Clinical Characteristics and Risk Factors of Delayed Ophthalmoplegia Following Cavernous Sinus Exploration in Endoscopic Pituitary Adenoma Surgery

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Background & Objective

Background:
- Postoperative cranial nerve (CN) dysfunction varies widely (1.4–8%) following endoscopic endonasal surgery (EES) for cavernous sinus (CS) invasion
- Timing of onset and recovery patterns are not well characterized

Objective:
- To analyze **the incidence, risk factors, and temporal patterns** (early vs. delayed) of postoperative ophthalmoplegia following CS exploration

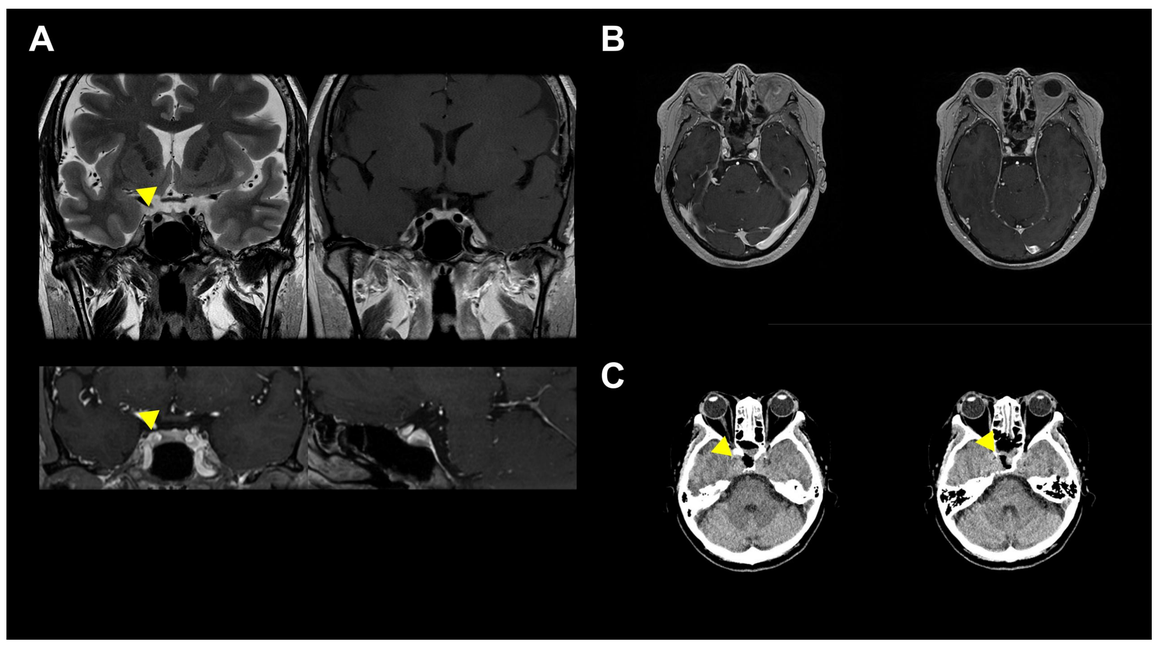

Figure 1. Illustrated Case of Delayed Ophthalmoplegia. (A) Preoperative MRI showing pituitary adenoma with cavernous sinus invasion. (B) Postoperative CT on POD 6 (at the onset of symptoms) revealing swelling of hemostatic agents within the cavernous sinus, leading to compression of cranial nerves.

Material & Methods

Study Design: Retrospective review of 127 patients (March 2020 – September 2024)
Inclusion: Endoscopic skull base surgery with CS exploration

Definitions:
- Early Onset: ≤ 3 days post-op
- Delayed Onset: > 3 days post-op
- Extensive Hemostatic Agent Use: ≥ 3 applications of flowable agent (Floseal/Collastat; containing 2,500 IU thrombin)

Table 1. Baseline Characteristics of Patients Undergoing Cavernous Sinus Exploration

