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MINI REVIEW

Pituitary apoplexy

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Abstract Pituitary apoplexy is a clinical syndrome of sudden headache and visual decline associated with acute hemorrhagic or ischemic change of an intrasellar mass, and comprises only a subset of hemorrhagic pituitary lesions. The most common presenting symptoms include headache, nausea, diminished visual acuity or visual field, ophthalmoplegia/paresis, and impaired mental status. Multiple risk factors have been reported, although the majority of cases have no identifiable precipitants. MRI is the most sensitive diagnostic modality, with specific imaging findings dependent on the timing post-hemorrhage. Early clinical suspicion is imperative to allow for corticosteroid replacement and hemodynamic stabilization when indicated. Transsphenoidal surgical decompression improves outcome in a majority of cases, although conservative management may be appropriate in select scenarios.

Keywords Pituitary apoplexy · Thunderclap headache · Pituitary adenoma · Pituitary hemorrhage · Adrenal insufficiency

Background

Pituitary apoplexy has become synonymous with hemorrhage within a pituitary lesion, and more properly should be designated as pituitary tumor apoplexy. However, classical apoplexy in the sense of a catastrophic event associated with acute onset of symptoms accompanies only a fraction of hemorrhagic pituitary lesions [1, 2]. The initial description of a clinical presentation of pituitary apoplexy is attributed to Bailey in 1898 [3], with credit of the designation "pituitary apoplexy" given to Brougham, Heusner, and Adams in 1950 to depict 5 cases of sudden death in which autopsy revealed hemorrhagic degeneration of a pituitary adenoma [4]. As noted, pituitary apoplexy should be more appropriately termed pituitary tumor apoplexy, since intrinsic hemorrhage within the pituitary gland reflects pathologies such as Sheehan's syndrome, and other instances of hemorrhage into a normal pituitary gland. In addition to pituitary adenomas, sellar hemorrhage has also been reported with benign cysts of the pituitary, metastases [5], other neoplastic lesions and trauma, although adenomas predominate [6].

Radiologic and surgical series report hemorrhage in 10–22 % of pituitary adenomas, although clinical pituitary apoplexy is associated with only 0.6–9 % of pituitary tumors [1, 7–14]. Hemorrhage into pituitary tumors can be classified as acute, subacute, and chronic [15]. Although the classic presentation of pituitary apoplexy evolves over hours to 1 or 2 days, a stuttering course of subacute symptoms may precede the full panorama of acute pituitary tumor apoplexy [1, 6]. In one case series, an average of 14 days elapsed between onset of symptoms until presentation to neurosurgery, with some delays exceeding 2 months [2]. Pituitary tumor apoplexy patients are statistically more likely to be unmarried, uninsured, and without a primary health care provider, when considering a strict definition of sudden deterioration of visual acuity with imaging and pathological evidence consistent with pituitary tumor hemorrhage [16]. These socioeconomics factors may lead to a failure to note antecedent warning signs and symptoms until a fulminant presentation results.

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Table 1 Presenting symptoms and signs of pituitary apoplexy

Presenting symptom	Incidence (%)
Headache	84–100
Nausea	80
Diminished visual acuity	56
Visual field deficit	34–70
Ocular paresis	45–57
Impaired mental status	13–30

Clinical presentation

The most common presenting signs and symptoms in pituitary tumor apoplexy are headache (84–100 %), nausea (80 %), diminished visual acuity (56 %), temporal visual field cut (34–70 %), some degree of ophthalmoparesis (45–57 %), and impaired mental status (13–30 %) (Table 1) [1, 2, 17]. Headache and meningismus are believed to result from stretching of the hypophyseal capsule and/or extension of the intratumoral bleeding into the subarachnoid space. Mass effect on adjacent optic nerves, optic chiasm, and the cavernous sinus produces the high incidence of visual and cranial nerve deficits. Loss of vision may manifest as decreased visual acuity, enlargement of the blind spot, generalized constriction of visual fields, a frequently asymmetric bitemporal hemianopia or superior quadrantanopia, occasional nasal field defect, or even unilateral or bilateral blindness [18, 19].

