

Isolated Third Cranial Nerve Palsy in Pituitary Apoplexy: Case Report and Systematic Review

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Objectives: To report a case of isolated third nerve palsy from pituitary apoplexy and perform a systematic literature review. *Materials and methods:* MEDLINE/EMBASE databases were searched up to September 2020. Inclusion criteria: Age ≥ 18 , isolated third nerve palsy from pituitary apoplexy. Exclusion criteria: Age < 18 , presence of other neurological findings, no hemorrhage or infarction of pituitary. *Results:* Case report: A 76-year-old woman presented with headache and right-sided ptosis. Right-eye exam revealed complete ptosis, absent pupillary constriction and accommodation, depressed and abducted eye on primary gaze, and -1 impaired depression, adduction, elevation, without other neurological findings. Brain MRI was suggestive of pituitary apoplexy. Pathology after transsphenoidal resection revealed an infarcted pituitary adenoma. Third nerve palsy resolved completely in 21 days. Systematic review: Twenty-three studies reporting 35 patients were selected from 182 abstracts. Twenty-nine (83%) had complete isolated third nerve palsy. Headache was reported in 31 (97%). Thirty-one had hemorrhage and 1 had infarction of pituitary. Cavernous sinus invasion occurred in 14 (50%). Twenty-eight were managed surgically (80%) and 7 medically (20%). Nerve palsy resolved completely in 27 (82%) and partially in 4 (11%). *Conclusions:* Pituitary apoplexy is an important differential diagnosis in patients with isolated third nerve palsy. Isolated third nerve palsy in apoplexy appears to have favorable prognosis.

Key Words: Oculomotor palsy—Third nerve palsy—Pituitary apoplexy—Pituitary adenoma—Transsphenoidal resection

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Introduction

Pituitary apoplexy (PA) is a rare medical emergency caused by an expanding mass within the sella turcica, resulting from a hemorrhage, or infarction or both of the pituitary gland or within a preexisting pituitary tumor such as an adenoma.¹ PA is a clinical syndrome characterized by sudden onset of headache, visual deficits, altered mental status, hormonal dysfunction and ophthalmoparesis, due to involvement of the third, fourth, or sixth cranial nerves. Isolated third cranial nerve palsy (I3NP) is a rare manifestation of PA. Here, we describe a patient who developed an acute I3NP associated with severe headache, as the presentation of pathologically proven PA. We performed a systematic review of I3NP caused by PA to further elucidate the clinical, anatomical/radiological, prognostic and endocrine features of this condition and to highlight the importance to include PA in the differential

