



Review

Pituitary Apoplexy in Patients with Pituitary Neuroendocrine Tumors (PitNET)

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Abstract: Various complications of pituitary neuroendocrine tumors (PitNET) are reported, and an intratumor hemorrhage or infarct underlying pituitary apoplexy (PA) represents an uncommon, yet potentially life-threatening, feature, and thus early recognition and prompt intervention are important. Our purpose is to overview PA from clinical presentation to management and outcome. This is a narrative review of the English-language, PubMed-based original articles from 2012 to 2022 concerning PA, with the exception of pregnancy- and COVID-19-associated PA, and non-spontaneous PA (prior specific therapy for PitNET). We identified 194 original papers including 1452 patients with PA (926 males, 525 females, and one transgender male; a male-to-female ratio of 1.76; mean age at PA diagnostic of 50.52 years, the youngest being 9, the oldest being 85). Clinical presentation included severe headache in the majority of cases (but some exceptions are registered, as well); neuro-ophthalmic panel with nausea and vomiting, meningism, and cerebral ischemia; respectively, decreased visual acuity to complete blindness in two cases; visual field defects: hemianopia, cranial nerve palsies manifesting as diplopia in the majority, followed by ptosis and ophthalmoplegia (most frequent cranial nerve affected was the oculomotor nerve, and, rarely, abducens and trochlear); proptosis (N = 2 cases). Risk factors are high blood pressure followed by diabetes mellitus as the main elements. Qualitative analysis also pointed out infections, trauma, hematologic conditions (thrombocytopenia, polycythemia), Takotsubo cardiomyopathy, and T3 thyrotoxicosis. Iatrogenic elements may be classified into three main categories: medication, diagnostic tests and techniques, and surgical procedures. The first group is dominated by anticoagulant and antiplatelet drugs; additionally, at a low level of statistical evidence, we mention androgen deprivation therapy for prostate cancer, chemotherapy, thyroxine therapy, oral contraceptives, and phosphodiesterase 5 inhibitors. The second category includes a dexamethasone suppression test, clomiphene use, combined endocrine stimulation tests, and a regadenoson myocardial perfusion scan. The third category involves major surgery, laparoscopic surgery, coronary artery bypass surgery, mitral valvuloplasty, endonasal surgery, and lumbar fusion surgery in a prone position. PA in PitNETs still represents a challenging condition requiring a multidisciplinary team from first presentation to short- and long-term management. Controversies involve the specific panel of risk factors and adequate protocols with concern to neurosurgical decisions and their timing versus conservative approach. The present decade-based analysis, to our knowledge the largest so far on published cases, confirms a lack of unanimous approach and criteria of intervention, a large panel of circumstantial events, and potential triggers with different levels of statistical significance, in addition to a heterogeneous clinical picture (if any, as seen in subacute PA).



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and a spectrum of evolution that varies from spontaneous remission and control of PitNET-associated hormonal excess to exitus. Awareness is mandatory. A total of 25 cohorts have been published so far with more than 10 PA cases/studies, whereas the largest cohorts enrolled around 100 patients. Further studies are necessary.

Keywords: pituitary neuroendocrine tumors; neurosurgery; pituitary apoplexy; hormone; surgery; anticoagulant; computed tomography; headache

1. Introduction

Various complications have been reported in the relationships of pituitary neuroendocrine tumors (PitNET); an intratumor hemorrhage or infarct/infarction, also named pituitary apoplexy (PA), is a less common feature, yet with a life-threatening potential, thus its importance in early recognition and prompt intervention. Of historical note, hemorrhages associated with pituitary tumors were first described in 1898 by Pearce Bailey, and in 1950 the term “pituitary apoplexy” was introduced by Brougham et al. [1]. PA is a medical emergency presenting as sudden onset headache, loss of vision, ophthalmoplegia, and altered consciousness in relationship with a prior known or unknown pituitary mass, mostly PitNETs (usually a nonfunctioning adenoma, but also, hormonally active tumors with or without previous specific therapy) [1–3].

The incidence of PA in the general population varies from 0.2% to 0.6%, and from 2% to 12% in selected subgroups diagnosed with different types of PitNETs [4,5]. Males are affected more frequently than females; even though any age may be involved, most cases are reported within the fifth or sixth decade of life, whereas pediatric incidence remains very low [6,7].

The underlying mechanisms of PA are not completely understood yet. The classical hypothesis states that a rapidly growing tumor exceeds vascular supply [8]. Other potential contributors are vascular endothelial growth factor (VEGF), tumor necrosis factor- α (TNF- α), pituitary tumor-transforming gene (PTTG), matrix metalloproteinase-2/9 (MMP-2/9) or MMP-9, hypoxia-inducing factor (HIF-1 α), a high proliferating index Ki-6 [9–11]; and high-mobility group box 1 (HMGB1), a nuclear DNA-binding protein with pro-inflammatory effects [12].

In terms of clinical presentations, sudden headache, often with retro-orbital location, is one of the most common presenting symptoms of PA, with an incidence of 92% up to 100% of the patients [13]. The PA-associated mechanism includes traction of intracranial pain-sensitive structures such as the dura mater, cranial nerves, blood vessels, and meningeal irritation caused by blood and necrotic tissue [14]. Other frequent symptoms are ophthalmological complaints such as visual loss, diplopia, and ophthalmoplegia [15]. Specific hormonal anomalies, caused either by hormonally active PitNETs or by PA-induced or tumor-related hypopituitarism, may also be identified at the moment of PA diagnostic [16]. Arterial hypertension, diabetes mellitus, non-endocrine major surgical procedures, head trauma, infections, and certain drugs targeting the endothelium or clotting profile are PA-associated risk factors [16]. Hemorrhage in prolactinomas is another common scenario, especially under specific medical therapy [17,18]. Cavernous sinus invasion or the presence of a large macroadenoma may also increase the risk of developing PA [18,19]. Socioeconomic factors potentially play a role in the development of PA, yet, not unanimously accepted [20].

The imaging tests used as a diagnostic aid are mostly represented by computed tomography (CT) and magnetic resonance imaging (MRI) [21]. Even though CT is used more often, MRI has a higher sensitivity [22]. The most commonly described MRI signs of PA are “sinus mucosal thickening” and “pituitary ring sign” [23]. Of note, the diagnostic of PA needs to be confirmed by imaging findings and/or associated post-operative pathological profile after suspicion of PA is raised from a clinical presentation with regard to a neuroendocrine and/or neurologic point of view [21–23].

PA management involves a multidisciplinary team, as it is considered a neuroendocrine emergency. The main source of mortality is caused by acute adrenal insufficiency. Therefore, prompt glucocorticoid replacement is crucial [24]. However, the exact protocol still represents a subject of controversy. Early surgery is necessary for patients with severe visual loss since decompression may lead to a better recovery of visual dysfunction [25], but not necessarily to complete hypopituitarism recovery [26]. Other data did not identify any differences regarding the outcome of eye profile and hormonal imbalance when comparing surgical to conservative management [27,28].

Aim

Our purpose is to overview PA as a complication of a pituitary tumor, particularly PitNETs, from clinical presentation to management and outcome.

2. Method

This is a narrative review of the English-language medical literature. Inclusion criteria are the following: clinically relevant papers concerning a PubMed-based search using the keywords “apoplexy”, “hemorrhage”, or “infarction” in association with “pituitary” (alternatively “hypophyseal”); the timeline of publication is between 2012 and 2022; we included original research, either studies or case reports/series. Exclusion criteria were PA associated with the following circumstances: pregnancy and postpartum period, infection with coronavirus amid the recent COVID-19 pandemic, and non-spontaneous PA meaning PA associated with treatment for a prior known PitNET: neurosurgery, pituitary radiotherapy, and medication for hormonally active PitNETs, for instance, dopamine analogs (cabergoline, bromocriptine) for prolactinomas and somatotropinomas, respectively, somatostatin analogs (octreotide, lanreotide, and pasireotide), and growth hormone (GH) receptor antagonist pegvisomant for somatotroph PitNETs.

3. PitNET Complicated with PA

According to our methodology, we identified 194 original papers that included 165 case reports, 5 case series, 22 retrospective studies, one case–control study, and one prospective study. Overall, 1452 patients with PA were included (926 males, 525 females, and one transgender male). In accordance with medical literature, we found a male predominance (male-to-female ratio of 1.76). The mean age of patients was 50.52 years, the youngest was 9, and the oldest was 85 years [29–222] (please see Table 1) (Figure 1).

Table 1. Original studies published between 2012 and 2022 concerning PA according to our methodology; the cited studies are displayed from 2012 to 2022; the data concern the clinical presentation and potential triggers of PA in addition to underlying pituitary disease (if any) [29–222].

