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Original Article

Clinical Differentiation of Painful Ophthalmoplegia: A Comparative Analysis of Diagnostic Groups

Hüseyin Nezih ÖZDEMİR, Elvin HASANLI, Figen GÖKÇAY, Neşe ÇELEBİSOY

Ege University Hospital, Department of Neurology, İzmir, Türkiye

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ABSTRACT

Objective: Painful ophthalmoplegia (PO) is a clinical syndrome with diverse etiologies, often presenting with overlapping features that complicate diagnosis. Early differentiation is essential to guide appropriate investigations and management. To identify clinical examination findings that differentiate the underlying etiologies of PO and to determine features that may aid in clinical decision-making.

Methods: This retrospective observational study included patients with PO evaluated at a tertiary neuro-ophthalmology center between January 2014 and January 2024. Clinical, demographic, and laboratory data were collected. Patients were classified into diagnostic groups based on etiology. Comparative analyses and binary logistic regression were used to identify clinical predictors that distinguish cavernous sinus-orbital apex (CS-OA) inflammatory syndrome from other causes.

Results: A total of 94 patients were included. CS-OA (28.7%) and carotid-cavernous fistula (CCF) (26.6%) were the most common etiologies. Ptosis was more frequent in CS-OA and was identified as an independent predictor (p=0.031). Chemosis and vision loss were more common in non-CS-OA etiologies and were independently associated with these conditions (p=0.041 and p=0.018, respectively). Chemosis was observed in 88% of CCF cases. Vision loss was most frequent in infectious etiologies, particularly invasive fungal sinusitis. Facial hypoesthesia showed a trend toward an association with CS-OA (p=0.073).

Conclusion: Specific clinical findings, particularly ptosis, chemosis, and vision loss, may help differentiate the underlying etiologies of PO. Careful clinical evaluation can provide valuable guidance for diagnostic decision-making, especially in settings with limited access to advanced investigations.

Keywords: Painful ophthalmoplegia, cavernous sinus, carotid-cavernous fistula, orbital diseases

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Corresponding Author:
Hüseyin Nezih ÖZDEMİR
Ege University Hospital, Department of Neurology, İzmir, Türkiye
huseyinnezihozdemir@gmail.com
ORCID ID: 0000-0002-0651-7276

INTRODUCTION

Painful ophthalmoplegia (PO) refers to a syndrome of periorbital or hemicranial pain with ipsilateral ocular motor nerve palsies.[1] Although it is uncommon, PO carries clinical importance due to the risk of visual and neurological morbidity.[2] Therefore, accurate and timely differentiation of the underlying etiologies is essential.

Different etiologies of PO may present with similar clinical presentations, complicating the diagnostic process.[3] The spectrum of causes includes vascular, inflammatory, neoplastic, and infectious conditions affecting the cavernous sinus, orbital apex, and orbit.[3] Infectious etiologies include bacterial and fungal infections involving the paranasal sinuses and adjacent structures, as well as systemic infections such as syphilis and mycobacterial disease.[4] Neoplastic causes include both primary and metastatic tumors. Vascular disorders encompass intracavernous carotid artery abnormalities, cavernous sinus thrombosis, and abnormal arteriovenous communications. In addition, infiltrative and systemic inflammatory conditions, including hematologic malignancies, connective tissue diseases, and large-vessel vasculitides, may involve these regions.[4] Tolosa-Hunt syndrome is characterized by idiopathic granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbital apex.[5]

While detailed imaging and laboratory investigations are required for a definitive diagnosis, clinical findings play a crucial role in guiding clinicians toward a provisional diagnosis and selecting appropriate diagnostic tests. The aim of this study was to identify clinical examination findings that differentiate the etiologies of PO and to identify features that may aid in clinical decision-making.

