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Prognostic factors for impaired plasma sodium homeostasis after transsphenoidal surgery

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ABSTRACT

Objective: Surgical manipulation of the pituitary stalk, neurohypophysis or the hypothalamus may disturb control of the plasma sodium level. The factors that might predict the risk of postoperative sodium imbalance are not clear, and were investigated in this study.

Methods: A retrospective survey of 129 surgical records for the occurrence of plasma sodium levels outside the normal range, following transphenoidal procedures. Median patient age was 49 (range 20-78) years, 65 female. 73 of the operated lesions were non functioning pituitary adenomas. Patients were considered to have impaired plasma sodium balance if the range of 135-145 mmol/L was not maintained.

Results: Of all 129 surgical cases, 68 (53%) experienced an imbalance in sodium levels. Severe sodium imbalance (≥149 or ≤ 131 mmol/L) was observed in 28 patients (22%). 13 showed hypernatraemia (median day 1), and 15 hyponatraemia (median day 6). Tumour size was associated with an increased incidence of sodium imbalance, particularly in patients younger than 49 years; surgery resulted in sodium imbalance in 38% of young patients operated on for tumours < 22 mm and in 76% of young patients, operated on for tumours ≥ 22 mm. Overall, tumour size increased with patients' age, and tumour size was less predictive for sodium disturbances in elderly patients. Median time in hospital was 5 days for patients without sodium imbalance, 6 days for patients with hypernatraemia and 11 days for patients with hyponatraemia.

Conclusions: Following pituitary surgery, patients with large tumours, in particular those of young age, are at higher risk for loosing control of their plasma sodium level. Increased ADH secretion (hyponatraemia), but not transient diabetes insipidus was associated with a prolonged hospital stay. Postoperative follow-up of patients with sellar tumours should include careful monitoring of plasma sodium levels within the first two postoperative weeks and clear patients' instructions.

1. INTRODUCTION

The sella turcica lays in close proximity to several important anatomical structures including the optic chiasm, the internal carotid arteries and the pituitary gland, which is connected to the hypothalamus.. Sellar tumours cause symptoms through volume expansion, compression or infiltration of the surrounding anatomical structures, or excessive or deficient hormonal secretion (1). Disturbance of the posterior pituitary gland interferes with antidiuretic hormone (ADH) secretion, resulting in central diabetes insipidus (DI) or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (2-4). Following transphenoidal surgery DI and SIADH may cause morbidity due to fluid and electrolyte imbalance and in particular disturbance of sodium homeostasis(5-17). While most changes are mild, symptoms can occur if the serum sodium level falls below 130 mmol/L or above 149 mmol/L. The condition is transient in the majority of cases, although the incidence of prolonged or permanent DI, as a result of a more central injury of the pituitary-hypothalamic region, has been reported to range from 1.6 to 31% (4, 6, 12, 18, 19).

In case of insufficient ADH secretion, high quantities of dilute urine can be lost and the serum sodium level and plasma osmolality may rise leading to the need for water replacement. In case of inappropriate or uncontrolled ADH release (not stimulated by increased plasma osmolality or hypovolemia; but triggered by brain signals or caused by neuronal damage), serum sodium usually drops unless water supply is markedly restricted (5).. Symptoms of sodium imbalance include dizziness, headaches, paraesthesias, nausea, vomiting and lethargy, but can progress to altered mental status and seizures if severe hyponatraemia or hypernatraemia occur (3). SIADH may occur after surgical manipulation of the pituitary stalk, neurohypophysis or the hypothalamus (3, 4, 18, 20).

Previous searches for predictors of central DI did not reveal a correlation between DI and tumour size (3, 5, 21). Some studies have reported a tendency for a higher rate of

DI in connection of microadenomas after endoscopic transnasal resection of pituitary lesions (2, 4, 21, 22) due to more extensive exploration of the sella, whilst other studies show a correlation of an increase of DI incidence with macroadenomas (1, 4, 9, 12, 21). No correlation has been found between DI and tumour size (3, 5, 21). Findings differ with respect to the patient's age; although Hans et al. describe old age as risk factor for hyponatraemia (23), while Nomikos et al. found no correlation between age and recovery of the pituitary function after surgery (1); similarly in respect of gender: Zada et al. detected females to have a higher risk to develop postoperative hyponatraemia (3), while Sigounas et al. as well as Hensen et al. found no impact of sex on the incidence of postoperative DI or hyponatraemia (4, 5)

The purpose of this study was therefore to assess whether prognostic factors could be identified pre-operatively. These included tumour size, patients' age, gender, and anatomical criteria in preoperative images.