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|---------------|--|---|---|---|
| Brar [29] 2012 | Case report | 29-year-old male | Headache, nausea, non-projectile vomiting, dizziness, hypotension (systolic BP = 86–90 mmHg, diastolic BP = 56–62 mmHg) | High altitude (4572 m) | * |
| Cagnin [30] 2012 | Case report | 80-year-old male | Headache, nausea, vomiting, drowsiness, neck rigidity, fever | Head trauma hypertension | * |
| Chan [31] 2012 | Case report | 30-year-old male | Headache, decrease in visual acuity, 3rd cranial nerve palsy Clinically manifested Cushing disease | | Corticotroph PitNET |
| Chentli [32] 2012 | Case report | 9-year-old boy | Retro-orbital headache, decrease in visual acuity, diplopia, papillary edema Gigantism (+5SD) | | Lactosomatotroph PitNET |
| Choudhry [33] 2012 | Case series | 4 female patients (mean age: 41.75 years) | Headache ($n = 4$), nausea and vomiting ($n = 3$), decreased visual acuity ($n = 4$), bitemporal hemianopia ($n = 4$), 3rd cranial nerve palsy ($n = 2$), facial numbness/pain ($n = 1$) Clinically manifested Cushing disease ($n = 4$) | DM, hypertension | Corticotroph PitNET |
| Enatsu [196] 2012 | Case report | 65-year-old female | Left 3rd cranial nerve palsy, decrease in visual acuity | | Nonfunctioning pituitary tumor |
| Komurcu [34] 2012 | Case report | 45-year-old male | Headache, bilateral 3rd cranial nerve palsy, proptosis, diplopia, loss of vision | Coronary artery bypass surgery | Null cell pituitary adenoma |
| Kruljac [35] 2012 | Case report | 77-year-old female | Headache, decrease in vision, ptosis, diplopia | Heparin-induced thrombocytopenia, 2DM, hypertension | Squamous cell carcinoma metastasis in the pituitary |
| Kurusu [36] 2012 | Case report | 68-year-old male | Headache, nausea, vomiting, 3rd cranial nerve palsy, coma | Hypertension | Nonfunctioning pituitary tumor |
| Liu [37] 2012 | Case report | 66-year-old male | Headache, vomiting, decreased visual acuity, right 3rd cranial nerve palsy, meningism | | Pituitary tumor with hypopituitarism |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|---------------------|--------------------|--|---|-------------------------------------|
| Mohindra [38] 2012 | Case report | 40-year-old female | Headache, vision loss, coma Acromegalic features | | Somatotroph PitNET |
| Paisley [39] 2012 | Case report | 67-year-old female | Headache, vomiting, partial loss of vision, left temporal hemianopia, light sensitivity | Hypertension | * |
| Tedd [40] 2012 | Case report | 37-year-old male | Headache, nausea, vomiting, photophobia, neck stiffness | | Pituitary tumor |
| Verma [41] 2012 | Case report | 36-year-old male | Headache, fever, loss of vision, 3rd cranial nerve palsy | | Pituitary tumor |
| Wildenberg [42] 2012 | Case report | 40-year-old male | Headache, vomiting | Dengue hemorrhagic fever, thrombocytopenia | Somatotroph PitNET |
| Yamamoto [43] 2012 | Two case reports | 56-year-old female | Headache, vomiting, visual disturbance, left 3rd cranial nerve palsy | Endocrine stimulation tests | Pituitary tumor |
| | | 73-year-old male | Progressive visual disturbance | Endocrine stimulation tests | Pituitary tumor |
| Zoli [44] 2012 | Case report | 59-year-old female | Headache, 6th cranial nerve palsy | | Pituitary tumor |
| Chou [45] 2013 | Case report | 64-year-old female | Headache, nausea, vomiting, fever, high BP, visual illusions | | Pituitary tumor |
| Cinar [46] 2013 | Case report | 38-year-old male | Headache, nausea, vomiting | DM, hypertension | Somatotroph PitNET |
| Delgado-Alvarado [47] 2013 | Case report | 70-year-old male | Headache, right total ophthalmoplegia | | * |
| Deshwal 2013 [48] | Case report | 29-year-old male | Headache, nausea, loss of appetite, fatigue, difficulty sleeping, hypotension | High altitude (5200 m) | No underlying condition |
| Fanous [49] 2013 | Case report | 39-year-old male | Headache, diplopia | | Pituitary macroadenoma |
| Haider [50] 2013 | Case report | 64-year-old woman | Headache, nausea, diplopia, right ptosis | Enoxaparin | Pituitary macroadenoma |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|---------------|--------------------|---|---|-------------------------------------|
| Hojo [51] 2013 | Case report | 29-year-old male | Headache, vomiting | | Lactotroph PitNET |
| Huang [52] 2013 | Case report | 77-year-old male | Headache, nausea, vomiting, ophthalmoplegia, visual field deficit | GnRH agonist for prostate cancer | Pituitary adenoma |
| Jiang [53] 2013 | Case report | 49-year-old male | Headache | Diabetic ketoacidosis | Somatotroph PitNET |
| Kobayashi [54] 2013 | Case report | 33-year-old female | Headache, nausea, malaise | Oral contraceptives | Nonfunctioning pituitary adenoma |
| Machado [220] 2013 | Case report | 36-year-old female | Spontaneous resolution of cushingoid features under no treatment | Hypertension | Corticotroph PitNET |
| Masui [55] 2013 | Case report | 68-year-old male | Headache, fatigue, anorexia, bitemporal hemianopia | | Pituitary melanoma metastasis |
| Mir [56] 2013 | Case report | 55-year-old male | Headache, vomiting, altered consciousness | 2DM | Somatotroph PitNET |
| Mohamed [57] 2013 | Case report | 37-year-old male | Headache, nausea, vomiting, neck pain, 3rd cranial nerve palsy, left temporal field defect, loss of visual acuity | | Pituitary adenoma |
| Ní Chróinín [58] 2013 | Case report | 75-year-old female | Headache, vomiting, diplopia, 3rd cranial nerve palsy | Hypertension, DM | Pituitary adenoma |
| Oh [59] 2013 | Case report | 42-year-old man | Headache, vomiting, fever, neck stiffness, left eye ptosis, hemianopia | Hypertension, chronic renal failure | Pituitary adenoma |
| Radhiana [60] 2013 | Case report | 44-year-old male | Headache, vomiting, coma | | Pituitary adenoma |
| Steinberg [218] 2013 | Case report | 43-year-old male | Visual loss, loss of consciousness | DM, hypertension | Lactotroph PitNET |
| Sun [221] 2013 | Case report | 49-year-old male | Exitus | Long restrain in sitting position | Gonadotroph PitNET |
| Tutanc [61] 2013 | Case report | 27-year-old female | Headache, vomiting, palpitation, sleep disturbance | Thyroxine therapy | Thyrotrophic PitNET |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|--|--|---|--|
| Uemura [219] 2013 | Case report | 84-year-old male | Retro-orbital pain, 3rd cranial nerve palsy | DM, dabigatran etexilate | Nonfunctioning pituitary adenoma |
| Witczak [62] 2013 | Case report | 67-year-old female | Panhypopituitarism, headache, 3rd cranial nerve palsy | | Pituitary metastases from breast cancer |
| Wong [63] 2013 | Case report | 62-year-old male | Headache, diplopia, 3rd, 4th, and 5th cranial nerve palsy | | Pituitary adenoma |
| Zieliński [64] 2013 | Case report | 59-year-old female | Headache, vomiting, nausea, altered consciousness, visual disturbances | Anticoagulation | Nonfunctioning pituitary adenoma |
| Berkenstock [65] 2014 | Case report | 50-year-old male | Headache, nausea, vomiting, unilateral loss of vision, diarrhea, polydipsia, polyuria | Hypertension | Pituitary adenoma |
| Bujawansa [66] 2014 | Retrospective analysis | 55 patients (35 males and 20 females) Mean age: 58.4 years | Acute headache ($n = 48$) Cranial nerve palsy ($n = 26$): 3rd cranial nerve palsy ($n = 16$), 6th cranial nerve palsy ($n = 5$), multiple palsies ($n = 5$) Diplopia ($n = 21$) Visual field defect ($n = 20$) Vomiting ($n = 14$) Photophobia ($n = 10$) Nausea ($n = 9$) Facial pain/trigeminal neuralgia ($n = 8$) Collapse ($n = 2$) | hypertension ($n = 11$), anticoagulation with warfarin ($n = 3$), aspirin ($n = 2$), coronary artery bypass grafting ($n = 2$), major orthopedic surgery ($n = 3$), clomiphene ($n = 1$) | Nonfunctioning pituitary adenomas in 45 cases (82%), lactotroph PitNETs in 6 cases (11.5%), somatotroph PitNETs in 4 cases (7.2%), multiple endocrine neoplasia syndrome in 2 cases |
| Chao [67] 2014 | Case report | 14-year-old female | Headache, nausea, blurred vision | | Pituitary adenoma |
| Cho [68] 2014 | Case report | 40-year-old female | Headache, diplopia, hemiparesis | Hypertension | * |
| Chao [67] 2014 | Case report | 14-year-old female | Headache, nausea, blurred vision | | Pituitary adenoma |
| Cho [68] 2014 | Case report | 40-year-old female | Headache, diplopia, hemiparesis | Hypertension | * |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|---------------------|--|--|--|---|
| Garg [197] 2014 | Case report | 20-year-old male | Visual impairment, bitemporal hemianopia | | Pituitary adenoma |
| Gupta [69] 2014 | Case report | 62-year-old male | Headache, 3rd cranial nerve palsy, visual field defects Acute coronary syndrome, hours after admission to hospital | DM | Pituitary macroadenoma |
| Jho [70] 2014 | Retrospective study | 109 patients (69 males and 40 females) mean age: 51 years | Headache Visual acuity/field deficits Cranial nerve palsies Vomiting Altered consciousness Meningism Fever | Anticoagulation ($n = 9$) | PitNET ($n = 98$) Rathke's cyst ($n = 8$) Primitive neuroectodermal tumor ($n = 1$) Craniopharyngioma ($n = 1$) Metastatic lung carcinoma ($n = 1$) |
| Lee [71] 2014 | Case report | 58-year-old male | Headache, visual disturbances, visual field defect, decreased sexual activity | T3 thyrotoxicosis | Gonadotroph PitNET |
| Maltby [72] 2014 | Case report | 11-year-old female | Headache, vomiting, lethargy, weight loss Tall stature, central obesity | | Possible gonadotroph PitNET |
| Man [73] 2014 | Case report | 52-year-old male | Headache, left sided weakness | | Bronchogenic carcinoma metastases |
| Mishra [74] 2014 | Case report | 43-year-old male | Headache, vomiting, loss of vision, bitemporal hemianopia, fever | Dengue hemorrhagic fever, thrombocytopenia | Pituitary adenoma |
| Mura [198] 2014 | Case report | 85-year-old male patient | 3rd cranial nerve palsy | Laparoscopic surgery, anticoagulation (dabigatran), hypertension | Nonfunctioning pituitary adenoma |
| Navarro-Bonnet [75] 2014 | Case report | 30-year-old male | Headache, decreased visual acuity, diplopia, right ptosis Within 24 h: confusion, left hemiplegia | | Giant lactotroph PitNET |
| Rebeiz [199] 2014 | Case report | 81-year-old female | Stupor, hypotension, bilateral blindness | Hypertension | Pituitary adenoma |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|---------------|------------------------------|--|--|-------------------------------------|
| Roerink [76] 2014 | Case report | 46-year-old transgender male | Headache, nausea, vomiting, blurred vision | DM during testosterone therapy | Somatotroph PitNET |
| Tan [77] 2014 | Case report | 53-year-old male | Headache, vomiting, left eye ptosis, right 6th cranial nerve palsy, right hemianopia, fever | Dengue hemorrhagic fever, thrombocytopenia | Lactotroph and gonadotroph PitNET |
| Villar-Taibo [78] 2014 | Case report | 51-year-old female | Headache, nausea, vomiting, photophobia, photophobia meningeal signs, fever | Meningitis | Somatotroph PitNET |
| Yoshida [200] 2014 | Case report | 74-year-old female | Asymptomatic apoplexy, anterior hypopituitarism, hyperthyroidism | | Pituitary adenoma |
| Yoshino [201] 2014 | Case report | 78-year-old male | Fever, respiratory distress, polyuria | Thoracic surgery | Pituitary adenoma |
| Zhang [79] 2014 | Case report | 42-year-old male | Headache, fever, loss of consciousness, visual disturbance | | Pituitary adenoma |
| Akakin [80] 2015 | Case report | 58-year-old male | Headache, blurred vision, bitemporal hemianopia, lethargy | Posterior lumbar fusion surgery | Pituitary adenoma |
| Asaithambi [81] 2015 | Case report | 54-year-old male | Headache, visual loss, partial 3rd, 4th, and 6th cranial nerve palsies | | Pituitary adenoma |
| Banerjee [82] 2015 | Case report | 56-year-old female | Headache, visual loss, followed by neurological deterioration (unresponsive, fixed and dilated right pupil, decerebrate response to stimuli) | Fall from standing | Pituitary macroadenoma |
| Fountas [83] 2015 | Case report | 45-year-old male | Headache, fever, photophobia, hypotension, confusion | | Pituitary adenoma |
| Kasl [202] 2015 | Case report | 14-year-old female | Upper limb weakness, mental status changes | | Lactotroph PitNET |
| Kasl [203] 2015 | Case report | 74-year-old female | Unilateral vision loss, 3rd cranial nerve palsy | Intravitreal injection of vascular endothelial growth factor inhibitor | Gonadotroph PitNET |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|---|--|---|--|
| Kim [84] 2015 | Case report | 69-year-old male | Headache, visual field defect, diplopia, 3rd, 4th, and 6th cranial nerve palsy | Mitral valvuloplasty | Pituitary adenoma |
| Man [85] 2015 | Case report | 82-year-old male | Headache, diplopia, bilateral 3rd and 6th cranial nerve palsies | | Pituitary adenoma |
| Roerink [86] 2015 | Two case reports | 41-year-old male | Neck pain, acromegalic features | DM | Somatotroph PitNET |
| | | 47-year-old female | Headache, a second episode of headache and visual impairment, Cushingoid features | DM, hypertension | Corticotroph PitNET |
| Saberifard [87] 2015 | Case report | 50-year-old female | Headache, vomiting, visual field defect | | Pituitary adenoma |
| Sasagawa [88] 2015 | Case report | 62-year-old male | Headache, 3rd cranial nerve palsy | GnRH agonist for prostate cancer | Gonadotroph PitNET |
| Sasaki [89] 2015 | Case report | 65-year-old male | Headache, visual impairment, symptoms of adrenal insufficiency | | Pituitary adenoma |
| Singh [90] 2015 | Retrospective analysis | 87 patients (55 males and 30 females) mean age: 50.9 years | Headache ($n = 78$, 89.7%) Cranial nerve palsy ($n = 34$, 39%) Visual field defects ($n = 30$, 34.1%) | Hypertension ($n = 34$, 39%) DM ($n = 11$, 12.6%) cardiothoracic surgery ($n = 2$, 2.3%) anticoagulant therapy ($n = 9$, 10.3%): heparin ($n = 2$, 22.2%) or warfarin ($n = 7$, 77.8%) antiplatelet drugs ($n = 17$, 19.5%) | Null cell ($n = 18$) Lactotroph PitNET ($n = 8$) |
| Teasdale [91] 2015 | Case report | 72-year-old male | Headache, nausea, vomiting, visual disturbances 5 years after the initial presentation: headache, vomiting, visual disturbances, diplopia, 3rd and 6th cranial nerve palsy, epistaxis | | Thyrotroph, gonadotroph PitNET 5 years after the initial presentation: malignant spindle and round-cell tumor |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|-----------------------|--|---|--|--|
| Zhu [92] 2015 | Case-control study | 2021 patients with pituitary tumors, out of which: 97 cases with PA (70 males and 27 females) mean age: 50.1 ± 13.9 years (PA), randomly matched with 194 controls | Headache ($n = 84$, 86.6%) Visual deterioration ($n = 60$, 61.86%) Vomiting ($n = 39$, 40.21%) Ptosis ($n = 25$, 25.77%) Diplopia ($n = 6$, 6.18%) | Hypertension DM (differences between cases and controls were not statistically significant) | Null (non-functional) PitNET ($n = 63$) Lactotroph PitNET ($n = 7$) Somatotroph PitNET ($n = 8$) Corticotroph PitNET ($n = 1$) Thyrotroph PitNET ($n = 2$) Gonadotroph PitNET ($n = 10$) Others ($n = 4$) Multiple staining ($n = 2$) |
| Zou [93] 2015 | Case report | 23-year-old male | Headache, nausea, decreased visual acuity, loss of consciousness, fever | | Somatotroph PitNET |
| Choudhury [94] 2016 | Case report | 75-year-old male | Headache, nausea, vomiting, photophobia | Antiplatelet drug | Pituitary adenoma |
| Doglietto [95] 2016 | Case report | 76-year-old female | Headache, visual disturbances, ophthalmoplegia, 3rd cranial nerve palsy | Anticoagulant therapy (dabigatran) | Nonfunctioning pituitary adenoma |
| Gambaracci [96] 2016 | Case report | 55-year-old female | Headache, decreased visual acuity, fever | | Pituitary adenoma |
| Giammattei [97] 2016 | Case series | 8 male patients mean age: 70 years | Headache ($n = 7$) Nausea and vomiting ($n = 4$) Decreased visual acuity ($n = 2$) Ophthalmoplegia ($n = 6$) Altered consciousness ($n = 1$) Photophobia ($n = 1$) | Anticoagulant ($n = 3$) Antiplatelet ($n = 1$) Hypertension ($n = 5$) DM ($n = 2$) Autoimmune hemolytic anemia with thrombocytopenia ($n = 1$) | Pituitary adenoma |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|---|--|--|--|
| Giritharan [98] 2016 | Case series | 31 patients (19 males, 12 females), mean age: 55 years | Headache (<i>n</i> = 31, 100%) Nausea/vomiting (<i>n</i> = 17, 55%) Visual field defect (<i>n</i> = 18, 58%) Decrease in visual acuity (<i>n</i> = 7, 23%) Ocular paresis (<i>n</i> = 12, 39%): 3rd cranial nerve (<i>n</i> = 8, 26%), 6th cranial nerve (<i>n</i> = 6, 19%) | Hypertension (<i>n</i> = 5, 16%) Oral anticoagulation (<i>n</i> = 3, 10%) Heparin therapy (<i>n</i> = 1, 3%) Pregnancy (<i>n</i> = 1, 3%) Previously known adenoma (<i>n</i> = 1, 3%) | Nonfunctioning adenomas (<i>n</i> = 21, 67.74%) Somatotroph PitNET (<i>n</i> = 2, 6.45%) Lactotroph PitNET (<i>n</i> = 1, 3.22%) Gonadotroph PitNET (<i>n</i> = 5, 16.12%) Corticotroph PitNET (<i>n</i> = 2, 6.45%) |
| Keane [99] 2016 | Case report | 67-year-old male | Headache, 3rd cranial nerve palsy | GnRH agonist for prostate cancer | Gonadotroph PitNET |
| Ogawa [100] 2016 | Retrospective study | 43 patients (30 males and 13 females) mean age: 56.67 years | Headache Cranial nerve palsies Aseptic meningitis Altered consciousness | | Nonfunctioning pituitary adenoma (<i>n</i> = 29) Lactosomatotroph PitNET (<i>n</i> = 5) Lactotroph PitNET (<i>n</i> = 4) Thyrotroph PitNET (<i>n</i> = 3) Somatotroph PitNET (<i>n</i> = 1) Corticotroph PitNET (<i>n</i> = 1) |
| Paschou [101] 2016 | Case report | 37-year-old male | Headache, nausea, fever, visual acuity decrease, 3rd cranial nerve palsy, neck stiffness, confusion | | Gonadotroph PitNET |
| Sussman [102] 2016 | Case report | 46-year-old male | Headache, dizziness, decrease in visual acuity, syncope, 3rd and 4th cranial nerve palsy, hemiparesis | Anti-hypertensive drugs | Pituitary adenoma |
| Balaparameswara Rao [103] 2017 | Case report | 45-year-old male | Headache, vomiting, altered consciousness | Dengue hemorrhagic fever | Corticotrophic PitNET |
| Grangeon [104] 2017 | Case report | 83-year-old male | Headache (hemicrania) | DM | Pituitary adenoma |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|---|---|--|--|
| Humphreys [105] 2017 | Prospective study | 10 patients, out of which 5 patients with PA (2 males and 3 females) mean age: 46 years | Headache ($n = 3$) Visual field defect ($n = 1$) Decreased visual acuity ($n = 1$) Irregular menses ($n = 1$) Hyponatremia ($n = 1$) Altered consciousness ($n = 1$) | | Gonadotroph PitNET ($n = 3$) Thyrotroph PitNET ($n = 1$) Null cell ($n = 1$) |
| Ishigaki [204] 2017 | Case report | 66-year-old male | Delayed 3rd cranial nerve palsy | Head trauma, hypertension, DM | Nonfunctioning pituitary adenoma |
| Law-Ye [106] 2017 | Case report | 29-year-old male | Headache, progression to coma | Bodybuilding exercises | Pituitary adenoma |
| Pasha [107] 2017 | Case report | 35-year-old female | Headache, vomiting, 3rd cranial nerve palsy, decrease in vision, acute right side motor deficits and speech impairment | | Pituitary adenoma |
| Patra [108] 2017 | Case report | 36-year-old male | Headache | Polycythemia | Somatotroph PitNET |
| Rais [205] 2017 | Case report | 86-year-old female | Functional decline | Hypertension, DM | Pituitary adenoma |