METHODS

Study Design and Participants

This retrospective observational study was conducted at a tertiary neuro-ophthalmology laboratory. Patients with PO were retrospectively identified through a review of medical records between January 2014 and January 2024. PO was defined as the presence of periorbital or hemicranial pain accompanied by ipsilateral ocular motor nerve involvement.[1]

Patients aged 18 years and older who were evaluated, diagnosed, and treated in the laboratory were included in the study. The diagnostic workup for PO was guided by the differential diagnosis and included laboratory and imaging studies. Laboratory evaluation comprised complete blood count, blood chemistry, inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), thyroid function tests, glycemic evaluation including glycated hemoglobin, and autoantibody testing, including markers for vasculitis and connective tissue diseases when clinically indicated. Serological tests for infectious etiologies were performed when appropriate. Imaging studies included contrast-enhanced cranial and orbital magnetic resonance imaging, with vascular imaging when indicated. Lumbar puncture was performed when clinically indicated. Patients without a complete diagnostic workup or with incomplete clinical data were excluded.

Data were extracted from medical records. Demographic and clinical variables included age, sex, and, when present, comorbidities such as diabetes mellitus, vascular risk factors, autoimmune thyroid disease, and other autoimmune disorders. Neuro-ophthalmological examination findings were recorded. Best-corrected visual acuity was measured in decimal units and converted to the logarithm of the minimum angle of resolution, according to the latest literature.[6] Recorded findings included diplopia, ptosis, proptosis, chemosis, visual loss, limitations of extraocular movements (inward, outward, upward, and downward gaze), and facial hypoesthesia.

Patients were classified into diagnostic groups according to the underlying etiology and predominant anatomical involvement. The diagnostic groups included cavernous sinus-orbital apex inflammatory syndrome (CS-OA), carotid-cavernous fistula (CCF), thyroid eye disease (TED), tumors, idiopathic orbital inflammatory disease (IOID), and infections. The CS-OA group comprised patients with inflammatory conditions involving the cavernous sinus and/or orbital apex, including idiopathic cases. Although these entities differed in etiology, they were grouped together because they shared similar inflammatory involvement of the cavernous sinus and/or orbital apex, with overlapping neuro-ophthalmological features. The tumor group included neoplastic lesions involving the cavernous sinus, orbital apex, or orbit. The infection group included patients with bacterial or fungal infections involving the cavernous sinus, orbital apex, or orbit. Final diagnoses were established based on clinical findings, imaging results, laboratory investigations, and follow-up data when available.

The independent variables in the study were demographic characteristics and findings on clinical examination, including age, sex, comorbidities, diplopia, ptosis, proptosis, chemosis, visual loss, limitations of extraocular movements, and facial hypoesthesia. The dependent variable was the diagnostic group.

Visual loss was defined as a reduction in best-corrected visual acuity compared with the normal expected range for age. Ptosis was defined as the upper eyelid margin positioned below the superior corneal limbus or asymmetrically positioned compared with the fellow eye, as observed on clinical examination. Proptosis was defined as anterior displacement of the globe identified clinically and, when available, supported by orbital imaging. Chemosis was defined as conjunctival edema observed on ophthalmological examination. Extraocular movement restriction was defined as a limitation of ocular excursion in the relevant gaze direction, documented during bedside assessment in the cardinal gaze positions. Fever was defined as a body temperature ≥38 °C at presentation or documented during clinical evaluation.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 26, IBM Corp., Armonk, NY, USA). Continuous variables were assessed for distribution and expressed as median and interquartile range (IQR). Categorical variables were presented as numbers and percentages. Comparisons between diagnostic groups were performed using the Kruskal-Wallis test for continuous variables. For categorical variables, the chi-square test or Fisher's exact test was used as appropriate.

Binary logistic regression was performed to identify clinical examination findings associated with CS-OA, compared with non-CS-OA etiologies. Variables were selected for inclusion in the regression model based on clinical relevance and univariate analysis, with a threshold of $p<0.10$. Multicollinearity was assessed before inclusion in the regression model. The results of the regression analysis were reported as odds ratios (OR) with 95% confidence intervals (CI). Model coefficients were estimated using maximum likelihood methods. A two-sided p value <0.05 was considered statistically significant.