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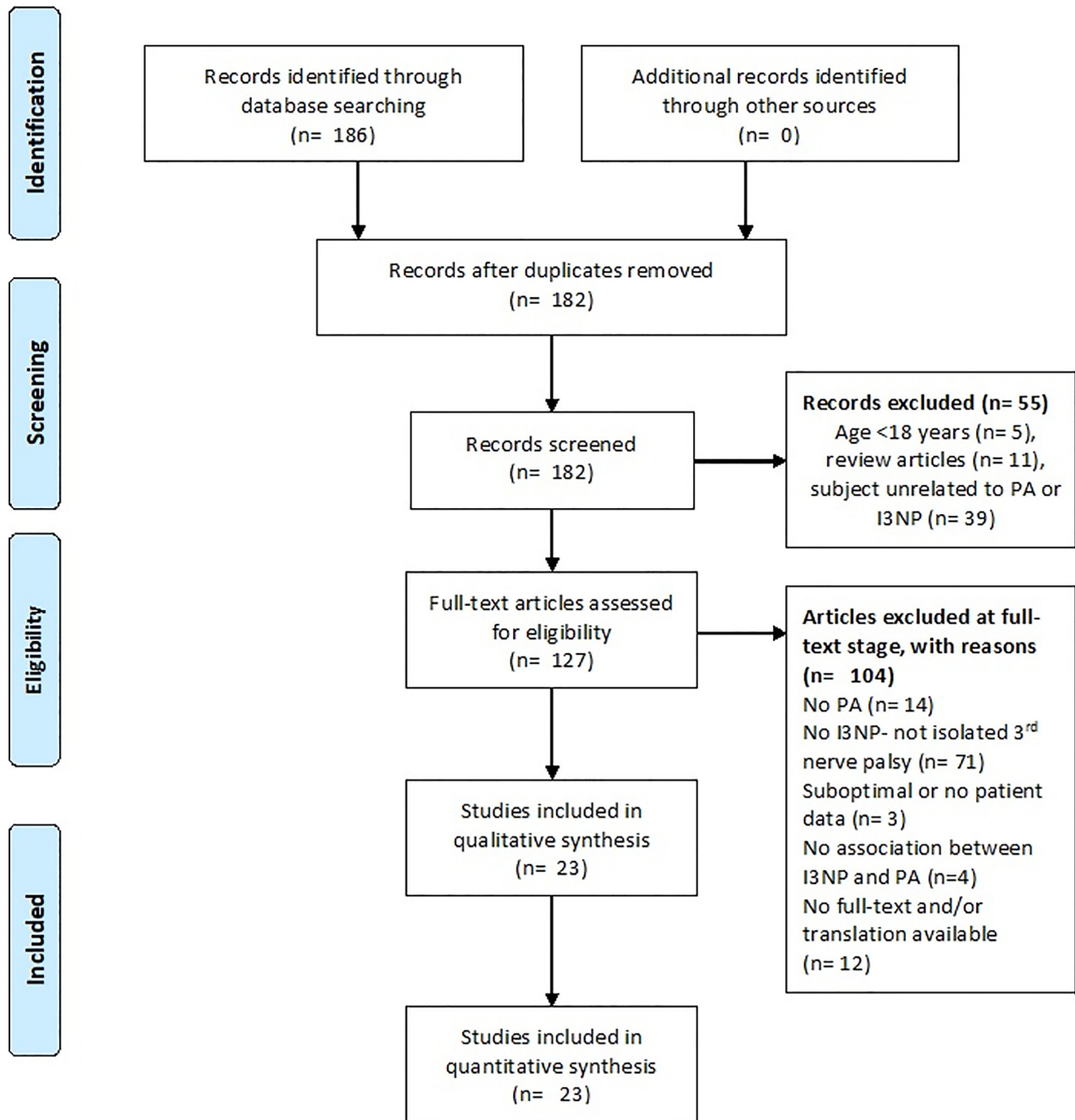


Fig. 1. PRISMA flowchart for study inclusion for isolated third cranial nerve palsy (I3NP) in pituitary apoplexy (PA).

diagnosis in patients presenting with acute I3NP, aside from intracranial aneurysm and microvascular ischemia.

Methods

MEDLINE and EMBASE databases were searched from inception to September 20, 2020 using a combination of the keywords: "oculomotor", "third nerve", "pituitary", "apoplexy", "hemorrhage", and "infarct". Retrieved abstracts were screened by authors SR and MR for inclusion in the full-text stage. Full-texts were screened if abstracts were unavailable. Selected full-text manuscripts from abstract

screening were then assessed for final inclusion in the systematic review (Fig. 1). Conflict resolution, when required at the full-text stage, was performed by SRL.

The inclusion criteria used were I3NP in patients with PA, age greater than or equal to 18 years, both hemorrhage and infarction of the pituitary gland, and both tumor and non-tumor hemorrhage in the pituitary. Exclusion criteria used were age less than 18 years, qualitative review articles, basic science studies, patients with other neurological findings in addition to third nerve palsy, such as but not restricted to, visual field defects, impaired visual acuity and other cranial nerve deficits. Records

were excluded if there was no definitive mention of hemorrhage or infarction in the pituitary or no specification of the third nerve palsy as the only neurological finding. Studies such as retrospective or prospective analyses not specifying individual patient level data were excluded. Studies were also excluded if English translations or full-text versions were not available in the institutional library database or through interlibrary loan transfer from other institutions in the United States.

The following variables were recorded: age, sex, side of third nerve involved, complete or partial palsy, aspects of third cranial nerve function involved (pupillary constriction, accommodation, extraocular movements, and eyelid elevation), radiological imaging features, size of the lesion, presence or absence of cavernous sinus invasion, presence or absence of hormonal derangements on laboratory evaluation, nature of management (medical or surgical), surgical pathology, outcome in terms of resolution of I3NP, partial or complete resolution, and time to any (complete or partial) resolution in days. Complete I3NP was defined as involvement of all three components of third nerve function and not complete loss or absence of one function. In patients without documented exact time to resolution, we included the post-discharge follow-up time interval with the first documentation of resolution. Both quantitative and qualitative analysis was performed in this study. Bias estimation was not performed for the case reports and case series. CARE guidelines checklists were created for the included case reports and case series (supplementary material). PRISMA guidelines were followed to perform the systematic review (supplementary material).

