



Fat and Fibrin Glue: Quo Vadis?

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ABSTRACT

AIM: To analyze the effectiveness of fat and fibrin glue to prevent postoperative cerebrospinal fluid (CSF) leak in pituitary surgery.

MATERIAL and METHODS: Two hundred and eleven patients affected by pituitary adenoma entered this study. Patients that underwent a microscopic transsphenoidal approach between January 2013 and April 2019 were included. All the patients that developed intraoperative CSF leak were treated with fat and fibrin glue. The presence or absence of postoperative CSF leak was considered as a parameter to test the effectiveness of the intraoperative reconstruction technique used.

RESULTS: Postoperative CSF leak was observed in 5 patients (2.4%). Among patients with an intraoperative low-grade CSF leak (1 or 2), 97.9% did not develop a postoperative CSF leak. In contrast, those who presented an intraoperative CSF leak of grade 3, had a worse prognosis.

CONCLUSION: Fat and fibrin glue is currently an effective method in the treatment of low-grade intraoperative CSF leak. In case of intraoperative CSF leak of grade 3, it should be used combined with the nasoseptal flap technique to obtain a safer reconstruction.

KEYWORDS: Cerebrospinal fluid leakage, Reconstructive phase, Pituitary surgery, Skull base

ABBREVIATIONS: CSF: Cerebro-spinal fluid, NSF: Naso-septal flap, EEA: Endoscopic endonasal approach, MRI: Magnetic resonance imaging

INTRODUCTION

Pituitary adenomas are usually benign lesions and their prevalence is increasing (18,41). Apart from prolactinomas, surgery represents the first-line treatment (37).

The most feared complication of this surgery is the postoperative cerebrospinal fluid (CSF) leak (9). The introduction of nasoseptal flap (NSF) (23), in the reconstructive phase of this surgery, determined a remarkable decrease of postoperative CSF leak rates (29). However, this successful technique was designed for the endoscopic approach (23). According to this, in all the articles that reported a favorable experience with

the NSF, the endoscopic-assisted technique was performed (22,34,43).

Up to date, there are few conditions where the nasoseptal flap (NSF) is not considered as a valid option in the reconstructive phase: 1) when the neurosurgeon does not use an endoscopic technique or 2) when the neurosurgeon uses an endoscopic technique, but there is no genuine indication for the mentioned flap. Therefore, the young skull base neurosurgeon is challenged to master other techniques (other than NSF) for the reconstructive phase, which should be chosen based on the existing shreds of evidence regarding their efficacy. Our team decided to study a reconstruction technique that has been used for a long time: crural fat and fibrin glue.

This study aims to analyze the effectiveness of fat and fibrin glue to prevent postoperative CSF leak in pituitary surgery.

■ MATERIAL and METHODS

Data were collected retrospectively and patients operated through a microscopic transsphenoidal approach between January 2013 and April 2019 were included. The senior author treated all patients. The ones operated through a transcranial approach and/or with history of previous pituitary adenoma surgeries or other types of sellar lesions were excluded.

The intraoperative videos of the patients included in our study were carefully reviewed to identify the presence of intraoperative CSF leak. Then, we stratified the patients according to their intraoperative CSF leak grade.

Surgical Technique

All the patients were treated by the same neurosurgeon (AC). The semi-sitting position was used, taking into account the concept of the sphenoseal point (2,3). A microscopic assisted endonasal trans-sphenoidal approach was performed (6). During the nasal phase, nasal structures were preserved.

After detecting the intraoperative CSF leak, crural fat and fibrin glue (Beriplast® P Combi set, CSL Behring, Montevideo, Uruguay) were placed.

The crural fat graft was collected using sterile dedicated instruments' set and was positioned in the space generated by the durotomy. The edges of the fat block were placed perfectly in-lay. Afterwards, the interface between the dura mater and the fat was sealed with fibrin glue. Finally, it was asked to the anesthesiologist to induce Valsalva's manoeuvre to assess the efficacy of reconstruction.

No other hemostatic agents were used. During the reconstructive phase, the nasoseptal flap was not harvested. Lumbar drainage was not positioned. In the postoperative period, the patients stayed in bed for 48 hours with the head at 30 degrees. Pre and postoperative MRIs with detailed intraoperative images of six patients are shown in the Figures (Figure 1-6).

Classification of the intraoperative CSF leak

Esposito et al. published a useful CSF leak grading system during the intraoperative stage (19). We can synthesize it as follows: Grade 0, no leak observed; Grade 1, small leak, confirmed by Valsalva manoeuvre, without obvious diaphragmatic defect; Grade 2, moderate leak with obvious diaphragmatic defect; or Grade 3, large diaphragmatic defect.