Ethical Aspect

The study was approved by the Ege University Ethics Committee. The approval number was 25-1.1T/38, and the approval date was 23 January 2025. The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Informed consent was obtained from each participant.

RESULTS

A total of 111 cases of PO were identified during the study period. After excluding nine patients with incomplete diagnostic workup and eight with incomplete clinical data, 94 patients were included in the study. The median age was 57 years (IQR: 42-65), and 51 patients (54.3%) were female. Table 1 summarizes the demographic features of the study cohort.

Of the 94 patients included in the analysis, 27 (28.7%) had CS-OA; 25 (26.6%) had CCF; 11 (11.7%) had TED; 11 (11.7%) had tumors; 10 (10.6%) had IOID; and 10 (10.6%) had infections. The CS-OA group included 15 cases of idiopathic cavernous sinus inflammation, two cases of cavernous sinus thrombosis, one case of cavernous sinus inflammation due to granulomatosis with polyangiitis, and nine cases of orbital apex inflammation. The tumor group included one malignant epithelial tumor, one chondroid tumor, two hemorrhagic pituitary macroadenomas, three meningiomas, one nasopharyngeal carcinoma, one lymphoma, one multiple myeloma, and one suspected metastatic lesion involving the cavernous sinus and orbit, with clival involvement. In the IOID group, eight patients had orbital myositis and two had orbital pseudotumor. The infection group included nine fungal infections (five cases of mucormycosis and four of aspergillosis) and one case of skull-base infection due to *Streptococcus pneumoniae*.

Table 1. Demographic and clinical characteristics of the study population

Variable	Value
Age, years, median (IQR)	57 (42-65)
Sex, female, n (%)	51 (54.3)
DM, n (%)	29 (30.9)
Vascular risk factors other than DM, n (%)	18 (19.1)
Autoimmune thyroid disease, n (%)	16 (17.1)
Autoimmune disease other than thyroid, n (%)	7 (7.4)
Diplopia, n (%)	78 (83.1)
Ptosis, n (%)	30 (31.9)
Proptosis, n (%)	41 (43.6)
Chemosis, n (%)	30 (31.9)
Vision loss, n (%)	50 (53.2)
Restricted inward gaze, n (%)	13 (13.8)
Restricted outward gaze, n (%)	60 (63.8)
Restricted downward gaze, n (%)	41 (43.6)
Restricted upward gaze, n (%)	17 (18.1)
Facial hypoesthesia, n (%)	27 (28.7)
High fever, n (%)	3 (3.2)

IQR: Interquartile range, DM: Diabetes mellitus.

Comparisons of demographic and clinical characteristics across diagnostic groups are presented in Table 2. Briefly, age differed significantly between groups (p=0.006), with patients in the infection group being older, whereas those with IOID tended to be younger. DM was significantly more frequent in the infection group (p=0.001). Autoimmune thyroid disease was strongly associated with TED (p<0.001).

Among the clinical findings, ptosis was more common in the CS-OA group (p=0.010). Proptosis was more frequently observed in the CCF and TED groups, whereas chemosis was predominantly seen in the CCF group (both p<0.001). Vision loss differed significantly between groups (p<0.001), with higher frequencies observed in the TED and infection groups.

Restricted outward gaze was significantly more frequent in CCF and IOID (p<0.001). Facial hypoesthesia was significantly associated with the CS-OA and tumor groups (p=0.002). No significant differences were observed with respect to sex, vascular risk factors other than diabetes, diplopia, restricted inward, upward, or downward gaze, or the presence of fever (all p>0.05).