Variable	Value (N=127)
Mean Age	63.5 ± 10.2 years
Tumor Size (Max. diameter)	26.3 ± 8.7 mm
Knosp Grade 3-4 (High grade)	91 (71.7%)
New Postop. Ophthalmoplegia	**17 (13.6%)**
Cranial Nerve VI (Abducens)	9 (52.9%)
Cranial Nerve III (Oculomotor)	7 (41.2%)
Onset Timing	
Delayed (>3 days)	**12 (70.6%)**
Early (≤3 days)	5 (29.4%)

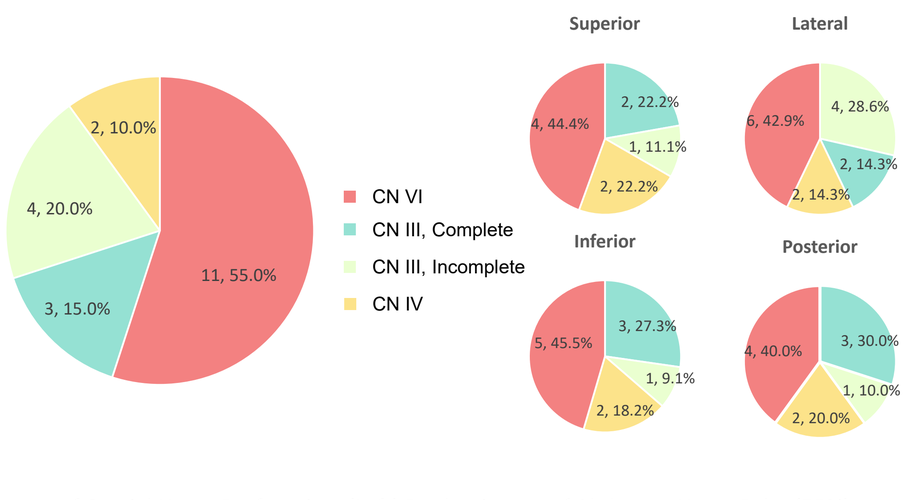

Figure 2. Patterns of Cranial Nerve Dysfunction. (Left) Predominance of Abducens Nerve Palsy (55%) (Right) Distribution by Cavernous Sinus Compartment (p > 0.05)

Results

A. Incidence & Characteristics
1. **Incidence:** 13.6% (17/125 patients) developed new ophthalmoplegia.
2. Affected Nerves: **CN VI** (52.9%) > CN III (41.2%) > CN IV (11.8%)
3. Timing: **Delayed** (>3 days) onset observed in **70.6%** of cases (Mean onset: **9 days**)

B. Key Risk Factors (Multivariate Analysis)
1. **Extensive Hemostatic Agent Use (≥ 3 ea)**: OR 15.57 (p < 0.001)
2. **Lateral Compartment** Involvement: OR 9.00 (p = 0.011)
3. Hypertension: Potential protective effect (OR 0.18, p = 0.054)

C. Distinct Onset Patterns (Early vs. Delayed)
1. **Early Onset (≤ 3 days, n=5):** Significantly associated with high **tumor invasiveness** compared to the delayed group
2. **Factors**: 100% rate of Lateral/Posterior compartment involvement and high Knosp Grade(all p < 0.05)

D. Recovery Outcomes
1. **Excellent Prognosis**: **94.1% (16/17**) completely recovered (**Median: 20 days**).
2. **Factors Delaying Recovery:** Patients with **extensive hemostatic agent use (p < 0.0001)** and **ophthalmalgia (p = 0.007)** showed significantly slower recovery