■ RESULTS

Of the 211 patients included in this study, 51 presented intra-

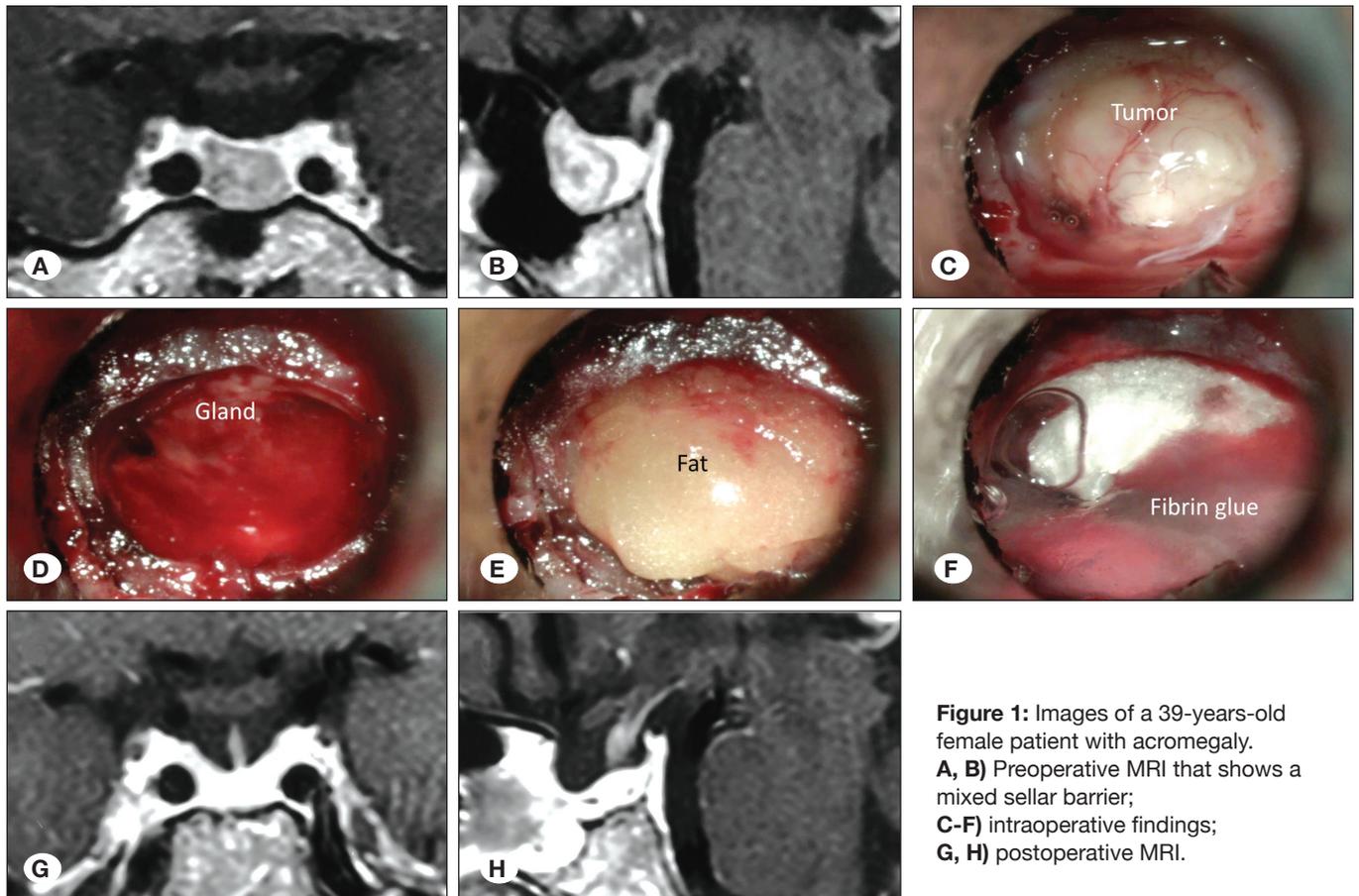


Figure 1: Images of a 39-years-old female patient with acromegaly. **A, B)** Preoperative MRI that shows a mixed sellar barrier; **C-F)** intraoperative findings; **G, H)** postoperative MRI.