To determine which clinical findings differentiate non-CS-OA etiologies from CS-OA, a binary logistic regression analysis was performed. Chemosis (OR =6.54, 95% CI: 1.03-41.53, p=0.041) and vision loss (OR =5.33, 95% CI: 1.32-21.42, p=0.018) were independently associated with non-CS-OA etiologies. In contrast, ptosis was negatively associated with non-CS-OA etiologies (OR =0.21, 95% CI: 0.05-0.86, p=0.031), indicating a higher likelihood of CS-OA in patients presenting with ptosis. The logistic regression model demonstrated acceptable goodness-of-fit according to the Hosmer-Lemeshow test (χ^2=4.481, p=0.811), with a Nagelkerke R^2 value of 0.515.

Other variables, including age, diabetes mellitus, autoimmune thyroid disease, proptosis, and restricted outward gaze, were not independently associated with non-CS-OA etiologies. Facial hypoesthesia showed a trend toward association with non-CS-OA etiologies (OR =0.27, 95% CI: 0.06-1.12, p=0.073), although this did not reach statistical significance (Table 3).

Table 2. Comparison of demographic characteristics and clinical examination findings across diagnostic groups in patients with painful ophthalmoplegia

Variable	CS-OA n=27	CCF n=25	Thyroid eye disease n=11	Tumors n=11	IOID n=10	Infections n=10	p value
Sex, female, n (%)	12 (44.4)	17 (68)	7 (63.6)	4 (36.3)	5 (50)	6 (40)	0.426
Age, years, median (IQR)	44 (35-65)	59 (47.5-66.5)	56 (54-58)	46 (38-62)	39 (26-64)	68 (61-73)	**0.006**
DM, n (%)	6 (22.2)	8 (32)	2 (18.2)	3 (27.3)	1 (10)	9 (90)	**0.001**
Vascular risk factors other than DM, n (%)	7 (25.9)	8 (32)	1 (9.1)	1 (9.1)	0 (0)	1 (10)	0.236
Autoimmune thyroid disease, n (%)	2 (7.4)	4 (16)	8 (72.7)	0 (0)	1 (10)	1 (10)	**<0.001**
Autoimmune disease other than thyroid, n (%)	2 (7.4)	2 (8)	1 (9.1)	1 (9.1)	1 (10)	0 (0)	0.980
Diplopia, n (%)	21 (77.8)	23 (92)	9 (81.8)	10 (90.9)	8 (80)	7 (70)	0.574
Ptosis, n (%)	15 (55.6)	3 (12)	2 (18.2)	3 (27.3)	2 (20)	5 (50)	**0.010**
Proptosis, n (%)	4 (14.8)	20 (80)	9 (81.8)	1 (9.1)	5 (50)	2 (20)	**<0.001**
Chemosis, n (%)	2 (7.4)	22 (88)	0 (0)	0 (0)	4 (40)	2 (20)	**<0.001**
Vision loss, n (%)	10 (37.1)	17 (68)	3 (27.2)	7 (63.6)	4 (40)	9 (90)	**<0.001**
Restricted inward gaze, n (%)	4 (14.8)	2 (8)	2 (18.2)	2 (18.2)	1 (10)	2 (20)	0.886
Restricted outward gaze, n (%)	14 (51.9)	23 (92)	2 (18.2)	7 (63.6)	9 (90)	5 (50)	**<0.001**
Restricted downward gaze, n (%)	10 (37)	9 (36)	6 (54.5)	6 (54.5)	4 (40)	6 (60)	0.660
Restricted upward gaze, n (%)	3 (11.1)	7 (28)	2 (18.2)	2 (18.2)	2 (20)	1 (10)	0.727
Facial hypoesthesia, n (%)	13 (48.1)	6 (24)	0 (0)	6 (54.5)	0 (0)	2 (20)	**0.002**
High fever, n (%)	1 (3.7)	0 (0)	1 (9.1)	0 (0)	0 (0)	1 (10)	0.412