2. METHODS

2.1 Group of surgical cases included

137 patients (68 males, 69 females) who had undergone transsphenoidal microsurgery on pituitary tumours in the Department of Neurosurgery at the University Hospital of Zurich between January 2000 and December 2004 were analysed. All operations were performed by a single surgeon (R.L.B.). Fourteen patients were excluded because of missing data. Some (of the remaining 123) patients underwent transsphenoidal surgery more than once during the study period; four patients (1 male, 3 females) underwent transsphenoidal surgery twice after developing a relapse and one male patient underwent transsphenoidal surgery three times because of recurrent haemorrhage due to persisting adenoma. This resulted in a total of 129 surgical events (64 male, 65 female),. The age at surgery of the patients ranged 20 to 78 years (median 49 years). For analysis two age groups were created above and below this median point,

Of the total 129 operated sellar lesions, 105 were primary lesions, 24 were recurrences.

Postoperative histological analysis revealed that the patients presented a large spectrum of sellar tumours, such as non functioning adenomas (n=73, 56.6%), GH-secreting adenomas (n=21, 16.3%), prolactinomas (n=17, 13.2%), ACTH producing adenomas (n=3, 2.3%), Rathke cleft cysts (n=7, 5.4%) and others (n=8, 6.2%).

2.2 Analysis of sellar tumour size on preoperative MRI

The preoperative MRI of the sellar region was acquired through T1-weighted sequences with and without gadolinium enhancement, as well as T2-weighted sequences. The largest diameter of the tumour measured in the coronal or sagittal plane was used in subsequent analysis as tumour size.

2.3 Peri-operative Management and surgical procedure

To cover the increased glucocorticoid requirement during and following surgery, steroids were given peri-operatively to all patients with potentially diminished ACTH secretion reserve and eventual adrenal insufficiency (Solucortef 300mg on the day of surgery, 200mg first postoperative day, 100mg on the second postoperative day and 37.5mg Cortisone on the third day). Surgical extirpation was performed using the unilateral endonasal-transsphenoidal approach.

2.4 Postoperative treatment

Electrolyte levels and metabolic panels were measured daily until the patient left the hospital (range 3 - 33 days, median 6 days). Patients in this study were considered to have serum sodium imbalance if the narrow range of 135-145 mmol/L was not maintained. If electrolyte imbalance became apparent, monitoring was increased to twice or 3 times a day, based on results. Urine output and fluid intake was measured closely in all cases for the first 24 hours. This time period was extended up to several days depending on the results.. In case of increased urine output (>4 L/24h), urine analysis and urine specific gravity were determined and electrolyte monitoring was intensified. The close monitoring was motivated by the fact that, due to the potential biphasic or triphasic responses of sodium imbalance, a primary mild imbalance does not exclude the possibility of a severe imbalance in the postoperative course.

Follow-up endocrinological controls were performed 4-12 weeks after surgery. Three months after surgery, an MRI examination of the sellar region was carried out.

2.5 Data presentation and statistics

Data presentation and statistical analysis was performed using Matlab (The Mathworks, Natick, MA, USA). A two-tailed probability value of the fraction of patients on a binomial distribution with a probability threshold at 0.05 was used to establish significant differences. All incidences are given in percent [%] with the borders of the 95% confidence interval, either in the text or as error bars in the plots. The equality of medians of two distributions was tested with the non-parametric Wilcoxon rank sum test. For nominal variables, statistical analysis was performed with SPSS 17.

