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DOI: https://doi.org/10.1530/EJE-10-0651

Accepted Preprint first posted on 6 October 2010 as Manuscript EJE-10-0651

PITUITARY APOPLEXY: RE-EVALUATION OF RISK FACTORS FOR BLEEDING INTO PITUITARY ADENOMAS AND IMPACT ON OUTCOME

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Short running title: Pituitary Apoplexy: risk factors and outcome

Word count (excluding title page, references and tables): 3372

ABSTRACT

Objective: To assess frequency, symptoms and outcome of pituitary apoplexy (PA) among pituitary adenoma patients, to gain better insight into risk factors for bleeding into pituitary adenoma, and to estimate the sequelae of PA by means of a matched control group.

Method: By reviewing charts of 574 patients with pituitary adenoma we analysed incidence, symptoms and outcome of PA, and potential risk factors for developing PA by means of a control group (patients with pituitary adenoma without PA).

Results: 42 suffered from PA; all had macroadenomas. 30/217 male (14%) and 12/179 female (7%) macroadenoma patients, 32/194 patients with clinically non-functioning (16.5%) and 10/202 with clinically active (5.0%) macroadenoma were affected. Antithrombotic therapy predisposed patients to PA ($p = 0.026$), diabetes mellitus and hypertension did not ($p = 1.00$). Patients with PA and pituitary adenoma patients without PA had similar frequencies of hypopituitarism (45 vs. 48%, $p > 0.05$) and visual field defects (38 vs. 55%, $p > 0.05$), but ophthalmoplegia was significantly more common (76 vs. 5%, $p < 0.001$) in patients with PA. Nearly all patients were treated by surgery; most recovered from ophthalmoplegia whereas visual function improved only moderately. Endocrine outcome was worse in patients with PA compared to patients without PA.

Conclusions: Male gender and characteristics of the adenoma itself (especially tumour size and tumour type) rather than patient's cardiovascular risk factors such as diabetes and hypertension seem to predispose to PA; antithrombotic therapy may also be important.

INTRODUCTION

Pituitary apoplexy (PA) is defined as an acute clinical syndrome characterized by sudden onset of headaches, visual impairment and ophthalmoplegia due to haemorrhage with enlargement of a pituitary adenoma (1). The majority of reports on PA consist of single cases or small case series describing this clinically impressive condition; most of these reports, however, do not allow more rigorous data analysis including statistical evaluation. We found 11 retrospective studies in the last 29 years with a large number of patients with PA (≥16) (1-11). The results and essential information of these studies are summarized in table 1. To the best of our knowledge there are no previous case-control studies comparing potential risk factors, symptoms and outcome of patients with PA with pituitary adenoma patients without PA.

The aims of our study were to assess frequency, symptoms and outcome of PA among pituitary adenoma patients and to analyse potential risk factors for developing PA by means of a matched control group. Knowledge and information about potential risk factors could help to prevent PA in pituitary adenoma (and incidentaloma) patients with risk factors by providing an early indication for surgery.

SUBJECTS AND METHODS

We performed a retrospective chart review of patients with pituitary adenoma presenting to the Division of Endocrinology, Department of Internal Medicine, University Hospital of Zurich. Patients were identified by a search in the electronic database of our Division with the following keywords: pituitary adenoma, pituitary tumour, hypopituitarism, prolactinoma, acromegaly and Cushing's disease.

Charts of 574 pituitary adenoma patients from 1980 to November 2007 were reviewed. Patients who suffered an apoplexy in their pituitary adenoma were identified. We diagnosed PA according to the clinical definition by Randeva et al.: Presence of a pituitary adenoma together with at least one of the following criteria: 1. Episode of acute severe headaches, 2. sudden visual disturbance such as visual field defects or ophthalmoplegia (5).

Patients with PA were compared with the total cohort of patients with pituitary adenoma during the same period. In order to analyse potential risk factors or associated factors for PA and to estimate sequelae of PA, we compared PA patients with a control group (matched case-control study-design). The control group was formed as follows: We assigned to each PA patient two pituitary adenoma patients without PA, who were matched for sex, tumour type, tumour size and age (downward order of relevance). For additional risk factors (i.e. oestrogens, antithrombotic therapy, diabetes mellitus, arterial hypertension, bilateral adrenalectomy, cardiac surgery and therapy with dopamine agonists) and outcome we compared the PA patients with the control group (5, 12, 13).

