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transsphenoidal pituitary adenoma surgery

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cirurgia transesfenoidal endoscópica de adenomas da hipófise

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Eu, Christiane Celeste Ferreira Sonnay, abaixo assinado, nº mecanográfico 201305390, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

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Faculdade de Medicina da Universidade do Porto, 15/03/2019

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Neurocirurgia

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Risk factors for cerebrospinal fluid leak following endoscopic transsphenoidal pituitary adenoma surgery

ORIENTADOR

Dra. Patrícia Maria Polónia Pinto

COORIENTADOR (se aplicável)

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTES TRABALHOS APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
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Faculdade de Medicina da Universidade do Porto, 15/03/2019

Assinatura conforme cartão de identificação: Christiane Celeste Ferreira Sonnay

Dedicatória

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Risk factors for cerebrospinal fluid leak following endoscopic transsphenoidal pituitary adenoma surgery

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Abstract

Purpose: To evaluate risk factors for intraoperative and/or postoperative cerebrospinal fluid (CSF) leak following endoscopic transsphenoidal surgery in patients with pituitary adenomas.

Methods: A retrospective cohort study of 219 pituitary adenomas submitted to transsphenoidal endoscopic surgery (2007 – 2017) at the Centro Hospitalar São João was performed. Age, sex, body mass index, smoking status, diabetes mellitus, hypertension, dyslipidemia, chronic obstructive pulmonary disease, asthma, obstructive sleep apnea syndrome (OSAS), tumor size and type, prior transsphenoidal surgery or radiotherapy were collected by clinical documentation analysis and phone interview. An univariate statistical analysis was performed to evaluate the association of risk factors with the occurrence of CSF leaks.

Results: 201 patients were included in the study (18 excluded due to insufficient data). The prevalence of intra and postoperative CSF leaks was 14.9% (30/201) e 5.0% (10/201), respectively. There was a statistically significant association between the appearance of intraoperative CSF leaks and the following risk factors: tumor size (19.9% macroadenomas, $p=0.001$) and tumor type (26.3% growth hormone (GH) secreting adenomas, $p=0.009$). Despite being non-statistically significant, intraoperative CSF leaks occurred with more frequency on patients with hypertension, asthma and OSAS. The risk of postoperative CSF leaks was significantly associated with the previous occurrence of intraoperative CSF leak ($p<0.001$) and they also appeared with more frequency on patients with asthma, OSAS and on GH-secreting tumors; every postoperative CSF leak occurred on macroadenomas.

Conclusion: Knowledge of patient's risk factors is an important tool in the preoperative assessment, especially given the risk arising from CSF leaks (meningitis).

Keywords

Pituitary adenoma, Cerebrospinal fluid leaks, Endoscopic transsphenoidal surgery, Risk factors

Introduction

Pituitary adenomas are benign intracranial neoplasms. They represent approximately 16% of all central nervous system tumors [1]. The gold-standard treatment is surgical, except for prolactinomas (tumors producing prolactin) in which the treatment in the majority of cases is based on pharmacological therapy (dopaminergic agonists) [2].

Over the years various surgical techniques have emerged. Transsphenoidal surgery, first described in 1906 by Schloffer, is currently the standard treatment [3]. The transsphenoidal endoscopic variant has gained relevance and popularity in recent years over the microsurgical technique as a minimally invasive technique. It demonstrated lower complication rates, shorter hospitalizations and better overall results [4-6]. However, despite improvements in this field, both techniques are associated with potentially serious surgical complications, such as cerebrospinal fluid (CSF) leak, which increase the likelihood of meningitis in these patients [7].

The current literature describes an occurrence of intraoperative CSF leaks between 18.1% and 53.2% [8] and postoperative CSF leaks between 1.4% and 16.9%, [7] being one of the most frequent surgical complications. Its occurrence often leads to longer hospitalizations, re-hospitalizations, and re-operations that imply higher costs for the health system [8].

Since most of the postoperative CSF leaks arise following the occurrence of intraoperative CSF leaks, it is of particular interest to evaluate the preoperative risk factors of both complications [9]. It was chosen to evaluate the relationship between the occurrence of intraoperative and postoperative CSF leaks and demographic data, habits and comorbidities, characteristics of the tumor and a preventive/treatment measure (use of lumbar drainage).

Based on current literature, several studies have shown a significant association between a high body mass index (BMI) at the time of surgery and the occurrence of intra and postoperative CSF leaks. Increased intra-abdominal pressure leading to an increased intracranial pressure (ICP) was one of the main reasons reported in these patients [10,11]. In view of this hypothesis, it is sought to associate other comorbidities with an increased intra-abdominal pressure, namely obstructive pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD) to the occurrence of CSF leaks. Furthermore, obstructive sleep apnea syndrome (OSAS) could also increase CSF leaks caused by the nocturnal hypoxia that these patients presents that lead to episodic increases in ICP [12].

The objective of this study was to evaluate risk factors for intra and postoperative CSF leaks after endoscopic transsphenoidal surgery in patients with pituitary adenomas. Another purpose was to describe some of the preventive and treatment measures used in the studied population.

Methods

Population

A retrospective cohort analysis of 219 patients with pituitary adenoma undergoing an endoscopic transsphenoidal surgery (ETS) between January 2007 and December 2017 in Centro Hospitalar São João was performed. Demographic data, patient's comorbidities, tumor features and perioperative data were collected through computerized clinical documentation. All available patients with missing values were called by phone interview. The study and its objectives were summarized to the patient via telephone and explicit consent was obtained if patients accepted to answer the questions. The inclusion criteria included having a follow-up of at least six months and a completed purely endoscopic endonasal transsphenoidal surgery. The exclusion criteria were patients under 18 years and incomplete data without contact available or unanswered telephone attempts. At the end, 201 patients were included and 18 patients were excluded due to insufficient data.