Statistical analysis was performed using IBM® SPSS® Statistics software version 20. Descriptive variables were reported as mean (\pm SD), median (IQR), or frequencies (percentages). Pearson/Spearman correlation, Chi-square test, and Mann-Whitney U-test were used to estimate associations between variables depending on normality of distribution of variables, which was assessed by Skewness and Kurtosis of the distribution. Based on the aforementioned criteria, final sample size obtained was small; therefore, we refrained from performing meta-analysis or inferential statistics such as Chi-Square testing or regression analysis for difference in outcomes based on age, sex, cavernous sinus invasion, or nature of treatment (medical versus surgical).

Results

Case report

A 76-year-old right-handed woman presented with sudden-onset severe pressure-like headache and drooping of the right eyelid for three days. There was no history of head trauma, loss of consciousness, neck stiffness, nausea or vomiting. Her comorbidities

included hypertension, type 2 diabetes, dyslipidemia, coronary artery disease, recent bilateral femoral deep-vein thrombosis treated with apixaban, and history of a poorly differentiated adenocarcinoma of the Ampulla of Vater treated with Whipple procedure in 2018. Comprehensive ophthalmic examination of the right eye demonstrated complete ptosis, depressed and abducted position in primary gaze, restriction of extraocular movements by -1 for depression, adduction, and elevation; fixed pupil at 3 mm with no constriction with light or accommodation; absence of APD and APD by reverse. Her left pupil was reactive to light and left eye extraocular movements were full. Visual acuity was 20/20 OU, fundi and visual fields were normal, anisocoria in room light was absent, and rest of the neurological exam was unremarkable. The findings were attributed to an isolated third-cranial nerve palsy. Given the acute onset severe headache and cranial nerve palsy; subarachnoid hemorrhage due to a ruptured aneurysm of the posterior communicating artery (PCom) was suspected. Non-contrast head CT and CT angiography head and neck showed no evidence of aneurysm or subarachnoid hemorrhage but revealed a 12 mm hypodense lesion in the sellar-suprasellar region. The patient was admitted to the neurology service for further management.

MRI of the brain with dedicated pituitary protocol with and without gadolinium (Fig. 2) revealed a heterogeneous $1.9 \times 1.8 \times 1.8$ cm sellar mass with suprasellar extension. The lesion demonstrated T1 iso/hyperintensity with thick peripheral enhancement and evidence of internal hemorrhage. The mass mildly compressed the superior aspect of the right cavernous sinus and adjacent cavernous internal carotid artery (ICA). There was no narrowing of the ICA lumen and no definite radiological invasion into the cavernous sinus. Laboratory evaluation showed evidence of secondary hypopituitarism with central hypothyroidism, hypogonadism and relative adrenal insufficiency. Low serum levels of gonadotropins (follicle stimulating hormone (FSH) 0.7 IU/l [postmenopausal normal value 25.8–134.8 IU/l], luteinizing hormone (LH) 0.4 IU/l [postmenopausal normal value 7.7–58.5 IU/l]; somatomedin C 0.08 ng/ml [normal value 0.39–4.08 ng/ml], cortisol 5.1 UG/dl [normal value 6.7–27.6 UG/dl], thyroid stimulating hormone (TSH) 0.08 mIU/ml [normal value 0.39–4.08 mIU/ml], and free T4 0.46 ng/dl [normal value 0.58–1.64 ng/dl]) were noted, while serum prolactin was normal at 6.7 ng/ml [normal value 3.4–24.1 ng/ml]. She was started on thyroxine and IV hydrocortisone replacement therapy. A diagnosis of pituitary apoplexy was made and neurosurgical decompression was performed via transsphenoidal approach. Pathology confirmed a partially infarcted pituitary adenoma with a sclerotic stroma. The patient had an uneventful post-operative period with complete resolution of the I3NP three weeks post-operatively.

