Clinical Findings Associated with Aneurysmal Third Nerve Palsy

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SUMMARY

Aims: To describe the clinical and etiological features of acquired third nerve palsy and to evaluate the associations and diagnostic performance of pupillary involvement, motor distribution, and other clinical findings for aneurysmal etiology.
Material and Methods: This retrospective observational study included 225 patients evaluated between 2014 and 2021. A palsy was operationally classified as complete when the superior, medial, and inferior rectus muscles and the levator palpebrae were all affected; pupillary function was analyzed separately. Thirteen aneurysmal cases were compared with 212 non-aneurysmal cases. Associations were assessed with Fisher exact tests and Firth penalized logistic regression.
Results: Initial pupillary involvement occurred in 10/13 aneurysmal and 67/212 non-aneurysmal cases (OR 7.21, 95% CI 1.92–27.07; p = 0.002). Complete motor palsy with pupillary involvement was also associated with aneurysm (OR 4.68, 95% CI 1.47–14.92; p = 0.009), whereas motor completeness alone was not. Initial pupillary involvement had 76.9% sensitivity, 68.4% specificity, a 13.0% positive predictive value, and a 98.0% negative predictive value. Three aneurysmal cases initially spared the pupil.
Conclusion: Pupillary involvement substantially increased the probability of aneurysmal third nerve palsy, whereas the complete or incomplete motor pattern did not provide additional discrimination. Pupil sparing reduced, but did not exclude, aneurysmal etiology. Clinical findings should therefore be interpreted together with the clinical course and neuroimaging.
Key words: oculomotor nerve diseases, intracranial aneurysm, pupil, ophthalmoplegia, neuroimaging

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INTRODUCTION

Acquired third nerve palsy is a heterogeneous neuro-ophthalmic syndrome, because the oculomotor nerve contains somatic motor fibers supplying the levator palpebrae and four extraocular muscles, together with parasympathetic fibers controlling the pupil and accommodation. Lesions anywhere from the midbrain to the orbit can produce variable ptosis, diplopia, ophthalmoplegia, and pupillary abnormalities. Causes include microvascular ischemia, intracranial aneurysm, trauma, neoplasia, inflammation, other vascular disorders, and neurosurgical complications [1–3].

The etiological distribution varies by population and clinical setting. In a 37-year population-based study from Minnesota, the annual incidence was 4.0 per 100,000 inhabitants; microvascular disease accounted for 42%, and aneurysmal compression for 6% of cases [1]. A 36-year inpatient series of 1,400 patients reported aneurysms in 10% [2], whereas a recent Korean tertiary-center series of 633 patients with isolated third nerve palsy found intracranial aneurysms in 14.1% [4].

Pupillary assessment has traditionally been central to distinguishing microvascular from compressive palsies. The 'pupil rule' reflects the superficial location of pupillomotor fibers in the subarachnoid segment, close to the posterior communicating artery, whereas microvascular ischemia may preferentially affect deeper endoneurial territories. The distinction is not absolute: some microvascular palsies cause anisocoria, and some compressive or aneurysmal lesions initially spare the pupil, particularly with partial external dysfunction or an intracavernous lesion [1,3,5,6,7,8,9]. Pain, age, and vascular risk factors alone are also insufficient to establish etiology [1,10,11].

The distribution of external motor dysfunction has been less extensively studied, and no universal definition of complete or incomplete palsy exists. Lee et al. distinguished partial from complete external dysfunction, and cautioned that pupil sparing is less reliable for excluding aneurysm when motor involvement is incomplete [3]. Sanders et al. found that vasculopathic pupil-sparing incomplete palsies usually had diffuse partial weakness, and hypothesized that aneurysms might more often produce focal patterns with complete preservation of one or more muscles; this required comparative validation [12]. We therefore described the clinical and etiological features of a cohort with acquired third nerve palsy and evaluated the associations and diagnostic performance of pupillary involvement, motor distribution, and other clinical and systemic factors for aneurysmal etiology.

MATERIAL AND METHODS

We conducted a retrospective observational study of an anonymized clinical database containing 225 patients with acquired third nerve palsy, evaluated at Centro Oftalmológico Virgilio Galvis between 2014 and 2021. Aneurysmal cases were compared with all non-aneurysmal etiologies. Variables included demographic characteristics, systemic history, laterality, presenting symptoms, visual acuity, symptom duration, recovery, pupillary involvement, the distribution and severity of dysfunction in the rectus muscles supplied by the third nerve, and ptosis.