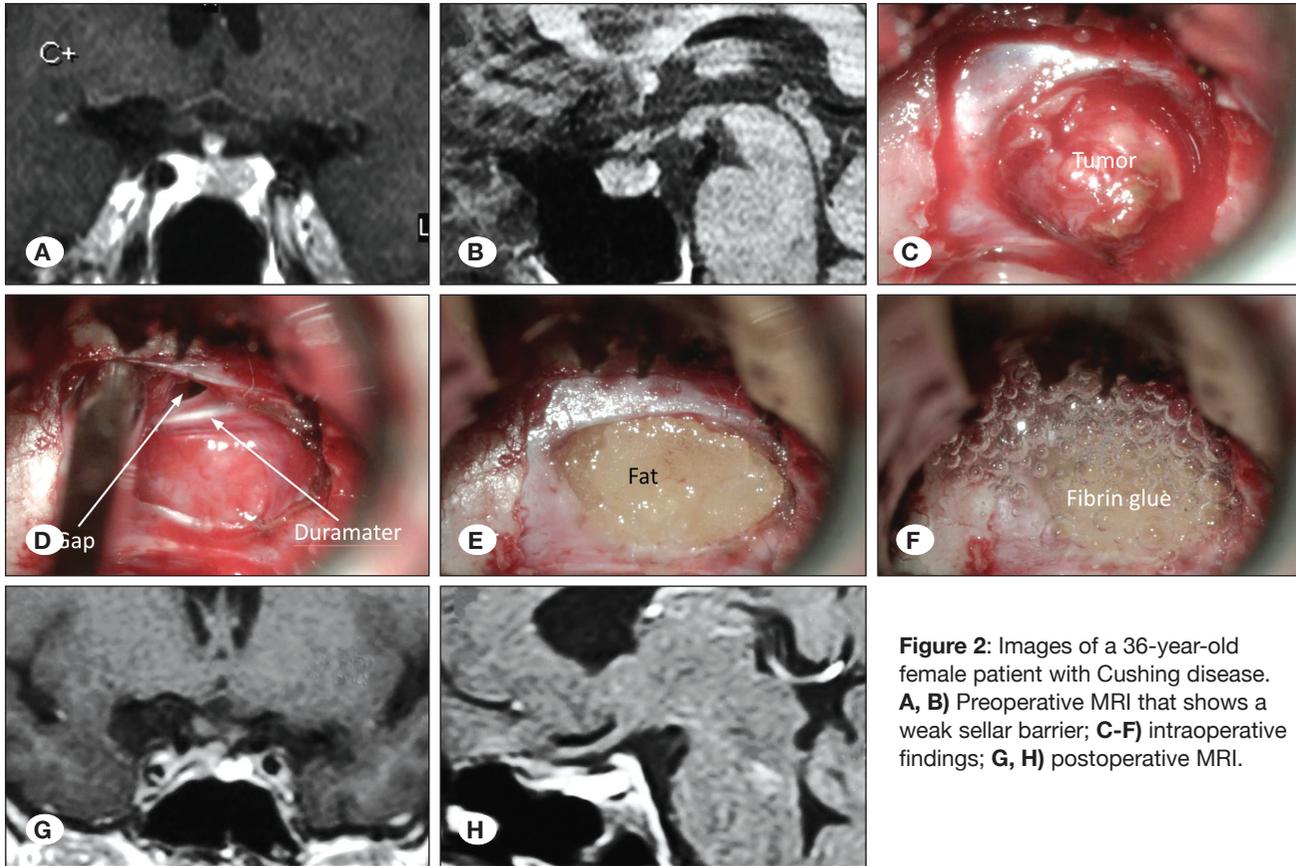


Figure 2: Images of a 36-year-old female patient with Cushing disease. **A, B)** Preoperative MRI that shows a weak sellar barrier; **C-F)** intraoperative findings; **G, H)** postoperative MRI.