The variables studied included patient *age, sex, BMI at the surgery's time (kg/m²), smoking, diabetes mellitus (DM), hypertension, dyslipidemia, COPD, asthma, OSAS, tumor size, tumor type, prior transsphenoidal surgery, history of previous radiotherapy (RT), use of lumbar drainage perioperatively*. The tumor size was classified in microadenoma (<10 mm) and macroadenoma (>10 mm) according to the maximum tumor diameter on magnetic resonance imaging. The tumor type according to the secreted hormones was classified into five categories: null cell, growth hormone (GH)–producing, adrenocorticotrophic hormone (ACTH)–producing, gonadotropin [follicle-stimulating hormone (FSH) and luteinizing hormone (LH)] –secreting and others adenomas (including prolactin–producing, thyroid-stimulating hormone (TSH)–producing and plurihormonal adenomas). Prolactinomas were only submitted to surgery after failure of the pharmacological treatment.

The primary outcome was the occurrence of intraoperative and postoperative CSF leak. The intraoperative CSF fluid leak was evaluated during the surgery by the neurosurgeon and was recorded in the surgery report. The postoperative CSF fluid leak was defined as a clinical evidence of CSF rhinorrhea during 30 days after the procedure.

Surgical technique

The surgeries were performed by the same team of two surgeons. The technique described below is the standard used actually by neurosurgeons at Centro Hospitalar São João. This has undergone some changes in the last 10 years mainly regarding the materials used in the reconstruction of the local anatomy.

1. Endoscopic access until the sphenoidal sinuses through unilateral nostril.
2. Lateral deviation of the middle turbinate.
3. Opening of the sphenoid rostrum.
4. Coagulation and removal of the sphenoid sinus mucosa.
5. Identification of the sellae turcica and opening of the bony floor with subsequent enlargement.
6. Coagulation and incision of the sellar dura.
7. Removal of the tumor by fragments and submission for definitive examination to pathologic anatomy.
8. Reconstruction of the local anatomy - reconstitution of the sellar floor.
9. Repositioning of the middle turbinate near the nasal septum. (In some ancient cases, at the end, a Foley catheter balloon was inflated)

Patients with evidence of intraoperative CSF fluid leak must remain flat in bed during 5 days with lumbar drain placed in the operating room at the end of the surgery in all cases.

Statistical analysis

Statistical analysis was carried out by using SPSS Statistics edition 24.0 (IBM Corp, Armonk, NY). Categorical variables are presented as frequency and percentage and continuous variables are presented as mean and standard deviation. Chi-square test and Fischer's exact test was used for categorical variables and independent samples t-test for continuous variables. A *P* value of <0.05 was considered as a statistically significant difference.

This study was approved by the ethical committee of the hospital.

Results

As shown in Table 1, data was collected from 201 patients with a mean age of 51 ± 15.7 years and a mean BMI of 28.9 ± 4.8 kg/m², classified as an overweight population. There were 46.8% male and 53.2% female patients. The study population was mostly non-smokers (82.1%). Regarding comorbidities, 23.9% had DM, 48.8% had hypertension and 52.2% had dyslipidemia. Concerning pulmonary diseases, only 3.5% showed a diagnosis of COPD, 5.5% of asthma and 9.5% of OSAS. As for tumor characteristics, the majority were macroadenomas (72.6%) and nonfunctioning (38.3%). Among the others, 19.4% were ACTH-producers, 18.9% were GH-producers, 11.9% produced sex hormones (FSH/LH) and the remaining (11.4%) included 17 pluri-hormonal tumors, 2 TSH-producers and 4 prolactin-producing tumors. In total, 30 patients had recurrences and had undergone previous surgery. Only 1 patient had undergone radiotherapy previously.

Intraoperative CSF leaks occurred in 30 patients, all of whom had external lumbar drainage placed at the end of surgery. Among these, only 7 CSF leaks were effective, i.e., loss of CSF was maintained postoperatively. Additionally, there were 3 cases of post-operative CSF leaks without evidence of prior intra-operative CSF leak.

TABLE 1. DEMOGRAPHIC DATA OF 201 PATIENTS

Characteristic	No. of cases (%)
Age (years), mean (SD)	51.0 (15.7)
Sex	
Male	94 (46.8)
Female	107 (53.2)
BMI (kg/m ²), mean (SD)	28.9 (4.8)
BMI by category	
<25	43 (21.4)
25-29.99	78 (38.8)
≥30	80 (39.8)
Smoking	
No	165 (82.1)
Yes	36 (17.9)
DM	
No	153 (76.1)
Yes	48 (23.9)
Hypertension	
No	103 (51.2)
Yes	98 (48.8)
Dyslipidemia	
No	96 (47.8)
Yes	105 (52.2)
COPD	
No	194 (96.5)
Yes	7 (3.5)
Asthma	
No	190 (94.5)
Yes	11 (5.5)
OSAS	
No	182 (90.5)
Yes	19 (9.5)
Tumor size	
Microadenoma	55 (27.4)
Macroadenoma	146 (72.6)
Tumor type	
Null	77 (38.3)
GH	38 (18.9)
ACTH	39 (19.4)
FSH/LH	24 (11.9)
Others	23 (11.4)
Previous surgery	
No	171 (85.1)
Yes	30 (14.9)
Previous RT	
No	200 (99.5)
Yes	1 (0.5)
Intraoperative CSF leak	
No	171 (85.1)
Yes	30 (14.9)
Lumbar drainage	
No	170 (84.6)
Yes	31 (15.4)
Postoperative CSF leak	
No	191 (95.0)
Yes	10 (5.0)

Abbreviations: SD=standard deviation.

In Table 2, it is presented the characteristic of all patients with a postoperative CSF leak. Patients' age varied between 32 and 69 years and 50% were male. All postoperative CSF leak were macroadenoma and the majority was GH-producing tumors. All patients with previous occurrence of intraoperative CSF leak had intraoperative lumbar drainage placement. The 3 postoperative CSF leaks without intraoperative CSF leak were diagnosed at day 2, day 10 and day 15 post surgery. Three patients with CSF leaks had meningitis (1 only intraoperative, 1 intraoperative + postoperative, 1 only postoperative). One patient with postoperative CSF leak had sinusitis. Of the 10 postoperative CSF leaks, 1 resolved only with bed rest, 7 resolved with bed rest plus external lumbar drainage and 2 required further surgical interventions.

