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Evaluating the Effect of Trans Surgical Fluorescein and its Relationship with Visual Prognosis in Patients with Pituitary Neuroendocrine Tumors

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ABSTRACT

Introduction: Sodium fluorescein is highly effective for neurosurgical procedures. However, its application in terms of color decompression of the vasa nervorum in sellar lesions compressing the chiasm and optic nerves remains unstudied. Additionally, the correlation between the degree of vasa nervorum filling and the visual prognosis of patient's post-surgical resection has yet to be established.

Objective: The aim is to describe the preliminary results of a potential prognostic scale and to assess whether the degree of filling of the optic nerve vasa nervorum and optic chiasm with sodium fluorescein influences the visual prognosis of patients with Pituitary Neuroendocrine Tumors (PitNETs).

Methods: Four patients diagnosed with PitNETs underwent preoperative visual acuity assessment and campimetry. Intraoperative administration of sodium fluorescein both before and after resection was conducted to evaluate the degree of vasa nervorum filling, using a scale developed by the authors. The relationship between fluorescein instillation and patients' visual prognosis was assessed.

Results: The disparity in vasa nervorum staining in the optic chiasm pre- and post-surgery did not impact the visual prognosis three months following surgical resection of pituitary adenomas. Statistical analysis revealed a paradoxical correlation between visual improvement and reduction in hemodynamic vasa nervorum filling. It was noted that a high preoperative score might correlate with better visual prognosis during follow-up.

Conclusion: This study provides insights into the use of fluorescein and its implications for visual prognosis in PitNETs. It was concluded that visual prognosis might be associated with a higher pre-resection score. A prospective study with a larger sample size is necessary to confirm these preliminary findings.

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Introduction

Fluorescence in neurosurgery has a long historical development, with several different biomarkers and biochemicals being used [1]. Sodium fluorescein is a coloring substance that, when exposed to the YELLOW 560 (YE560) filter on KINEVO 900 and PENTERO 900 microscopes (Carl Zeiss Meditec, Oberkochen, Germany), allows for differentiation between healthy tissue and tumor tissue in the brain [2].

It accumulates in specific areas of the brain as a result of compromised blood-brain barrier leakage [3]. An incidence of 9.72% of adverse effects of fluorescein has been described (náusea, vomiting, urticaria and bronchospasm [4]. Currently, in neurosurgery, the incorporation of fluorescein is associated with a higher percentage of total brain tumor resections (77.5% vs. 27.1%) and skull base tumors [5,6].

Intrathecal fluorescein is proved with high specificity and sensitivity to detect cerebrospinal fluid leak in endoscopic endonasal procedures [7]. Also, in the bibliography is described fluorescein sodium video angiography to evaluate blood flow within vessels and exclusion of aneurysm after surgical clipping with safer manipulation [8]. It is an effective and safe tool for the biopsy or tumor resection of patients suspected of having non-Hodgkin B-cell lymphoma with preoperative MRI showing homogeneous lesions with contrast [9]. Another use of fluorescein in neurosurgery is that it enables visualization of the most compromised nerve bundles, identification of target fascicles for biopsy, and increased diagnostic certainty of peripheral nerve biopsies [10].

Patients diagnosed with pituitary adenomas exerting a mass effect on the optic chiasm present with two significant characteristics. First, they exhibit visual field defects or visual acuity impairments and second, they have the peculiarity that, upon administering sodium fluorescein, certain patients experience filling defects of the vasa nervorum in the optic chiasm [11]. The approach if it is transcranial or transsphenoidal should be preferred according to the location of the pathology and anatomical and histological characteristics of this region in this study, there was only realized the transcranial approach because the need for the YELLOW 560 filter in the microscopes [12].

Patients with PitNETs could exert a mass effect on the optic chiasm and exhibit visual field defects on campimetry [13]. Upon administration of sodium fluorescein, certain individuals experience filling defects in the vasa nervorum of the optic chiasm.

This study aimed to describe a new scale developed by the collaborators in patients with pituitary macroadenomas who were administered trans-surgical fluorescein, and its relationship with the improvement of visual prognosis.

Materials and Methods

Four consecutive patients of all ages attending our Neurosurgery Department between 2021 and 2022 years of age were included in the study.

All individuals with brain MRI findings suggestive of PitNETs, confirmed by histopathology, were included.

Pre- and post-surgical assessments of visual acuity and campimetry were performed by an ophthalmology service.