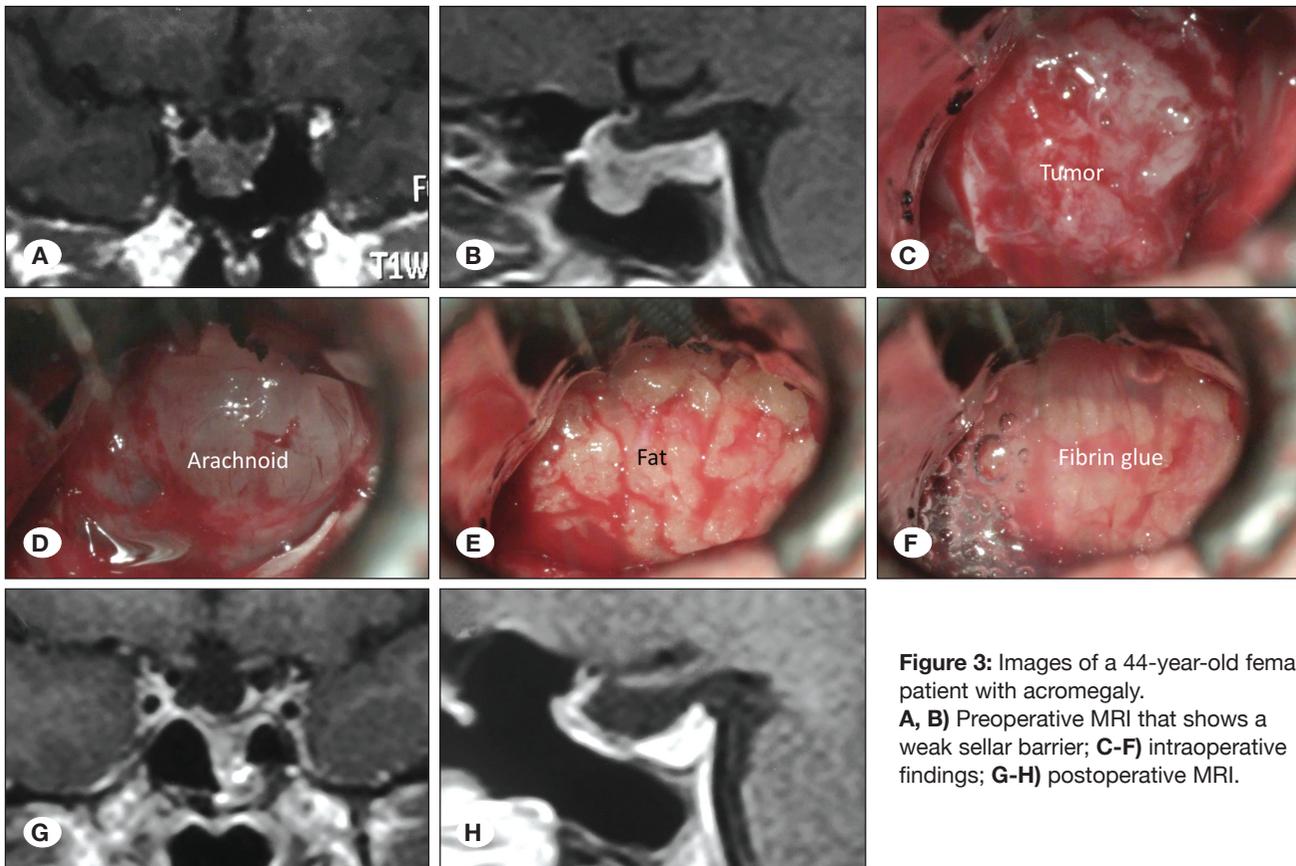


Figure 3: Images of a 44-year-old female patient with acromegaly. **A, B)** Preoperative MRI that shows a weak sellar barrier; **C-F)** intraoperative findings; **G-H)** postoperative MRI.