3. RESULTS

3.1 Incidence, type and timing of serum sodium imbalance

A total of 68 (53% [44 62]%) patients suffered from sodium imbalance (Figure 1 a). 34 of 65 women (52%), and 34 of 64 men (53%) had sodium concentrations outside the norm; 45 (35%) developed hypernatraemia (Na >145 mmol/L) with peak sodium levels at a median of 2 days (mean 2.3 days) following surgery (Figure 1 b), and 23 patients (18%) developed hyponatraemia (Na <135 mmol/L) with nadir sodium levels at a median of 6 days (mean 6.4 days) postoperative (Figure 1 c). Out of these 68 patients, 13 developed a second episode of sodium imbalance: 10 of 13 (77%) became hyponatremic after initial hypernatraemia and two hypernatremic after hyponatraemia (Figure 1 a). A severe sodium imbalance (≥149 or ≤ 131 mmol/L) was observed in 28 patients (22%). Among them 13 (10%) showed hypernatraemia (149-153 mmol/L) on median day 1 (mean 1.7), and 15 (12%) hyponatraemia (115-130 mmol/L) on median day 6 (mean 6.7). The median time in hospital was 5 (range 2-13) days for the 61 patients without sodium imbalance, 6 (range 3-14) days for the 45 patients with hypernatraemia, and 11 (range 3-33) days for the 23 patients with hyponatraemia. If hyponatraemia as well as hypernatraemia occurred in the postoperative time period, the most extreme excursion entered the subsequent analysis.

3.2 Incidence of sodium imbalance vs. tumour size

Figure 2 a shows the extreme sodium level as a function of maximal tumour diameter. The distribution of tumour size does not differ significantly from the normal distribution (Lilliefors test) and the median tumour size was 24 mm for our patient population (Figure 2 b).

To investigate the effect of tumour size, the fraction of patients showing an imbalance was computed for five groups of tumour sizes (Figure 2 c). Whereas less than 50% of the patients experienced an imbalance in the quintiles of small tumour sizes, more than 50% of the patients experienced an imbalance in the quintiles of large tumour sizes. In an exploratory analysis we then determined a tumour size where the difference between a small tumour group and a large tumour group was largest. This tumour size turned out to be a maximal diameter of 22 mm (Figure 2 d). Analysis with nominal variables revealed that the incidence of sodium imbalance is significantly correlated with tumour size (Spearman correlation = 0.174, $p = 0.049$)

3.3 Tumour size vs. patient age

Patient’s age at surgery ranged between 20 and 78 years. Figure 3 a shows the tumour size as a function of the age of the patient. Age and tumour size are positively correlated ($\rho=0.27$, $p<0.003$, Pearson's linear correlation coefficient). The linear regression reveals an increase in tumour size of 0.22 mm/y ($p<0.0004$) over the whole group of patients. The age distribution of the patient group does not differ significantly from the normal distribution (Figure 3 b, Lilliefors test). The age distribution has a median of 49 y, which was used as a cut-off to divide the patients into two age groups: A younger group with 58 cases aged < 49 years, and an elder group with 71 cases aged ≥ 49 years at the time of surgery. The median tumour size was smaller for the patient group < 49 years (18.1 mm) than for the patient group ≥ 49 years of age (28.0 mm) (Figure 3 c). The difference in medians between the two size distributions is significant ($p<0.001$, Wilcoxon rank sum test).

3.4 ANOVA of sodium imbalance, tumour size and age

Since older patients have larger tumours (Figure 3), we were interested whether the effect of tumour size on the incidence of sodium concentration imbalance holds for both the young and the old patient group separately. Figure 4 shows extreme sodium values for young/old patients with small/large tumours separately. For the group of elder patients, small and large tumours led to a similar incidence (small: 11 of 21 disturbed = 52% [30 74] %, large: 27 of 50 disturbed = 54% [39 68] %). This difference was not significant ($p = 0.9$, Mann-Whitney U test). The largest difference appeared for young patients, where small tumours lead to sodium imbalance in only 14 of 37 patients (38% [22 55] %), whereas for large tumours, 16 of 21 patients experienced a sodium imbalance (76% [53 92] %). This difference was significant ($p < 0.001$, Mann-Whitney U test, not corrected for multiple comparisons). In this latter group of young patients with large tumours, 6 of 7 men and 10 of 14 women showed sodium imbalance, thus making gender specificity improbable.