Motor classification was based on the superior, medial, and inferior rectus muscles, each recorded as preserved or as showing mild, moderate, or complete paresis. A margin-reflex distance (MRD) of at least 4 mm indicated no ptosis and preserved levator function; an MRD below 4 mm indicated levator involvement. A palsy was operationally classified as complete when all three evaluated rectus muscles showed some degree of paresis or paralysis, and ptosis indicated levator involvement; thus, every assessed motor structure was affected. It was classified as incomplete when at least one rectus muscle was fully preserved, or levator function was preserved. In this definition, 'complete' denotes the distribution of involvement across all assessed structures and does not necessarily imply total loss of function in each muscle. Pupillary function was analyzed independently and dichotomized as involved or spared.

Continuous variables were summarized as mean and standard deviation, or median and interquartile range, as appropriate; categorical variables were reported as frequencies and percentages. Aneurysmal and non-aneurysmal groups were compared with Welch's t test, the Mann-Whitney U test, or the two-sided Fisher exact test. Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

The diagnostic performance of complete motor palsy with pupillary involvement, initial pupillary involvement, and pupillary involvement at any time was evaluated with sensitivity, specificity, predictive values, likelihood ratios, and accuracy; 95% CIs for proportions were calculated with the Wilson method. Analyses were stratified by initial pupillary status, and subgroup analyses were performed in patients with incomplete palsy. Statistical analyses used R version 4.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Because there were few aneurysmal events, and complete separation occurred, multivariable models were estimated with Firth penalized logistic regression, adjusted for age and sex, using Jeffreys-prior penalized likelihood. Tests were two-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

The study included 225 patients with a mean age of 61.2 ±15.5 years; 126 (56.0%) were men and 99 (44.0%) women. The right eye was affected in 124 cases (55.1%). Hypertension was present in 111 patients (49.3%), diabetes mellitus in 100 (44.4%), cerebrovascular disease in 10 (4.4%), and previous head trauma in 28 (12.4%).

Diplopia was present in 161 patients (71.6%), headache in 104 (46.2%), ocular pain in 93 (41.3%), and other neurological symptoms in 45 (20.0%). Compared with patients reporting diplopia, those without diplopia had worse presenting visual acuity (median 0.35 logMAR [IQR 0.18–1.00] vs 0.30 logMAR [IQR 0.10–0.48]; $p = 0.008$), and more often had visual acuity of 1.00 logMAR or worse (17/64 [26.6%] vs 16/161 [9.9%]; OR 3.28, 95% CI 1.54–6.99; $p = 0.003$). Incomplete motor palsy occurred with similar frequency (16/64 [25.0%] vs 48/161 [29.8%]; OR 0.78, 95% CI 0.41–1.52; $p = 0.516$). Complete ptosis (MRD ≤ 0 mm) was more frequent without diplopia (47/64 [73.4%] vs 96/161 [59.6%]), although the difference was not statistically significant (OR 1.87, 95% CI 0.99–3.54; $p = 0.065$).

The median interval from symptom onset to evaluation was 7.0 days (IQR 3.0–20.0; range 0–6,570). Mean follow-up was 9.87 ±4.46 months, with a median of 6.5 months (IQR 3.2–13.1; range 0.3–21.1). Complete recovery of third nerve function was recorded in 56 patients (24.9%), after a mean of 6.07 ±4.69 months and a median of 5.0 months (IQR 3.0–8.0; range 0.3–19.0). None of the 13 aneurysmal cases achieved documented complete recovery, compared with 56/212 non-aneurysmal cases (26.4%; $p = 0.042$). Sex, diabetes mellitus, and documented complete recovery differed significantly between etiological groups (Table 1).

Table 1. Demographic, clinical, and follow-up characteristics according to etiology