TABLE 2. DESCRIPTION OF PATIENTS WITH POSTOPERATIVE CSF LEAK AND RESPECTIVE TREATMENTS/COMPLICATIONS

Postoperative CSF Leak (n=10)							
ID	Age	Sex	Type	Size	Intraop. events	Complication(s)	Postop. treatment
1	57	M	Null	Macro	None	D15: Postop. CSF leak + Sinusitis	RP
2	62	M	ACTH	Macro	None ^a	D10: Postop. CSF leak + Meningitis	RP + LD + 3 reop.
3	44	M	FSH/LH	Macro	Intraop. CSF leak; LD	Postop. CSF leak	RP + LD
4	46	M	GH	Macro	Intraop. CSF leak; LD	Postop. CSF leak	RP + LD
5	59	F	GH	Macro	Intraop. CSF leak; LD	Postop. CSF leak; D1: Meningitis	RP + LD + 1 reop.
6	69	F	Null	Macro	Intraop. CSF leak; LD	Postop. CSF leak	RP + LD
7	39	M	GH	Macro	Intraop. CSF leak; LD	Postop. CSF leak	RP + LD
8	32	F	GH	Macro	Intraop. CSF leak; LD	Postop. CSF leak	RP + LD
9	52	F	GH	Macro	Intraop. CSF leak; LD	Postop. CSF leak	RP + LD
10	43	F	Null	Macro	None	D2: Postop. CSF leak	RP + LD

^aThe suprasellar portion of the adenoma was densely adherent to the sellar diaphragm.

Abbreviations: n=sample size; ID=identification; Intraop. =intraoperative; Postop. =postoperative; M=male; F=female; LD=lumbar drainage; D=postoperative day; RP=reclined position; reop. =reoperation.

Intraoperative CSF leak

30 (14.9%) intraoperative CSF leaks were verified. The variables associated with the occurrence of intraoperative CSF leak were tumor size and tumor type. Being a macroadenoma (19.9%, $p=0.001$) was a highly predictive factor of developing an intraoperative CSF leak. The tumor type significantly affected intraoperative CSF leak rates. Namely, 26.3% of GH-producing tumors leaked, whilst 20.8% of non-functioning tumors leaked, 8.3% of FSH/LH-producing tumors leaked, 2.6% of ACTH-producing tumors leaked and 4.3% of the others (which include prolactin-producing, TSH-producing and plurihormonal adenomas). The remaining variables did not show a statistically significant association (Table 3).

TABLE 3. UNIVARIATE ANALYSIS OF PATIENT CHARACTERISTICS ASSOCIATED WITH INTRAOPERATIVE CSF LEAK

	Intraoperative CSF leak		P Value
	No, n (%)	Yes, n (%)	
Age (years), mean (SD)	51 (16)	50.4 (13)	0.827
Sex			
Male	78 (83.0)	16 (17.0)	0.552
Female	93 (86.9)	14 (13.1)	
BMI (kg/m ²), mean (SD)	29.0 (4.8)	28.5 (4.5)	0.665
BMI by category			
<25	35 (81.4)	8 (18.6)	0.691
25 – 29.99	68 (87.2)	10 (12.8)	
≥30	68 (85)	12 (15)	
Smoking			
No	140 (84.8)	25 (15.2)	0.999
Yes	31 (86.1)	5 (13.9)	
DM			
No	127 (83.0)	26 (17.0)	0.169
Yes	44 (91.7)	4 (8.3)	
Hypertension			
No	90 (87.4)	13 (12.6)	0.429
Yes	81 (82.7)	17 (17.3)	
Dyslipidemia			
No	80 (83.3)	16 (16.7)	0.556
Yes	91 (86.7)	14 (13.3)	
COPD			
No	165 (85.1)	29 (14.9)	0.719
Yes	6 (85.7)	1 (14.3)	
Asthma			
No	162 (85.3)	28 (14.7)	0.51
Yes	9 (81.8)	2 (18.2)	
OSAS			
No	157 (86.3)	25 (13.7)	0.132
Yes	14 (73.7)	5 (26.3)	
Tumor size			
Microadenoma	54 (98.2)	1 (1.8)	0.001
Macroadenoma	117 (80.1)	29 (19.9)	
Tumor type			
Null	61 (79.2)	16 (20.8)	0.009
GH	28 (73.7)	10 (26.3)	
ACTH	38 (97.4)	1 (2.6)	
FSH/LH	22 (91.7)	2 (8.3)	
Others	22 (95.7)	1 (4.3)	
Previous surgery			
No	146 (85.4)	25 (14.6)	0.476
Yes	25 (83.3)	5 (16.6)	
Previous RT			
No	171 (85.5)	29 (14.5)	0.149
Yes	0 (0)	1 (100)	

Significant p values are in bold.

Abbreviations: n=sample size; SD=standard deviation.

Postoperative CSF leak

10 (5.0%) postoperative CSF leaks were verified. Occurrence of an intraoperative CSF leak (23.3% vs 1.8%, $p<0.001$), the consequent lumbar drainage placement at the end of the surgery (22.6% vs 1.8%, $p<0.001$) and no dyslipidemia (9.4% vs 1.0%, $p=0.007$) were reported as statistically significant predictors. The remaining variables did not show a statistically significant association (Table 4).

TABLE 4. UNIVARIATE ANALYSIS OF PATIENT CHARACTERISTICS ASSOCIATED WITH POSTOPERATIVE CSF LEAK

	Postoperative CSF leak		P Value
	No, n (%)	Yes, n (%)	
Age (years), mean (SD)	51 (16)	50 (11)	0.894
Sex			
Male	89 (94.7)	5 (5.3)	0.990
Female	102 (95.3)	5 (4.7)	
BMI (kg/m ²), mean (SD)	28.9 (4.8)	28.4 (3.3)	0.745
BMI by category			
<25	41 (95.3)	2 (4.7)	0.844
25 – 29.99	73 (93.6)	5 (6.4)	
≥30	77 (96.2)	3 (3.8)	
Smoking			
No	156 (94.5)	9 (5.5)	0.694
Yes	35 (97.2)	1 (2.8)	
DM			
No	145 (94.8)	8 (5.2)	0.999
Yes	46 (95.8)	2 (4.2)	
Hypertension			
No	97 (94.2)	6 (5.8)	0.748
Yes	94 (95.9)	4 (4.1)	
Dyslipidemia			
No	87 (90.6)	9 (9.4)	0.007
Yes	104 (99.0)	1 (1.0)	
COPD			
No	184 (94.8)	10 (5.2)	0.999
Yes	7 (100)	0 (0)	
Asthma			
No	181 (95.3)	9 (4.7)	0.438
Yes	10 (90.9)	1 (9.1)	
OSAS			
No	174 (95.6)	8 (4.4)	0.241
Yes	17 (89.5)	2 (10.5)	
Tumor size			
Microadenoma	55 (100)	0 (0)	0.065
Macroadenoma	136 (93.2)	10 (6.8)	

Significant p values are in bold.