To improve the power of statistical testing, we grouped all values into nominal variables. This resulted in nominal variables AGE (young/old: patient age < 49 y or ≥ 49 y), SIZE (small/large: maximal tumour diameter < 22 mm or ≥ 22 mm), MALE (male or female patient) and NAEX (Na imbalance/no Na imbalance: extreme sodium value within or outside the normal range 135-145 mmol/L). Then we tested the effect of tumour size and patient age on sodium imbalance by performing an ANOVA with fixed factors AGE and SIZE and dependent variable NAEX. This statistical approach avoids the problem of multiple comparisons. The analysis shows a non-significant effect of patient age (AGE, $p = 0.68$), a significant effect of tumour size (SIZE, $p = 0.03$), and a significant interaction between the two (AGE*SIZE, $p = 0.05$). The presence of an interaction effect implies that the effect of tumour size on the incidence of sodium concentration imbalance varies as a function of patient age, as illustrated in Figure 4. This indicates that tumour size has an impact especially in young patients.

4. DISCUSSION

The principle finding of this study is that larger tumours cause significantly more sodium disturbance. The incidence of a plasma sodium disturbance was 61% in the group with larger tumours and 43%. in the group with tumours <22mm.This supports the findings of an earlier study, which stated that patients with macroadenomas are more at risk to develop delayed hyponatraemia than patients with smaller tumours (9). This contrasts with the study of Hensen et al. (4) suggesting that tumour size was of borderline significance for the development of hyponatraemia.

The analysis of the tumour size in our study showed that tumour size increases with age. This implies that in older patients more time passes until symptoms occur which result in presenting to a doctor who makes the diagnosis. However comparing the size of the tumour with the age of the patient and the occurrence of sodium disturbance, the elder group of patients showed a similar incidence of sodium imbalance with small as well as with large tumours (52% small, 54% large). Thus for the younger patient group the size of the tumour was the largest influence. Elder patients appear to be more robust with respect to large tumours, younger patients with tumours ≥ 22mm seem to be at a particularly high risk of developing postoperative serum sodium disturbances; small tumours lead to sodium disturbance in only 38%, large tumours in 76%. Thus this study does not agree with either Hans et al. (23) who reported old age to be a risk factor for hyponatraemia nor Nomikos et al. (1) who found no correlation between age and recovery of the pituitary function after surgery. Our data showing that male and female patients are affected with equal frequency (of 54% and 53%, respectively), supports reports stating that there is no difference between the two sexes regarding incidence of postoperative sodium imbalances (4, 5)

Length of hospital stay was longer for patients with hyponatraemia compared to patients with hypernatraemia or without sodium imbalance. It appears that decreased ADH secretion (inadequate response to increasing plasma osmolality), i.e. (transient) diabetes insipidus has less impact on length of stay than increased ADH secretion. Lack of ADH can be compensated for by increased water intake or administration of hypotonic fluids or DDAVP when required but is usually transient (permanent diabetes insipidus is rare). On the other hand, hyponatraemia was related to a prolonged stay in hospital. It is unclear, however, whether hyponatraemia *per se* is causing or contributing to a prolonged hospital stay or whether it is merely reflecting a situation where a non-osmotically driven, the osmotic stimulus overruling ("inadequate") ADH release occurs in response to injury and stress. ADH is difficult to measure, but more recent data have suggested that copeptin, the stable peptide of the vasopressin/ADH precursor which is co-secreted with ADH, could be measured as a surrogate marker to monitor non-osmotic stress in severely ill patients (25). Whereas a prognostic value of copeptin values is usually not specific for the mode of injury but merely reflects the severity of stress, changes in ADH release may be of particular interest and relevance in patients undergoing pituitary surgery. It appears that in our patients the target of ADH action, plasma sodium, i.e. the resulting hyponatraemia, reflects more severe disease, a response to stress/injury in patients following pituitary surgery.

We cannot exclude the possibility that the high incidence of sodium disturbance was related to the manner in which glucocorticoids and fluids were routinely applied following surgery in the patients included in our study; however, only randomized controlled trials could clarify the impact of the postoperative treatment.

5. CONCLUSIONS

Plasma sodium imbalance is common after transsphenoidal resection of sellar lesions. The visibility of the pituitary or its stalk turned out to be without predictive value with regard to postoperative serum sodium imbalance, possibly since intraoperative MR imaging capacitates the surgeon to localize normal gland and stalk after partial removal of the adenoma.