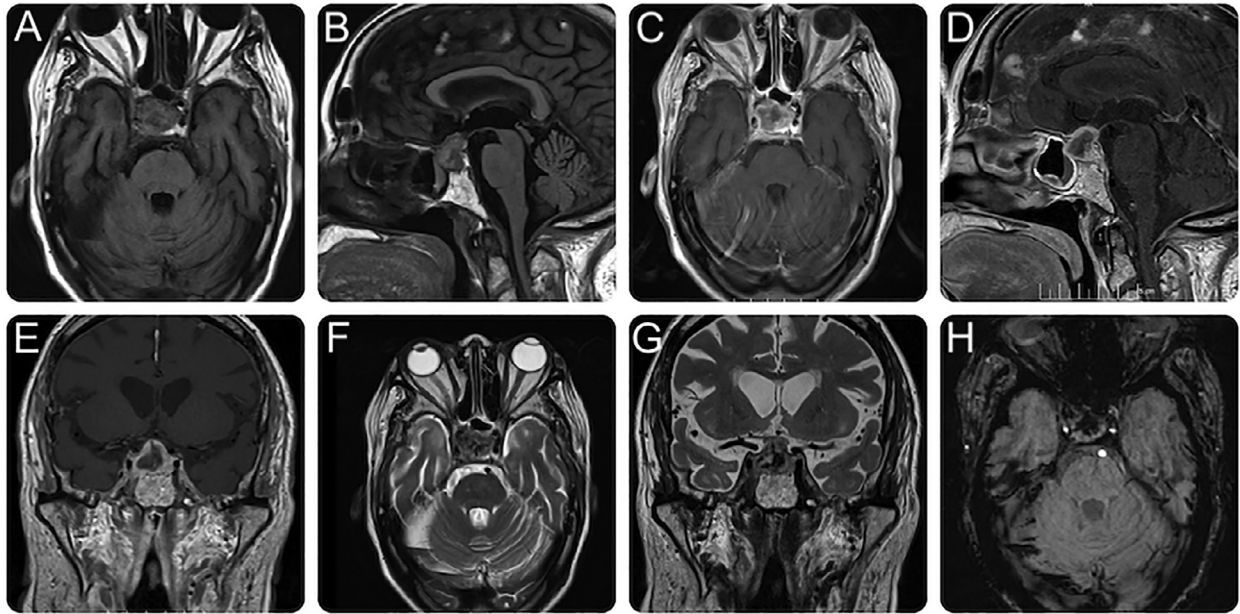


Fig. 2. MRI of the brain with dedicated pituitary protocol showing a heterogeneous $1.9 \times 1.8 \times 1.8$ cm sellar mass with suprasellar extension. (A) Axial, (B) coronal T1-weighted; (C) axial, (D) coronal, (E) sagittal T1-weighted post-gadolinium; (F) axial, (G) coronal T2-weighted; (H) susceptibility weighted imaging MRI brain sequences. The lesion demonstrates T1 iso-hyperintensity (A, B) with thick peripheral enhancement (C–E) and evidence of internal hemorrhage (H). The mass mildly compresses the superior aspect of the right cavernous sinus and adjacent cavernous internal carotid artery.

Systematic review

One hundred eighty-two abstracts were screened after removal of duplicates. Fifty-five abstracts were excluded at initial screening. One hundred and twenty-seven full-text articles were examined and one-hundred and four were excluded due to the presence of other neurological findings or no specification of I3NP ($n=71$), no PA ($n=14$), PA but with no specified relation to I3NP ($n=4$), and I3NP in PA but patient characteristics and outcomes not reported ($n=3$). We identified a total of 35 patients with I3NP in PA from 23 studies using the above criteria. This comprised of 18 case reports (less than 3 patients reported), 4 retrospective analysis (all medical records review), and 1 case series (3 or more patients reported). Among the case series and retrospective analyses included, 35 patients were excluded due to absent PA

($n=2$), no third nerve palsy ($n=16$), other ophthalmological or neurological findings (not I3NP, $n=17$).

Patient age ranged from 20 to 82 years with a mean of 54 ± 15.9 years. Twenty-eight patients were male (80%) and 7 were female (20%). I3NP was right-sided in 23 patients (66%), left-sided in 8 (27%), and bilateral in 1 patient. Headache associated with the I3NP was reported in 31 patients (97%). Twenty-nine patients (83%) had complete I3NP characterized by the presence of pupillary palsy, impaired extraocular movements, and ptosis. Six patients had partial I3NP with sparing of one or more components of third nerve function (17%) (Table 1). Among patients with partial palsy, 4 had pupillary sparing, one patient had extraocular movement sparing, and one patient had both pupils and extraocular movements spared.

Table 1. Clinical characteristics of 35 patients with I3NP and pituitary apoplexy.