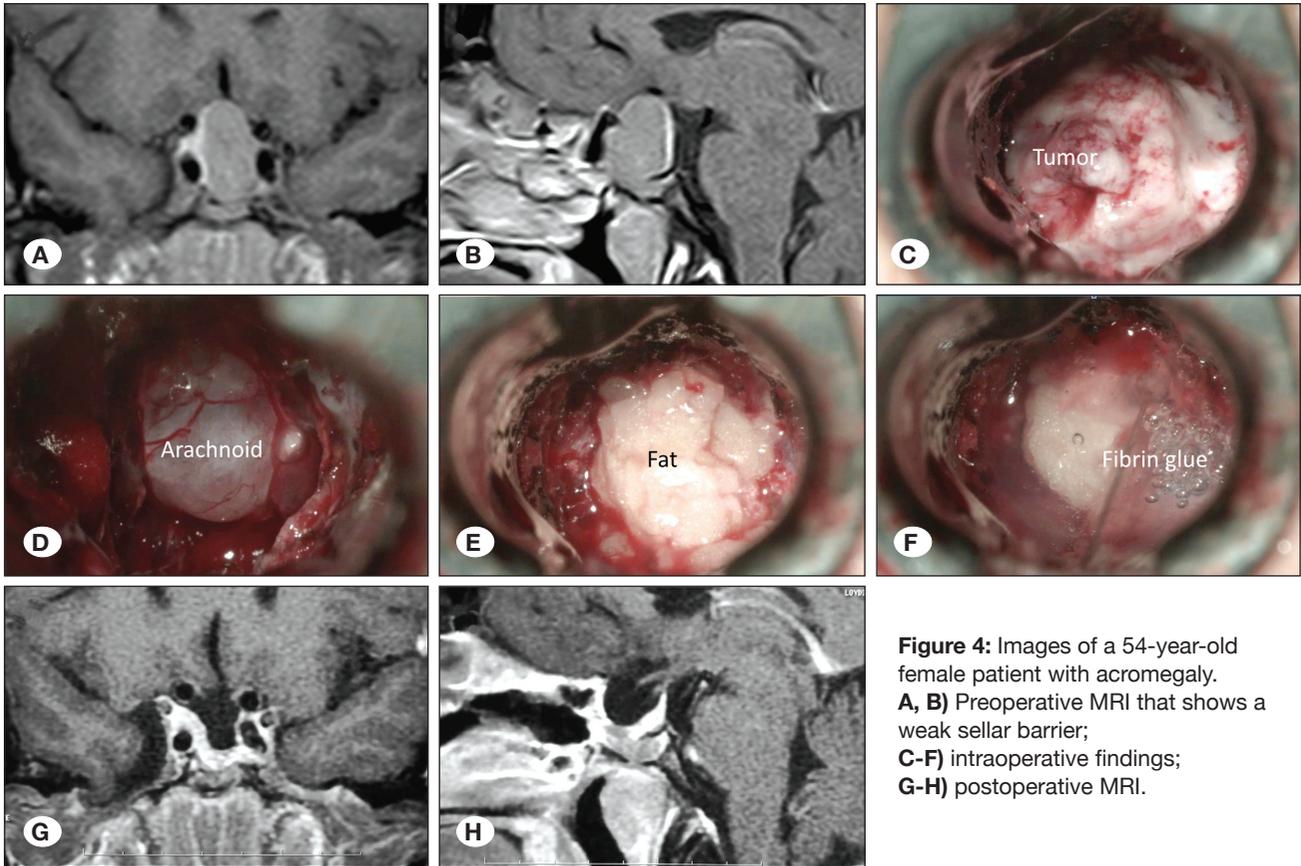


Figure 4: Images of a 54-year-old female patient with acromegaly. **A, B)** Preoperative MRI that shows a weak sellar barrier; **C-F)** intraoperative findings; **G-H)** postoperative MRI.

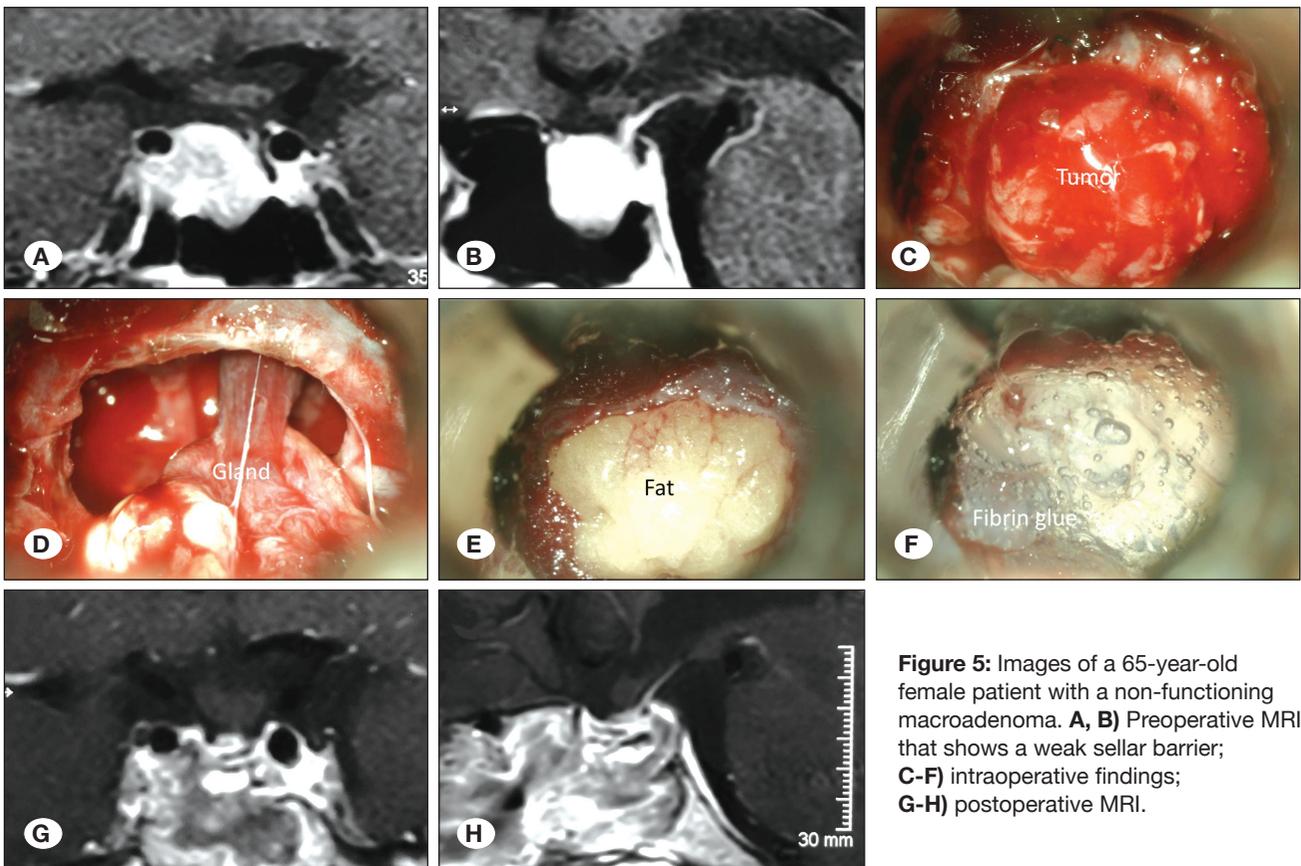


Figure 5: Images of a 65-year-old female patient with a non-functioning macroadenoma. **A, B)** Preoperative MRI that shows a weak sellar barrier; **C-F)** intraoperative findings; **G-H)** postoperative MRI.