Abbreviations: n=sample size; SD=standard deviation.

TABLE 4. CONTINUED

	No, n (%)	Postoperative CSF leak	
		Yes, n (%)	<i>P</i> Value
Tumor types			
Null	74 (96.1)	3 (3.9)	0.183
GH	33 (86.8)	5 (13.2)	
ACTH	38 (97.4)	1 (2.6)	
FSH/LH	23 (95.8)	1 (4.2)	
Others	23 (100)	0 (0)	
Previous surgery			
No	162 (94.7)	9 (5.3)	0.999
Yes	29 (96.7)	1 (3.3)	
Previous RT			
No	190 (95.0)	10 (5.0)	0.999
Yes	1 (100)	0 (0)	
Intraoperative CSF leak			
No	168 (98.2)	3 (1.8)	<0.001
Yes	23 (76.7)	7 (23.3)	
Lumbar drainage			
No	167 (98.2)	3 (1.8)	<0.001
Yes	24 (77.4)	7 (22.6)	

Significant *p* values are in bold.

Abbreviations: n=sample size; SD=standard deviation.

Discussion

Cerebrospinal fluid leaks continue to be a potentially life-threatening complication of skull base surgery despite all the technological advances. Currently, risk factors for intraoperative and postoperative CSF leaks are still poorly defined. The reason is mainly due to a wide variety of studies on the subject with disparate results. This study adds the reality of Centro Hospitalar São João, a Portuguese tertiary health care center, in this panorama.

Concerning the incidence of CSF leak on the studied population, there were 14.9% of intraoperative CSF leaks, being just slightly below the range of percentages described in the literature (18.1-53.2%) [8]. Increased incidences of intraoperative CSF leaks are more correlated with aggressive tumor resections by surgeons, attempting complete resection, than with the type of surgical technique used (microscopic VS endoscopic) [13]. The rate of postoperative CSF leaks was 5.0%, which coincides with that reported in other studies (1.4-16.9%) [7]. These rates are institution-specific and team surgeon-specific.

After analyzing the data, the variables with statistically significant association with occurrence of intraoperative CSF leaks were the tumor size and the tumor type.

The fact that macroadenomas increase the risk of intraoperative CSF leak is already a known association in the literature. Several studies [3,14-16] associate them with an increased risk of intra and postoperative CSF leaks. It should be noted that, although the association between postoperative CSF leak and macroadenomas were not statistically significant, 100% of the postoperative CSF leak were macroadenomas ($p=0.065$). These tumors are larger and have a tendency to extend beyond the normal position of the gland, therefore more invasive surgeries are required [17]. Consequently, the surgeon had to work closer to the sellar diaphragm to remove the maximum of tumor mass [3]. On the other hand, the expansion of the tumor itself may weaken the sellar diaphragm, leading to its protrusion through the open bony floor and thus exposing the arachnoid membrane [18]. One study [19] concluded that each 1 mm increase in tumor size, the odds of having an intraoperative CSF leak increased 3%.

It has also been shown that the type of hormone secreted by the tumor increases the risk of CSF leaks. GH-producing adenomas increased the occurrence of both intraoperative and postoperative CSF leaks, although the latter was not statistically significant. In this particular case, it has been revealed that tumor size and tumor type are intrinsically interconnected characteristics. In this sample, the majority of GH-producing tumors (65.8%) and non-functioning tumors (94.8%) were macroadenomas, in contrast to ACTH-producing tumors that were mostly microadenomas (82.1%, $p<0.001$). A previous study [20] also found an increase of intraoperative CSF leaks in GH-producing adenomas, hypothesizing the possibility of excess growth hormone altering the properties of the sellar diaphragm. Another study [21] underline the fact that the surgical technique used in functioning adenomas tend to be more aggressive to attempt a curative resection.

Regarding the risk factors that had increased the occurrence of postoperative CSF leaks in this study. Intraoperative CSF leak leading to an increased risk of this postoperative complication is a well-established association. Some studies even say that it is one of the most predictive factors of its occurrence [16]. The incidence of postoperative CSF leak is estimated to be 6-fold higher in patients having a CSF leak intraoperatively [8]. In fact, as found in the 3 patients of this sample, the occurrence of postoperative leak without intraoperative leak is possible although it is uncommon, occurring mostly in cases of macroadenomas that extensively deform the local anatomy. This explains the importance of correctly identifying the CSF leaks during surgery to allow a rigorous sealing reconstruction and a prolonged attentive follow-up in order to prevent recurrence [15]. For some authors, the reconstruction technique used in intraoperative CSF leaks is the most important factor to avoid postoperative leaks [22].

Naturally, the presence of a lumbar drain placed during the surgery is also related to an increased risk of postoperative CSF leaks. As in others previous studies that also reported this association [23,24], the

explanation raised for this trend is based on the surgeons' decision to place a lumbar drain in patients who are already more likely to have a postoperative CSF leak, namely a prior occurrence of an intra-operative CSF leak [23]. So, the risk is not directly related to the lumbar drainage but it is to the cause for why it had been collocated. The use of lumbar drain is motivated by preventing the increase of ICP that may disadvantage a normal local healing of surgical reconstruction [25,23]. A recent prospective study [26] with a population not restricted to pituitary adenomas concluded that the junction of a reconstruction with vascularized nasoseptal flap with a perioperative lumbar drainage prevented the occurrence of postoperative CSF leaks.

Despite the result obtained in how not to have dyslipidemia was a statistically significant predictor for the occurrence of postoperative CSF leaks, after a careful analysis of the data, it was concluded that there was an important information collection bias, leading to an incorrect association.