| Simsek Bagir [109] 2017 | Case report | 32-year-old male | Headache, nausea, vomiting, hiccups, acromegalic features | | Lactosomatotroph PitNET |
| Souteiro [110] 2017 | Case report | 77-year-old female | Headache, nausea, vomiting, psychomotor impairment, visual acuity loss | Hypertension, 2DM | Corticotroph PitNET |
| Waqar [111] 2017 | Retrospective study | 47 patients with pituitary apoplexy (33 males and 14 females) mean age: 54 ± 15 years - patients were compared with 50 surgically treated patients with nonfunctioning pituitary adenomas | Headache ($n = 42$) Nausea/vomiting ($n = 25$) Visual field defect ($n = 26$) Visual acuity defect ($n = 18$) Cranial nerve palsy ($n = 19$) Altered consciousness ($n = 4$) | Hypertension ($n = 11$) Anticoagulation-antiplatelet therapy ($n = 4$) | Pituitary adenoma |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|---|---|---|---|
| Zoli [112] 2017 | Retrospective study | 75 patients (45 males and 30 females) mean age: 52.4 ± 16.2 years | Headache (<i>n</i> = 75, 100%) Anterior hypopituitarism (<i>n</i> = 51, 68%) Visual disturbances (<i>n</i> = 55, 73.4%) Ophthalmoplegia (<i>n</i> = 38, 50.7%) Altered consciousness (<i>n</i> = 2, 2.6%) | | Pituitary adenoma |
| Abbara [113] 2018 | Retrospective study | 52 patients (25 males and 27 females) mean age: 46.7 years | Headache (<i>n</i> = 40/43) Vomiting (<i>n</i> = 22/43) 3rd cranial nerve palsy only (<i>n</i> = 12/35) 6th cranial nerve palsy only (<i>n</i> = 8/35) 3rd and 6th palsy (<i>n</i> = 3/35) Decreased visual acuity (<i>n</i> = 14/35) Visual fields defects (<i>n</i> = 13/35) | Hypertension (<i>n</i> = 17) Intrapartum/puerperal (<i>n</i> = 7) DM (<i>n</i> = 4) Antiplatelet or anticoagulant (<i>n</i> = 3) Dopamine agonists (<i>n</i> = 2) Radiotherapy (<i>n</i> = 2) None (<i>n</i> = 24) | Nonfunctioning adenoma or gonadotroph PitNET (<i>n</i> = 47) Lactotroph PitNET (<i>n</i> = 5) |
| Bettag [114] 2018 | Case report | 75-year-old female | Headache, diplopia, decreased consciousness | | Gonadotroph PitNET |
| Fan [115] 2018 | Case report | 79-year-old male | Headache, decreased vision, diplopia, 3rd cranial nerve palsy | | Pituitary adenoma |
| Hodgson [206] 2018 | Case report | 71-year-old female | Proptosis | | Lactotroph PitNET |
| Jang [207] 2018 | Case report | 41-year-old female | Diplopia, visual disturbances, 6th cranial nerve palsy | Chemotherapy (doxorubicin and cyclophosphamide) | Pituitary macroadenoma |
| Joo [116] 2018 | Case report | 73-year-old male | Headache, 3rd cranial nerve palsy | Lumbar fusion surgery in prone position | Pituitary macroadenoma |
| Komshian [117] 2018 | Case report | 56-year-old male | Headache, diplopia, 3rd cranial nerve palsy | | Nonfunctioning pituitary adenoma |
| Kuzu [118] 2018 | Case report | 30-year-old male | Headache, 3rd cranial nerve palsy | Dexamethasone suppression test | Corticotroph PitNET |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|---------------------------|--|--|--|---|
| Myla [119] 2018 | Case report | 59-year-old male | Headache, stiff neck, nausea | Hypertension | Nonfunctioning pituitary macroadenoma |
| Raj [208] 2018 | Case report | 18-year-old male | Vomiting, adrenal insufficiency | Varicella infection, thrombocytopenia | Corticotroph PitNET |
| Ricciuti [120] 2018 | Case series | 17 patients (12 males and 5 females) mean age: 58.76 years | Headache ($n = 5$) Vomiting ($n = 4$) 3rd cranial nerve palsy ($n = 10$) 6th cranial nerve palsy ($n = 4$) Visual acuity deficit ($n = 4$) Neck stiffness ($n = 1$) | Hypertension ($n = 3$) Previous radiation therapy ($n = 1$) | |
| Rutkowski [121] 2018 | Retrospective study | 32 patients (21 males and 11 females) mean age: 49 years | Headache ($n = 32$, 100%) Nausea/vomiting ($n = 10$, 31%) Encephalopathy ($n = 6$, 19%) Nuchal rigidity ($n = 4$, 12%) Hypopituitarism ($n = 28$, 88%) Decrease in visual acuity ($n = 31$, 97%) Cranial nerve palsy (3rd, 4th and/or 6th) ($n = 16$) | | Nonfunctional adenoma (70%) Clinically hypersecreting adenoma (15%) Lactotroph PitNET Somatotroph PitNET Corticotroph PitNET |
| Salehi [209] 2018 | Case report | 78-year-old male | Ophthalmoplegia, 3rd and 4th cranial nerves palsy, altered consciousness | | Pituitary adenoma |
| Ward [210] 2018 | Case report | 63-year-old male | Fever, hypotension, tachycardia, altered consciousness | Closed head injury | Nonfunctioning pituitary adenoma |
| Yamada [122] 2018 | Case report | 50-year-old male | Headache, visual impairments, loss of consciousness | | * |
| Almeida [123] 2019 | Retrospective analysis | 67 patients (41 males and 26 females) mean age: 57.4 +/− 16.2 years | Headache ($n = 60$) Visual deficit ($n = 44$) Hypopituitarism ($n = 40$) Cranial nerve palsy ($n = 32$): 3rd ($n = 17$), 4th ($n = 8$), 6th ($n = 8$) Altered levels of consciousness ($n = 10$) | | Pituitary adenoma |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|--|--|---|--|
| Crisman [124] 2019 | Case report | 43-year-old male | Headache, cranial nerve palsies (3rd, 4th, and 6th) | Endoscopic Retrograde Cholangiopancreatography | Pituitary adenoma |
| Dupont [125] 2019 | Case report | 83-year-old female | Headache, bilateral vision loss | Dual anti-aggregation | Pituitary adenoma |
| Ghalaenovi [126] 2019 | Case report | 28-year-old male | Resolution of initial symptoms (headache, nausea, photophobia, bitemporal hemianopia at diagnosis of a pituitary macroadenoma) | | Lactotroph PitNET |
| Harju [127] 2019 | Case report | 48-year-old male | Headache, diplopia, 3rd cranial nerve palsy, visual field defect, fever | Endoscopic endonasal surgery | Non-functional macroadenoma |
| Hosmann [128] 2019 | Retrospective analysis | 76 patients (53 males and 23 females) mean age: 53.7 +/-14.3 years | Headache ($n = 63$, 82.9%) Nausea/vomiting ($n = 26$, 34.2%) Decrease in visual acuity ($n = 42$, 54.9%) Visual field deficit ($n = 48$, 63.3%) Cranial nerve palsy: 3rd ($n = 35$, 46.1%), 6th ($n = 22$, 28.9%) Altered levels of consciousness ($n = 12$, 15.8%) | Hypertension ($n = 23$, 30.3%) Oral anticoagulation ($n = 14$, 18.4%) DM ($n = 9$, 11.8%) Extracranial surgery within 24 h before apoplexy ($n = 4$, 5.3%) | Clinically nonfunctioning PitNETs (81%): gonadotroph PitNET (37.9%), null-cell (29.3%), plurihormonal (8.6%), corticotroph (3.5%), somatotroph (1.7%) Clinically functioning PitNETs: lactotroph (10.4%), corticotroph (6.9%), somatotroph (1.7%) |
| Kirigin Biloš [129] 2019 | Case report | 74-year-old male | Headache, nausea, vomiting, vertigo, 3rd cranial nerve palsy | | Pituitary adenoma |
| Krug [130] 2019 | Case report | 45-year-old male | Headache, diplopia | | Crooke cell adenoma |
| Mittal [131] 2019 | Case report | 38-year-old male | Headache, nausea, 3rd cranial nerve palsy, visual field deficits | DM | Nonfunctioning pituitary adenoma |
| Naito [132] 2019 | Case report | 14-year-old female | Headache, visual impairment | Cardiac surgery | Pituitary adenoma |
| Nioi [133] 2019 | Case report | 50-year-old female | Headache, visual impairment, vertigo Hemodynamic collapse after placement of nasogastric tube | TSS, incorrect placement of nasogastric tube | Pituitary adenoma |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|---------------|--|--|---|---|
| Pedro [134] 2019 | Case report | 79-year-old male | Headache, photophobia, vomiting | | Pituitary adenoma |
| Santos [135] 2019 | Case report | 74-year-old female | Headache, vomiting, decrease in visual acuity, bitemporal hemianopia | Systemic anticoagulation, DM | Pituitary adenoma |
| Sanz-Sapera [136] 2019 | Case report | 50-year-old male | Headache, acromegalic features | | Somatotroph PitNET |
| Singhal [137] 2019 | Case report | 65-year-old female | Headache, vision loss, rhinorrhea | | Corticotroph PitNET |
| Swaid [138] 2019 | Case report | 65-year-old female | Headache, 3rd cranial nerve palsy | Coronary angiography, anticoagulation (heparin), 2DM, hypertension | Pituitary adenoma |
| Thomas [139] 2019 | Case report | 85-year-old male | Headache, 3rd cranial nerve palsy | Dengue fever-induced thrombocytopenia | Pituitary adenoma |
| Uneda [140] 2019 | Case report | 51-year-old male | Headache, 3rd cranial nerve palsies (ophthalmoplegia) | Vardenafil therapy | Pituitary adenoma |
| Wang [141] 2019 | Case report | 21 patients (15 males and 6 females), with a mean age of 50.7 ± 15.0 years | Headache ($n = 21$) Nausea ($n = 15$) Vomiting ($n = 14$) Visual disturbances: visual field defects ($n = 17$) decreased visual acuity ($n = 17$) Cranial nerves palsies ($n = 10$) Electrolyte disturbances ($n = 12$) Menstrual disturbances and galactorrhea ($n = 4/6$) Fever ($n = 3$) Altered consciousness ($n = 3$) | Hypertension ($n = 9$) Coagulation disturbances ($n = 9$) Diabetes mellitus ($n = 4$) Antiplatelet therapy ($n = 1$) Chronic renal insufficiency ($n = 1$) Atrial fibrillation ($n = 1$) Old myocardial infarction ($n = 1$) | Nonfunctioning pituitary adenoma ($n = 18$) Lactotroph PitNET ($n = 2$) Somatotroph PitNET ($n = 1$) |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|---------------------|--|---|---|-------------------------------------|
| Waqar [142] 2019 | Case report | 51-year-old male | Headache, vomiting, diplopia, 6th cranial nerve palsy | | Nonfunctioning pituitary adenoma |
| Ahn [211] 2020 | Case report | 78-year-old male | Stupor, hemiparesis | Hypertension | Pituitary adenoma |
| Brown [143] 2020 | Case report | 56-year-old male | 2 episodes of acute-onset headache, vomiting, and a cranial nerve palsy | | Switching phenotypes |
| Catarino [144] 2020 | Case report | 55-year-old female | Headache, 3rd cranial nerve palsy | DM, Pituitary fungal infection | Corticotroph PitNET |
| Eichberg [145] 2020 | Case report | 46-year-old female | Headache, nausea, vomiting, blurred vision | | Nonfunctioning pituitary adenoma |
| Elarjani [146] 2020 | Case report | 31-year-old male | Headache, hemiparesis, unilateral decreased visual acuity | | Pituitary adenoma |
| Franzese [147] 2020 | Case report | 60-year-old male | Headache, nausea, weakness, diplopia, 3rd cranial nerve palsy | Coronary artery bypass grafting | Null cell adenoma |
| Klimko [148] 2020 | Case report | 41-year-old male | Headache, fatigue, weight loss | | Somatotroph PitNET |
| Lee [149] 2020 | Case report | 75-year-old male | Headache, vomiting, dizziness, 3rd, 4th, and 5th nerve palsies | Hypertension, DM, hemodialysis | Nonfunctioning pituitary adenoma |
| Marzoughi [150] 2020 | Case report | 70-year-old male | Headache, diplopia, 3rd cranial nerve palsy | Hypertension, DM, anticoagulant | Pituitary adenoma |
| Pangal [151] 2020 | Retrospective study | 50 patients (31 males, 19 females) mean age: 53 years | Headache (86%) Vision loss (62%) Cranial nerve palsy (40%) Decrease in consciousness (14%) | | Pituitary adenoma |
| Patel [152] 2020 | Case report | 60-year-old male | Headache, nausea, vomiting, monocular vision loss | Autologous hematopoietic cell transplantation | Somatotroph PitNET |
| Romano [212] 2020 | Case report | 65-year-old male | Blindness, hemiparesis, decreased alertness | | Pituitary macroadenoma |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|--|---|--|-------------------------------------|
| Shetty [153] 2020 | Case report | 49-year-old female | Headache, palpitations, nausea, vomiting, neck stiffness | Regadenoson myocardial perfusion scan | Nonfunctioning pituitary adenoma |
| Siwakoti [154] 2020 | Case report | 59-year-old female | Headache, nausea, dizziness | | Corticotroph PitNET |
| van Boven [155] 2020 | Case report | 31-year-old female | Headache, nausea, vomiting | 2DM | Corticotroph PitNET |
| Yang [213] 2020 | Case report | 70-year-old female | Confusion, hypotension, fever, chills, cough | | Pituitary microadenoma |
| Alam [156] 2021 | Case report | 40-year-old male | Headache acromegalic feats | | Somatotroph PitNET |
| Aljabri [157] 2021 | Case report | 74-year-old male | Headache and vomiting 2 h after goserelin injection, dizziness, diplopia | Androgen deprivation therapy (goserelin) for prostate cancer | Pituitary macroadenoma |
| Alkhaibary [214] 2021 | Case report | 65-year-old male | Diplopia, 3rd cranial nerve palsy | Coronary bypass graft surgery | Pituitary adenoma |
| Ambrose [158] 2021 | Case report | 84-year-old male | Headache, bruising 5 days after admission: bilateral ptosis, ophthalmoplegia | Immune thrombocytopenia | Pituitary macroadenoma |
| Bhagal [215] 2021 | Case report | 63-year-old male | Myxedema coma | | Pituitary adenoma |
| Bukhari [159] 2021 | Case report | 59-year-old male | Headache, loss of vision, 3rd cranial nerve palsy | Hypertension | Pituitary adenoma |
| Cavalli [160] 2021 | Retrospective study | 30 patients (22 males, 8 females) mean age: 54 years | Visual disturbance (86.7%) Headache (96%) Nausea and vomiting (33.3%) | Hypertension (53.8%) Invasive procedures (30.7%) Anticoagulation (23%) Trauma (7.7%) Antiplatelet therapy (7.7%) | PitNET |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|--|--|---|--|
| de Silva [161] 2021 | Case report | 35-year-old female | Headache, visual loss Cushingoid features | | Crooke cell tumor |
| Elsehety [216] 2021 | Case report | 60-year-old female | Vision loss, vomiting, coma | | Nonfunctioning pituitary adenoma |
| Falhammar [162] 2021 | Retrospective study | 33 patients (18 male and 15 female) mean age: 46.5 years | Headache (82%) Visual disturbances (36%) Nausea (36%) | Antithrombotic therapy $n = 7$ (21%) | PitNET |
| Gohil [163] 2021 | Case report | 56-year-old male | Headache, diplopia, 3rd cranial nerve palsy during hospitalization for leptospirosis | Leptospirosis | Pituitary adenoma |
| Hanna [164] 2021 | Case report | 49-year-old male | Headache, diplopia, 3rd cranial nerve palsy | | Nonfunctioning pituitary adenoma |
| Huang [165] 2021 | Case report | 72-year-old male | Headache, nausea, vomiting, 3rd cranial nerve palsy | | Nonfunctioning pituitary adenoma |
| Iqbal [166] 2021 | Retrospective study | 55 patients (26 males and 29 females) mean age: 50 years | Headache Confusion Visual field defect Cranial nerve palsy | Hypertension Anticoagulation Antiplatelet Previous stroke Radiotherapy | Somatotroph PitNET Lactotroph PitNET |
| Komić [167] 2021 | Case report | 54-year-old male | Headache, vomiting, photophobia | | Pituitary adenoma |
| Marx [168] 2021 | Retrospective study | 46 patients (29 males and 17 females) mean age: 47.3 years | Meningism ($n = 20$) Headache ($n = 38$) Visual acuity decrease ($n = 11$) Visual field defect unilateral impairment bitemporal impairment ($n = 20$) Cranial nerve palsies: 3rd ($n = 19$), 4th ($n = 6$), 6th ($n = 13$) Impaired Glasgow Coma Scale (< 15) ($n = 2$) | GnRH analogs ($n = 2$) Anticoagulant ($n = 1$) Cabergoline ($n = 2$) Recent major surgery ($n = 3$) Recent rugby play without head trauma ($n = 1$) Pregnancy ($n = 3$) | Nonfunctioning adenoma ($n = 31$) Corticotroph PitNET ($n = 1$) Lactotroph PitNET ($n = 12$) Somatotroph PitNET ($n = 1$) |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|--|--|--|---|
| Nakhleh [169] 2021 | Retrospective study | 27 patients (14 males and 13 females) mean age: 40.7 ± 12.5 years | Headache (<i>n</i> = 25) Visual field defect (<i>n</i> = 9) Cranial nerve palsy (<i>n</i> = 3) Altered consciousness (<i>n</i> = 2) | Hypertension (<i>n</i> = 5) DM (<i>n</i> = 3) Antiplatelet therapy (<i>n</i> = 3) | Nonfunctioning pituitary adenoma (<i>n</i> = 21) Lactotroph PitNET (<i>n</i> = 5) Somatotroph PitNET (<i>n</i> = 1) |
| Oudghiri [170] 2021 | Case series | 4 patients (2 males and 2 females) mean age: 78.25 years | Headache (<i>n</i> = 2) Vomiting (<i>n</i> = 2) Visual disturbance (<i>n</i> = 1) Cranial nerve palsy (<i>n</i> = 3) | Anticoagulant (<i>n</i> = 2) Hypertension (<i>n</i> = 1) DM (<i>n</i> = 1) | Nonfunctioning pituitary adenoma |
| Pan [171] 2021 | Case report | 44-year-old male | Headache, vomiting, dizziness | Diabetic ketoacidosis Acute pancreatitis Hypertension | Somatotroph PitNET |
| Pattankar [172] 2021 | Case report | 20-year-old female | Headache, lethargy, altered sensorium Progressive neurological deterioration: hemiparesis, unilateral ophthalmoplegia | Diabetic ketoacidosis | Nonfunctioning pituitary adenoma |
| Pokhrel [217] 2021 | Case report | 26-year-old male | Vision reduction, retro-orbital pain, dizziness, vomiting, right limbs weakness Acromegalic features | No apparent trigger | Somatotroph PitNET |
| Rosso [173] 2021 | Case report | 76-year-old female | Headache, 3rd cranial nerve palsy | 2DM apixaban | Pituitary adenoma |
| Seaman [25] 2021 | Retrospective study | 44 patients (24 males and 20 females) median age: 55 years | Headache (<i>n</i> = 40) Visual disturbances (<i>n</i> = 30): visual field disturbances (<i>n</i> = 16), decreased visual acuity (<i>n</i> = 9), cranial nerve palsies: 3rd (<i>n</i> = 18), 4th (<i>n</i> = 6), 5th (<i>n</i> = 1), 6th (<i>n</i> = 6) Nausea/vomiting (<i>n</i> = 7) Altered mental status (<i>n</i> = 7) Hormone-related complains (<i>n</i> = 4) | Hypertension (<i>n</i> = 22) DM (<i>n</i> = 13) Anticoagulation (<i>n</i> = 4) | Nonfunctioning adenoma (<i>n</i> = 38) Functioning PitNET (<i>n</i> = 6) |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|--|--|---|---|
| Sun Z [174] 2021 | Retrospective study | 24 patients (13 males and 11 females) mean age: 46.46 ± 14.95 years | Headache (<i>n</i> = 20, 83.33%) Nausea and vomiting (<i>n</i> = 17, 70.83%) Loss of vision (<i>n</i> = 18, 75.00%) Visual field defects (<i>n</i> = 8, 33.33%) Ophthalmoplegia attributed mainly to 3rd and 6th cranial nerve palsies (<i>n</i> = 7, 29.17%) Decreased libido (<i>n</i> = 2, 8.33%) Amenorrhea (<i>n</i> = 2, 8.33%) Loss of consciousness (<i>n</i> = 1) | | Nonfunctioning adenomas (<i>n</i> = 7) Lactotroph PitNET (<i>n</i> = 3) Corticotroph PitNET (<i>n</i> = 1) Gonadotroph PitNET (<i>n</i> = 1) Lactocorticotroph PitNET (<i>n</i> = 1) |
| Teramoto [175] 2021 | Retrospective study | 45 patients (33 males and 12 females) mean age: 56 years | Headache (<i>n</i> = 40) Visual impairment (<i>n</i> = 18) Ophthalmoplegia (<i>n</i> = 19) Hypopituitarism (<i>n</i> = 23) | Hypertension (<i>n</i> = 12) DM (<i>n</i> = 10) Antithrombotic therapy (<i>n</i> = 7) | Nonfunctioning adenoma (<i>n</i> = 37) Somatotroph PitNET (<i>n</i> = 5) Lactotroph PitNET (<i>n</i> = 3) |
| Tumyan [176] 2021 | Case report | 67-year-old male | Headache, nausea, peripheral vision defect, decreased consciousness within 48 h; 3rd cranial nerve palsy, progressive confusion | DM | Pituitary adenoma |
| Van Dong [177] 2021 | Case report | 38-year-old female | Headache, decreased visual acuity, aphasia, hemiparesis, decreased consciousness | | Pituitary adenoma |
| Vargas [178] 2021 | Case report | 53-year-old female | Headache, vomiting, 3rd cranial nerve palsy, progressive neurological deterioration | | Pituitary macroadenoma |
| Yoshida [179] 2021 | Case report | 78-year-old male | Headache, nausea, hemianopia, collapse | | Gonadotroph PitNET |
| Zhu JD [180] 2021 | Case report | 48-year-old male | Headache, vomiting, 3rd cranial nerve palsy, decreased vision unilaterally within 48 h: consciousness disturbance, hemiplegia, hyperthermia | | Nonfunctioning pituitary adenoma |