Variable	Total (n = 225)	Aneurysmal (n = 13)	Non-aneurysmal (n = 212)	p value
Age, years	61.2 ±15.5	64.4 ±13.4	61.0 ±15.6	0.397
Female sex	99 (44.0%)	13 (100.0%)	86 (40.6%)	<0.001
Right eye	124 (55.1%)	5 (38.5%)	119 (56.1%)	0.257
Hypertension	111 (49.3%)	7 (53.8%)	104 (49.1%)	0.782
Diabetes mellitus	100 (44.4%)	1 (7.7%)	99 (46.7%)	0.007
Cerebrovascular disease	10 (4.4%)	3 (23.1%)	7 (3.3%)	0.014
Head trauma	28 (12.4%)	2 (15.4%)	26 (12.3%)	0.668
Ocular pain	93 (41.3%)	2 (15.4%)	91 (42.9%)	0.079
Diplopia	161 (71.6%)	8 (61.5%)	153 (72.2%)	0.526
Headache	104 (46.2%)	4 (30.8%)	100 (47.2%)	0.391
Other neurological symptoms	45 (20.0%)	5 (38.5%)	40 (18.9%)	0.143
Time from onset, days	7.0 (3.0–20.0)	2.0 (1.0–45.0)	7.0 (3.0–16.2)	0.654
Documented complete recovery	56 (24.9%)	0 (0.0%)	56 (26.4%)	0.042

Data are mean ± standard deviation, n (%), or median (interquartile range), as appropriate. P values were obtained with Welch's t test, the Mann-Whitney U test, or the two-sided Fisher exact test

Microvascular disease was the most frequent etiology (149 cases, 66.2%), followed by trauma (26, 11.6%). Aneurysmal and neoplastic causes were each identified in 13 patients (5.8%) (Table 2).

Using the operational definition, 161 patients (71.6%) had complete and 64 (28.4%) incomplete motor palsy. At presentation, 62 patients (27.6%) had complete palsy with pupillary involvement, 99 (44.0%) complete palsy with pupil sparing, 15 (6.7%) incomplete palsy with pupillary involvement, and 49 (21.8%) incomplete palsy with pupil sparing. Pupillary involvement was present initially in 77 patients (34.2%); 4 additional patients developed it during follow-up, giving 81 cases (36.0%) with pupillary involvement at any time.

Complete palsy with pupillary involvement occurred in 8/13 aneurysmal cases (61.5%) and 54/212 non-aneurysmal cases (25.5%) (OR 4.68, 95% CI 1.47–14.92; p = 0.009). Initial pupillary involvement was also associated with aneurysm (OR 7.21, 95% CI 1.92–27.07; p = 0.0015), as was pupillary involvement at any time (OR 6.62, 95% CI 1.77–24.81; p = 0.0025) (Table 3). Motor classification alone was not associated with aneurysmal etiology: aneurysms

Table 2. Etiological distribution of third nerve palsy

Etiology	n	%
Microvascular	149	66.2
Traumatic	26	11.6
Aneurysmal	13	5.8
Neoplastic	13	5.8
Idiopathic	8	3.6
Inflammatory	6	2.7
Orbital apex syndrome	5	2.2
Carotid-cavernous fistula	4	1.8
Paraneoplastic syndrome	1	0.4
Total	225	100.0

Table 3. Motor presentation and pupillary involvement according to etiology

Etiology	n	Complete + pupil	Complete, pupil spared	Incomplete + pupil	Incomplete, pupil spared	Initial pupil involvement	Pupil involvement at any time
Microvascular	149	19 (12.8%)	84 (56.4%)	9 (6.0%)	37 (24.8%)	28 (18.8%)	30 (20.1%)
Traumatic	26	22 (84.6%)	2 (7.7%)	0 (0.0%)	2 (7.7%)	22 (84.6%)	22 (84.6%)
Neoplastic	13	5 (38.5%)	4 (30.8%)	1 (7.7%)	3 (23.1%)	6 (46.2%)	7 (53.8%)
Aneurysmal	13	8 (61.5%)	2 (15.4%)	2 (15.4%)	1 (7.7%)	10 (76.9%)	10 (76.9%)
Idiopathic	8	2 (25.0%)	1 (12.5%)	2 (25.0%)	3 (37.5%)	4 (50.0%)	4 (50.0%)
Inflammatory	6	1 (16.7%)	2 (33.3%)	1 (16.7%)	2 (33.3%)	2 (33.3%)	3 (50.0%)
Orbital apex syndrome	5	1 (20.0%)	3 (60.0%)	0 (0.0%)	1 (20.0%)	1 (20.0%)	1 (20.0%)
Carotid-cavernous fistula	4	4 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (100.0%)	4 (100.0%)
Paraneoplastic syndrome	1	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Complete and incomplete refer to the operational motor classification used in this study. "Pupil" denotes pupillary involvement

were found in 10/161 complete palsies (6.2%) and 3/64 incomplete palsies (4.7%; OR for incomplete vs complete palsy 0.74, 95% CI 0.20–2.79; p = 0.763).