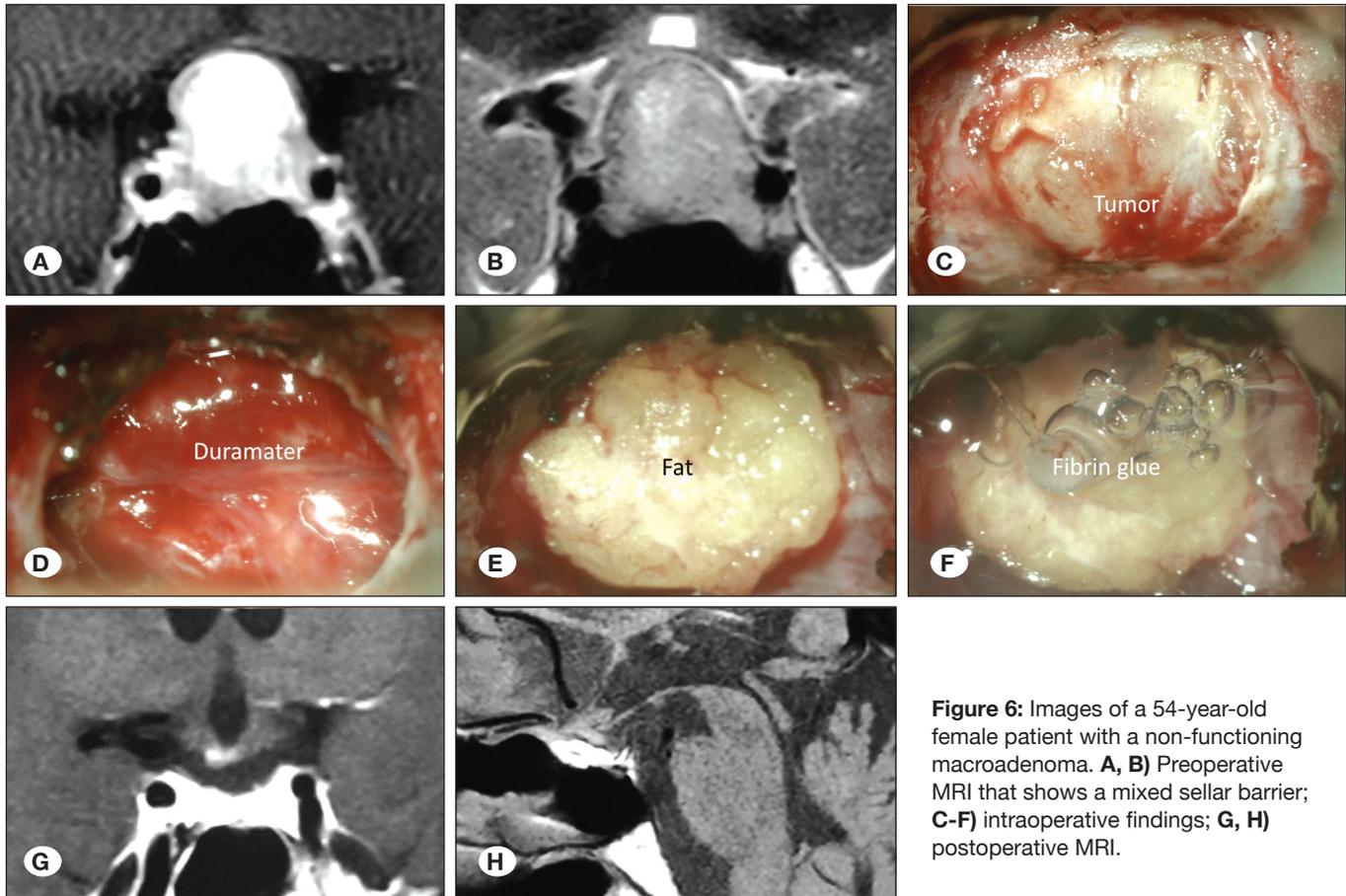


Figure 6: Images of a 54-year-old female patient with a non-functioning macroadenoma. **A, B)** Preoperative MRI that shows a mixed sellar barrier; **C-F)** intraoperative findings; **G, H)** postoperative MRI.

operative CSF leak and 5 patients developed postoperative CSF leak (Table I).