In patients experiencing postoperative CSF leaks during 30 days after the procedure, the first treatment initiated was based on conservative measures like placing a lumbar drain in patients without it, resting in bed at least 5 days and avoiding maneuvers that increase ICP (at an intermediate care unit). Only in two cases, those who manifested a diagnosis of meningitis, it was necessary to return to surgery, and one of them required 3 successive re-operations. It is worthy of note that the recurrence of CSF leak after surgical repair is rare [25]. The surgical technique of pavement reconstruction currently with better results in several studies and with statistically significant association in the prevention of postoperative CSF leak is the vascularized pedicled nasoseptal flap [9,22,24]. It has even been reducing the rates of postoperative CSF leaks to less than 5% [22,24]. For some authors, an early surgical approach is preferable when CSF leak occur [24,8]. For others [27,14], placement of a lumbar drain and bed rest for 5 days is sufficient for most of small leaks. And even there are those who argue that most postoperative CSF leak would resolve between 2 to 10 days without any treatment [28]. There is no great consensus in this area between conservative measures or early surgical exploration. An advantage of early re-exploration cited would be the avoidance of prolonged hospitalizations in cases where conservative therapy fails and surgery is necessary [8].

After a brief review of the literature, there are other risk factors that have been associated with increased CSF leaks that were not found statically significant in this study.

Among them, the increased risk of intra and postoperative CSF leak with increased BMI [9,7,12,10,15] stands out. In this way, they recommend a more solid and rigid surgical reconstruction of the floor in obese patients. Dlouhy et al. demonstrated that an increase of BMI of 5 kg/m² increases the risk of postoperative CSF rhinorrhea by 1.61 times [10]. Increased intra-abdominal pressure leading to an increased intracranial pressure was one of the main reasons reported in these patients [11,10]. It is possible that this cohort's BMI was not high enough to increase the risk of CSF leaks.

Regarding the hypothesis raised of the possible increase of postoperative CSF leak in patients with respiratory diseases (asthma, COPD and OSAS), the association was non-statistically significant. The prevalence of asthma in this study (5.5%) is slightly lower than that described in Portugal (6.8%) [29]. In the same sense, the prevalence of COPD (3.5%) is much lower than that described for the Portuguese population (14.2%) [30], and may have altered the power of the expected results. However, the results showed that intraoperative and postoperative CSF leaks occurred with more frequency on patients with asthma and OSAS. This is in line with the results of a nationally based study concluded that chronic cough and asthma were statistically significant risk factors for the appearance of postoperative CSF leaks based on the instantaneous increase of ICP [12]. As for OSAS, an article reported this comorbidity as a risk factor for increasing spontaneous CSF leaks. The explanation comes from episodic increases in ICP due to nocturnal hypoxia occurring in these patients which, in turn, contributes to hypercapnia and leads to cerebral vasodilation [12]. In patients with severe OSAS, even when awake, they maintain an elevated ICP [31]. The absence of a statistically significant association between OSAS and CSF leak may have been due to the fact that it was not taken into account the disease modifiers (severity, treatment, stability, exacerbations). Actually, it is described that the treatment of

OSAS can restore the ICP to normal values [31]. It is also worth noting the importance of continuous positive airway pressure (CPAP) in the treatment of this condition and its relative contraindication in the postoperative period of these patients. Despite this, the perfect timing for the reintroduction of CPAP is also not well understood [32].

Despite being non-statistically significant, intraoperative CSF leaks occurred with more frequency on patients with systemic hypertension. As the explanation raised for elevated intra-abdominal pressure increasing ICP and the propensity for idiopathic intracranial hypertension in patients with CSF leaks, it is known that arterial hypertension, more specifically the mean arterial pressure (MAP), also has influence on intracranial pressure (Cerebral Perfusion Pressure = MAP – ICP) [10,33] .

Some positive points should be highlighted. This study aimed to present an overview of the possible risk factors to be taken into account in the preoperative evaluation of the patients, for which a large number of variables were selected to be tested. As for all studies, the starting point is to correctly define the variables to be studied and the desired outcomes in the methods section, which was taken into account in the elaboration of the study protocol. This allows studies of the same area to be comparable between them for revisions of the theme. In addition, the collection of data from the hospital's clinical database was performed by only one investigator with the concern of confirming unavailable or doubtful information with the patients themselves. It contributes to a standardized data collection. Finally, to study surgical events like those discussed, a smaller single-institution analysis can report events more accurately and with finer details.

The weaknesses of these studies include its retrospective design that may lead to possible biases. Consideration should be given to the possibility of intraoperative CSF leaks' underdiagnosis what hence the importance of a standardized method for their detection. In this study, the type of intraoperative CSF leak (low or high-flow) and the defect size (small or large) were not subdivided due to lack of information. Furthermore, few cases of CSF leaks were found in the cohort studied, which impaired the multivariate analysis initially predicted. Additionally, some risk factors studied are uncommon in the general population, so drawing solid conclusions about the risk turns out to be difficult. Consequently, the external validity of this study is limited.

Conclusion

This series of 201 patients with pituitary adenoma following endoscopic transsphenoidal pituitary surgery present an overview of the risk factors, frequency and management of CSF leaks. Intra and postoperative CSF leaks were appreciated in 14.9% and 5.0% of patients, respectively.

Despite the current literature, demonstrating that BMI increases the risk of CSF leaks, this association was not statistically significant in this study. However, it demonstrates that there is a significant association between the occurrence of intraoperative CSF leaks and two risk factors: macroadenomas and GH-producing tumors. Despite being non-statistically significant, intraoperative CSF leaks also occurred with more frequency on patients with hypertension, asthma and OSAS. All of them being pathologies that can lead to increased ICP. The risk of postoperative CSF leaks was statistically significantly increased in patients with intraoperative CSF leak. They also appeared with more frequency on patients with asthma, OSAS and on GH-secreting tumors. It is worth mentioning that every postoperative CSF leak occurred on macroadenomas.

A broad understanding of the major risk factors for CSF leaks is really important to enable the development of preoperative risk assessments to identify high-risk patients and thus proposing individualized information relating to preventive and management measures to be taken on each patient. In the future, as this is a Portuguese single-institutional study, it would be interesting to raise the interest in this matter in other medical institutions to achieve a national multi-institutional study.

Conflict of Interest: The authors declare that they have no conflict of interest.