All patients underwent a computer tomography scan (CT) and / or magnetic resonance imaging (MRI) of the sellar region. In the PA group 11 patients (26%) had a CT, 23 patients (55%) had a MRI and 8 patients (19%) had both. In the control group 26 patients (31%) had a CT, 43 patients (51%) had a MRI and 15 patients (18%) had both. Tumours measuring less than 1 cm in diameter (as determined by neuroimaging) were classified as microadenomas, and larger tumours as macroadenomas. Tumour type was mostly determined on histology, but sometimes histological analysis only showed necrosis. In these cases tumour type was defined by clinical presentation and endocrine studies at diagnosis. Clinical presentation of gonadotropin-secreting tumours is similar to that of clinically non-functioning tumours. Therefore, these tumours were included under the term of clinically non-functioning tumours. Tumours with no further characteristics or endocrine activity were assigned to that group, too. Endocrine function was evaluated at the time of admittance to the hospital (before medical and surgical treatment), as well as 12 months after surgery. Secondary adrenal failure was defined by the perceived need for glucocorticoid replacement therapy with concomitant low (in the majority <200 nmol/L) serum cortisol levels in the early morning. Secondary hypothyroidism was defined by previously repeatedly low (usually <10 pmol/L) serum free thyroxine levels. We defined male hypogonadism as having low serum testosterone (usually <12 nmol/L) and gonadotropin levels (usually FSH and LH both <2 mU/mL), and female hypogonadism as having amenorrhoea and low oestradiol (usually <70 pmol/L) without rising gonadotropin levels (usually FSH and LH both <5 mU/mL).

Median and range were used for descriptive statistics. Fisher's exact test was used to analyse categorical variables and groups. Mc Nemar test was used to analyse differences in categorical variables within the group (14). Multivariate logistic regression analyses adjusting for age, sex and tumour size were conducted with the whole group. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Version 16.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

42 of 574 patients (7.3%) with pituitary adenoma fulfilled the diagnostic criteria for classical PA as defined above. In 41 of the 42 patients with classical PA, pituitary adenoma had been unknown before PA occurred. The median age of PA-patients was 53.5 (range 21-85) years. The median age of the control group was 50.0 (range 23-84) years.

Tumour size

All 42 patients with PA had a macroadenoma. 354 patients (67%) without PA had a macroadenoma, 160 (30%) had a microadenoma, and 18 (3%) had an adenoma of unknown size.

Sex

Although women (317; 55%) presented overall more frequently with pituitary adenoma than men (257; 45%), PA occurred about 3 times more often in men (30/257 men; 12%) than in women (12/317 women; 4%) (odds ratio = 3.36, CI = 1.68 – 6.71, $p < 0.001$). Since PA occurred only in macroadenomas, the analysis was performed only in macroadenoma patients. Men with macroadenoma had a significantly increased risk for PA compared to women (30/217 men (14 %) and 12/179 women (7 %) with PA; odds ratio = 2.23, CI = 1.11 – 4.50, $p = 0.022$) (table 2).

Tumour type

The most frequent types of pituitary macroadenoma were clinically non-functioning tumours (49%) and prolactinomas (32%), followed by GH-secreting tumours (16%). Cushing's disease (3%) and Nelson's syndrome (0.5%) were quite rare (table 2).

Most of the PA patients had clinically non-functioning tumours. 32/194 (16.5%) patients with clinically non-functioning and 10/202 (5.0%) with clinically active macroadenoma developed PA, resulting in a significantly higher risk for PA in clinically non-functioning macroadenomas (odds ratio = 3.79, CI = 1.81 – 7.95, $p < 0.001$). Male sex and clinically non-functioning tumour type were found to be independent risk factors for PA ($p < 0.001$).

Predisposing factors

We compared the frequencies of potential risk factors (i.e. oestrogens, antithrombotic therapy, diabetes mellitus, arterial hypertension, bilateral adrenalectomy, cardiac surgery and therapy with dopamine agonists) between PA

patients and the control group of matched patients with pituitary adenomas (table 3) (5, 12, 13). Sex, age, tumour size and tumour type (matched parameters) revealed no significant difference between PA and control group.