The surgical procedure included a transcranial pterional approach, with an incision at the level of the upper edge of the zygomatic arch. Subgaleal dissection of the flap was performed, followed by temporal muscle detachment. Subsequently, a craniotomy with two burr holes was performed: one behind the frontozygomatic suture, below the superior temporal line, and the other behind the spheno-temporal suture at the level of the squama of the temporal bone. Durotomy was performed [14].

The microsurgical techniques were performed using a KINEVO 900 and/or PENTERO 900 microscope (Carl Zeiss Meditec, Oberkochen, Germany). Cisternal dissection was conducted from proximal to distal to expose the optic nerve and the chiasm. Once the visual pathway was exposed, the YELLOW 560 (YE560) filter of the KINEVO 900 and/or PENTERO 900 microscopes was employed. Prior to surgical tumor resection, intravenous 0.4 ml was administered intravenously, followed by 20 ml of saline solution 0.9% were administered. The hemodynamic filling pattern of the vasa nervorum was observed in the arterial, capillary, and venous phases of both the optic nerves and the chiasm.

After gross total resection (GTR), the same technique was performed again to assess the immediate postsurgical hemodynamic filling pattern.

We developed a new classification based on a scoring system after fluorescein administration in patients with PitNETs. The static and hemodynamic filling patterns of the vasa nervorum in the arterial, capillary, and venous phases of the optic nerves and chiasm were evaluated before and after the GTR. Scores were awarded based on the filling quadrants, with one point for each quadrant capturing the contrast. A minimum score of 0 points and maximum score of 16 points were obtained. We performed static and dynamic analyses of the vasa nervorum, in which the static analysis proved that based on the quadrant division of filling, if it filled the four quadrants–four points, three quadrants–three points, two quadrants–two points, and one quadrant–one point, without fill–cero points. In the dynamic analysis, a point was assigned based on hemodynamic filling in the arterial, capillary, and venous phases in each quadrant. If it presented filling in three phases, three points, in two phases, two points, and one phase, one point. Without filling, cero points [Figure 1].

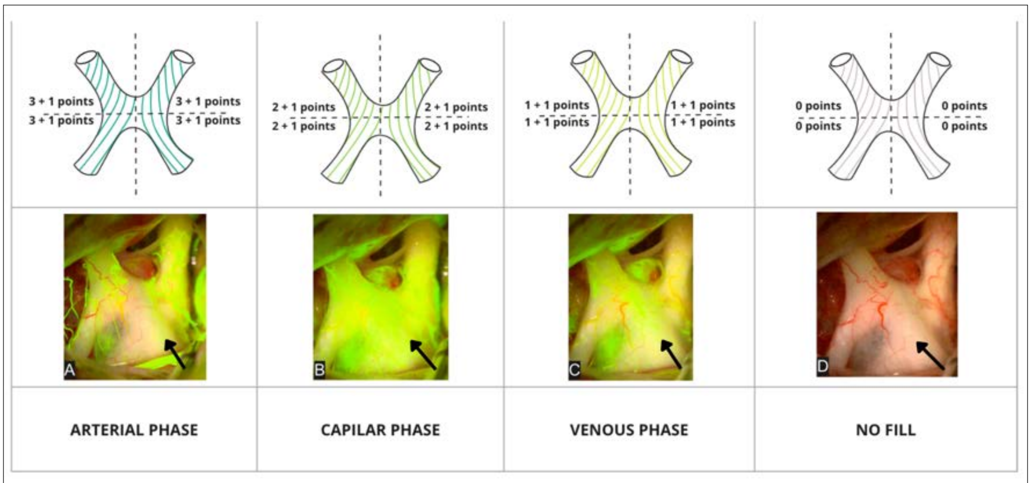

Figure 1: Static and Hemodynamic Filling

Static and dynamic analysis where it is evidence of the three phases of hemodynamic filling (arterial, capillary and venous phase). The optic chiasm is divided into four quadrants to make a score for the hemodynamic filling of the vasa nervorum (16 points in total). If there is filling in the four quadrants, it is given one point for each quadrant. If there is filling in the three phases of hemodynamic filling, it is given one point for each phase in every quadrant.

Individuals were reassessed by the ophthalmology service three months after discharge.

A comparison was made between pre- and post-resection scores and their relationship with visual acuity and campimetry. The Pearson's coefficient was used to determine correlations.

Statistical analysis was performed using IBM SPSS Statistics (version 23.0; SPSS Inc., Chicago, IL, USA).
All the included patients who agreed to participate signed an informed consent form. This study was approved by the local Ethics Committee.

Results

Case 1

In the first case there was a high score before the resection of the tumor (16 points) and posterior to the resection there was a reduction of the score (12 points) with improvement of the visual acuity in three months [Figure 2].