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- ANEXO I –

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REFERENCES

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2. This result was later contradicted by Becker and Seligman [5].
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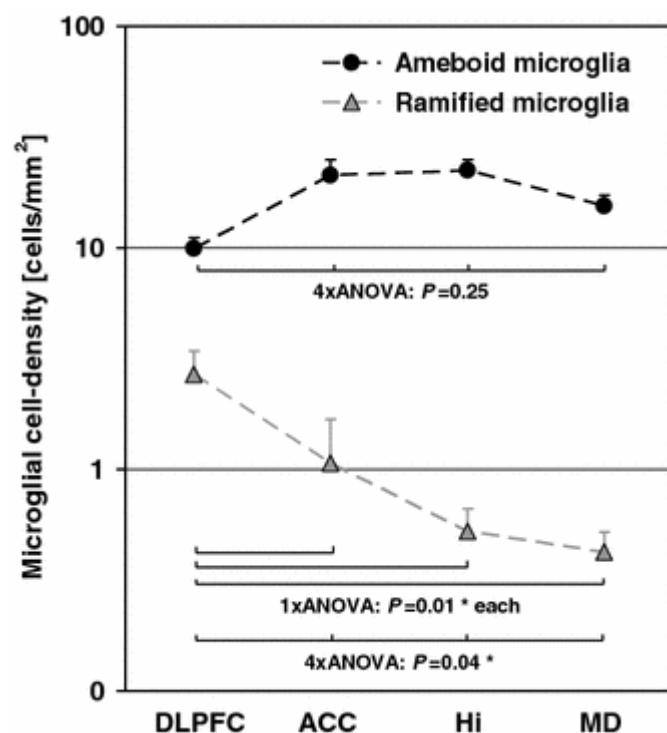
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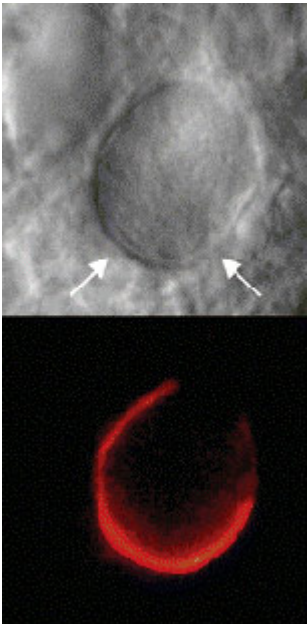
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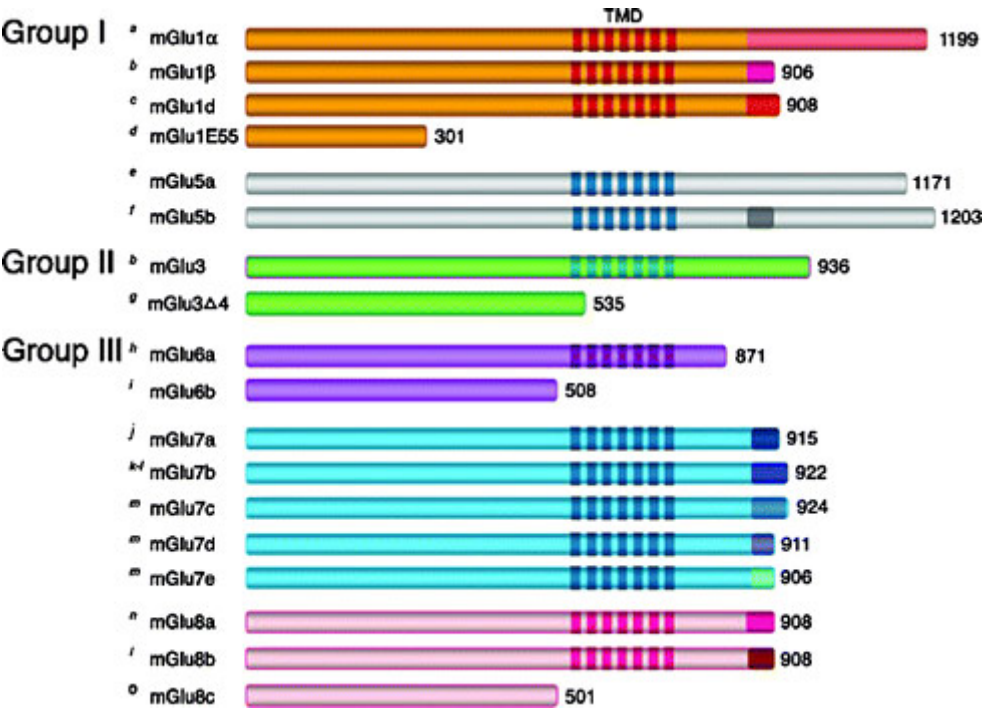
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Tomei conhecimento. Nada a opor.

01 de Outubro de 2018

A Coordenadora da Unidade de Investigação

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Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar de São João

Nome do Investigador Principal:

Christiane Celeste Ferreira Sonnay

Título da Investigação:

Fatores de risco pré-operatório para fistula de líquido cefalorraquidiano
na cirurgia endoscópica transesfenoidal de adenomas da hipófise.

Pretendendo realizar no(s) Serviço(s) de: Neurocirurgia

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Porto, 3 de Julho de 2018.

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Parecer da Comissão de Ética para a Saúde do
Centro Hospitalar de São João / Faculdade de Medicina da Universidade do Porto

Título do Projeto: Fatores de risco pré-operatório para fistula de líquido cefalorraquidiano na cirurgia endoscópica transesfenoidal de adenomas da hipófise

Nome da Investigadora Principal: Christiane Celeste Ferreira Sonnay, estudante do Mestrado Integrado em Medicina da FMUP

Onde decorre o Estudo: No Serviço de Neurocirurgia do CHSJ. Dispõe de autorização do Prof. Doutor Rui Vaz. O profissional de ligação será a Dra. Patrícia Maria Polónia Pinto, que também é a orientadora.

Objectivos do Estudo: Estudo retrospectivo que pretende avaliar a associação entre os fatores de risco pré-operatório, nomeadamente a existência de um índice de massa corporal elevado, de doenças pulmonares obstrutivas e de síndrome de apneia obstrutiva do sono, com a ocorrência de fistulas de líquido cefalorraquidiano (LCR) intra-operatória e pós-operatória na cirurgia endoscópica transesfenoidal em doentes com adenomas da hipófise. Para tal, serão selecionados os doentes operados entre 2007 e 2016 no Serviço de Neurocirurgia do Hospital de São João. Os dados serão extraídos do SClinico e confirmados via entrevista telefónica pela Doutora Patrícia Polónia caso estejam incompletos. Uma análise estatística multivariada será efetuada para investigar a associação entre os fatores de risco e a ocorrência de fistulas de LCR.