Risk for PA was significantly elevated in patients with antithrombotic drugs (vitamin K antagonist or platelet inhibitors) (Odds ratio = 2.96, CI = 1.16 – 7.58, p = 0.026), but not in patients with cardiovascular risk factors such as diabetes mellitus (Odds ratio = 1.00, CI = 0.28 – 3.53, p = 1.00) and arterial hypertension (Odds ratio = 0.93, CI = 0.38 – 2.29, p = 1.00).

Remarkably none of the 42 PA patients, but 11 of the 84 control patients received dopamine agonist treatment, suggesting that treatment with dopamine agonists could be protective. Oestrogen treatment tended to be a risk factor in female patients with macroprolactinoma (n = 2 in PA group and n = 4 in control group), but for this potential risk factor statistical analysis was not performed due to small sample size.

Symptoms

Symptoms at presentation are listed in table 4. Ophthalmoplegia was significantly more frequent in the PA group than in the control group (Odds ratio = 64.0, CI = 18.71 – 218.93, $p < 0.001$). Visual field defects due to chiasma compression were slightly more frequent in the control group, but this result did not reach significance.

Pituitary function

At presentation, 45% of patients with PA, and 48% of the control group were suffering from hypopituitarism such as secondary adrenal failure (7% versus 10%), secondary hypothyroidism (14% versus 15%) and hypogonadism (43% versus 48%).

Outcome

39 of 42 patients with PA, and 81 of 84 control patients were treated by surgery. Two PA patients were not operated on their pituitary lesion due to their poor general condition. One of them died 77 days after diagnosis. In a third patient PA was not diagnosed until 40 days after the event at which stage surgery was postponed. In two control patients with macroprolactinoma treatment with dopamine agonists was initiated and surgery became unnecessary. One control patient with an endocrine inactive macro-incidentaloma refused surgery.

Patients with ophthalmoplegia recovered better from their visual disturbances than patients with visual field defects. Nearly all patients (33/36) recovered from ophthalmoplegia without sequelae, whereas visual field defects persisted in about 24% of patients (15/62), both in the PA and the control group (table 5). Endocrine outcome was worse in patients with PA than in the control group: The frequency of hypopituitarism increased (from 45 at presentation to 71% during follow-up, Odds ratio = 4.7, CI = 1.30 – 25.33, p = 0.013) in the PA

group, while it did not change in the control group (from 48 at presentation to 55% during follow-up, Odds ratio = 1.5, CI = 0.68 – 3.41, p = 0.362) (table 5). Secondary adrenal failure and secondary hypothyroidism increased in the PA (from 7 to 55% and from 14 to 52%) as well as in the control group (from 10 to 33% and from 15 to 44%, both p <0.001) (table 5).

DISCUSSION

In our retrospective series 7.3% of patients with pituitary adenoma presented with PA. In previous series the incidence of PA in patients with all kinds of pituitary adenoma amounted to 1.6 – 12.8% (1, 3-5, 10, 11).

In contrast to some case-reports demonstrating that PA may occur also in small pituitary tumours, we postulate that a large tumour size is associated with a significantly increased risk for PA, because all of our patients with PA had a pituitary macroadenoma (13, 15). This finding is in line with the study of Da Motta et al., in which all patients had a pituitary tumour with important suprasellar extension (4). An additional major risk factor in our series was male gender. Men suffered significantly more frequently from PA than women, irrespective of tumour size. Some, but not all authors report that male sex is an independent risk factor for PA (1, 4, 5, 8, 11-13, 16, 17).

Yet another major risk factor represents tumour type. In agreement with some but not all previously published series, the incidence of PA was significantly higher in our patients with clinically non-functioning tumours (1, 2, 4-6, 8, 11, 12). Wakai et al. did not find a significant difference in the incidence of PA among different tumour types in their study of 560 pituitary adenoma patients and 51 PA patients (1). However, Da Motta et al., Randeva et al., Sibal et al. and Semple et al. reported an increased risk for PA in clinically non-functioning tumours (between 60% to 77%) (4-6, 8).