Variable	Result	Result
Age (Mean \pm SD) ($n=35$)	54 ± 15.9 years	Range- 20–82 years
Sex ($n=35$)	Male- 28 (80%)	Female- 7 (20%)
I3NP side ^A ($n=32$)	Right- 23 (66%)	Left- 8 (27%)
I3NP completeness ($n=35$)	Complete- 29 (83%)	Partial- 6 (17%)
Adenoma ($n=29$)	Functioning- 6 (21%)	Non-functioning- 23 (79%)
Vascular lesion ($n=33$)	Hemorrhage- 31 (94%)	Infarct- 2 (6%)
Cavernous sinus invasion ($n=28$)	Invaded- 14 (50%)	Not invaded- 14 (50%)
Any resolution [#] ($n=33$)	Yes- 31 (94%)	No resolution- 2 (6%)
Treatment	Surgical- 28 (80%)	Medical- 7 (20%)

I3NP: isolated third cranial nerve palsy. ^AOne patient had bilateral I3NP. [#]Partial or complete resolution.

Thirty-one patients had pituitary hemorrhage and two patients had infarction. The nature of PA was not reported for 2 patients. Thirty-three patients had an underlying pituitary tumor. The size of the pituitary lesion ranged from 0.4 cm to a maximum of 4.6 cm across, recorded across any dimension. Mean size could not be estimated due to lack of uniform reporting of the size dimensions. Cavernous sinus invasion was noted in 14 patients (50%). No data was available regarding cavernous sinus involvement in 7 patients (20%). The pituitary lesion was reported as non-functioning in 23 patients (79%) and functioning adenoma with hormone secretion in 6 patients (21%) (Table 1); of which three had prolactinomas, two had Cushing's syndrome, and one had a growth hormone secreting tumor. Hormonal deficiencies were observed in 13 patients (40%), involving all the pituitary hormone lineages. Only one patient had pan-hypopituitarism.

Twenty-eight patients (80%) were managed surgically and 7 were managed conservatively (20%). Any (complete or partial) degree of resolution of the I3NP was noted in 31 patients (94%). Twenty-seven patients had complete resolution of I3NP (82%) and four had partial resolution (12%). Defect of pupillary constriction was the persistent finding in the three of four patients with partial resolution. Two patients had no improvement in I3NP. Time to any resolution of I3NP ranged from 8 days to 90 days with a median time of 29 days (IQR 19-63). Two studies documented complete resolution in the "immediate" and "early" post-operative period with no specified time duration.

In patients with cavernous sinus invasion (n=14), 12 (85.7%) had complete I3NP and 2 (14.3%) had partial I3NP. In patients without invasion, 11 (78.5%) had complete and 3 had partial I3NP (21.5%). Eleven patients (78.5%) had any resolution of I3NP (partial or complete) in patients with cavernous sinus invasion and 13 patients (92.8%) had any resolution in patients without invasion. Median time to resolution in patients with cavernous sinus invasion was 30 days (IQR 14-51) and 28.5 days (IQR 24-73) in patients without invasion (Table 2).

Overall, 28 patients were managed surgically (20%) and 7 were managed medically (20%). All patients had data on presence or absence of any resolution (partial or complete). Nineteen patients and three patients among surgical and medical management respectively had specific time to resolution mentioned in days. In patients who were managed

surgically, 25 (89%) had any resolution of I3NP and median time to resolution was 29 days (IQR 21-49). With medical management, 6 patients (87%) had any resolution of I3NP and median time to resolution was 90 days (IQR 14-90) (Table 2). Further inferential analyses such as correlation between age/sex and time to resolution of I3NP, relation between cavernous sinus invasion and resolution of I3NP, and difference in time to resolution or any resolution between medical and surgical management were not performed due to small sample size and missing data for several variables among these patients.

Discussion

We report a patient who presented with acute I3NP and was diagnosed with pathologically proven PA. PA is a rare medical emergency caused by an expanding mass within the sella turcica, resulting from hemorrhage or infarction of the pituitary gland or within a preexisting pituitary adenoma.¹ According to recent epidemiological studies, its prevalence is about 6.2 cases per 100,000² and its incidence is 0.17 per 100,000 per year.³ PA is often the first presentation of an underlying pituitary tumor in over 80% of patients⁴ and is characterized by sudden onset headache, which is usually the most common initial symptom, associated with visual disturbances, oculomotor nerve palsy⁵ and acute onset hypopituitarism. Visual disturbances are present in more than half of PA patients⁵⁻⁷ and are due to a sudden increase in tumor mass leading to compression of the optic chiasm or optic nerves from upward expansion of the tumor.⁷ Third cranial nerve palsy is also frequent, affecting 52% of patients⁸ with PA, and it is usually related to a lateral expansion of the pituitary mass.