Table 1. Cont.

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|------------------------|---|---|---|---|
| Zhu Q [181] 2021 | Retrospective study | 46 patients (35 males and 11 females) mean age: 46.78 ± 12.32 | Headache ($n = 44$) Visual disturbance ($n = 41$) Nausea/vomiting ($n = 27$) Hypogonadism ($n = 39$) Asymptomatic apoplexy ($n = 1$) | | PitNET |
| Cross [182] 2022 | Retrospective study | 59 patients (40 males and 19 females) median age: 54 years | Headache ($n = 59$) Cranial nerve deficits ($n = 46$): 3rd cranial nerve palsy ($n = 26$, 44%), 4th cranial nerve palsy ($n = 1$), 6th cranial nerve palsy ($n = 12$, 20%) Vision loss ($n = 5$) | | PitNET |
| Geyik [183] 2022 | Retrospective study | 143 patients with pituitary adenoma, out of which 8 patients with PA (4 males and 4 females, mean age: 26.75 years) | Headache ($n = 7$) Visual disturbances ($n = 4$) Amenorrhea and galactorrhea ($n = 4$) | | Lactotroph PitNET ($n = 5$) Nonfunctioning adenoma ($n = 3$) |
| Hamrick [184] 2022 | Case report | 31-year-old male | Headache, nausea, vision decrease, | Systemic chemotherapy (bleomycin, etoposide, cisplatin) | Somato- and corticotroph PitNET |
| Hsu [185] 2022 | Case report | 53-year-old male | Headache, fever, pruritic skin rash, abdominal pain, fatigue | | Gonadotroph PitNET |
| Liu [186] 2022 | Case report | 33-year-old male | Headache, nausea, vomiting, bitemporal hemianopia, diplopia, 3rd cranial nerve palsy, Cushingoid features | | Corticotroph PitNET |
| Mills [187] 2022 | Case report | 65-year-old female | Headache, reduced visual acuity, bitemporal hemianopia | | Metastatic breast carcinoma into gonadotroph PitNET |
| Oldfield [188] 2022 | Case report | 57-year-old male | Headache, thirst, polydipsia, weakness | | Pituitary adenoma |

Table 1. *Cont.*

| Author Reference Number/ Year of Publication | Type of Study | Population | Clinical Presentation at Admission for PA | Potential Triggers/ Predisposing Factors | Underlying Pituitary Condition * |
|--|----------------|--------------------|---|---|-------------------------------------|
| Puglisi [189] 2022 | Case report | 81-year-old female | Headache, bilateral vision loss, altered consciousness, hematuria | Anticoagulant (acenocoumarol), hypertension | PitNET |
| Rai [190] 2022 | Case report | 64-year-old male | Headache, nausea, vomiting, decreased visual acuity, ophthalmoplegia | Hypertension, DM, polysubstance abuse | Pituitary macroadenoma |
| Shrestha [191] 2022 | 2 case reports | 56-year-old male | Headache, 3rd cranial nerve palsy, diplopia, decrease in vision | Hypertension | PitNET |
| | | 50-year-old male | 3rd cranial nerve palsy (ptosis) | | |
| Singh A. [192] 2022 | Case report | 36-year-old male | Chronic headache, sudden diplopia, 6th cranial nerve palsy | | Somatotroph PitNET |
| Singh V. [193] 2022 | Case report | 52-year-old female | Headache, visual field changes | | Nonfunctioning pituitary adenoma |
| Syed [194] 2022 | Case report | 36-year-old male | Headache, diplopia, abducens nerve palsy | | Pituitary adenoma |
| Viola [195] 2022 | Case report | 63-year-old male | Headache, asthenia, diplopia | | Pituitary adenoma |

* there are some reports where imaging findings did not identify an actual pituitary tumor at the moment of PA confirmation. Of note, due to the changes of terminology during the last decade, we used the type of pituitary tumor according to the original papers unless there were clear criteria for what we currently consider PitNET. Abbreviations: BP = blood pressure; DM = diabetes mellitus; 2 DM = type 2 diabetes mellitus; GnRH = gonadotropin-releasing hormone; T3 = triiodothyronine; PA = pituitary apoplexy; *n* = number of patients (the name of the original article “study” or “series” was used according to the original publication).



Figure 1. Flowchart according to our methodology.

3.1. Clinical Presentation in Cases with PA: Neurologic and Ophthalmic Elements

Sudden headache was the most frequent symptom and occurred in more than two-thirds of patients. (Table 1) Headache was severe, often described as the most painful headache episode an individual has ever experienced, and graded, for example, as high as 9 on a scale from 0 to 10, with 10 being the most severe in one study [31]. For practical purposes we point out that headache was absent in some cases; thus, an index of suspicion should be provided by other endocrine and non-endocrine clinical elements [43,86,196–216]. For instance, Enatsu et al. reported a 65-year-old woman admitted for a nonfunctioning pituitary adenoma-associated PA who presented third cranial nerve palsy and sudden decrease in visual acuity unaccompanied by headache [196]. Another example is a 65-year-old male who developed PA as a post-operative complication after a coronary artery surgery; he only presented diplopia and third cranial nerve palsy [214]. Other circumstances without headaches involve a comatose status. The case presented by Bhogal et al. involves a 63-year-old man with bradycardia and hypotension due to myxedema coma as part PA-associated hormonal picture [215]. Elsehety et al. reported a 60-year-old woman with vision loss and progression to coma due to an acute stroke as a surrounding event to PA [216].

Other common symptoms include nausea and vomiting, either with a neurological or endocrine component (acute secondary adrenal insufficiency) [25,29,30,33,36–121,128–171,174,176,178–208,217]. As mentioned, altered consciousness of various degrees up to coma was identified in 24 papers [56,64,70,79,93,97,100,103,111,112,114,122,123,141,151,169,174,177,189,209,210,215,216,218]. Weakness as a distinct clinical element was specified in five clinical cases (as a neurologic or endocrine consequence) [73,147,188,202,217].

Another important clinical finding is meningism, a crucial clue for differentiating between two life-threatening conditions: PA presenting as aseptic meningitis and bacterial meningitis. PA mimics neurological conditions, such as bacterial [30,37,39,59,63,78,83,106,119,168] or aseptic [100,176] meningitis, making differential diagnosis difficult. Both PA and meningitis share a similar clinical presentation with nuchal rigidity [30,59,70,78,83,119,168],

positive Kernig and Brudzinski signs [37,78], fever [30,59,78,83], photophobia [39,70,83], and altered states of consciousness [30,83,106,176]. Moreover, laboratory findings consistent with bacterial meningitis, such as neutrophilic pleocytosis [30,39,59,78,119,176], and high protein content [39,59,83,119,176] were also observed in PA. In terms of glucose content of cerebrospinal fluid (CSF), patients presented with normal [59,78,83,119] or high [176] levels in CSF. In spite of findings suggestive of bacterial meningitis, all CSF cultures were sterile [30,39,59,78,83,100,119,176]. In one case, differential diagnosis was particularly difficult [78]. Villar-Taibo et al. presented a patient with clinical presentation (nuchal rigidity, positive Kernig and Brudzinski signs, and fever) and CSF analyses consistent with bacterial meningitis, whose state improved under antibiotics. Following this event, the subject was diagnosed with PA based on MRI findings and pathological examination. The authors hypothesized that meningitis might have led to PA due to vasculitis. However, it remained unclear whether PA mimicked meningitis or if previous meningitis led to PA [78]. Considering that both PA and bacterial meningitis can be life-threatening, prompt differential diagnosis and treatment are essential. Current findings suggest that the presentation of a clinical picture suggestive of meningitis includes differential diagnosis with PA, especially in patients with sterile CSF, knowing that PA may cause aseptic, irritant chemical, bacterial-like meningitis [39].

PA may associate cerebral ischemia through either extrinsic compression or vasospasm, leading to neurological deterioration (mental status changes, motor deficits, speech impairment) in patients who suffered from acute ischemic stroke following PA [79,107,146,199].

PA-associated visual disturbances include decreased visual acuity in most cases [11,25,31–33,37,57,70,75,80,93,96–98,101,102,105,110,113,120,121,128,135,146,168,177,187,190,196]. Complete blindness was reported in two papers [199,212]. Visual field defects varied from (mostly common) hemianopia [33,39,55,80,126,135,179,187,197] to cranial nerve palsies manifesting as diplopia in the majority of these cases [32,34,35,49,50,58,63,66,68,75,84,85,91,92,114,115,117,127,130,142,147,150,157,163,164,186,191,194,195,207,214] followed by ptosis [34,35,50,59,75,77,79,92,107,146,157,191,199,206] and ophthalmoplegia [47,52,95,140,158,172,190,209]. The most frequent cranial nerve affected was the oculomotor nerve, but rarely, patients also presented with abducens [25,44,77,81,84,85,91,98,113,120,121,123,124,128,142,168,174,182,192,207] and trochlear [25,63,81,84,102,121,123,124,149,168,182,209] nerves palsies. Optic chiasm compression was specified in 18 articles [32,33,46,55,62,63,65,69,80,123,125,169,177,185,186,191,192,218] or, rarely, an invasion of the cavernous sinus [44,63,65,196]. Interestingly, two patients, a 45-year-old male [34] and a 71-year-old female [207] were admitted for PA-associated proptosis.

3.2. PA and Hormonal Imbalance at First Diagnostic

Endocrine features in subjects admitted for PA include PitNETs-associated hormonal excess, even though most patients were nonfunctioning tumors, respectively, tumor- or PA-caused hypopituitarism (as mentioned, we did not include patients with previously recognized and treated PitNETs). In terms of clinical presentation, Cushingoid features (corticotroph PitNET) are reported in 5 studies (less than 0.005% of the patients): two males of 30, respective 33 years [31,186], a cases series of 4 females aged between 26 and 45 years [33], and other two women of 35, respective 47 years [86,161]. Acromegaly (caused by somatotroph or lactosomatotroph PitNET) was recognized in 8 patients (0.005%) aged between 26 and 50 years; a male [86,109,136,148,156,217] to female [38,78] ratio of 6 to 2. One case of gigantism (+5 SD) was reported on a 9-year-old boy with lactosomatotroph PitNET [32]. Hypopituitarism included elements of hypogonadism [127–129,131,135] like disturbances of menstrual cycle in women of reproductive age [171,172], etc., but, also, with a more severe potential, hypotension [29,48,83,199,210,213].