Mechanisms for the development of PA are not fully understood. As discussed by Bjerre et al., blood supply to the anterior pituitary lobe is provided by portal vessels through the infundibulum. As the perfusion pressure is very low in these portal vessels, pituitary adenomas are particularly susceptible to even minor increments in intrasellar pressure caused by a tumour (18). Beside an elevated intrasellar pressure a further important factor for developing PA could be the degree and type of vascularisation of the tumour. Some authors suggest that pituitary adenomas can outgrow their blood supply resulting in ischemic necrosis followed by haemorrhage (5, 8). Cardoso and Petersen have postulated that an intrinsic vasculopathy in pituitary adenomas renders them more susceptible to infarction and haemorrhage (17). McCabe et al. found a markedly raised vascular endothelial growth factor (VEGF) mRNA expression in the tissue of clinically non-functioning tumours compared with other types of pituitary tumours and normal pituitaries, which could indicate that angiogenesis may be different, and that properties of tumour vessels could contribute to an increased risk for PA in clinically non-functioning

tumours (19). The results of these studies, including ours, are consistent with proposed theories on the pathogenesis of PA: beside male sex, large tumours and non-functioning tumour type are major risk factors for developing PA.

In addition to these three major risk factors, other potential risk factors have been discussed in the literature: arterial hypertension, sudden changes in arterial blood pressure, diabetes mellitus, head trauma, transient elevations of intracranial pressure, cardiac surgery, dynamic tests of pituitary function with releasing factors, antithrombotic therapy, oestrogens, dopamine agonists, somatostatin analogues and radiotherapy (5, 12, 13). Of these risk factors we could confirm antithrombotic therapy (vitamin K antagonist or platelet inhibitors) as significant in our study.

Suffering a head trauma may also be associated with an elevated risk for PA, but because of its rare occurrence (3 in PA group and none in control group) statistical analysis was not undertaken. The mechanism of posttraumatic PA is not yet fully understood. Bao et al. speculate that the change of blood flow in pituitary adenomas due to fluctuations of intracranial pressure and blood pressure following severe head injury leads to the apoplectic event in a pituitary adenoma (20).

Similarly, statistical analysis was not possible for oestrogen treatment in female patients with prolactinoma due to the small sample size. Oestrogens may enhance growth and activity of prolactinoma cells, may increase perfusion demand and stimulate tumour vascularisation. Furthermore oestrogen treatment was reported to stimulate the production of VEGF in cells isolated from prolactinoma (21).

Treatment with dopamine agonists in prolactinoma patients, by contrast, did not appear to be harmful in our series. Given that these agents decrease growth and activity of prolactinoma cells, we suggest that dopamine agonist treatment should no longer be included in the list of risk factors for PA, despite previous case reports suggesting the opposite (3, 12).

Diabetes mellitus and arterial hypertension were not found to be significant risk factors for PA in our series suggesting that the overall cardiovascular risk profile (which predicts stroke) does not predict bleeding into a pituitary adenoma.

Few studies address the long term outcome of patients with PA. In our study most patients recovered from ophthalmoplegia, whereas outcome in patients with visual field defects was worse. Since the three ocular motor cranial nerves (III, IV, and VI) are peripheral nerves, they can undergo regeneration. The optic nerve as part of the white matter cannot recover after axonal disruption. In the series of Onesti et al. and Bills et al. visual outcome was also better in patients with ophthalmoplegia than in those with visual field defects (2, 22).

Concerning the endocrine outcome, an event of PA may lead to irreversible loss of pituitary cells, thus leaving the majority of our PA patients with (at least partial) pituitary insufficiency. These observations are in line with some other studies (10, 23) Zayour et al. speculate that the rapid increase in intrasellar contents after haemorrhagic infarction of a pituitary adenoma may lead to a sudden increase in intrasellar pressure, resulting in ischemic necrosis of the anterior pituitary and limiting the potential for functional recovery after decompression (23). However, Liu et al. have found that some recovery of hormone deficiencies in their PA patients occurred following surgery (11).

With increasing use of CT scans and MRI studies incidentally discovered pituitary adenomas become more frequent. Most pituitary adenoma patients are assigned for treatment, especially when a clinically active adenoma or threatening visual field defects by a large macroadenoma is found. Based on our findings, we cannot comment on the best management of such patients, but our observations may be helpful in management decisions for patients with pituitary macro-incidentalomas. According to our results, the threat of bleeding is highest in large, clinically non-functioning tumours in patients who are taking antithrombotic therapy for prevention or treatment of atherosclerosis and its complications. Therefore, among patients with pituitary incidentaloma, we would propose to treat those with macroadenoma and atherosclerosis by surgery even if there are no tumour-related signs and symptoms, to prevent PA.