Tumour size had an impact on the incidence of plasma sodium imbalance in patients younger than 49 years: In this young group, 76% of patients with tumour diameter ≥ 22mm experienced either hypernatraemia or hyponatraemia, or both. If hyponatraemia occurred, the median time spent in hospital was prolonged from 5 to 11 days. Therefore, postoperative treatment of young patients with large tumours should include especially careful monitoring of their plasma sodium level within the first two postoperative weeks and clear patients' instructions.

AUTHOR CONTRIBUTIONS

RB, PW, CS designed the study and treated the patients; RB performed surgery; RS compiled the data; JS performed statistical analysis; RS, JS, CS, RB wrote the paper.

DECLARATION OF INTEREST

The authors report no declarations of interest.

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FIGURE CAPTIONS

Figure 1: Extreme Na levels over time in the postoperative course. a) All patients in whom a sodium level outside the normal range was detected are presented with a symbol (o first occurrence, □ second occurrence). Numbers indicate first occurrences (i.e. the incidence of the event). Of the 13 cases with two occurrences, in 10 cases hypernatraemia occurred before hyponatraemia. b) Number of patients with hypernatraemia, plotted against the postoperative day at which the peak hypernatraemia was reached. c) Number of patients with hyponatraemia, plotted against the postoperative day at which the nadir in hyponatraemia was reached.

Figure 2. Extreme sodium levels *vs.* maximal tumour diameter. a) Scatter plot of extreme sodium levels for all patients. The range of normal sodium concentration is delineated by the dotted lines. In 68 of the 129 patients, a sodium level outside of the normal range was detected. b) The size distribution of tumours, median diameter 24 mm (dotted line). c) Fraction of cases where the sodium level showed an imbalance for different tumour sizes. More than 50% of cases experienced an imbalance for the three large tumour size groups. d) The largest difference between groups appeared if a tumour size of 22 mm was taken as a threshold.

Figure 3. Tumour size *vs.* patient age. a) Scatter plot of maximal tumour diameter for all surgical cases. The regression line has a slope of 0.22 mm/y. b) The age distribution of cases, median age 49 y (dotted line). c) Tumour size distributions are shown as box plots for the age groups above and below the median age. The boxes have lines at the lower quartile, median, and upper quartile values. Whiskers extend from each end of the box to the most extreme values within 1.5 times the interquartile range from the

ends of the box. The two size distributions do not have equal medians ($p<0.003$, Wilcoxon rank sum test).

Figure 4. Distribution of extreme sodium levels for 4 patient subgroups. Incidence of sodium concentration imbalance for young and old patients with small and large tumours. Tumour size has an impact especially in young patients.