Other signs and symptoms at PA presentation include lactotroph PitNET-associated galactorrhea [141,174,183]; hyperthermia [180], pruritic skin rash associated with central adrenal insufficiency-related cortisol deficit [185], hiccups [109], epistaxis [91], hema-

turia [189], phonophobia [78], visual illusions [45], and symptomatic diabetic ketoacidosis [53,171,172].

In terms of the PitNET stain profile (regardless clinical expression) non-functional type was followed by somatotroph PitNETs [32,38,42,46,53,56,66,76,78,86,92,93,98,100,108,109,121,128,136,141,148,152,156,166,168,169,171,175,192,217], lactotroph PitNETs [66,75,77,90,98,100,113,121,126,128,141,166,168,169,174,175,183,202,206], gonadotroph PitNETs [71,72,77,88,91,98,99,101,105,113,114,128,179,185,187,203,221], corticotroph PitNET [31,33,92,98,100,103,118,121,128,137,144,154,155,168,174,184,186,208,220], lactosomatotroph [32,100,109], and thyrotroph PitNETs [61,92,100,105]. Other pathologic features of pituitary masses complicated with PA include: Crooke cell adenoma [130,161], tumor with switching phenotypes [143], malignant spindle and round-cell tumor [91], Rathke's cyst [70,194], primitive neuroectodermal tumor [70], craniopharyngioma [70], and pituitary metastasis from squamous cell carcinoma [35], melanoma [55], lung and bronchogenic carcinoma [70,73], respectively, and breast carcinoma [62,187].

3.3. Potential Triggers and Circumstantial Events of PA

Our decade-based analysis showed that high blood pressure may be regarded as the most frequent co-morbidity (or risk factor) followed by diabetes mellitus in individuals admitted for PA. (Table 1) Two cases reported severe, complicated diabetes with diabetic ketoacidosis [53,171,172], and chronic kidney failure [59]. Another endocrine contributor was T3 thyrotoxicosis in one patient [71].

Infectious triggers were also found and include pituitary fungal infection [144], dengue hemorrhagic fever [42,74,77,103,139], varicella [208], and leptospirosis [163]. Of note, Catarino et al. presented the case of a 55-year-old woman who suffered from a corticotroph PitNET-associated PA in relationship to a fungal infection that was surgically treated without anti-fungal treatment [144]. Dengue hemorrhagic fever led to PA in five patients. The underlying mechanism is thrombocytopenia which favors bleeding at the level of PitNET. All patients had pituitary adenomas, with one corticotroph PitNET [103], one somatotroph PitNET [42], and one lactotroph–gonadotroph PitNET [77]. Three patients underwent transsphenoidal surgery (TSS) [42,74,103], one patient was treated conservatively [139], and another patient underwent TSS after initial conservative treatment with cabergoline and dexamethasone due to visual deterioration [77]. The 56-year-old patient introduced by Gohil et al. presented leptospirosis; the proposed mechanisms through which leptospirosis might induce PA include non-inflammatory vasculopathy, as well as platelet dysfunction, rather than thrombocytopenia [163]. An interesting finding was conducted by Humphreys G et al., who analyzed in a prospective study the sphenoid sinus mucosal microbiota characteristics in 10 patients with PA. The authors observed abnormal sinus bacteria like *Enterobacteriaceae* in patients with PA [105].

Traumatic causes are identified; for instance, head trauma [30,160,204], recent rugby play without an actual head trauma [168], and bodybuilding exercises [106].

Anticoagulation [25,64,66,70,128,135,138,160,166,173,195,198] and antiplatelet therapy [90,94,97,113,141,160,166,169] are the most important iatrogenic elements. For instance, we mention rivaroxaban, enoxaparin, dabigatran etexilate, warfarin, heparin, apixaban, and aspirin. Other vascular and clotting triggers include Takotsubo cardiomyopathy [213], heparin-induced thrombocytopenia [35], thrombocytopenia of other causes [97,208], and polycythemia [108]. Medical treatments in point are further on (at the statistical level of rare case reports): androgen deprivation therapy for prostate cancer [52,88,99,157,168], systemic chemotherapy like bleomycin, etoposide, cisplatin [184], doxorubicin, cyclophosphamide [207], and thyroxine therapy [61].

Oral contraceptives may contribute to PA [54]. Kobayashi et al. presented a 33-year-old female with ischemic PA of a nonfunctioning macroadenoma following the use of oral contraceptives for 1.5 years. The patient fully recovered under conservative treatment with analgesics and hormone replacement with hydrocortisone and thyroxine. The hypercoagulable state induced by estrogens was hypothesized as an underlying mechanism of PA [54]. Additionally, a vardenafil-triggered PA was reported [140]. Uneda et al. reported a 51-year-old male with signs and symptoms of PA (severe headache and oculomotor nerve palsy) the morning after taking vardenafil for erectile dysfunction for the first time in three months. He was diagnosed with apoplexy of a pituitary adenoma based on CT and MRI findings and was surgically treated. Even though the underlying mechanisms remain unclear, possible mechanisms of PA under phosphodiesterase 5 (PDE) inhibitors are hypotension, vasodilation, and antiplatelet effects [140].

Iatrogenic components may include diagnostic tests and procedures: dexamethasone suppression test [118], clomiphene use [66], combined endocrine stimulation tests [43], regadenoson myocardial perfusion scan [153], and MRI scan [46]. Among non-pituitary-surgery-related triggers, we identified major surgery [66,128,132,168,201], laparoscopic surgery [199], coronary artery bypass surgery [34,66,214], mitral valvuloplasty [84], endonasal surgery [127], and lumbar fusion surgery in prone position [80,116]. Interestingly, Naito Y et al. reported a case of PA in a 14-year-old girl with Carney complex who underwent successful resection of a cardiac myxoma, but the day after surgery she experienced headache and visual disturbances requiring urgent surgical decompression for PA [132].

Other therapeutic procedures include the intravitreal injection of vascular endothelial growth factor inhibitor [204], autologous hematopoietic cell transplantation [152], endoscopic retrograde cholangiopancreatography [124], and radiotherapy [113,166].

Two case reports presented individuals with PA caused by exposure to high altitudes (the first case was published in 2012). Both subjects were 29-year-old males without underlying pituitary conditions who ascended slowly to altitudes of over 4500 m. The initial diagnosis was acute mountain sickness in both cases. However, due to low blood pressure and findings of adrenal insufficiency, PA was suspected, and later MRI scans confirmed PA. Neither patient displayed visual disturbances [29,48]. The management included transfer to a lower altitude (as a specific approach in this distinct type of PA) as well as glucocorticoid replacements (100 mg of hydrocortisone every eight hours, the first two days, followed by 7.5 mg of prednisolone daily due to persistent hypocortisolism [29], respective 100 mg of hydrocortisone every six hours followed by full recovery [48].

Of note, two unusual triggers are polysubstance abuse [191] and long restraint in a sitting position [221]. The patient presented by Sun et al., a 49-year-old male, died in custody due to a gonadotroph PitNET-associated PA following restraint in a sitting position for four days [221] (Figure 2).

3.4. PA Management

The management of the patients recognized with PA is summarized in Table 2. Essentially, the subjects were managed surgically (80%) or conservatively. Although the majority are TSSs, five papers introduced patients undergoing craniotomies [36,60,127,159,217]. Craniotomies were necessary for intracranial hemorrhage [36], subarachnoid hemorrhage [60], previous nasal surgery [127], and technical challenges such as cavernous sinus invasion with encasement of the internal carotid artery [159], respectively, encasing of both carotid arteries [217].

Table 2. Management and outcome in patients PitNET-PA [29–222].