Pituitary adenomas are rarely known at the time of presentation of PA; it is therefore not surprising that all epidemiological data on PA derive from retrospective studies with their obvious drawbacks. Apart from being retrospective, another limitation of our study is its long period of time. The quality of documentation of some elder cases was variable, and although neuroimaging by MRI or CT scan was performed in all patients, the exact tumour size and tumour infiltration were not always described in sufficient detail. Some tumours were possibly overestimated in size because of bleeding. However, in 36 of our 42 PA patients (86%) suprasellar and/or parasellar extensions were documented by brain imaging studies. Among the remaining 6 PA patients, 4 had a tumour diameter of 2 cm and only 2 had too fragmentary data about tumour dimensions. Therefore we feel confident that the vast majority of our PA patients had macroadenomas before the event of PA. Without precise assessment of the tumour size in all patients it was not possible to prove whether large tumour size and non-functioning tumour type were independent risk factors for PA. It can be argued that non-functioning tumours may be diagnosed at a later stage of disease due to late compression symptoms caused only by large tumours. Unfortunately, as long as we have only crude figures about tumour size (i.e. tumour size less than 1 cm or more than 1 cm) in some of the patients, we are unable to further determine any independency between these two risk factors. Moreover, concerning the endocrine status of the patients, we had only limited data on insulin

hypoglycaemia stress tests, considered as gold standard for determination of secondary adrenal failure. However, serum basal cortisol levels in the early morning may be used as first-line test in the assessment of the hypothalamic–pituitary–adrenal axis both preoperatively and postoperatively, as well (24).

The strengths of our study are both the large number of included patients and the matched case-control study design comparing patients suffering from PA with a group of patients having comparable tumours without PA from the same institution and time period.

We conclude that the risk for PA depends mainly on properties of the tumour itself (tumour size and type) and on the patient's gender. Antithrombotic therapy and possibly also head trauma and oestrogen treatment in patients with prolactinoma may enhance or trigger such an event. Over the following months, most patients recovered from ophthalmoplegia but few from pituitary failure. Early diagnosis of partial pituitary failure by careful history and examination may help to discover pituitary adenoma in some -especially male - patients at an earlier stage, and thus reduce the risk for PA.

COMPETING INTERESTS, FUNDING AND AUTHOR'S CONTRIBUTION

We do not have any conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Authors' contribution: DLM-G wrote the manuscript and was responsible for data-collection. CS, MB and KL revised the manuscript. MB and DLM-G calculated the statistics. KL made most of the ophthalmologic examinations and RLB most of the surgeries. All authors contributed to the quality of this manuscript by helpful critical review of the results and the discussion.

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Table 1: Summary of previous large retrospective studies about pituitary apoplexy

	Total number of patients	Cases of PA (n)	Incidence of PA (%)	essential information
Wakai S (1981) (1)	560	51	9.1	PA is not correlated with sex, endocrine function or histological type of the adenoma, but with age.
Bills DC (1993) (2)		37		In stable patients with PA surgical decompression should be performed as soon as possible, because delays beyond 1 week may retard the return of visual function.
Bonicki W (1993) (3)	799	39	4.9	Authors suggest surgical treatment in every case of PA to enhance neurological and endocrine recovery.
Da Motta LA (1999) (4)	125	16	12.8	In PA surgical treatment was associated with better outcome than treatment with dexamethasone.
Randeva HS (1999) (5)	982	35	3.2	Hypertension may be an important predisposing factor for PA. Transsphenoidal surgery is safe and effective. It is indicated if there are associated abnormalities of visual acuity or visual fields.
Sibal L (2004) (6)		45		Patients with classical PA and without any or only with mild, non-progressive neuro-ophthalmic signs can be managed conservatively in the acute stage.
Nomikos P (2004) (7)*	721	27	3.7	Anterior pituitary function was more frequently preserved, normalized or even improved after transsphenoidal surgery compared to transcranial surgery in patients with non-functioning pituitary adenomas.
Semple PL (2005) (8)		62		Emergency surgery is required in patients with a diminished level of consciousness, deteriorating vision or sudden onset of blindness. Isolated cranial nerve palsies may be successfully managed conservatively.
Nielsen EH (2006) (9)*	192	41	21	PA occurs more frequently than usually assumed. In patients operated on for non-functioning pituitary adenoma, survival is independent of the occurrence of PA.
Dubuisson AS (2007) (10)	1540	24	1.6	PA is a rare event. Complete recovery is possible if the diagnosis is rapidly obtained and adequate management is initiated in time. Surgical results are very satisfactory in the majority of cases.
Liu ZH (2010) (11)	262	25	9.5	Classical PA is a rare event. The incidence of subclinical PA is higher than classical PA. Patients with classical PA have a higher mean age and most patients were male (68%). Visual improvement is better in subclinical PA than in classical PA. In both classical and subclinical PA anterior pituitary function is able to recover.