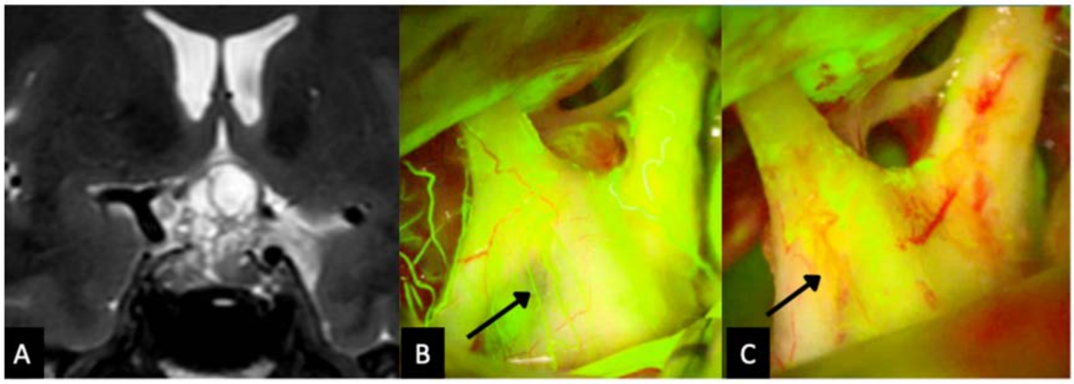

Figure 2: A 53-year-old Male with a Pituitary Adenoma Underwent Microsurgical Resection

A) MRI in the coronal cut T2 sequence showing a pituitary adenoma with severe compression of the optic chiasm with size of 24.6 x 17.7 x 14.7 mm. B) Hemodynamic filling of the vasa nervorum before surgical resection with filling of the four quadrants in the three phases of hemodynamic filling demonstrating 16 points. C) Hemodynamic filling of the vasa nervorum posterior to surgical resection where there is evidence of filling of three quadrants in the three stages of hemodynamic filling. There is absence of filling in two quadrants in the capilar phase when it demonstrates 12 points.

Case 2

The case 2 presented is a female of 87 years old with pituitary apoplexy and amaurosis. This result indicated that the score prior to microsurgical resection was low (6 points), with an improvement in the score after resection (8 points), without presenting improvement in campimetry at the three month-follow up [Figure 3].

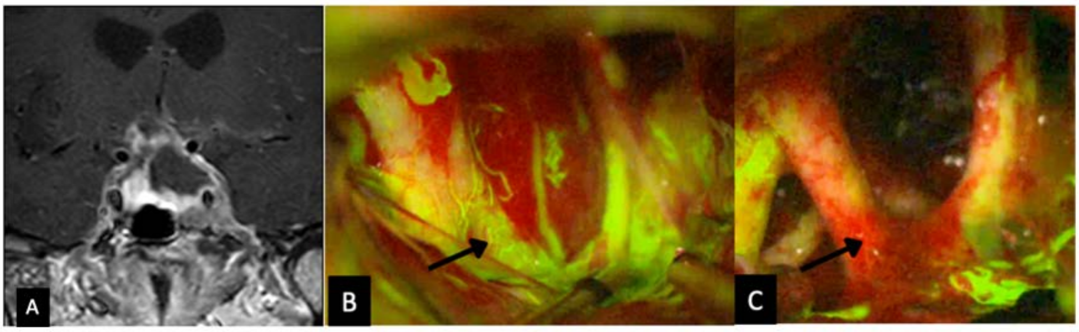

Figure 3: Female of 73 Years Old with Diagnosis of Pituitary Adenoma and Apoplexy

A) MRI in coronal cut and T1 sequence showing pituitary adenoma with invasion of the cavernous sinus, pituitary apoplexy and displacement of the optic chiasm. B) Hemodynamic filling of the vasa nervorum previous to surgical resection with filling of the inferior quadrants in the three phases of hemodynamic filling with score of 6 points. C) Hemodynamic filling of the vasa nervorum posterior to surgical resection with filling of the right superior and inferior quadrants in the three phases of hemodynamic filling with a score of 8 points.

Case 3

The third case presented a patient who had a preoperative score of 14 points and posterior to the surgical resection the patient had 12 points. In the follow-up, the patient had an improvement in the visual acuity [Figure 4].