Figure 3

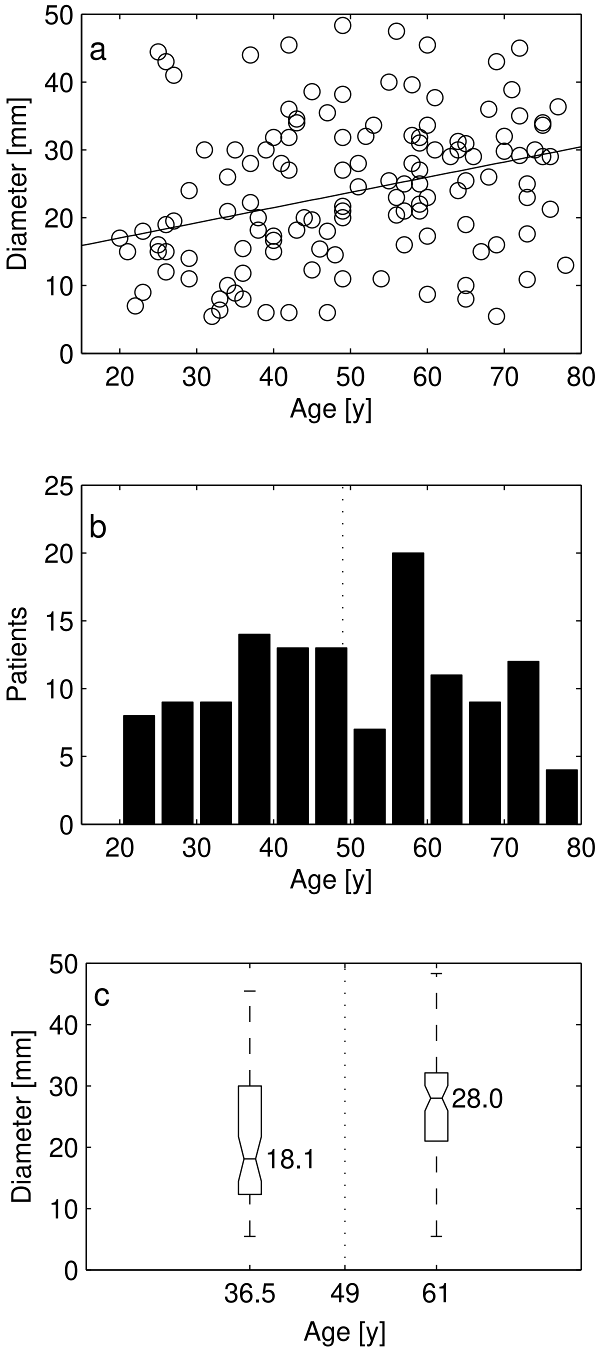
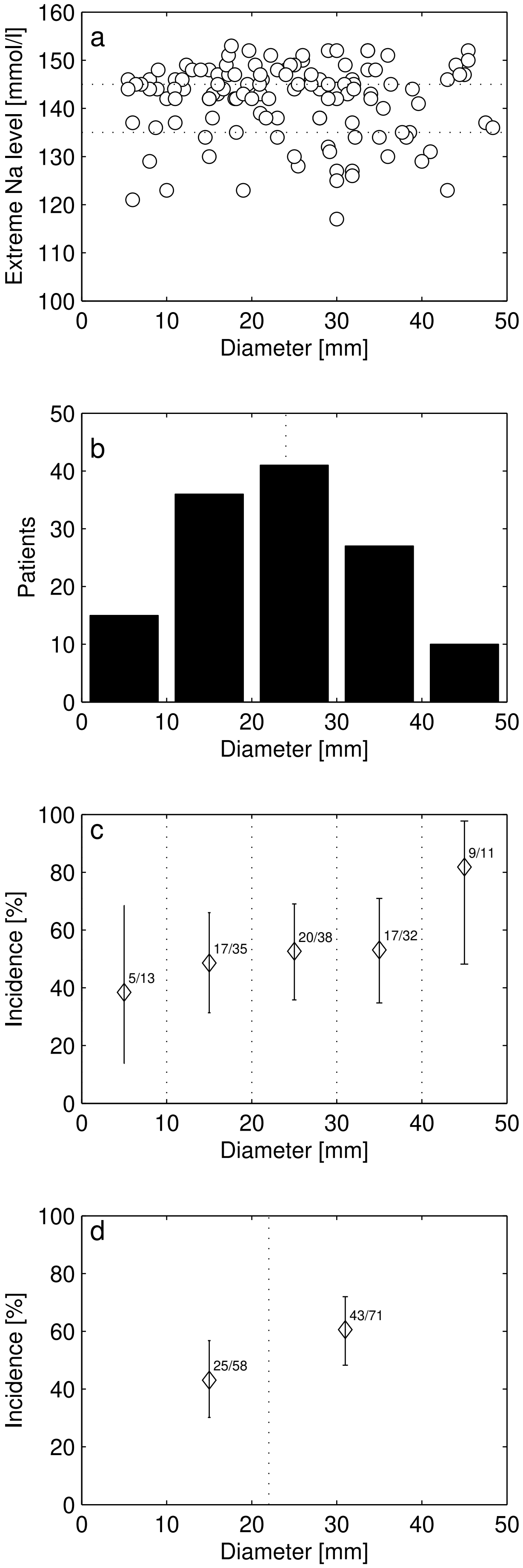

a
Diameter [mm]
Age [y]
b
Patients
Age [y]
c
Diameter [mm]
18.1
28.0
36.5
49
61
Age [y]