| Author (Reference) | Management | Outcome |
|--------------------|---|--|
| Brar [29] | Transfer to a lower altitude glucocorticoid replacement | Adrenal insufficiency |
| Cagnin [30] | C | Resolution of neurological symptoms, hypopituitarism |
| Chan [31] | TSS Hormonal replacement (postoperative hypopituitarism) | 3 years follow-up: remission of the pituitary tumor, regression of Cushingoid features, permanent anterior hypopituitarism and central diabetes insipidus |
| Chentli [32] | C | 2 months follow-up: visual acuity normalized, spontaneous reduction in pituitary tumor (MRI) |
| Choudhry [33] | TSS ($n = 4$) Hormonal replacement (postoperative hypopituitarism) | Postoperatively: vision recovery and biochemical remission of Cushing's disease ($n = 4$) 6 months follow-up: regression of cushingoid features ($n = 4$), weight-loss ($n = 4$), hypertension remission ($n = 3$), DM resolution ($n = 3$), DM improvement ($n = 1$) 40 months follow-up: biochemical remission and postoperative anterior hypopituitarism ($n = 4$) |
| Enatsu [196] | TSS | 3rd cranial nerve palsy improved Complete removal of the mass (MRI) Endocrine profile recovery |
| Komurcu [34] | TSS | 4 months follow-up: complete visual recovery 6 months follow-up: complete tumor removal, no recurrence (CT) |
| Kruljac [35] | TSS | Exitus 1 month later |
| Kurisu [36] | Craniotomy, evacuation of the hemorrhage, tumor resection through anterior interhemispheric approach | Exitus within 1 month (PA causing intracerebral hemorrhage) |
| Liu [37] | C | 3 months follow-up: normal pituitary hormones secretion, complete disappearance of pituitary mass (MRI) |
| Mohindra [38] | Ventriculo-peritoneal shunt | Exitus within 48 h |
| Paisley [39] | TSS Glucocorticoid replacement | Visual recovery, partial hypopituitarism |
| Tedd [40] | Glucocorticoid replacement | |
| Verma [41] | TSS Glucocorticoid replacement | Clinical improvement |
| Wildenberg [42] | TSS | |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|-----------------------|---|--|
| Yamamoto [43] | TSS | Symptoms resolved postoperatively and vision returned |
| | Transient desmopressin replacement | |
| Zoli [44] | TSS | 3 months follow-up: radical tumor removal, resolution of neurological symptoms |
| | TSS | |
| Chou [45] | TSS | Resolution of visual disturbances |
| Cinar [46] | TSS | Remission of acromegaly |
| Delgado-Alvarado [47] | TSS | Resolution of ophthalmoplegia |
| Deshwal [48] | Transfer to a lower altitude + C | Full recovery |
| Fanous [49] | TSS | Near complete resolution of visual disturbances |
| Haider [50] | C (+ Dexamethasone) | Complete recovery of 3rd cranial nerve function |
| Hojo [51] | Initial C → TSS following hematoma expansion | No visual disturbances |
| Huang [52] | TSS | Vision improvement |
| Jiang [53] | C | Patient refused further treatment |
| Kobayashi [54] | C | Recovery without sequela |
| Machado [220] | C | 28 months follow-up: clinical remission |
| Masui [55] | TSS | Anterior pituitary hormonal deficits, diabetes insipidus |
| Mir [56] | TSS | Remission of DM; normalization of GH levels |
| | Glucocorticoid replacement | Central hypothyroidism, hypogonadism, and hypocortisolism |
| Mohamed [57] | TSS | Postoperatively: partial improvement of vision and 3rd cranial nerve palsy |
| Ní Chróinín [58] | C | Clinical improvement |
| Oh [59] | TSS | Clinical improvement |
| Radhiana [60] | Craniotomy, decompression, tumor excision | Exitus |
| Steinberg [218] | Patient refused surgery | Tumor size decreased, necrotic zone in the pituitary (MRI) |
| | C (Cabergoline) | |
| Uemura [219] | C (Glucocorticoid, levothyroxine replacement) | Resolution of signs and symptoms |
| Witczak [62] | TSS | Exitus after 3 months (due to breast cancer) |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|---------------------|---|--|
| Wong [63] | TSS | Recovery of nerve palsies |
| Zieliński [64] | C (Glucocorticoid, levothyroxine replacement) | Tumor regression (MRI); resolution of ophthalmic and neurological symptoms |
| Berkenstock [65] | TSS | Resolution of nerve palsy, persistent visual field defects, panhypopituitarism |
| Bujawansa [66] | Pituitary surgery ($n = 33$, 55%): early emergency surgery ($n = 23$), delayed elective surgery ($n = 18$) conservative ($n = 22$, 40%) | Complete resolution of visual field defects (65%) Partial improvement of visual field defects (85%) Complete resolution of cranial nerve palsies ($n = 23$) Partial resolution of cranial nerve palsies ($n = 26$) Anterior pituitary deficits ($n = 47$, 85.5%) Central adrenal insufficiency ($n = 40$, 72.7%) Central hypothyroidism (29 patients, 52.7%) Severe growth hormone deficiency ($n = 21$, 38.2%) Hypogonadism ($n = 27$ male patients) Diabetes insipidus ($n = 2$) |
| Chao [67] | TSS | Visual field improvement |
| Cho [68] | C | Partial recovery, no endocrine dysfunctions |
| Garg [197] | TSS | |
| Gupta [69] | Coronary artery bypass → TSS | Resolution of nerve palsy, persistent visual field defects |
| Jho [70] | TSS ($n = 101$) C ($n = 8$) | Resolution of symptoms ($n = 48$) Improvement of symptoms ($n = 12$) Stationary ($n = 1$) |
| Lee [71] | TSS Glucocorticoid replacement, anti-thyroid drugs | |
| Maltby [72] | C | Panhypopituitarism, empty sella |
| Man [73] | Palliative care, dexamethasone, brain radiotherapy | |
| Mishra [74] | TSS | Visual improvement |
| Mura [198] | Conservative | Hypogonadotrophic hypogonadism |
| Navarro-Bonnet [75] | Fronto-temporoparietal craniectomy | Postoperatively: hemiplegia, hormonal substitution (prednisone, levothyroxine), cabergoline treatment 6 months follow-up: amelioration of paralysis, normalized prolactin levels, small residual tumor |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|--------------------|--|---|
| Rebeiz [199] | TSS | No improvement |
| Roerink [76] | C (Hydrocortisone, levothyroxine, lanreotide, scheduled TSS) | 3 months follow-up: normalized IGF-1 levels |
| Tan [77] | C (Cabergoline, dexamethasone) → TSS due to visual deterioration | Hypopituitarism, persistent visual defects, residual tumor |
| Villar-Taibo [78] | C (Hormonal replacement) | Resolution of symptoms, improvement of acromegaly signs and symptoms, hypopituitarism, diabetes insipidus |
| Yoshida [200] | TSS Hormonal replacement | Hypopituitarism, resolution of hyperthyroidism, with subsequent hypothyroidism |
| Yoshino [201] | C (Glucocorticoid replacement) | Resolution of pituitary hemorrhage |
| Zhang [79] | TSS Hormonal replacement | Symptoms improvement |
| Akakin [80] | TSS Hormonal replacement | Visual defects improvement, no residual tumor |
| Asaithambi [81] | TSS | Postoperatively: bitemporal hemianopia, left and right partial 3rd cranial nerve palsy |
| Banerjee [82] | TSS | No improvement |
| Fountas [83] | TSS Hormonal replacement | Hypopituitarism |
| Kasl [202] | TSS | Improvement of neurological symptoms |
| Kasl [203] | TSS | Recovery of symptoms |
| Kim [84] | TSS | Complete recovery |
| Man [85] | TSS | Partial improvement of 3rd cranial nerve palsy |
| Roerink [86] | C C → elective TSS | |
| Saberifard [87] | C | Empty sella |
| Sasagawa [88] | TSS | Complete resolution of nerve palsy |
| Sasaki [89] | C | |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|--------------------|---|--|
| Singh [90] | Surgery during acute stage ($n = 61$, 70.1%) Delayed surgery ($n = 8$, 9.2%) Conservative ($n = 18$, 20.7%) | Improvement/complete resolution of visual defects in all survivors HRT with levothyroxine (62.7%) or cortisol (60%) Diabetes insipidus at 3-month follow-up (23%) Tumor regrowth ($n = 7$, 8.6%) Exitus ($n = 4$, 4.6%) |
| Teasdale [91] | TSS 5 years after the initial presentation: sphenoidotomy, radiotherapy | Visual improvement, panhypopituitarism 5 years after the initial presentation: exitus |
| Zhu [92] | TSS ($n = 93$, 95.88%) Transcranial surgery ($n = 4$, 4.12%) | Electrolyte disturbance ($n = 18$, 18.56%) Diabetes insipidus ($n = 69$, 71.13%) Cerebrospinal rhinorrhea ($n = 2$, 2.06%) Postoperative hemorrhage ($n = 1$, 1.03%) Postoperative infection ($n = 1$, 1.03%) Exitus ($n = 1$, 1.03%) |
| Zou [93] | Surgery | Improvement of symptoms and radiological findings |
| Choudhury [94] | C | Considerable reduction in pituitary tumor |
| Doglietto [95] | TSS | Recovery of nerve palsy, complete removal of pituitary adenoma (MRI) |
| Gambaracci [96] | TSS | |
| Giammattei [97] | TSS ($n = 8$) Hormonal replacement | Hypopituitarism |
| Giritharan [98] | C ($n = 11$, 35%) Surgery ($n = 20$, 65%) | Hormone deficiency ($n = 26$, 84%) Resolution of visual disturbances ($n = 18$, 72%) Improvement of visual symptoms ($n = 6$, 24%) |
| Keane [99] | TSS | Complete resolution of symptoms |
| Ogawa [100] | TSS ($n = 43$) | Resolution of neurological symptoms ($n = 38$) Persistence of nerve palsy ($n = 3$) Prolonged visual problems ($n = 1$) Exitus due to leukemia ($n = 1$) |
| Paschou [101] | TSS | Resolution of symptoms, central hypothyroidism |
| Sussman [102] | TSS | 6 weeks follow-up: partial recovery of lower limb paresis, persistence of upper limb paresis, full recovery of 3rd and 4th cranial nerve palsies, partial 6th cranial nerve palsy |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|---------------------------|---|--|
| Balaparameswara Rao [103] | TSS | Improvement of vision Anterior hypopituitarism |
| Grangeon [104] | C | Headache resolution |
| Humphreys [105] | TSS (<i>n</i> = 5) Radiotherapy (<i>n</i> = 2) | Hypopituitarism treated with HR (<i>n</i> = 4) |
| Ishigaki [204] | TSS | Resolution of nerve palsy |
| Law-Ye [106] | C | Full recovery |
| Pasha [107] | TSS | Recovery of neurological deficits |
| Patra [108] | C | Remission of acromegaly and polycythemia |
| Rais [205] | C | |
| Simsek Bagir [109] | TSS | Remission of symptoms, central hypothyroidism and hypogonadism, GH deficiency |
| Souteiro [110] | C | Resolution of hypercortisolism, disappearance of the tumor (MRI) |
| Waqar [111] | TSS (<i>n</i> = 36) Conservative (<i>n</i> = 11) | Hypopituitarism (<i>n</i> = 45) Diabetes insipidus (<i>n</i> = 3) |
| Zoli [112] | TSS (<i>n</i> = 75) | Anterior hypopituitarism (<i>n</i> = 15, 20%) Diabetes insipidus (<i>n</i> = 4, 5.3%) Ophthalmoplegia resolution/improvement (71%) Visual symptoms improvement (85.5%) Conscious regain in both patients |
| Abbara [113] | C (<i>n</i> = 33/52) Surgery (<i>n</i> = 19/52) | Partial resolution of visual symptoms (<i>n</i> = 19/19) Full resolution of visual symptoms (<i>n</i> = 5/16) Hypopituitarism: long-term hypocortisolism (<i>n</i> = 27), hypothyroidism (<i>n</i> = 15) Diabetes insipidus (<i>n</i> = 2) |
| Bettag [114] | TSS | Partial improvement of hemiparesis, persistent visual loss |
| Fan [115] | C | Complete resolution of visual disturbances after 6 months |
| Hodgson [206] | Embolization, surgical resection | Reduction in pain |
| Jang [207] | TSS | Improvement of visual disturbances |
| Joo [116] | TSS | Full recovery |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|--------------------|--|---|
| Kuzu [118] | TSS | Recovery of symptoms, panhypopituitarism |
| Myla [119] | TSS | Hormonal replacement |
| Raj [208] | C | Remission of central adrenal insufficiency |
| Ricciuti [120] | Surgery ($n = 13$) C ($n = 4$) | Symptoms resolved in up to 6 months Hormonal substitution ($n = 6$) Residual tumor ($n = 6$) |
| Rutkowski [121] | Surgery ($n = 32$, 100%) | Improvement of visual symptoms (77%) Resolution of visual symptoms (38%) Resolution of oculomotor palsies (81%) Partial hormone recovery following preoperative hypopituitarism 6 (21%) of 28 |
| Salehi [209] | TSS | Complete recovery |
| Ward [210] | TSS Hormonal replacement | Stable vision, improved mental status |
| Yamada [122] | C | Panhypopituitarism |
| Almeida [123] | Surgery ($n = 49$) C ($n = 18$) | Last follow-up: Visual status: worsening ($n = 1$), stationary ($n = 3$), partial improvement ($n = 12$), complete recovery ($n = 24$) Cranial nerve palsies: partial improvement ($n = 9$), complete recovery ($n = 17$) Hormonal function: hypothyroidism ($n = 3$), hypocortisolism ($n = 11$), panhypopituitarism ($n = 27$), diabetes insipidus ($n = 4$) |
| Crisman [124] | TSS | Resolution of cranial nerve palsy |
| Dupont [125] | TSS | Slight regain of vision postoperatively |
| Ghalaenovi [126] | Lost during follow-up | The patient experienced spontaneous resolution of initial symptoms |
| Harju [127] | Craniotomy Glucocorticoid replacement | Persistent visual defects, anosmia, diabetes insipidus |
| Hosmann [128] | TSS ($n = 72$, 94.7%) Surgery with sub-frontal approach ($n = 4$, 5.3%) | Decreased visual acuity (12.3%) Visual field deficit (35.4%) Impaired eye movement (14.1%) Hormonal replacement (72.3%): hypothyroidism (61.3%), hypocortisolism (52.3%), hypogonadism (29.2%), permanent diabetes insipidus (9.2%), GH deficiency (4.6%) |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|---------------------|---|---|
| Kirigin Biloš [129] | C | Improvement of 3rd cranial nerve deficit, diplopia, panhypopituitarism, partial empty sella |
| Krug [130] | TSS | Recovery of symptoms |
| Mittal [131] | C → TSS | |
| Naito [132] | C | Resolution of symptoms |
| Nioi [133] | | Exitus |
| Pedro [134] | C | |
| Santos [135] | C | Resolution of symptoms, hypopituitarism |
| Sanz-Sapera [136] | C (Hormonal replacement) | Acromegaly remission |
| Singhal [137] | TSS | |
| Swaid [138] | TSS | 1 month follow-up: persistence of 3rd cranial nerve palsy |
| Thomas [139] | C | Full recovery of ptosis |
| Uneda [140] | TSS | Improvement of nerve palsy |
| Wang [141] | TSS (<i>n</i> = 21) | Hypopituitarism requiring hormonal replacement (<i>n</i> = 6) Resolution of visual field defects (<i>n</i> = 13), improvement of visual field defects (<i>n</i> = 4) Resolution of visual acuity (<i>n</i> = 15), improvement of visual acuity (<i>n</i> = 2) Recovery of cranial nerve palsies (<i>n</i> = 10/10) Residual tumor (<i>n</i> = 4) Hemiplegia (<i>n</i> = 1) |
| Waqar [142] | TSS | Resolution of nerve palsy |
| Ahn [211] | TSS | Neurological improvement; resolution of ICA stenosis |
| Brown [143] | TSS Radiotherapy | Lost to follow-up |
| Catarino [144] | TSS | Clinical improvement |
| Eichberg [145] | C → TSS 4 years later due to tumor recurrence | Resolution of symptoms No hormonal deficits |
| Elarjani [146] | TSS | Neurological improvement |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|--------------------|---|---|
| Franzese [147] | TSS | Resolution of symptoms |
| Klimko [148] | TSS | Remission of acromegalic features |
| Lee [149] | C | Gradual improvement of headache and nerve palsies |
| Marzoughi [150] | C due to multiple comorbidities | Resolution of diplopia and 3rd cranial nerve palsy, central hypothyroidism |
| Pangal [151] | TSS ($n = 50$) | Headache improvement (87%) Vision loss improvement (86%) Resolution of cranial nerve palsy resolved (72%) Partial improvement of cranial nerve palsy (11%) Panhypopituitarism persistence (48%) Development of panhypopituitarism (6%) |
| Patel [152] | Stress dose corticosteroids, TSS | Resolution of symptoms, vision improvement |
| Romano [212] | TSS | Visual and functional improvement |
| Shetty [153] | TSS | |
| Siwakoti [154] | C | |
| van Boven [155] | C | |
| Yang [213] | C | |
| Alam [156] | No specific treatment | Acromegaly remission |
| Aljabri [157] | C | Tumor regression, restart of goserelin treatment without side effects, hormonal substitution (corticosteroids, levothyroxin) |
| Alkhaibary [214] | C | Visual acuity and nerve palsy improvement, hypoadrenalism, hypothyroidism |
| Ambrose [158] | C → surgical decompression | Minor neurological improvement |
| Bhogal [215] | C | Tumor size reduction |
| Bukhari [159] | Fronto-temporoparietal craniotomy for tumor excision | Panhypopituitarism |
| Cavalli [160] | Conservative $n = 20$ (66.7%) + 8 patients undergoing delayed elective surgery Emergency surgery $n = 10$ (33.3%) Hormonal replacement $n = 28$ (93.3%) | Resolution of visual acuity defects in 61% Resolution of visual field defects in 64% Resolution of cranial nerve palsies in 69% Poor endocrine outcomes with various degrees of hypopituitarism |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|--------------------|--|--|
| de Silva [161] | TSS | Gradual improvement, normalization of cortisol levels |
| Elsehety [216] | TSS | Exitus |
| Falhammar [162] | Immediate pituitary surgery $n = 3$ Delayed pituitary surgery $n = 8$ | Visual defect and nerve palsies improved Hormonal deficits did not regress 3 deaths of unrelated causes during follow-up |
| Gohil [163] | C | Resolution of visual disturbances and nerve palsy; regression of adenoma Persistent hypothyroidism and hypocortisolism |
| Hanna [164] | C | Resolution of symptoms within 4 days |
| Huang [165] | TSS | Resolution of visual disturbances and nerve palsy Hormonal replacement therapy |
| Iqbal [166] | TSS (9/33) | Deterioration of pituitary function $n = 5$ Improvement of pituitary function $n = 13$ |
| Komić [167] | C (Hormonal replacement) | Resolution of symptoms after conservative treatment |
| Marx [168] | C ($n = 27$) TSS ($n = 19$) | Resolution of visual acuity defects ($n = 10/11$) Resolution of visual field defects ($n = 16/17$) Resolution of cranial nerve palsies ($n = 21/23$) Hormonal deficits: corticotropic ($n = 17$), thyrotropin ($n = 24$), gonadotropic ($n = 20$), somatotropin ($n = 6$) Residual tumor ($n = 17$) Tumor recurrence ($n = 4$) |
| Nakhleh [169] | C ($n = 10$) TSS ($n = 17$) | Corticotropin deficiency ($n = 13$) Secondary hypothyroidism ($n = 8$) Testosterone replacement therapy ($n = 7$) Central diabetes insipidus ($n = 4$) Cabergoline treatment ($n = 2$) Persistence of visual field defect ($n = 2$) Persistence of cranial nerve palsy ($n = 2$) |
| Oudghiri [170] | C ($n = 3$) TSS ($n = 1$) | Resolution of cranial nerve palsy; hormonal replacement therapy |
| Pan [171] | TSS | Central hypothyroidism and hypocortisolism |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|--------------------|--|--|
| Pattankar [172] | C | Left hemiparesis |
| Pokhrel [217] | Emergency craniotomy and tumor excision | Significant improvement of neurological and visual disturbances |
| Rosso [173] | TSS | Resolution of the nerve palsy |
| Seaman [25] | TSS: within 24 h ($n = 34$) within 24–48 h ($n = 3$) after 7 days ($n = 7$) | All cranial nerve palsies were resolved Visual field disturbances resolved in 13/16 cases Visual acuity decrease resolved in 6/9 cases Hormonal deficits (unresolved/acquired): hypothyroidism ($n = 11$) hypocortisolism ($n = 6$) hypogonadism (low testosterone) ($n = 3$) panhypopituitarism ($n = 11$) transient diabetes insipidus ($n = 8$) permanent diabetes insipidus ($n = 3$) |
| Sun [174] | TSS | Total tumor resection ($n = 21$, 87.50%) Headache resolution in all patients Cranial nerve palsies: full recovery ($n = 4$); improvement ($n = 3$) Vision: returned to normal ($n = 14$); improvement ($n = 3$); stationary ($n = 1$) Resolution of hormonal deficits ($n = 5$) |
| Teramoto [175] | TSS | |
| Tumyan [176] | TSS | Significant improvement of neurological and visual symptoms Hormonal replacement therapy |
| Van Dong [177] | TSS | No residual tumor; transient central adrenal insufficiency Improvement of visual and neurological symptoms |
| Vargas [178] | | Condition worsened, family withdrew care |
| Yoshida [179] | TSS | Residual tumor (MRI); visual acuity improvement |
| Zhu [180] | TSS | Resolution of neurological symptoms; persistence of visual disturbances |

Table 2. Cont.

| Author (Reference) | Management | Outcome |
|--------------------|---|--|
| Zhu [181] | TSS (<i>n</i> = 45) C (<i>n</i> = 1) | Decrease visual acuity (<i>n</i> = 7) Visual field deficit (<i>n</i> = 3) Resolution of all ocular palsy Endocrine dysfunction: hypocortisolism (<i>n</i> = 26) hypothyroidism (<i>n</i> = 19) hypogonadism (<i>n</i> = 24) |
| Cross [182] | TSS | Cranial nerve palsies: resolution (72%), improvement without resolution (16%) Diabetes insipidus (<i>n</i> = 5) Exitus due to heparin induced thrombocytopenia (<i>n</i> = 1) |
| Geyik [183] | TSS | |
| Hamrick [184] | TSS | Resolution of visual disturbances, central hypothyroidism |
| Hsu [185] | TSS | Hypopituitarism; hormone replacement therapy |
| Liu [186] | TSS | Remission of hypercortisolism, hypopituitarism, HRT |
| Mills [187] | TSS | 12 days postoperatively: exitus due to sepsis |
| Oldfield [188] | C | No residual tumor (MRI after 5 months) |
| Puglisi [189] | C | |
| Rai [190] | TSS | Improvement of visual symptoms |
| Shrestha [191] | TSS | Resolution of nerve palsy, residual tumor |
| Singh [192] | TSS | Resolution of 6th cranial nerve palsy; normal IGF-1 levels |
| Singh [193] | TSS | Remission of panhypopituitarism, normalization of visual field |
| Syed [194] | C | Resolution of pituitary adenoma and abducens palsy |
| Viola [195] | C | Panhypopituitarism requiring hormonal replacement; resolution of ophthalmologic and neurologic symptoms |

Abbreviations: C = conservative approach; CT = computed tomography; DM = diabetes mellitus; GH = growth hormone; IGF-1 = insulin-like growth factors; MRI = magnetic resonance imaging; PA = pituitary apoplexy; TSS = transsphenoidal surgery.