All 4 assessed motor components were affected in 161 patients (71.6%), 3 in 39 (17.3%), 2 in 24 (10.7%), and 1 in 1 (0.4%). The superior rectus was fully preserved in 22 patients (9.8%), the medial rectus in 18 (8.0%), and the inferior rectus in 48 (21.3%). Grade 0, corresponding to mild paresis, was recorded in 1 medial rectus and 4 inferior rectus muscles. Mean MRD was -0.6 ±2.0 mm, and median MRD was -1.0 mm (IQR -2.0 to 1.0); only 2 patients (0.9%) had MRD ≥ 4 mm and no ptosis (Table 4). No differences between aneurysmal and non-aneurysmal cases were found in the number of motor components affected, ordinal severity of any rectus muscle, or MRD; ptosis was nearly universal and had no discriminatory value (Table 5).

Table 4. Frequency and severity of motor involvement

Variable	Category	n	%
Motor components involved (of 4 assessed)	1	1	0.4
	2	24	10.7
	3	39	17.3
	4	161	71.6
Superior rectus	Normal	22	9.8
	Grade 0	0	0.0
	Grade 1	56	24.9
	Grade 2	59	26.2
	Grade 3	88	39.1
Medial rectus	Normal	18	8.0
	Grade 0	1	0.4
	Grade 1	40	17.8
	Grade 2	68	30.2
	Grade 3	98	43.6
Inferior rectus	Normal	48	21.3
	Grade 0	4	1.8
	Grade 1	45	20.0
	Grade 2	62	27.6
	Grade 3	66	29.3
Levator palpebrae	No ptosis (MRD ≥ 4 mm)	2	0.9
	Ptosis (MRD < 4 mm)	223	99.1

MRD – margin-reflex distance

Aneurysm was present in 10/77 patients with initial pupillary involvement (13.0%), and in 3/148 with initial pupil sparing (2.0%; OR 7.21, 95% CI 1.92–27.07; p = 0.0015). Among patients with pupillary involvement, aneurysm occurred in 8/62 complete and 2/15 incomplete palsies (OR 0.96, 95% CI 0.18–5.08; p = 1.000). With pupil sparing, it occurred in 2/99 complete and 1/49 incomplete palsies (OR 0.99, 95% CI 0.09–11.19; p = 1.000). Three of the 13 aneurysmal cases (23.1%) were incomplete; 2 had initial pupillary involvement and 1 had pupil sparing. Their mean age was 57.3 ±21.0 years, compared with 60.0 ±15.7 years in 61 non-aneurysmal incomplete cases (p = 0.751).

In bivariate analysis, complete separation by sex occurred, because all 13 aneurysmal cases were women (p < 0.001). Cerebrovascular disease, complete palsy with pupillary involvement, initial pupillary involvement, and pupillary involvement at any time were associated with aneurysm; diabetes mellitus was less frequent in the aneurysmal group. No significant associations were observed for hypertension, head trauma, ocular pain, diplopia, headache, other neurological symptoms, complete motor palsy alone, delayed pupillary involvement, or ptosis (Table 6).

Initial pupillary involvement had the highest sensitivity for aneurysmal etiology (76.9%), with 68.4% specificity, 13.0% positive predictive value, and 98.0% negative predictive value. Complete palsy with pupillary involvement had lower sensitivity (61.5%), but higher specificity (74.5%) and accuracy (73.8%). Considering pupillary involvement at any time did not increase sensitivity and slightly reduced specificity to 66.5%. All 3 indicators had low positive predictive values (12.3%–13.0%), high negative predictive values (96.9%–98.0%), and modest positive likelihood ratios (2.30–2.43) (Table 7).

In a Firth penalized logistic regression model adjusted for age and sex, complete palsy with pupillary involvement remained associated with aneurysmal etiology (adjusted OR 4.82, 95% CI 1.46–15.90; p = 0.010). In a separate model with the same adjustment, initial pupillary involvement also remained significant (adjusted OR 6.10, 95% CI 1.68–22.10; p = 0.006) (Table 8).