However, an I3NP as presentation of PA is distinctly an uncommon event.

Third nerve palsy is characterized by a combination of ptosis, impaired pupillary constriction, and ophthalmoparesis, depending on the localization of the lesion anywhere along its course between the midbrain and the orbit.^{9,10} Major causes of I3NP are microvascular ischemia secondary to diabetes mellitus or systemic hypertension; inflammatory processes such as giant cell arteritis; trauma, and compressive mass lesions, most commonly intracranial tumors or aneurysms.⁹

Table 2. Any resolution (partial or complete) and time of resolution of I3NP based on cavernous sinus invasion and nature of management (medical or surgical).

Variable	Result	Any resolution (partial or complete)	Median time to resolution in days (IQR)
Cavernous sinus invasion	Yes (n=14)	11 (78.5%)	30 (14-51)
	No (n=14)	13 (92.8%)	28.5 (24-73)
Management	Surgical (n=28)	25 (89%)	29 (21-49)
	Medical (n=7)	6 (87%)	90 (14-90)

*statistical significance/p- values not estimated due to low sample size. I3NP: isolated third cranial nerve palsy. IQR: interquartile range.

The differential diagnosis and localization of lesions causing I3NP can be narrowed by the impairment of the pupillomotor function of third cranial nerve and by the presence or absence of associated pain (painful third nerve palsy). An isolated complete third nerve palsy with normal pupillary function is usually a hallmark of ischemic lesions^{9,11} while pupillary involvement is a red flag for compressive lesions, in particular aneurysms. Ischemic lesions tend to involve the central core of the nerve that has oculomotor functions, while the superficial parasympathetic pupillomotor fibers are usually spared.¹² On the other hand, compressive lesions, such as a PCom aneurysm or a tumor, usually affect both the superficial and deep fibers, causing partial or complete oculomotor deficits associated with pupillary dysfunction.^{11–13}

Painful third nerve palsy is a well-known presenting sign of a PCom aneurysm, while visual field defects are a common sign of pituitary adenomas and PA. Despite these common presentations, PA, pituitary adenoma and PCom aneurysm may unfavorably mimic each other. Varma et al.¹⁴ described a patient who presented with a painful third nerve palsy with pupillary dysfunction highly suspicious for PCom aneurysm, diagnosed eventually with a pituitary adenoma with parasellar extension. In contrast, Bonfield et al.¹⁵ reported a case presenting with sudden complete vision loss found with a suprasellar hemorrhage, initially diagnosed with PA but ultimately found with a ruptured PCom aneurysm. Because of the potentially drastic consequences of overlooking a Pcom aneurysm, the latter should always be considered in the differential of PA and pituitary adenoma, and when suspicion is high a formal angiogram is recommended prior to surgical exploration.¹⁵

Several mechanisms have been proposed to explain the occurrence of third nerve palsy in PA. The oculomotor nerve is often the first cranial nerve involved with lateral expansion of a pituitary tumor or a hematoma, since the nerve is located horizontally in the same plane as the pituitary gland in the lateral wall of the cavernous sinus.¹⁶ An abrupt pressure increase in the pituitary region secondary to an acute hemorrhage, infarction, or necrosis of the pituitary gland is transmitted relatively easily to the third cranial nerve resulting in palsy^{16–18} due to the exquisite sensitivity of cranial nerves to increased pressure.¹⁸ Acute onset third nerve palsy secondary to infarction or necrosis in a pre-existing pituitary mass can also result from compromise of the blood supply to the nerve due to compression of the vasa nervorum originating in the ICA.¹⁹

Our patient's imaging revealed a sellar and suprasellar mass with an acute hemorrhagic component with mild mass effect on the right cavernous sinus. The etiology of I3NP in our patient is most likely a pressure effect on the right third cranial nerve or by a compromise of the vascular supply to the nerve due to compression of the vasa nervorum originating in the ICA.