n = number of patients, PA = pituitary apoplexy
* In these studies only patients with non-functioning pituitary adenomas were included.

Table 2 : Tumour-type

macroadenoma patients	with PA		without PA		Total	
	n	%	n	%	n	%
total	42	100	354	100	396	100
men	30	71	187	53	217	55
women	12	29	167	47	179	45
non-functioning	32	76	162	45	194	49
prolactinoma	7	17	119	34	126	32
GH-secreting	1	2	62	18	63	16
Cushing’s disease	1	2	10	3	11	3
Nelson’s syndrome	1	2	1	1	2	1

n = number of patients, PA = pituitary apoplexy

Table 3: Predisposing factors for PA

patients	with PA		control group		p-value **
	n	%	n	%	
total	42	100	84	100	
antithrombotic therapy	12	29	10	12	0.026
diabetes mellitus	4	10	8	10	1.00
arterial hypertension	9	21	19	23	1.00
dopamine agonists	0	0	11	13	-
oestrogens (depot injection)*	2	100	0	0	-
bilateral adrenalectomy	1	2	0	0	-
cardiac surgery	1	2	0	0	-
head trauma	3	7	0	0	-

n = number of patients, PA = pituitary apoplexy

*These calculations include only women with macroprolactinoma (n = 2 and 4 respectively)

**Statistical analysis done by Fisher's exact test

Table 4: Symptoms at presentation

patients	with PA		control group		p-value**
	n	%	n	%	
total	42	100	84	100	
ophthalmoplegia	32	76	4	5	<0.001
visual field defects	16	38	46	55	0.091
chronic headaches	5	12	20	24	0.156
amenorrhoea*	6	50	9	38	0.499
galactorrhoea*	2	17	4	17	1.00
hypopituitarism at presentation	19	45	40	48	0.851

n = number of patients, PA = pituitary apoplexy

*These calculations include only women (n = 12 or 24 respectively)

** Statistical analysis done by Fisher's exact test

Table 5: Visual and endocrine outcome

patients		with PA (n = 42)		control group (n = 84)		PA vs. control group
		n	%	n	%	p-value**
ophthalmoplegia	at presentation	32	76	4	5	<0.001
	outcome	3	7	0	0	-
present. vs. outc.:	p-value***	n.a.		n.a.		
visual field defects	at presentation	16	38	46	55	0.091
	outcome	2	5	13	15	0.142
present. vs. outc.:	p-value***	n.a.		n.a.		
hypopituitarism*	at presentation	19	45	40	48	0.851
	outcome	30	71	46	55	0.084
present. vs. outc.:	p-value***	0.013		0.362		
secondary adrenal failure	at presentation	3	7	8	10	0.750
	outcome	23	55	28	33	0.034
present. vs. outc.:	p-value***	n.a.		<0.001		
hypogonadism	at presentation	18	43	40	48	0.705
	outcome	23	55	39	46	0.451
present. vs. outc.:	p-value***	0.332		1.000		
hypothyroidism	at presentation	6	14	13	15	1.000
	outcome	22	52	37	44	0.450
present. vs. outc.:	p-value***	n.a.		<0.001		
diabetes insipidus	at presentation	1	2	0	0	-
	outcome	1	2	8	10	0.270
present. vs. outc.	p-value***	n.a.		n.a.		

n = number of patients, n.a. = McNemar test not applicable, outc. = outcome, PA = pituitary apoplexy, present. = at presentation, vs. = versus

*The term “hypopituitarism” includes any (including partial) pituitary failure such as ACTH, TSH or gonadotropin deficiency.

** Statistical analysis done by Fisher’s exact test

***Statistical analysis done by McNemar test