Table 5. Distribution and severity of motor involvement according to aneurysmal etiology

Variable	Aneurysmal (n = 13)	Non-aneurysmal (n = 212)	p value
Motor components involved (0–4)	4.0 (4.0–4.0)	4.0 (3.0–4.0)	0.642
Superior rectus, ordinal score	4.0 (2.0–4.0)	3.0 (2.0–4.0)	0.406
Medial rectus, ordinal score	3.0 (3.0–4.0)	3.0 (2.0–4.0)	0.889
Inferior rectus, ordinal score	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.326
MRD, mm	0.0 (-2.0 to 1.0)	-1.0 (-2.0 to 1.0)	0.719

Data are median (interquartile range). MRD – margin-reflex distance

Table 6. Bivariate analysis of factors associated with aneurysmal etiology

Variable	Aneurysmal	Non-aneurysmal	OR	95% CI	Fisher p value
Female sex	13/13 (100.0%)	86/212 (40.6%)	∞	Not estimable	<0.001
Hypertension	7/13 (53.8%)	104/212 (49.1%)	1.21	0.39–3.73	0.782
Diabetes mellitus	1/13 (7.7%)	99/212 (46.7%)	0.10	0.01–0.74	0.007
Cerebrovascular disease	3/13 (23.1%)	7/212 (3.3%)	8.79	1.97–39.14	0.014
Head trauma	2/13 (15.4%)	26/212 (12.3%)	1.30	0.27–6.20	0.668
Ocular pain	2/13 (15.4%)	91/212 (42.9%)	0.24	0.05–1.12	0.079
Diplopia	8/13 (61.5%)	153/212 (72.2%)	0.62	0.19–1.96	0.526
Headache	4/13 (30.8%)	100/212 (47.2%)	0.50	0.15–1.67	0.391
Other neurological symptoms	5/13 (38.5%)	40/212 (18.9%)	2.69	0.83–8.65	0.143
Complete palsy (operational definition)	10/13 (76.9%)	151/212 (71.2%)	1.35	0.36–5.06	0.763
Complete palsy + pupillary involvement	8/13 (61.5%)	54/212 (25.5%)	4.68	1.47–14.92	0.009
Initial pupillary involvement	10/13 (76.9%)	67/212 (31.6%)	7.21	1.92–27.07	0.002
Pupillary involvement at any time	10/13 (76.9%)	71/212 (33.5%)	6.62	1.77–24.81	0.002
Delayed pupillary involvement	0/13 (0.0%)	4/212 (1.9%)	0.00	Not estimable	1.000
Ptosis (MRD < 4 mm)	13/13 (100.0%)	210/212 (99.1%)	∞	Not estimable	1.000

OR – odds ratio, CI – confidence interval, MRD – margin-reflex distance

Table 7. Diagnostic performance for identifying aneurysmal etiology

Clinical finding	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR+	LR-	Accuracy, %
Complete palsy + pupillary involvement	61.5 (35.5-82.3)	74.5 (68.3–79.9)	12.9 (6.7–23.4)	96.9 (93.0–98.7)	2.42	0.52	73.8
Initial pupillary involvement	76.9 (49.7–91.8)	68.4 (61.9–74.3)	13.0 (7.2–22.3)	98.0 (94.2–99.3)	2.43	0.34	68.9
Pupillary involvement at any time	76.9 (49.7–91.8)	66.5 (59.9–72.5)	12.3 (6.8–21.3)	97.9 (94.1–99.3)	2.30	0.35	67.1

CI – confidence interval, PPV – positive predictive value, NPV – negative predictive value, LR+ – positive likelihood ratio, LR- – negative likelihood ratio

Table 8. Firth penalised logistic regression for aneurysmal etiology

Model	Variable	Adjusted OR	95% CI	p value
Model 1	Age, per year	1.02	0.98–1.06	0.318
Model 1	Female sex	34.33	2.22–530.83	0.011
Model 1	Complete palsy + pupillary involvement	4.82	1.46–15.90	0.010
Model 2	Age, per year	1.02	0.98–1.06	0.292
Model 2	Female sex	31.31	2.02–485.56	0.014
Model 2	Initial pupillary involvement	6.10	1.68–22.10	0.006

OR – odds ratio, CI – confidence interval

DISCUSSION

We classified third nerve palsy as incomplete when at least one assessed motor component – the superior, medial, or inferior rectus, or the levator palpebrae – was fully preserved, irrespective of dysfunction elsewhere. This approach was informed by Rucker's descriptions of fragmentary deficits in aneurysmal lesions [5,6] and Sanders et al.'s contrast between focal preservation and the diffuse partial weakness often seen in vasculopathic palsies [12]. Lee et al., however, defined partial external dysfunction by partial ptosis and/or incomplete restriction, and complete dysfunction by complete ptosis and ophthalmoplegia [3]. Our operational definition therefore prioritized anatomical distribution, rather than deficit intensity, and requires independent validation.