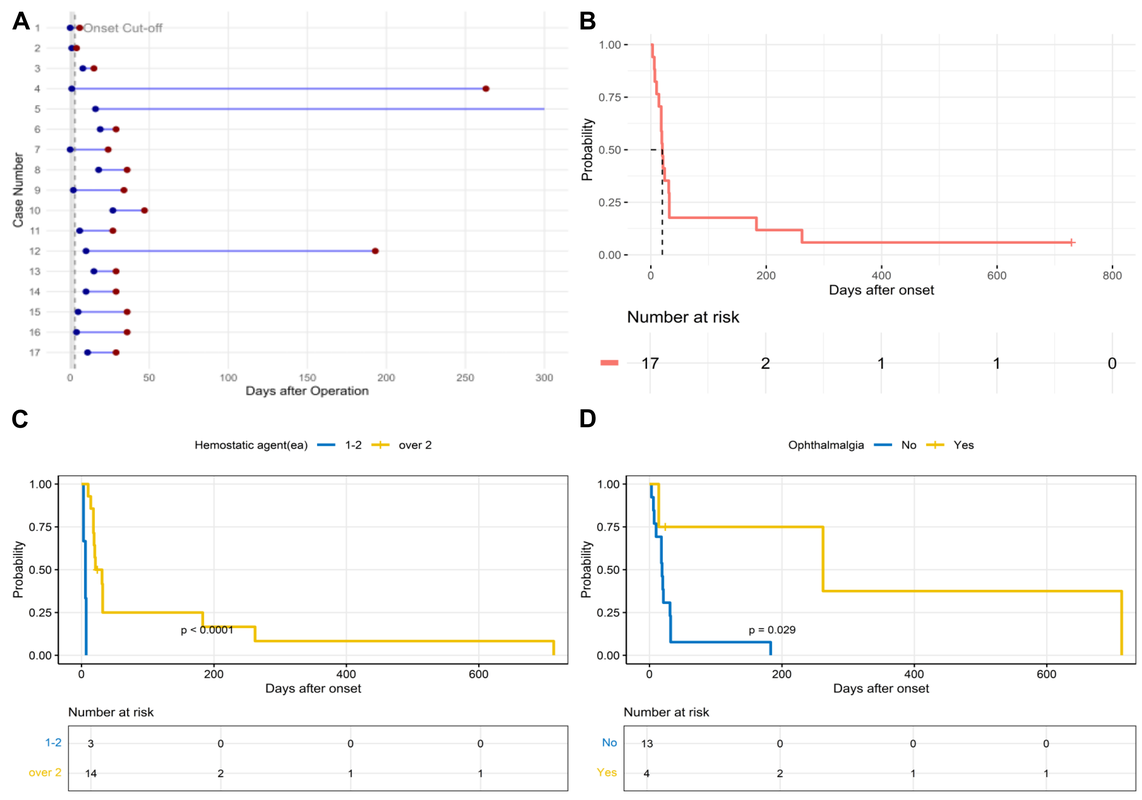

Figure 3. Temporal Patterns and Recovery Analysis of Delayed Ophthalmoplegia. (A) Distribution of Onset and Resolution Timing. (B) Overall Cumulative Recovery Rate (Kaplan-Meier Analysis). (C) Delayed Recovery in Extensive Hemostatic Agent Use Group. (D) Delayed Recovery in Ophthalmalgia Group

Table 2. Multivariable Analysis: Risk Factors for the Occurrence of Delayed Ophthalmoplegia.

Variables	Adjusted OR (95% CI)	P-value
Extensive Hemostatic Agent Use (≥ 3 ea)	**15.57** (3.56 – 98.51)	**< 0.001***
Lateral Compartment Involvement	**9.00** (1.89 – 60.18)	**0.011***
Hypertension	0.18 (0.03 – 0.88)	0.054
Postoperative Hematoma	7.31 (0.51 – 129.43)	0.143
Age	0.72 (0.43 – 1.20)	0.208
Ki-67 Index	1.13 (0.92 – 1.39)	0.225
Functioning Tumor	2.39 (0.49 – 14.75)	0.305

Discussion

Mechanism of Delayed Palsy:
- **Mechanical Compression:** Likely caused by the **expansion of gelatin-thrombin** hemostatic agents or resultant **venous congestion** within the confined CS
- Not associated with inflammatory markers

Early vs. Delayed: Distinct Entities:
- **Early Onset :** Driven by **surgical trauma** in invasive tumors (100% lateral/posterior compartment involvement)
- **Delayed Onset** : Occurred even in less invasive cases, primarily driven by hemostatic agent volume, **independent of surgical complexity**

Conclusions

- **Extensive use of hemostatic agents (≥ 3 ea)** is the most significant predictor for both the occurrence and prolonged duration of symptoms
- Patients with extensive CS exploration should be counseled about **delayed onset** (mean 9 days)

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Declarations

Ethical Approval: This study was approved by the Institutional Review Board of SNUH (IRB No. 2501–082–1607)
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