Concepção e Pertinência do estudo: As fistulas de líquido cefalorraquidiano são uma complicação importante da cirurgia endoscópica transesfenoidal, largamente empregue atualmente para o tratamento cirúrgico de adenomas da hipófise. Sendo que a maioria das fistulas pós-operatórias surgem no seguimento da ocorrência de fistula intra-operatória, revela-se de particular interesse avaliar os fatores de risco pré-operatórios de ambas estas complicações. No futuro, os resultados obtidos poderão permitir avaliar o risco individual de cada paciente pré-operatoriamente e, deste modo, adequar a técnica cirúrgica, planear e aconselhar o pós-operatório de cada doente. O trabalho proposto não apresenta quaisquer riscos.

Benefício/risco: Não aplicável

Confidencialidade dos dados: A informação a publicar não revelará a identificação dos participantes em estudo. Trata-se de um estudo retrospectivo de dados existentes, sem qualquer intervenção em doentes, em que a recolha de dados passará apenas pela consulta de registos clínicos eletrónicos e, quando necessário, confirmação via telefónica de dados incompletos. O anonimato de tais dados recolhidos será salvaguardado.

Respeito pela liberdade e autonomia do sujeito de ensaio: Em face da natureza do estudo, a obtenção de consentimento informado é dispensável.

Curriculum da investigadora: Adequado à investigação.

Data previsível da conclusão do estudo: Março de 2019

Conclusão: Proponho um parecer favorável à realização deste projecto de investigação.

Porto, 27 de Julho de 2018

A handwritten signature in black ink, appearing to read 'Manuel Pestana', with a stylized, cursive script.

O Relator da CES, Manuel Pestana



Questionário para submissão de Investigação

Exmo. Sr. Presidente da Comissão de Ética do Centro Hospitalar de São João/
Faculdade de Medicina da Universidade do Porto,

Pretendo realizar a investigação infracitada, solicito a V. Exa., na qualidade de Investigador, a sua apreciação e a elaboração do respetivo parecer. Para o efeito, anexo toda a documentação requerida.

IDENTIFICAÇÃO DO ESTUDO

Título da investigação: Fatores de risco pré-operatório para fístula de líquido cefalorraquidiano na cirurgia endoscópica transesfenoidal

Nome do investigador: Christiane Celeste Ferreira Sonnay

Endereço eletrónico: christiane_sonnay@hotmail.com

Contacto telefónico: 965020288

Caracterização da investigação:

☒ Estudo retrospectivo

☐ Estudo observacional

☐ Estudo prospetivo

☐ Inquérito

☐ Outro. Qual? _____

Tipo de investigação:

☐ Com intervenção

☒ Sem intervenção

Formação do investigador em boas práticas clínicas (GCP): ☐ Sim ☒ Não

Promotor (se aplicável): _____

Nome do orientador de dissertação/tese (se aplicável): Patrícia Maria Polónia Pinto

Endereço eletrónico: titapolonia@yahoo.com.br

Local/locais onde se realiza a investigação: Serviço de Neurocirurgia do Hospital de São João

Data prevista para início: 01 / 08 / 2018

Data prevista para o término: 31 / 03 / 2019

PROTOCOLO DO ESTUDO

Síntese dos objetivos:

Com este trabalho, pretende-se avaliar a associação entre os fatores de risco pré-operatório, nomeadamente a existência de um índice de massa corporal elevado, de doenças pulmonares obstrutivas e de síndrome de apneia obstrutiva do sono, e o risco de ocorrência de fístulas de líquido cefalorraquidiano (LCR) intra-operatória e pós-operatória na cirurgia endoscópica transesfenoidal em doentes com adenomas da hipófise. Para tal, serão selecionados os doentes operados entre 2007 e 2016 no Serviço de Neurocirurgia do Hospital de São João. Os dados serão extraídos do SCLínico e confirmados via entrevista telefónica pela Doutora Patrícia Polónia caso estejam incompletos. Uma análise estatística multivariada será efetuada para investigar a associação entre os fatores de risco e ocorrência de fístulas de LCR.

Fundamentação ética (ganhos em conhecimento/ inovação; ponderação benefícios/ riscos):

As fístulas de líquido cefalorraquidiano são uma complicação importante da cirurgia endoscópica transesfenoidal, largamente empregue atualmente para tratamento cirúrgico de adenomas da hipófise. Sendo que a maioria das fístulas pós-operatórias surgem no seguimento da ocorrência de fístula intra-operatória, revela-se de particular interesse avaliar os fatores de risco pré-operatórios de ambas estas complicações. No futuro, os resultados obtidos poderão permitir avaliar o risco individual de cada paciente pré-operatoriamente e, deste modo, adequar a técnica cirúrgica, planear e aconselhar o pós-operatório de cada doente. O trabalho proposto não apresenta quaisquer riscos.

CONFIDENCIALIDADE

De que forma é garantida a anonimização dos dados recolhidos de toda a informação?

A informação a publicar não revelará a identificação dos participantes em estudo.

O investigador necessita ter acesso a dados do processo clínico? ☒ Sim ☐ Não

Está previsto o registo de imagem ou som dos participantes? ☐ Sim ☒ Não

Se sim, está prevista a destruição deste registo após o sua utilização? ☐ Sim ☐ Não

CONSENTIMENTO

O estudo implica recrutamento de:

Doentes: ☐ Sim ☒ Não

Voluntários saudáveis: ☐ Sim ☒ Não

Menores de 18 anos: ☐ Sim ☒ Não

Outras pessoas sem capacidade do exercício de autonomia: ☐ Sim ☒ Não

A investigação prevê a obtenção de Consentimento Informado: ☐ Sim ☒ Não

Se não, referir qual o fundamento para a isenção:

Trata-se de um estudo retrospectivo de dados existentes, sem qualquer intervenção em doentes, em que a recolha de dados passará apenas pela consulta de registos clínicos eletrónicos e, quando necessário, confirmação via telefónica de dados incompletos. O anonimato de tais dados recolhidos será salvaguardado.