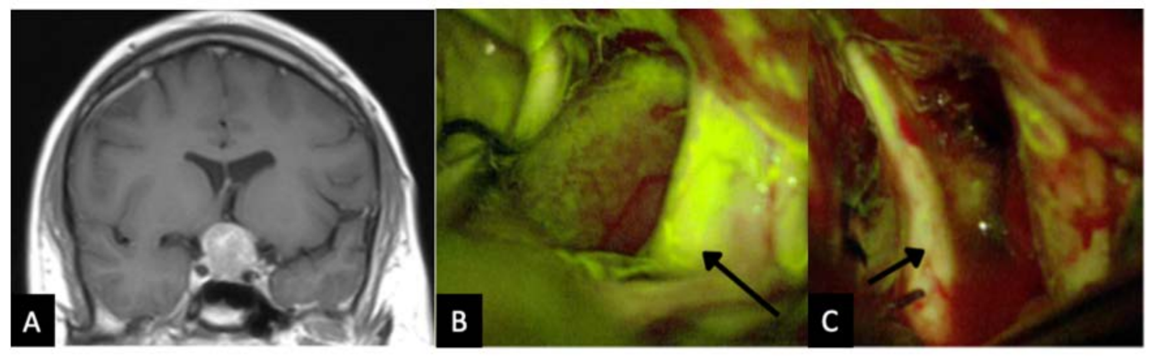

Figure 4: Male 38 Years Old with a Pituitary Adenoma

A) MRI in coronal cut and T1 sequence showing pituitary adenoma with size of 21 x 22 mm. B) Hemodynamic filling previous to surgical resection with absence of filling of the three phases in the superior left quadrants and inferior right quadrants with an absence of filling in the venous phase in the superior right quadrant giving a score of 14 points (shown in arrow). C) Hemodynamic filling posterior to resection of the pituitary adenoma. The patient showed hemodynamic filling in the three phases in the superior left quadrant and in both right quadrants showing an absence of filling in the left inferior quadrant with a total score of 12 points (shown in arrow)

Case 4

The fourth case was the only patient with an increase in the postoperative score (15 to 16 points), with improvement in visual acuity at three months of follow-up [Figure 5].

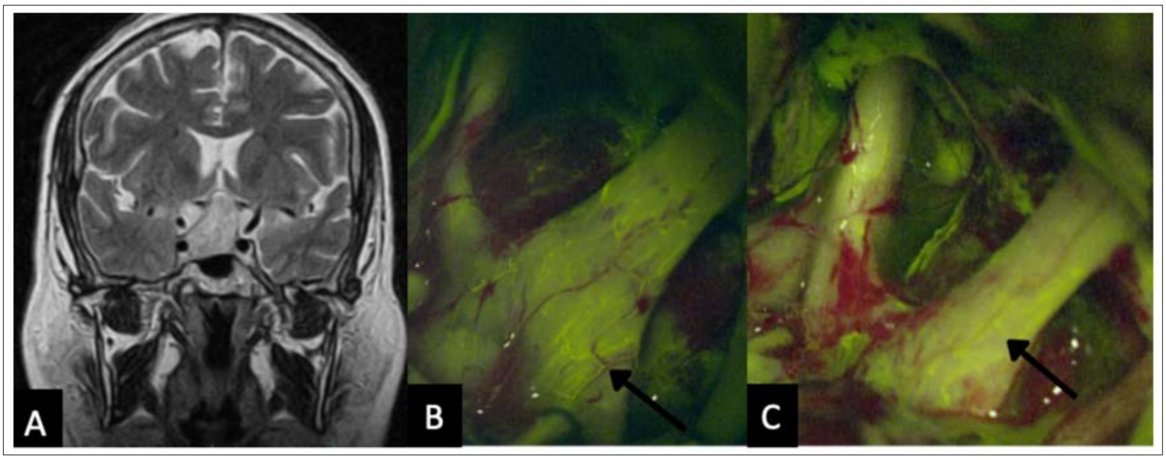

Figure 5: Female 58 Years Old with a Pituitary Adenoma

A) Skull MRI in the coronal section and T2 sequence with pituitary adenoma with size of 25 x 20 mm with displacement of the optic chiasm. B) Hemodynamic filling of the vasa nervorum previous to surgical resection with filling in the arterial phase of the two left quadrants and the right superior quadrant, filling of the four quadrants in the capillary phase and in the venous phase giving a score of 15 points. C) Hemodynamic filling of the vasa nervorum posterior to surgical resection. The patient presented a filling of the four quadrants in the three phases of hemodynamic filling with a total score of 16 points.

Statistical Analysis

In the statistical analysis, a paradoxical correlation was found between the degree of visual improvement and lower postoperative hemodynamic filling measured with the Pearson correlation with a value of - 0.8, which demonstrates an inverse correlation; nevertheless, this difference was not significant ($p = 0.1$). The size of the sample limits the significance of this analysis but guides us in understanding the behavior of the data. Table 1 describes the four patients' pre- and post-surgical scores [Table 1].