Conservative management [21–215,218–220] included vital signs monitoring, hydro-electrolytic balance, glucocorticoid substitution (intravenous hydrocortisone during the first 48 h followed by oral replacement), as well as substitution with levothyroxine and desmopressin (if needed) [123,168]. A management decision was based on the severity of clinical presentation and progression of the neurologic, eye, and hormonal features. The patients analyzed by Marx et al. were treated surgically when they presented severe visual acuity decrease, worsening of ophthalmological symptoms, resistant headache, or altered consciousness [168]. Similar criteria were applied by Almeida et al. and Bujawansa et al. [66,123]. Clinically stable individuals remained under a conservative approach [66, 123,168], as well as subjects to contraindications for performing neurosurgery [123] or those refusing it [218].

A few cases under the “wait and see” approach were later referred to TSS due to worsening conditions: hematoma expansion [51] or sudden visual deterioration [77,158].

We identified three clinically relevant studies that compared conservative management versus TSS in terms of evolution [123,160,168]. Almeida et al. found that visual, cranial nerve, and endocrine outcomes are similar between the two subgroups [123]. Cavalli et al. analyzed the clinical presentation, surgical methods, and treatment outcomes of patients with PA. The authors advocated for conservative management in patients without visual impairment and suggested that a tumor with a vertical diameter greater than 35 mm should be referred to neurosurgery in the presence of visual deficits. The only statistical difference between surgically treated patients and patients under conservative treatment was the higher ratio of achieving resolution of visual field defects at the latest follow-up in the group who underwent emergency surgery [160]. Marx et al. found that following surgery, a higher number of patients presented adrenal insufficiency and hypogonadotropic hypogonadism than those who were managed conservatively, but no statistically significant difference was identified in terms of visual acuity and visual field consequences [168]. Bujawansa S et al. suggested conservative treatment as a safe and adequate approach for selected patients (those with mild and non-progressive neuro-ophthalmic defects) [66]. The findings suggest that surgical treatment yields a higher risk of associating endocrine deficiencies [168], but a higher ratio of visual field defects improvement [161], but with similar outcomes in terms of visual acuity [123,160,168].

We mention some isolated reports with uncommon management such as radiotherapy for a subject diagnosed with a null cell tumor and a gonadotroph PitNET [105]; palliative care with dexamethasone and brain radiotherapy for an individual diagnosed with bronchogenic carcinoma metastases-associated PA [73]; transfer to a lower altitude, as prior mentioned, in specific cases with climbing-induced PA [29,48]; for an intraorbital-induced PA, the patient was offered orbital surgery, preceded by embolization through direct puncture techniques combined with a transarterial approach via the right ophthalmic artery [206]. Additionally, functional PitNET continued medical therapy for specific hormonal excess with cabergoline [75,77,168,170,199,218] or somatostatin analogs [76].

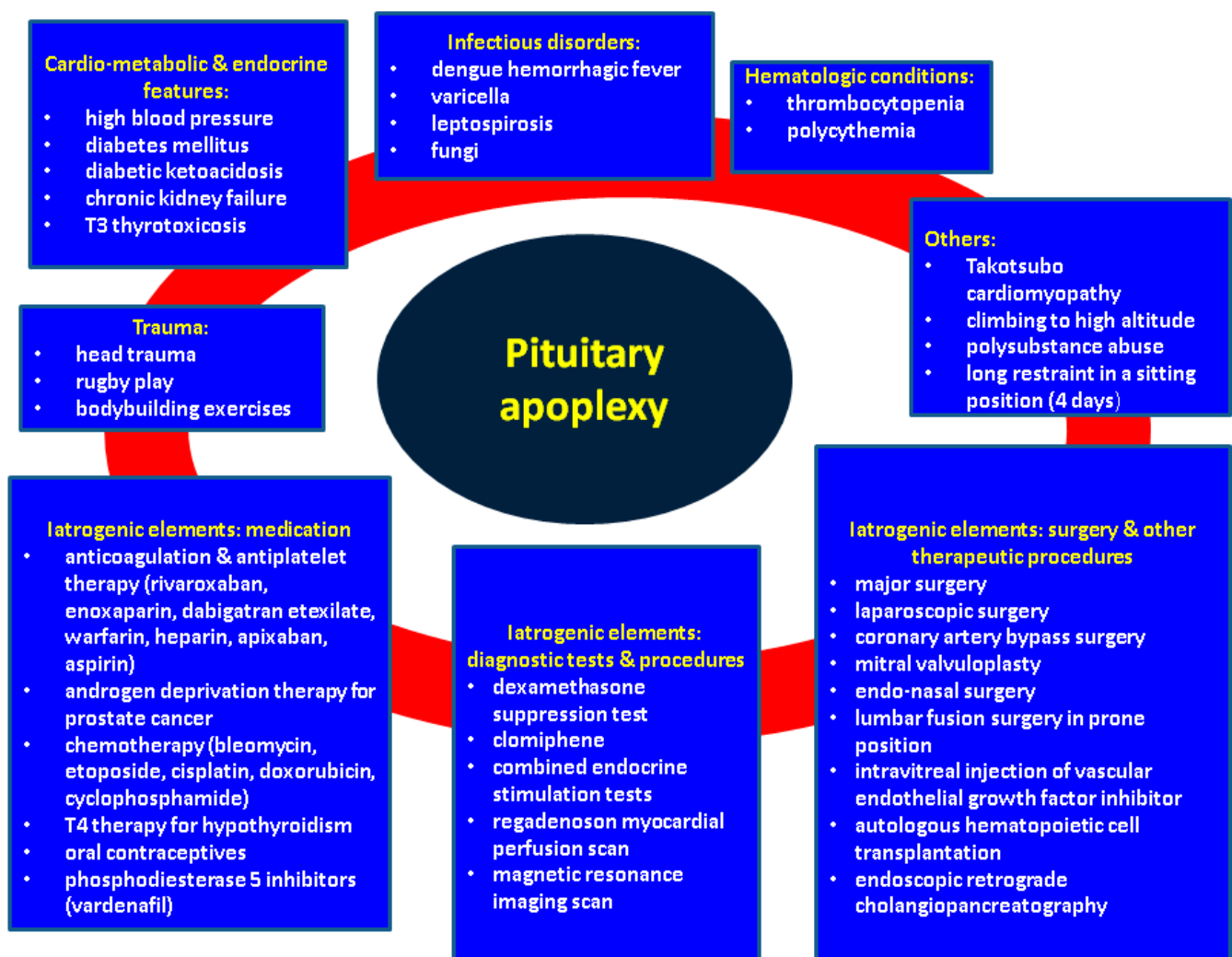


Figure 2. Qualitative analysis of potential contributors to spontaneous PA in PitNETs that are not previously treated (outside pregnancy and coronavirus infections). Abbreviations: T3 = triiodothyronine; T4 = thyroxine.

3.5. PA-Related Outcome

A large number of patients required hormonal replacement due to PA-associated hypopituitarism manifested as hypocortisolism which is the most important aspect in terms of an immediate life-threatening approach [25,29–31,56,65,66,75,80,90,92,123,128,144,163,168,169,208], central hypothyroidism [25,56,65,66,72,75,101,109,123,144,163,168,169,180,184,200], and hypogonadotropic hypogonadism [25,56,65,66,72,109,128,168,169,180,198]. GH deficiency was also reported [109,128,168], whereas spontaneous acromegaly remission was reported in four papers [46,136,156,208] or partial improvement of acromegaly-related GH excess [78]. Long-term therapy with desmopressin for permanent diabetes insipidus was reported, as well as [25,31,55,66,78,90,91,111–113,127,128,182]. Microadenomas underlying PA had a better clinical (including endocrine) outcome when compared to macroadenomas which are also associated with a higher rate of multiple hormonal deficiencies [169]. A retrospective study by Ogawa Y et al. found that ischemic rather than hemorrhagic lesions in PA correlated with an increased progression rate [100].

As mentioned, some small studies evaluated the outcome in terms of conservative versus neurosurgical management. A retrospective study (N = 46 patients with PA) showed that individuals with non-severe neuro-ophthalmological deficits were treated conservatively (N = 27), whereas the patients with a pituitary apoplexy score (PAS) ≥ 4 were treated

surgically (N = 19); the only statistically significant difference regarding the outcome was the higher rate of hormonal deficits in the second group [168]. Another study included 49 subjects who were referred for neurosurgery and 18 patients who were conservatively managed and showed similar improvement in visual and cranial nerve palsies [123]. A retrospective study (N = 24 subjects who underwent TSS) showed a complete tumor resection in 87.5% of cases; 94.44% of patients experienced an improvement of visual acuity; diabetes insipidus developed in 16.66% of individuals [174].

The timing of surgery was also taken into consideration by some studies, as a contributor to PA outcome. A study conducted by Rutkowski M et al. (N = 32 patients with acute PA who underwent TSS) included two groups depending on surgery timing: within 72 h of symptom onset and after 72 h; the second group had a statistically significant higher prevalence of hypopituitarism at presentation. However, in terms of hypopituitarism and visual dysfunction recovery, the outcome was similar [121].

The spontaneous resolution of PitNET through PA was reported with a favorable outcome [87,126,154,220]. Ghalaenovi H et al. published the case of a 28-year-old male with spontaneous regression of a nonfunctioning pituitary adenoma over the course of one year with the spontaneous resolution of headache, bitemporal hemianopia, and photophobia [126]. Machado et al. presented a 36-year-old female with spontaneous resolution of a corticotroph PitNET with symptoms remission within 28 months (conservative approach) [220]. Siwakoti et al. introduced a 59-year-old woman with tumor shrinkage and biochemical remission of Cushing's disease through conservative treatment [154]. Tumor resolution with empty sella following conservative management was reported by Saberifard et al. [87].

Fatal outcome surrounding PA was registered as an early event, for instance, within 48 h [38] or after 5 years since initial TSS [91]. Overall, we identified 14 publications [35, 36,38,60,62,90–92,100,133,182,187,216,221]. Some of the subjects were comatose at presentation [36,38,60,216], PA causing an intracerebral hemorrhage [36]; similarly, one case of the following is reported: fulminant heparin-induced thrombocytopenia [182]; fatal outcome 12 days following TSS due to sepsis [187]; or 3 months since PA in a patient with breast cancer [62] or leukemia [100]. Interestingly, two studies reported a mortality death of 1.03% (N = 97) [92], respective of 4.6% (N = 87) [90].

Of note, we identified through our analysis a single case of PA in the transgender population: a 46-year-old transgender male under testosterone therapy for 3 years who was admitted for severe headache, central hypocortisolism, and hypothyroidism. IGF-1 (insulin-like growth factor) levels, however, were high. The patient was diagnosed with somatotroph PitNET-associated PA and received surgical treatment with normalization of IGF-1 and improvement of secondary diabetes mellitus. Particularly, testosterone therapy in this situation may mask acromegaly features [76] (please see Table 2).

4. Discussion

4.1. Subentities concerning PA

An unusual case of “pneumo-apoplexy” was described by Singhal A et al.; a 65-year-old female had a PA-associated hemorrhage accompanied by pneumosella and manifested as rhinorrhea as well as classical symptoms of PA including headache and visual loss. The patient needed flap replacement of the nasoseptal defect [137].

“Recurrent” apoplexy was reported by Hosmann A et al. in 4 out of 76 patients (5.3%) after initial neurosurgery. Potential factors include residual post-operative tumor, cavernous sinus invasion of PitNET, and ophthalmoplegia [128]. However, a recurrent tumor after initial TSS due to PA-PitNET may be found as seen in the general population with PitNET who were previously candidates for neurosurgery [145,168].

Some patients presented “subacute” PA, with little to no symptoms, thus the importance of imaging assessments like MRI scans that point out infarction or hemorrhage [166]. The term “subacute” is used for PA associated with clinical symptoms less severe than fully manifested (or “acute”) PA, thus the importance of awareness since many cases may be

under-diagnosed [166,222]. Iqbal F et al. published a retrospective analysis on 55 patients (33 with acute PA and 22 with subacute PA). Severe headache and hyponatremia were more frequent in the acute group whereas the ratio of individuals who were referred to surgery was similar between the two subgroups [166]. Garg M et al. described the case of a 22-year-old female with vision reduction as the single symptom [197]. Klimko A et al. also reported a 41-year-old acromegalic male with subacute PA and panhypopituitarism [148].

4.2. Controversies in PA Domain

PA is an emergency that typically presents a sudden and severe headache and visual symptoms; however, subacute cases or those without headaches should not be missed. The most frequent cause is hemorrhage or ischemia in a nonfunctioning pituitary adenoma, but hormonally active PitNET may embrace a PA scenario. Middle-aged males are affected with the highest frequency, but both pediatric and elderly cases are shown in Table 1. The most common risk factors are high blood pressure, diabetes mellitus, and anticoagulation/antiplatelet therapy; however, at the level of case reports, uncommon conditions are reported as we prior pointed out. (Table 1) Differential diagnosis is sometimes crucial, as PA can mimic a number of conditions including meningitis or temporal arteritis [134]. Controversies around the exact panel of PA contributors still exist since there are still pathogenic elements that remain unclear. Whether the mentioned comorbidities as displayed in Figure 1 are directly connected to PA or are incidental is still a matter of debate.

The optimal treatment approach remains debated, but the main treatment options are TSS or conservative management. Due to possible complications from surgery, as well as a higher rate of pituitary insufficiencies after surgical treatment when compared with conservative management, careful evaluation is necessary. The individual multidisciplinary decision is mandatory. Surgical management should be reserved for patients with visual impairment due to cranial nerve palsies and optic chiasm compression, or patients with other neurological deficits. Conservative treatment is usually an adequate approach for stable patients with mild and stationary visual deficits and without further neurological impairments. When choosing conservative management, the risk of PA recurrence should also be taken into account. (Figure 3).

In terms of outcome, headaches and visual disturbances may resolve following both conservative and surgical treatment. Patients can present different degrees of anterior hypopituitarism and diabetes insipidus. Factors for a worse prognosis may be the presence of a large macroadenoma and an ischemic type of apoplexy. PA is a condition that can lead to a favorable outcome with the remission of symptoms and underlying pituitary disorder in some patients, whereas for others it can be life-threatening and invalidating when fatal cases are reported (as we already mentioned). Specific algorithms of management are still necessary.