Intraoperative CSF leak rate was 24.2% (n=51). All of these patients were treated with autologous fat and fibrin glue without using flaps.

The overall postoperative CSF leak rate was 2.4% (n=5). The rate of postoperative CSF leak in patients with evidence of intraoperative CSF leak was 9.8% (n=5). In these patients, lumbar drainage was positioned and revision surgery was performed: the first reconstruction was removed and a second fat graft, collected from the same crural site, was placed inside the osteodural defect and sealed with an external layer of fibrin glue. No further complications were noted.

The intraoperative CSF leak grade distribution, according to the mentioned classification, was: 75.8% with grade 0 (n=160), 7.1% with grade 1 (n=15), 15.2% with grade 2 (n=32), and 1.9% with grade 3 (n=4).

Table I shows the number of patients with intraoperative CSF leak according to their grades and evidence of postoperative CSF leak. Among the patients with intraoperative CSF leak of grade 1 (n=15), no cases of postoperative CSF leak were observed. Patients with evidence of intraoperative CSF leak of grade 2 (n=32) presented postoperative CSF leak in 1 case (3.1%).

Table I: Number of Patients with Postoperative CSF Fistula according to Their Grade of Intraoperative CSF Leak

Intraoperative CSF Leak Grade	Number of Patients	Postoperative CSF fistula
0	160	0
1	15	0
2	32	1
3	4	4

All patients with intraoperative CSF leak of grade 3 (n=4) presented postoperative CSF leak (100%). Within the patients with postoperative CSF leak (n=5), 80% (n=4) were classified with an intraoperative CSF leak of grade 3 and 20% (n=1) a grade 2.

Among all the patients included in the series (n=211), 97.6% (n=206) did not develop postoperative CSF leak.

During the early postoperative period one case of crural subcutaneous hematoma (n=1) was recorded as the only complication of the fat donor site. No crural wound infections were detected.

■ DISCUSSION

Intra and Postoperative CSF Leak Rates

Several authors report global rates of postoperative CSF leak ranging from 3-5%. Currently, this rate is similar for both microscopic and endoscopic techniques (30).

In the present study, using fat and fibrin glue as the only anti-CSF leak method, the overall CSF leak rate was 2.4%. The data and the results of the most recent published papers regarding sellar floor reconstruction techniques were analyzed. Our findings are aligned with the data previously reported (Table II) (1,4,5,12-15,17,20,21,24-26,32,35,39,42).

Intraoperative CSF leak rates depend on several factors: the type of sellar barrier (7,40), invasion of the third ventricle (19), BMI (20), and the surgeon's learning curve (21).

Strickland et al. reported that among their patients, 37.4% developed an intraoperative CSF leak (38). In our series, intraoperative CSF leak rate was 24% (n=51).

To calculate the overall CSF leak rate, the entire series of patients (with or without intraoperative CSF leak) was taken into account. However, the authors believe the effectiveness of an anti-CSF leak method should not be quantified on the overall postoperative CSF leak rate. For this reason, to

determine the effectiveness of fat and fibrin glue as an anti-CSF leak method, we included, in our analysis, just the patients with evidence of intraoperative CSF leak.

Consequently, it is not possible to affirm that the effectiveness of the reconstruction technique used was represented by the overall percentage of patients without postoperative CSF leak 97.6% (n=206) because it would be conceptually wrong. The fat and fibrin glue method's effectiveness should not be estimated on the overall rate of postoperative CSF leak of 2.4% (n=5); in fact, this data has been calculated considering all the patients in the series (n=211). The evaluation of the fat and fibrin glue reconstruction method's effectiveness should be based on the postoperative rate (9.8%, n=5) of CSF leak in patients who presented intraoperative CSF leak (n=51). Accordingly, it is represented by the rate of patients with intraoperative CSF leak who did not develop postoperative CSF leak (90.2%, n=46).

Comparing the success of the several anti-CSF leak methods reported in literature is not easy; according to that, as discussed in the previous section, the results generally show postoperative CSF leak rates, without specifying how many patients showed intraoperative CSF leak. Indeed, it is useful to distinguish, in the previous literature, intraoperative and postoperative CSF leaks rates (7).