Table 1: Static and Dynamic Analysis of Hemodynamic Filling of the Vasa Nervorum in the Optic Chiasm

Case	Visual acuity and campimetry pre resecction	Score pre-resection	Score post-resection	Visual acuity and campimetry in 3 month follow-up
1	Right eye: 20/70 Left eye : 20/20 Normal campimetry of both eyes.	16 points	12 points	Left eye: 20/20 Righ eye: 20/25 Normal campimetry in both eyes
2	Right eye: Total loss of visual acuity Left eye: Total loss of visual acuity Non-assemble campimetry	6 points	8 points	Left eye: Total loss of visual acuity. Right eye: Total loss of visual acuity. Non-assemble campimetry.
3	Right eye: 20/20 Left eye: 20/50 Left upper quadrantanopia	14 points	12 points	Right eye: 20/20 Left eye: 20/20 Normal campimetry.
4	Right eye: 20/20 Left eye: 20/20 Bitemporal superior quadrantopia	15 points	16 points	Right eye: 20/20 Left eye : 20/20 Normal campimetry

Full description of case series. Correlation between the score visual acuity and campimetry pre-resection, score pre-resection, score post resection and prognosis at three-month follow-up.

Discussion

In the present study, the degree of hemodynamic filling of the vasa nervorum of the optic chiasm, evaluated using sodium fluorescein, was analyzed to predict the visual prognosis of patients with PitNETs.

According to the literature, there are several studies that have evaluated the efficacy of other fluorescent agents, such as indocyanine green or 5-aminolevulenic acid, mainly in the resection of brain tumors, CSF fistula and aneurysmal disease [3, 5-8].

Recent studies have shown that the use of fluorescein has a few adverse effects that are reversible in the first 48 h and also low dose injection of intrathecal fluorescein is safe in patients who underwent endoscopic, endonasal approaches [4,15]. As a relatively safe drug in neurosurgical approaches, the use of sodium fluorescein allows the evaluation of its usefulness in patients diagnosed with PitNET; however, this has not been reported in the literature but it is reported the use of fluorescein to improve visualization and resection of other CNS tumors based on blood brain barrier alteration, with a growing evidence base background [16].

A prognostic scale was used, and the relationship between pre- and post-surgical enhancement with fluorescein of the optic chiasm evaluated in quadrants in its different filling phases was evaluated using transcranial approaches.

In the analysis, a paradoxical correlation was found between improvement in visual prognosis and a reduction in the filling of the vasa nervorum in the postoperative period.

In the first and third cases, the individuals presented a decrease in the postsurgical score compared to the presurgical score, obtaining a contradictory result, both with visual improvement, which suggests that the difference in the hemodynamic filling of the vasa nervorum probably does not influence the prognostic vision.

In the second case, the patient 's post-surgical score improved with respect to the previous one, without improving the visual field, which was probably due to a history of pituitary apoplexy, which could be an important variable that compromises the results of this study. According to the literature on patients with pituitary apoplexy, no significant improvement in visual acuity or visual fields has been observed during the postoperative follow-up [17-20]. Therefore, it can be inferred that despite the improvement in the hemodynamic filling score, there was no clinical improvement.

In the fourth case, there was an increase in the postoperative score with subsequent improvement in follow-up campimetry, which suggests that these results could positively influence the visual prognosis.

Despite the paradoxical results in the difference in the pre- and post-resection scores compared to clinical improvement, it was found that the visual prognosis at follow-up could be related to a high pre-surgical score, which could suggest that the microvascular involvement of the nerve optics is compensated and allows for better functional recovery during follow-up.

At the same time, it is important to highlight that this scale is only useful in transcranial approaches using previously described microscopes. Currently, with the advent of transnasal endoscopic approaches in minimally invasive surgery, the lack of filters that allow the use of fluorescein means that this approach cannot be used in the present study.

Likewise, considering that PitNETs are one of the most common tumors in skull base surgery, it is important to carry out additional prospective, longitudinal studies with a larger sample size to determine whether this scale could positively influence visual prognosis in long-term follow-up.

Conclusion

The present study offers a general view of the use of fluorescein and visual prognosis in PitNETs. We expected that filling of the vasa nervorum would improve after tumor resection; however, we observed a paradoxical correlation in the results. We concluded that visual prognosis was related to a better pre-resection score. It is important to consider that this retrospective study is a pilot study to evaluate the feasibility of conducting a prospective study, including more variables that could affect the visual prognosis of patients.

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