 2011, we found no statistical difference in outcomes from these strategems (data not shown). It is important to recognise that all patients do not respond equally to low sodium levels, and therefore, it may be of value to assess not only sodium levels but also symptoms. Timing appears to be important, and in the current study, readmissions from hyponatraemia were between POD 4 and POD 11, suggesting that an assessment at POD 7 is too late in some cases. Therefore, it may be beneficial with clinical assessment already at POD 4 in selected groups. Potentially this could be daily telephone assessment at POD 4 combined with pragmatic advice for patients with sodium <130 mmol/L to restrict fluid intake and have sodium checks accordingly, which may reduce the risk of readmission.
Conclusions

We found that after TSS, 2.7% of all patients were readmitted within 30 days with hyponatraemia, and all readmissions with hyponatraemia were between the 4th and the 10th PODs. No specific risk factors were identified after surgery. One week after TSS, 8.3% developed hyponatraemia, which lasted 6 weeks post surgery. A tumour pressing on the chiasm or a decline in sodium levels at POD 1 were associated with hyponatraemia at POD 7. However, assessment of serum sodium levels 5–7 days after surgery may alert the clinician to hyponatraemia and allow for advice regarding fluid restriction. It remains to be seen if this procedure will in the future decrease such re-admissions.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-17-0879.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement
J K, S C and A G contributed to the study conception and design. J K collected data, performed the analysis and drafted the manuscript. All authors contributed to the interpretation of results, all revised the manuscript critically for important intellectual content and all approved the final manuscript. J K is the guarantor.

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