CS-OA: Cavernous sinus-orbital apex, CCF: Carotid-cavernous fistula, DM: Diabetes mellitus, IOID: Idiopathic orbital inflammatory disease, IQR: Interquartile range

Table 3. Binary logistic regression analysis of factors associated with non-cavernous sinus-orbital apex etiologies in patients with painful ophthalmoplegia

Variable	OR	95% CI	p value
Age (years)	1.02	0.97-1.06	0.339
Autoimmune thyroid disease	1.26	0.17-9.29	0.815
DM	0.66	0.13-3.40	0.624
Ptosis	0.21	0.05-0.86	**0.031**
Proptosis	2.11	0.43-10.20	0.352
Chemosis	6.54	1.03-41.53	**0.041**
Vision loss	5.33	1.32-21.42	**0.018**
Restricted outward gaze	1.89	0.47-7.57	0.365
Facial hypoesthesia	0.27	0.06-1.12	0.073

OR: Odds ratio, CI: Confidence interval, DM: Diabetes mellitus

DISCUSSION

This study indicated that specific clinical examination findings may help differentiate the underlying etiologies of PO and provide practical clues for the differential diagnosis. In particular, ptosis was more frequently observed in CS-OA, whereas chemosis and vision loss were more suggestive of alternative etiologies. Facial hypoesthesia also showed a trend toward an association with CS-OA.

Ptosis was most frequent in the CS-OA group, and multivariable analysis demonstrated that it was an independent predictor of CS-OA (p=0.031). Involvement of the oculomotor nerve in the cavernous sinus and orbital apex explains the increased frequency of ptosis in patients with CS-OA.[7,8] The oculomotor nerve innervates the levator palpebrae superioris, and its involvement results in impaired eyelid elevation (ptosis).[8] In our cohort, one patient with granulomatosis with polyangiitis and two patients with cavernous sinus thrombosis were included in the CS-OA group. Cavernous sinus involvement due to granulomatosis with polyangiitis has been reported.[9] Cavernous sinus thrombosis is a rare cause of cavernous sinus involvement.[10] The remaining patients were classified as having idiopathic inflammation of the cavernous sinus, known as Tolosa-Hunt syndrome.[7] Idiopathic orbital apex inflammation reflects a similar inflammatory process confined to the orbital apex and is considered part of the same disease spectrum.[11]

Chemosis refers to edema of the conjunctiva, resulting from impaired venous drainage and increased vascular permeability.[12] CCF is an abnormal arteriovenous communication connecting the carotid arterial system to the cavernous sinus and resulting in elevated pressure in the orbital venous system.[12] This venous hypertension impairs the normal drainage of the conjunctival and episcleral veins, resulting in conjunctival edema and the characteristic appearance of chemosis.[13] In our cohort, chemosis was observed in 88% of patients with CCF and identified as an independent predictor of non-CS-OA etiologies in logistic regression analysis (p=0.041). In addition to its diagnostic value, chemosis may have clinical implications. Direct CCFs, defined as high-flow communications between the intracavernous internal carotid artery and the cavernous sinus, are often characterized by an abrupt onset of chemosis and require early intervention.[13-15]

In our cohort, vision loss was most frequent in patients with PO due to infectious etiologies. Among these, invasive fungal sinusitis, particularly mucormycosis and Aspergillus, was the most common cause. Vision loss was also identified as an independent predictor of non-CS-OA etiologies in logistic regression analysis (p=0.018). This is consistent with the literature, in which these organisms are also reported to be the most frequent causes.[16] Fungal sinusitis can lead to vision loss when the infection invades the optic nerve.[17] On the other hand, CCF was the second most common cause of vision loss in our cohort. Vision loss in CCF is caused by venous hypertension, which impairs orbital venous drainage and increases intraocular pressure, ultimately affecting optic nerve function.[12] In addition, chronic venous congestion may compromise retinal and optic nerve perfusion, leading to ischemic optic neuropathy or retinal vascular dysfunction. Delayed diagnosis and persistent venous hypertension may therefore result in irreversible visual impairment.[12]