The treatment of patients with PA includes both medical and surgical management. Intravenous steroid administration is mandatory until surgery in order to prevent acute adrenal insufficiency. Neurosurgical decompression via a transsphenoidal approach is the definitive treatment for pituitary apoplexy and early decompression may partially or completely restore pituitary function leading to preservation of third cranial nerve function.²⁰ Neurosurgical decompression was performed via transsphenoidal approach and pathological evaluation confirmed the diagnosis of PA. Our patient had uneventful post-operative period with complete resolution of the I3NP in three weeks.

This is the first systematic review of I3NP in pituitary apoplexy to our best knowledge based on literature search. The aim of this review was to analyze the clinical features, anatomical findings, diagnostic evaluation, management, and outcomes of I3NP in PA. We identified a total of 35 patients with I3NP in PA from 23 studies. We noted that this phenomenon may occur in a wide age group between 20–82 years with a mean age of 54 years and a male preponderance of 80%. Headache was reported in almost all patients (97%) and can both precede and accompany the onset of I3NP. Involvement of all three components of third nerve function (complete palsy) was noted in over 80% of patients. Although pituitary tumors were found to be non-functioning in 79%, deranged hormone levels were seen in up to 40% of patients, likely due to acute necrosis and compressive effect on the normal pituitary gland. The size of the lesion on imaging, albeit reported non-uniformly and only in eleven patients, ranged from 0.4 to 4 cm. The wide size range, the ability of sub-centimetric lesions to cause I3NP, and the high percentage of complete palsies all point to the major role played by sudden expansion within the lesion as compared to gross lesion size.

Invasion of the cavernous sinuses was noted only in 50%, indicating that third nerve palsy may occur due to other aforementioned processes related to an expansive lesion such as compression of the cavernous sinus without invasion and damage to vasa nervorum. Patients with and without cavernous sinus invasion had similar completeness (85.7% and 78.5% respectively) and median time to resolution of I3NP (30 days and 28.5 days respectively). Whether these differences were statistically significant was not estimated due to low sample size and missing data. However, these results provide an impression that cavernous sinus invasion does not confer a poor prognosis in terms of extent or recovery of third nerve palsy.

Surprisingly, almost all patients (94%) had some resolution of palsy with a significant proportion showing complete resolution (82%), indicating an overall good prognosis for I3NP in PA. Surgical intervention carried a trend towards earlier median time to resolution of I3NP [29 days (21–49)] as compared to conservative treatment

[90 days (14–90)]; however this analysis is severely limited by low number of medically managed patients ($n=7$), of whom time-to-resolution is reported only in three patients. Therefore, significance of the difference cannot be estimated. In the real-world scenario, the presence of disabling visual symptoms resulting from an expansive pituitary tumor steers decision making towards urgent surgical intervention, which may confer excellent prognosis for I3NP as noted above.

Our systematic review was limited by small sample size and non-reported data. We were unable to include patients from studies of third cranial nerve palsy in PA with unreported clinical or imaging characteristics and outcomes. This could be a potential source of literature bias. In addition, the validity of the imaging findings from the case reports could not be assessed since we did not have access to the original imaging. Studies with unavailable English translation were excluded which may cause language bias. Due to the above limitations, the results reported may therefore not be generalizable. The findings from our systematic review are discussed with an aim to provide an overview of the characteristics and outcome of patients with I3NP in PA.

Conclusions

Pituitary apoplexy is an important diagnostic consideration in patients presenting with I3NP. I3NP from PA appears to have favorable prognosis. The effect of cavernous sinus invasion on prognosis and the difference in outcomes with different lines of treatment requires further study.

Author contributions

Michela Rosso- Case Report, systematic review, statistical analysis, manuscript draft, manuscript revisions

Srinath Ramaswamy- Case Report, systematic review, statistical analysis, manuscript draft, manuscript revisions

Heidi Sucharew- Manuscript draft, statistical analysis, manuscript revisions for important scientific content.

Achala Vagal- Manuscript draft, manuscript revisions for important scientific and neuroimaging content.

Yaacov Anziska- Manuscript draft, manuscript revisions for important scientific content.

Steven R. Levine- Manuscript draft, manuscript revisions for important scientific content.

MR and SR contributed equally to this manuscript.

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Yaacov Anziska: no conflicts to disclose.

Steven R. Levine: no conflicts to disclose.

Declarations of Competing Interest

The authors have no conflicts of interest to declare.

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Supplementary materials

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