Figure 2



a
Extreme Na level [mmol/l]
Diameter [mm]
b
Patients
Diameter [mm]
c
Incidence [%]
5/13
17/35
20/38
17/32
9/11
Diameter [mm]
d
Incidence [%]
25/58
43/71
Diameter [mm]

Figure 1

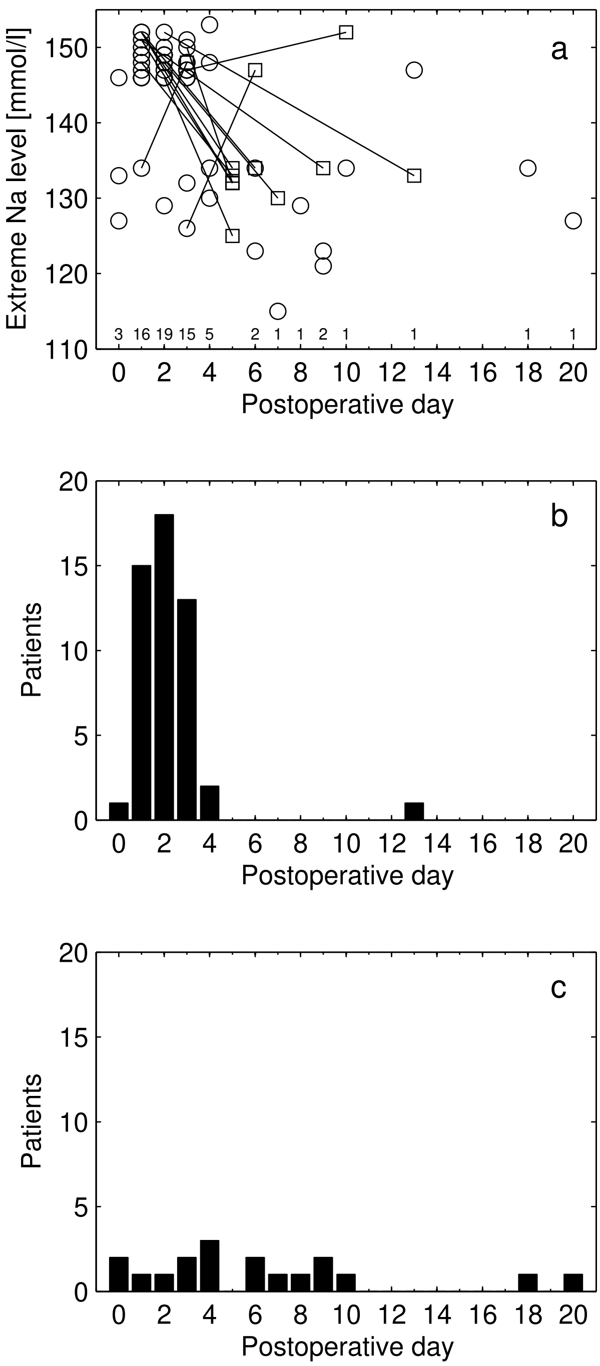
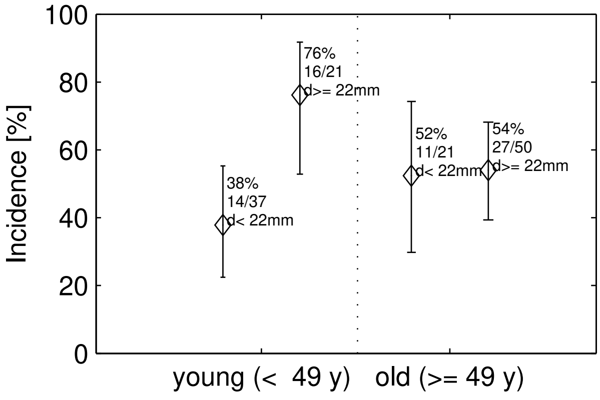

a
b
c
Extreme Na level [mmol/l]
Patients
Postoperative day
3 16 19 15 5 2 1 1 2 1 1 1 1

Figure 4



Incidence [%]
0
20
40
60
80
100
38%
14/37
d< 22mm
76%
16/21
d>= 22mm
52%
11/21
d< 22mm
54%
27/50
d>= 22mm
young (< 49 y)
old (>= 49 y)