Pupillary status does not determine whether the external motor palsy is complete or incomplete. Failure to separate external motor dysfunction from internal pupillary dysfunction has caused ambiguity in the literature,

including the erroneous use of 'complete palsy' to imply pupillary involvement. Pupillary function should be analyzed independently, because involvement or sparing can coexist with either complete or incomplete motor patterns [3,9,12,13].

Microvascular disease was the leading etiology (66.2%), and aneurysm accounted for 5.8%, close to the 6% reported by Fang et al., although the microvascular proportion was higher than in that population-based cohort and in the hospital series of Kim et al. [1,4]. These differences probably reflect patient selection, etiological criteria, and referral patterns.

The combined phenotype of complete motor palsy with initial pupillary involvement was associated with aneurysm, but motor completeness alone was not. Among patients with pupillary involvement, aneurysm frequency was almost identical in complete and incomplete palsies (12.9% vs 13.3%); with initial pupil sparing, it was 2.0% in both groups. The association of the combined phenotype therefore appears to have been driven mainly by pupillary status, with no additional discrimination from motor distribution once the pupil was considered. Precision was limited by the small number of aneurysms. Rucker, Trobe, and Lee had already cautioned that aneurysms may produce partial or progressive deficits, and that the pupil rule should not be applied rigidly when external involvement is incomplete [3,5–7].

Initial pupillary involvement showed the strongest clinical association with aneurysmal etiology. Aneurysm was found in 13.0% of patients with initial pupillary involvement and in 2.0% of those with pupil sparing. The high negative predictive value (98.0%) indicates that pupil sparing was associated with a low probability of aneurysm in this cohort, but did not exclude it, because three aneurysmal cases initially spared the pupil. Conversely, the low positive predictive value (13.0%) shows that most patients with pupillary involvement did not have an aneurysm, partly because aneurysms were uncommon.

Pupillary status modifies, but does not determine, aneurysm probability. Rucker described pupil sparing in 2/64 presumed aneurysmal cases [5], and Kissel et al. found initially normal pupils in 7/51 internal carotid-posterior communicating artery aneurysms; 5 later developed pupillary involvement [9]. In Fang et al., 6 out of 9 aneurysmal palsies initially spared the pupil, whereas initial pupillary involvement was also present in 10/61 presumed microvascular palsies [1]. Jacobson found generally mild pupillary abnormalities in 10/26 diabetic palsies [8], and Bartleson et al. reported pupil sparing in 3/12 patients with minimal oculomotor paresis [13]. Other reports confirm pupil sparing in aneurysms, especially with partial deficits, atypical compression, or non-classic locations [14–23].

Rectus muscle severity, the number of involved motor components, and MRD did not distinguish aneurysmal from non-aneurysmal palsies. Fang et al. likewise found no significant etiological difference in complete external dysfunction [1], while our classification did not confirm that focal preservation preferentially indicates aneurysm [12]. Ocular pain and headache were also non-discriminatory [2,11,24]. Lower diabetes prevalence in the aneurysmal group probably reflects the large microvascular comparison group rather than protection, while the cerebrovascular-disease association was exploratory because events were few.

All 13 aneurysmal cases occurred in women. This is compatible with the female predominance described for posterior communicating artery aneurysms, and with the higher prevalence and rupture risk of intracranial aneurysms among women, particularly at internal carotid and posterior communicating artery sites [25–27]. Nevertheless, complete separation and wide CIs preclude using sex as an exclusion criterion. The absence of documented complete recovery in aneurysmal cases should also be interpreted cautiously, because follow-up was not uniform; substantial oculomotor improvement has been reported after surgical aneurysm treatment [28].

Limitations include the retrospective design, few aneurysms, heterogeneity of the comparison group, lack of uniform quantitative measurements of motility and anisocoria, and no specific inferior oblique assessment. The motor classification is reproducible with the available variables, but is not a validated severity scale. Strengths include individual auditing of motor components, stratified analyses, and Firth penalized regression.

CONCLUSION

Generalized involvement of the three assessed rectus muscles and the levator did not independently identify aneurysmal etiology. Complete motor involvement combined with pupillary involvement, and initial pupillary involvement considered alone, significantly increased the probability of aneurysm. Preservation of the pupil or of one motor component reduced this probability, but did not exclude aneurysm. Clinical findings should therefore be integrated with the clinical course and neuroimaging.

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