To our knowledge, this is the largest analysis of published cases concerning spontaneous PA (outside pregnancy and COVID-19 infection). A timeline of published papers from 2012 to 2022 according to our methodology is displayed below. The largest studies addressing individuals with PA included 109, 97, and 87 subjects, respectively [29–222]. (please see Tables 1 and 3 and Figure 4)

Table 3. Retrospective studies with minimum 10 patients confirmed with PA/study according to our methodology [25,66,70,90,100,111–113,120,121,123,128,141,151,160,162,166,168,169,174,181–183].

| Author Reference Number/ Year of Publication | Population | Underlying Pituitary Condition |
|--|---|---|
| Bujawansa [66] 2014 | 55 patients (35 males and 20 females) Mean age: 58.4 years | Nonfunctioning pituitary adenomas in 45 cases (82%), lactotroph PitNETs in 6 cases (11.5%), somatotroph PitNETs in 4 cases (7.2%), multiple endocrine neoplasia syndrome in 2 cases |
| Jho [70] 2014 | 109 patients (69 males and 40 females) mean age: 51 years | PitNET ($n = 98$) Rathke's cyst ($n = 8$) Primitive neuroectodermal tumor ($n = 1$) Craniofaringioma ($n = 1$) Metastatic lung carcinoma ($n = 1$) |
| Singh [90] 2015 | 87 patients (55 males and 30 females) mean age: 50.9 years | Null cell ($n = 18$) Lactotroph PitNET ($n = 8$) |
| Ogawa [100] 2016 | 43 patients (30 males and 13 females) mean age: 56.67 years | Nonfunctioning pituitary adenoma ($n = 29$) Lactosomatotroph PitNET ($n = 5$) Lactotroph PitNET ($n = 4$) Thyrotroph PitNET ($n = 3$) Somatotroph PitNET ($n = 1$) Corticotroph PitNET ($n = 1$) |
| Waqar [111] 2017 | 47 patients with pituitary apoplexy (33 males and 14 females) mean age: 54 ± 15 years Patients were compared with 50 surgically treated patients with nonfunctioning pituitary adenomas | Pituitary adenoma |
| Zoli [112] 2017 | 75 patients (45 males and 30 females) mean age: 52.4 ± 16.2 years | Pituitary adenoma |
| Abbara [113] 2018 | 52 patients (25 males and 27 females) mean age: 46.7 years | Nonfunctioning adenoma or gonadotroph PitNET ($n = 47$) Lactotroph PitNET ($n = 5$) |
| Ricciuti [120] 2018 | 17 patients (12 males and 5 females) mean age: 58.76 years | |
| Rutkowski [121] 2018 | 32 patients (21 males and 11 females) mean age: 49 years | Nonfunctional adenoma (70%) Clinically hypersecreting adenoma (15%) Lactotroph PitNET Somatotroph PitNET Corticotroph PitNET |
| Almeida [123] 2019 | 67 patients (41 males and 26 females) mean age: 57.4 ± 16.2 years | Pituitary adenoma |
| Hosmann [128] 2019 | 76 patients (53 males and 23 females) mean age: 53.7 ± 14.3 years | Clinically nonfunctioning PitNETs (81%): gonadotroph PitNET (37.9%), null-cell (29.3%), plurihormonal (8.6%), corticotroph (3.5%), somatotroph (1.7%) Clinically functioning PitNETs: lactotroph (10.4%), corticotroph (6.9%), somatotroph (1.7%) |

Table 3. Cont.

| Author Reference Number/ Year of Publication | Population | Underlying Pituitary Condition |
|--|---|---|
| Wang [141] 2019 | 21 patients (15 males and 6 females), with a mean age of 50.7 ± 15.0 years | Nonfunctioning pituitary adenoma ($n = 18$) Lactotroph PitNET ($n = 2$) Somatotroph PitNET ($n = 1$) |
| Pangal [151] 2020 | 50 patients (31 males, 19 females) mean age: 53 years | Pituitary adenoma |
| Cavalli [160] 2021 | 30 patients (22 males, 8 females) mean age: 54 years | PitNET |
| Falhammar [162] 2021 | 33 patients (18 male and 15 female) mean age: 46.5 years | PitNET |
| Iqbal [166] 2021 | 55 patients (26 males and 29 females) mean age: 50 years | Somatotroph PitNET Lactotroph PitNET |
| Marx [168] 2021 | 46 patients (29 males and 17 females) mean age: 47.3 years | Nonfunctioning adenoma ($n = 31$) Corticotroph PitNET ($n = 1$) Lactotroph PitNET ($n = 12$) Somatotroph PitNET ($n = 1$) |
| Nakhleh [169] 2021 | 27 patients (14 males and 13 females) mean age: 40.7 ± 12.5 years | Nonfunctioning pituitary adenoma ($n = 21$) Lactotroph PitNET ($n = 5$) Somatotroph PitNET ($n = 1$) |
| Seaman [25] 2021 | 44 patients (24 males and 20 females) median age: 55 years | Nonfunctioning adenoma ($n = 38$) Functioning PitNET ($n = 6$) |
| Sun Z [174] 2021 | 24 patients (13 males and 11 females) mean age: 46.46 ± 14.95 years | Nonfunctioning adenomas ($n = 7$) Lactotroph PitNET ($n = 3$) Corticotroph PitNET ($n = 1$) Gonadotroph PitNET ($n = 1$) Lactocorticotroph PitNET ($n = 1$) |
| Teramoto [175] 2021 | 45 patients (33 males and 12 females) mean age: 56 years | Nonfunctioning adenoma ($n = 37$) Somatotroph PitNET ($n = 5$) Lactotroph PitNET ($n = 3$) |
| Zhu Q [181] 2021 | 46 patients (35 males and 11 females) mean age: 46.78 ± 12.32 | PitNET |
| Cross [182] 2022 | 59 patients (40 males and 19 females) median age: 54 years | PitNET |
| Geyik [183] 2022 | 143 patients with pituitary adenoma, out of which 8 patients with PA (4 males and 4 females, mean age: 26.75 years) | Lactotroph PitNET ($n = 5$) Nonfunctioning adenoma ($n = 3$) |

Abbreviations: PitNET = pituitary neuroendocrine tumor; PA = pituitary apoplexy; n = number of patients.

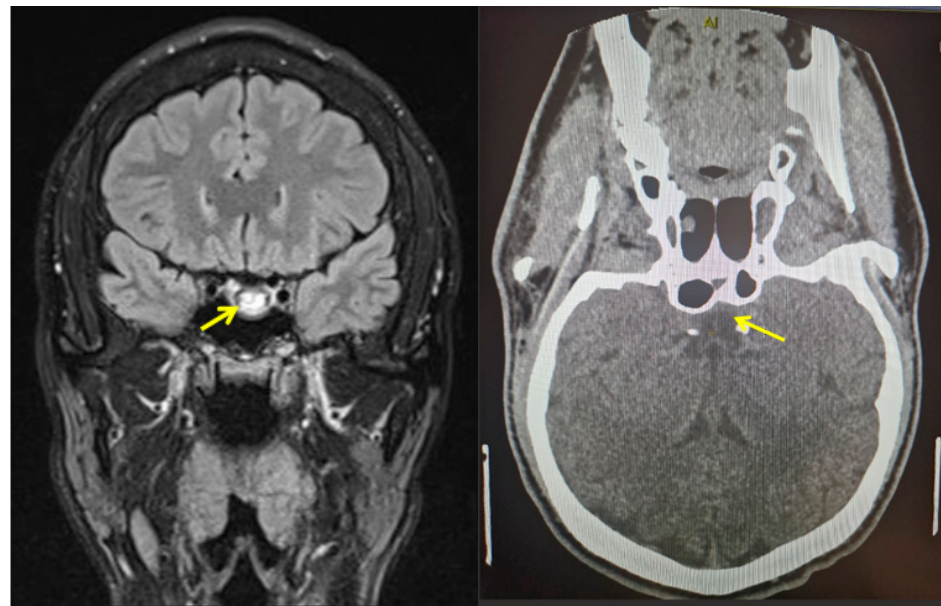


Figure 3. Imaging capture of a pituitary apoplexy. This is a male patient in his late 20s diagnosed with pituitary apoplexy with no prior medical or surgical history. On first presentation as an outpatient (due to severe headache), magnetic resonance imaging (performed as an emergency) shows a pituitary mass of 2.5 cm maximum diameter with inhomogeneous pattern suggesting hemorrhage (yellow arrow) at the level of a pituitary tumor (**left**). Intravenous contrast computed tomography (10 months since transsphenoidal surgery) shows a tendency to empty sella and no tumor remnants (yellow arrow) at the same level (**right**). Both captures are coronal plane.

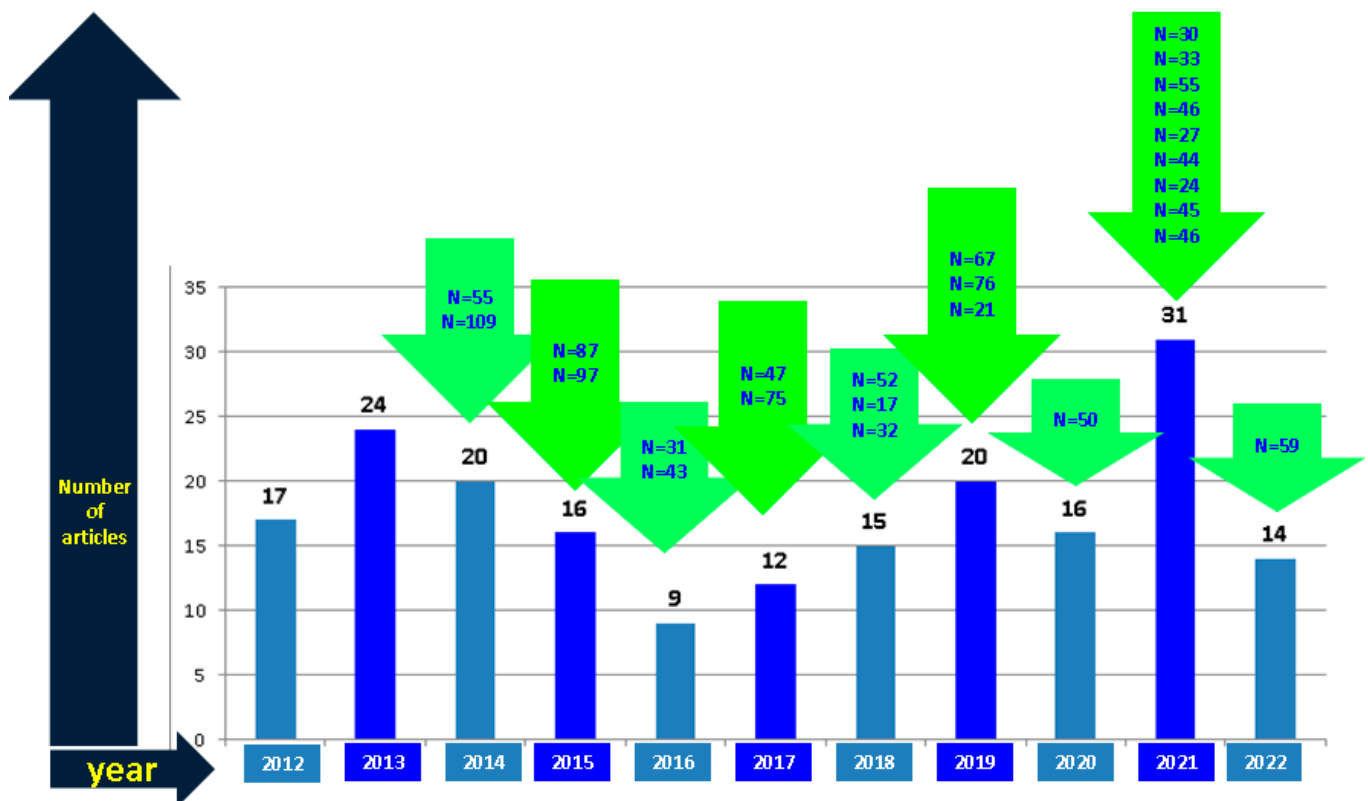


Figure 4. The timeline of original papers specifically addressing PA according to our methodology: the sample size analysis of original publications (please see references according to Table 1).

Abbreviations: N represents the number of patients included in studies with at least 10 subjects with PA per article (of note: in Table 1 we used the term “case series” or “study” according to the original publication; in this figure, we strictly included the original research depending on the number of patients).

Notably, PitNETs terminology and associated concepts massively changed since the WHO 2022 classification. Our 10-year analysis included cases with PA in relationship with different tumors that were diagnosed according to the criteria at that time. Recently, “PitNET” replaced “pituitary adenoma” which, however, is still allowed to be used. Grossly, there are three types of tumors arising from the anterior lobe: PitNET, pituitary blastoma, and craniopharyngioma (two specific subtypes). The modern approach of these tumors massively takes into consideration the role of immunohistochemistry for mainly five elements: PIT1, TPIT, SF-1, GATA3, and ER α in order to profile PitNET subtypes. The major changes are, a part from this new terminology: null cell tumors and unclassified pluri-hormonal tumors as a subtype of PitNETs with negative staining for transcription factors; “metastatic” PitNET replaced “metastatic carcinoma” that should be differentiated from a neuroendocrine carcinoma; immature (formerly “silent”) or mature PIT1-lineage tumor are determined based on PIT1 immunostaining; and mammosomatotroph, acidophil stem cell tumors in addition to mixed somatotroph/lactotroph tumors are distinct types with respect to PIT-1 lineage of PitNET [223–226] (Figure 5).

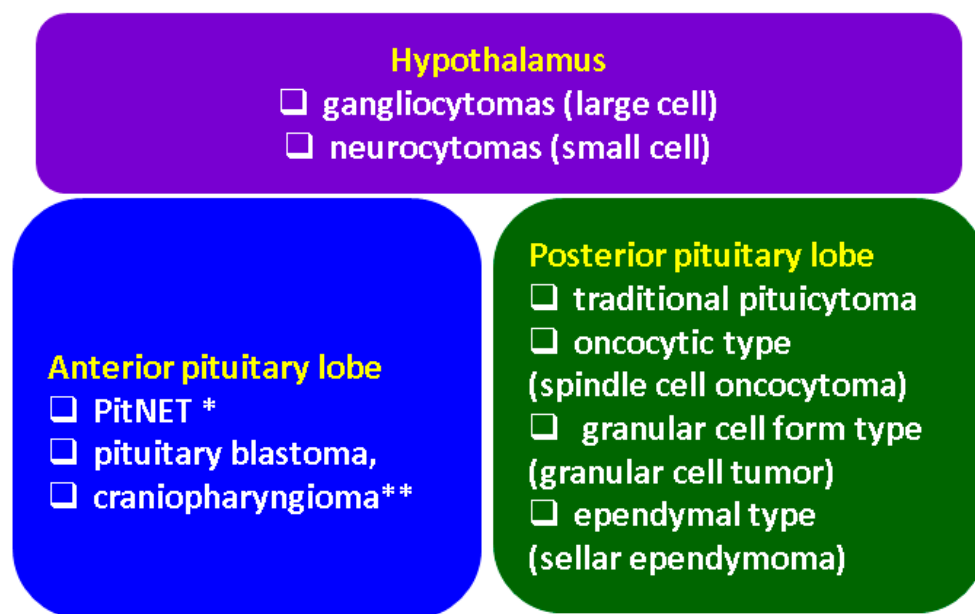


Figure 5. Integrating hypothalamic-pituitary tumors to new WHO 2022 criteria [223–226]. PitNET = pituitary neuroendocrine tumors; * well-differentiated adenohypophyseal tumors (formerly pituitary adenomas); ** two specific subtypes.

4.3. Limitations

We acknowledge that the current review did not follow the PRISMA guidelines for systematic review and may have missed some studies because only PubMed was used for the literature search.

5. Conclusions

PA in PitNETs still represents a challenging condition requiring a multidisciplinary team from first presentation to short- and long-term management. Controversies involve the specific panel of risk factors and adequate protocols with concern to surgical decisions and their timing. The present decade-based analysis, to our knowledge the largest so far on published cases, confirms a lack of unanimous approach and criteria of intervention, a

large panel of circumstantial events and potential triggers with different levels of statistical significance, in addition to a heterogeneous clinical picture (if any, as seen in subacute PA) and a spectrum of evolution that varies from spontaneous remission and control of PitNET-associated hormonal excess to exitus. Awareness is mandatory. A total of 25 cohorts have been published so far with more than 10 PA cases/studies, whereas the largest cohorts enrolled around 100 patients. Further studies are necessary.

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Abbreviations

| | |
|----------------|------------------------------------|
| CT | computed tomography |
| CSF | cerebrospinal fluid |
| HIF-1 α | hypoxia-inducing factor |
| HMGB1 | high-mobility group box 1 |
| HR | hormonal replacement |
| GH | growth hormone |
| IGF-1 | insulin-like growth factor |
| MMP | matrix metalloproteinase |
| MRI | magnetic resonance imaging |
| PA | pituitary apoplexy |
| PAS | pituitary apoplexy score |
| PitNET | pituitary neuroendocrine tumor |
| PDE | phosphodiesterase |
| PTTG | pituitary tumor-transforming gene |
| TNF- α | tumor necrosis factor- α |
| TSS | trans-sphenoidal surgery |
| VEGF | vascular endothelial growth factor |

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