Existe informação escrita aos participantes: ☐ Sim ☒ Não

PROPRIEDADE DOS DADOS

A investigação e os seus resultados são propriedade intelectual de:

☒ Investigador ☐ Promotor ☐ Ambos ☐ Serviço onde é realizado

☐ Não aplicável Outro: _____

BENEFÍCIOS, RISCOS E CONTRAPARTIDAS PARA OS PARTICIPANTES

Benefícios previsíveis:

Associação de fatores de risco pré-operatório e o risco de ocorrência de fístulas de líquido cefalorraquidiano na cirurgia endoscópica transesfenoidal em doentes com adenomas da hipófise. No futuro, poderá permitir avaliar o risco individual de cada paciente pré-operatoriamente e, deste modo, adequar a técnica cirúrgica, planejar e aconselhar o pós-operatório de cada doente.

Riscos/incómodos previsíveis:

Ausência de riscos/incómodos previsíveis.

São dadas contrapartidas aos participantes:

· pela participação ☐ Sim ☐ Não ☒ Não aplicável

· pelas deslocações ☐ Sim ☐ Não ☒ Não aplicável

· pelas faltas ao emprego ☐ Sim ☐ Não ☒ Não aplicável

· por outras perdas e danos ☐ Sim ☐ Não ☒ Não aplicável

CUSTOS / PLANO FINANCEIRO

Os custos da investigação são suportados por:

☐ Investigador ☐ Promotor ☐ Serviço onde é realizado

☒ Não aplicável Outro: _____

Existe protocolo financeiro? ☐ Sim ☒ Não

LISTA DE DOCUMENTOS ANEXOS

- ☒ Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João (se aplicável)
- ☐ Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto (se aplicável)
- ☒ Protocolo do estudo
- ☒ Declaração do Diretor de Serviço onde decorre o estudo
(sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)
- ☒ Profissional de ligação
- ☒ Informação dos orientadores
- ☐ Informação ao participante
- ☐ Modelo de consentimento
- ☐ Instrumentos a utilizar (inquéritos, questionários, escalas, p.ex.): _____
- ☒ Curriculum Vitae abreviado (máx. 3 páginas)
- ☐ Protocolo financeiro
- ☐ Outros:

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.

Porto, 13 de Julho de 2018

Nome legível: Christiane Celeste Ferreira Sonnay

Christiane Sonnay

assinatura

Parecer da Comissão de Ética do Centro Hospitalar de São João/FMUP

Emitido na reunião plenária da CE de 14 / 09 / 18

A Comissão de Ética para a Saúde
APROVA por unanimidade o parecer do
Relator, pelo que nada tem a opor à
realização deste projecto de investigação.

Prof. Doutor Filipe [illegible]
Presidente da [illegible]

Comissão de Ética

De: Christiane sonnay [christiane_sonnay@hotmail.com]
Enviado: quinta-feira, 10 de Janeiro de 2019 12:13
Para: comissao.etica@chs.j.min-saude.pt
Assunto: Pedido de adenda ao protocolo

Exma CES,

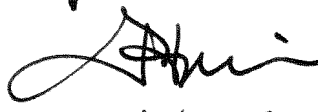
Venho por este meio pedir uma adenda ao protocolo do projecto 'Fatores de risco pré-operatório para fístula de líquido cefalorraquidiano na cirurgia endoscópica transesfenoidal de adenomas da hipófise' aprovado pela CES e autorizado pelo CA para alterar a amostra de doentes seleccionados inicialmente prevista entre 2007 e 2016 para incluir os doentes de 2017, passando a ser estudada a amostra de doentes operados no Serviço de Neurocirurgia do Hospital de São João de 01/01/2007 a 31/12/2017.

Esta alteração advém da necessidade de aumentar a amostra de doentes recolhida e de eventos ocorridos para obter uma análise estatística mais sólida e válida, visto tratar-se de eventos raros. Esta alteração foi aconselhada pela minha orientadora.

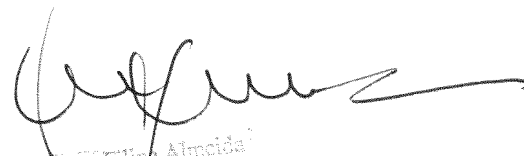
Agradeço desde já a vossa atenção.

Com os melhores cumprimentos,

Christiane Sonnay
Estudante de 6º ano do MIMED na FMUP

Propunha a aprovação da adenda pelo CES da CHUSJ

18.1.2019

Leu e aprova em nome do CES
do CE 21.01.18


Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

-ANEXO IV-

Disclosure of potential conflicts of interest

Disclosure of potential conflicts of interest

Authors must disclose all relationships or interests that could have direct or potential influence or impart bias on the work. Although an author may not feel there is any conflict, disclosure of all relationships and interests provides a more complete and transparent process, leading to an accurate and objective assessment of the work. Awareness of real or perceived conflicts of interest is a perspective to which the readers are entitled. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate. For examples of potential conflicts of interests *that are directly or indirectly related to the research* please visit:

www.springer.com/gp/authors-editors/journal-author/journal-author-helpdesk/publishing-ethics/14214

Corresponding authors of papers submitted to Pituitary
[include name of journal] must complete this form and disclose any real or perceived conflict of interest. The corresponding author signs on behalf of all authors.

The corresponding author will include a statement in that reflects what is recorded in the potential conflict of interest disclosure form. Please check the Instructions for Authors where to put the statement which may be different dependent on the type of peer review used for the journal. Please note that you cannot save the form once completed. Please print upon completion, sign, and scan to keep a copy for your files.

The corresponding author should be prepared to send the potential conflict of interest disclosure form if requested during peer review or after publication on behalf of all authors (if applicable).

☒ We have no potential conflict of interest.

Category of disclosure	Description of Interest/Arrangement

Article title Risk factors for cerebrospinal fluid leak following endoscopic transsphenoidal pituitary adenoma surgery

Manuscript No. (if you know it)

Corresponding author name Christiane Sonnay

Herewith I confirm, on behalf of all authors, that the information provided is accurate.

Author signature Christiane C.F. Sonnay Date 15/03/2019