Table II: Intra and Postoperative CSF Leak Rates Reported in the Previous Literature

Authors	Institution City, Country	Study Design	Interval	N	IOP CSF Leak Rate (%)	POP CSF Leak Rate (%)
Aijan et al. (1)	California, USA	Retro	2007-2012	176	NA	4.5
Bokhari et al. (4)	Kogarah, Australia	Retro	1998-2010	79	19%	2.5
Boling et al. (5)	Multicentric	Retro	2002-2014	982	NA	5.5
Cerina et al. (12)	Zagreb, Croatia	Pro	2012-2013	70	NA	NA
Chabot et al. (13)	NY - Illinois, USA	Retro	2009-2014	39	53.8	10.3
Chi et al. (14)	Renji, China	Retro	2011-2012	80	20	5
Chohan et al. (15)	NY, USA	Retro	2003-2014	62	69	1.6
Dallapiazza et al. (17)	Virginia, USA	Retro	2010-2013	56	58	7.1
Gondim et al. (20)	Fortaleza, Brasil	Retro	1998-2009	301	10.3	2.6
Gondim et al. (21)	Fortaleza, Brasil	Retro	2000-2012	374	NA	3.7
Hofstetter et al. (24)	NY, USA	Pro	2004-2010	71	60.6	1.4
Jakimovski et al. (25)	NY, USA	Retro	2003-2011	203	61	3.0
Jang et al. (26)	Changwon, South Korea	Retro	1998-2014	331	14	1.8
Qureshi et al. (32)	Illinois, USA	Retro	2006-2012	78	10.3	1.3
Robins et al. (35)	Leeds, UK	Retro	2009-2016	142	19.6	3.7
Thawani et al. (39)	Pennsylvania, USA	Retro	2009-2014	203	40.4	10.3
Zhan et al. (42)	Shandong, China	Retro	2008-2014	313	NA	3.8

Retro: Retrospective, **Pro:** Prospective, **N:** Number of patients, **IOP:** Intraoperative, **POP:** Postoperative, **CSF:** Cerebro-spinal fluid.

The use of fat and fibrin glue as reconstruction method in a microscopic transsphenoidal approach

Several reference centres of pituitary pathology do not use a full endoscopic technique (37). It may be explained with two main reasons: 1) they do not want to abandon the microscopic technique because of the good outcomes achieved or 2) they are in a transition stage between both techniques and they practice a kind of “assisted endoscopy”.

The NSF was designed to be used with the endoscopic technique (31). An easy and correct preparation, following the original work’s landmarks, is not achievable with the microscopic technique. Hence, centres that do not use or master the endoscopic technique could not take advantage of NSF during the reconstructive phase. The authors believe that the use of fat and fibrin glue represents a valid alternative for these groups.

NSF is not indicated in standard pituitary surgery. Generally, its application is reserved for the reconstructive phase of extended EEA (21,33). Within the standard approach context, the use of fat and fibrin glue could be considered as an alternative reconstruction method.

When the surgeon, who masters the endoscopic technique, performs a standard approach and there is evidence of intraoperative CSF leak (usually grade 1 or 2), fat and fibrin glue could be used in the reconstructive phase, without performing the NSF.

In the case of an extended EEA, fat and fibrin glue could be used as the only method for intraoperative low-grade CSF leak (grade 1 or 2) or combined with the NSF if the intraoperative CSF leak is of higher entity (grade 3). Cappabianca et al. describe in their series a successful way to combine them through the “3F” technique (11).

Two concepts must be kept in mind in order to make proper use of fat and fibrin glue plus NSF: the different kinds of intraoperative CSF leaks and the indications of extended EEA in pituitary surgery.

In pituitary surgery the indication of extended EEA with the eventual use of NSF is limited to specific cases of pituitary adenomas: dumb-bell shape, supra or para sellar extension (e.g., invasion of III ventricle and encasement of carotid artery), fibrous or rubbery consistency or recurrent tumour (8,10,27,28).

In a recent publication, Cappabianca et al. presented an innovative and useful technique named “3F” (i.e. fat, flap, flash) (11). This technique demonstrates that the fat and fibrin glue could be perfectly combined with the NSF.

The use of fat and fibrin glue proved to be, in our experience, an effective method during the microscopic stage.

Authors believe, according to Cappabianca et al., that it is not useful to be keen on a technique alone (16). Our team is currently undergoing a transition stage and moving to a fully endoscopic technique for pituitary surgery. Some

publications demonstrate the efficacy of fat and fibrin glue in the endoscopic era (36) and this reconstruction technique will continue to be performed in our department.

For these reasons, the fat and fibrin glue reconstruction method is far from being an old-fashioned tool; on the contrary, it is part of the vanguard in pituitary surgery.

Limitations

All patients in this series were treated with a microscopic technique. In the present study, the potential use of this method in the endoscopy field, alone or combined with the NSF technique, is discussed. In order to demonstrate the real clinical application of these conclusions, it is necessary to include patients treated with endoscopic technique. With this intent, our team is working alongside other groups, who masterfully performs the endoscopic technique.

CONCLUSION

The use of fat and fibrin glue is currently an effective method of treating intraoperative low-grade CSF leak (1 or 2). It represents an effective anti-CSF leak method that should be considered an essential resource in the skull base neurosurgeon’s arsenal of the 21st century.

Nevertheless, other studies with a more extensive series are needed to validate this hypothesis.

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