Although facial hypoesthesia did not reach statistical significance, it showed a trend toward predicting CS-OA in multivariable analysis (p=0.073). This finding can be explained by the involvement of the trigeminal nerve within the cavernous sinus, where its ophthalmic and maxillary divisions are located.[18] Among non-CS-OA etiologies, facial hypoesthesia was most frequent in the tumor group in our cohort. Tumors invading the cavernous sinus may produce similar sensory deficits by affecting the trigeminal nerve within this region.

Ninety percent of patients with infectious etiologies had DM; however, multivariable analysis did not demonstrate its predictive value for non-CS-OA etiologies. This may be explained by the immunosuppressive effects of DM, which impair host defense mechanisms and increase susceptibility to opportunistic infections, including invasive fungal infections.[19,20] Although DM was not independently associated with non-CS-OA etiologies in the multivariable analysis, the high prevalence of DM among patients with infectious etiologies remains clinically important, likely reflecting the increased susceptibility of diabetic patients to invasive fungal infections. Autoimmune thyroid disease was most frequently observed in patients with TED. The underlying mechanism is autoimmune inflammation directed against orbital fibroblasts, leading to expansion of orbital tissues and involvement of the extraocular muscles.[21] Notably, TED may occur in the absence of overt thyroid dysfunction.[22]

Our findings are generally consistent with previous studies reporting that inflammatory cavernous sinus syndromes commonly present with PO accompanied by cranial nerve involvement, particularly ptosis and sensory deficits.[2] Similarly, chemosis and proptosis are characteristic findings in CCF secondary to orbital venous congestion, whereas vision loss has been reported more frequently in invasive fungal infections and in compressive lesions of the orbital apex.[12,17] Previous studies have also emphasized the association between diabetes mellitus and invasive fungal infections, particularly mucormycosis.[17]

Overall, our findings support the existing literature and highlight specific clinical patterns that may assist in the differential diagnosis of PO in routine clinical practice.

These findings may be particularly helpful in busy and resource-limited clinical settings, where immediate access to advanced imaging and laboratory investigations may be restricted. Recognition of specific clinical patterns may assist clinicians in narrowing the differential diagnosis and prioritizing appropriate diagnostic tests. Ultimately, such an approach may facilitate a more efficient diagnostic process through the integration of clinical findings with targeted investigations. Although the regression model demonstrated acceptable goodness-of-fit, the findings should be considered exploratory and interpreted with caution because of the relatively small sample size and subgroup heterogeneity.

Study Limitations

This study has several limitations. First, its retrospective design may have introduced selection and information bias. Second, the study was conducted at a single center, which may limit the generalizability of the findings. In addition, the sample sizes of certain diagnostic subgroups were relatively small, potentially affecting statistical power; therefore, the findings should be interpreted with caution. Finally, the heterogeneity of underlying etiologies may have contributed to variability in clinical presentation.

CONCLUSION

Specific clinical examination findings may assist in differentiating the underlying etiologies of PO. Ptosis may suggest CS-OA inflammatory syndrome, whereas chemosis and vision loss may indicate alternative etiologies. Although definitive diagnosis relies on imaging and laboratory investigations, careful clinical evaluation may help guide the diagnostic process and support more targeted investigations.

Ethics

Ethics Committee Approval: The study was approved by the Ege University Ethics Committee. The approval number was 25-1.1T/38, and the approval date was 23 January 2025.

Informed Consent: Informed consent was obtained from each participant.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.N.Ö., F.G., N.Ç., Concept: F.G., N.Ç., Design: H.N.Ö., E.H., Data Collection or Processing: E.H., Analysis or Interpretation: H.N.Ö., Literature Search: H.N.Ö., E.H., Writing: H.N.Ö., F.G., N.Ç.

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