Ocular paresis is most commonly due to oculomotor palsy, followed by abducens palsy, and infrequently, trochlear or multiple cranial nerve involvement [18, 20–22]. Oculomotor dysfunction may result from direct cavernous sinus invasion by tumor, transmitted pressure on the lateral wall of the cavernous sinus, vascular occlusion of the nerve, or compression between tumor and the interclinoid ligament as the third nerve enters the cavernous sinus at the oculomotor trigone [21, 23, 24]. Isolated abducens palsy suggests posterior expansion of tumor toward Dorello's canal [23]. Trochlear weakness usually accompanies deficits in one or more other cranial nerves, although rare cases of isolated trochlear palsy have been reported in macroadenomas [25]. Even though divisions of the trigeminal nerve also course along the lateral wall of the cavernous sinus, it maintains its function even when stretched to four times its original length [26], and trigeminal dysfunction can signify tumor invasion into the external wall of the cavernous sinus or beyond [27].

Although the most frequent presentation of pituitary tumor apoplexy includes headache and visual impairment, the most feared consequence is sudden death, presumably from acute adrenal insufficiency [4, 28]. Infarction or necrosis of the gland itself results in hypopituitarism (usually permanent) in 70–80 % of patients [1, 29]. Prompt recognition of pituitary hormonal axis dysfunction and corticosteroid supplementation is critical. Hypocortisolemia also triggers vasopressin release and increased retention of water, both resulting in hyponatremia. Hydrocephalus due to suprasellar extension of the pituitary tumor can further confound the etiology of altered mental status and headache [6].

Etiology and pathogenesis

Several hypotheses exist on the pathogenesis of pituitary tumor apoplexy. Both infarction and hemorrhage are observed in apoplexy, not always concurrently. Ischemic necrosis and hemorrhagic conversion in any setting reflect an imbalance of blood flow and perfusion to the target organ. A classic scenario leading to such imbalance portrays a rapidly growing tumor that outstrips its vascular supply [4, 30]. Although this explanation intuitively applies for the vast majority of hemorrhagic macroadenomas, it becomes more tenuous in cases of hemorrhagic microadenomas with an apoplectic presentation [1, 7]. An alterative hypothesis proposes compression of portal vessels by a growing pituitary mass, with consequent ischemic necrosis, with or without hemorrhage (Fig. 1) [6]. The primary juncture of vulnerability is thought to involve the crossing of the superior hypophyseal artery at the diaphragmatic aperture. This contradicts angiographic evidence which suggests that most pituitary adenomas are supplied by the inferior hypophyseal artery. The observation that pituitary adenomas appear more prone to hemorrhage than other intracranial neoplasms [8] leads to further speculation on underlying intratumoral vascular fragility and vasculopathy [31].

Precipitating factors for apoplexy have been attributed to large size of tumor [32, 33], cavernous sinus invasion [32], hypertension [1], trauma [4], increased intracranial pressure, coughing and sneezing, prior radiation [34], endocrine stimulation tests [35], pregnancy and exogenous estrogen therapy [31], active and withdrawal of bromocriptine therapy [36], cardiac surgery [37], an anticoagulated state [6], and thrombocytopenia [2, 8, 9, 17, 31, 38].

The reported risk factors have been synthesized into 4 categories: (1) acute increase in hypophyseal blood flow; (2) reduced blood flow to the pituitary tumor; (3) hormonal stimulation of the pituitary gland and tumor; and (4) an anticoagulated state [17]. Sudden increase in blood flow to the pituitary gland may result from hypertension or microvascular degeneration, as seen in diabetes. Pituitary hypoperfusion from a transient increase in intracranial pressure or systemic procedures such as cardiac surgery accounts for another subset of apoplexy cases. This

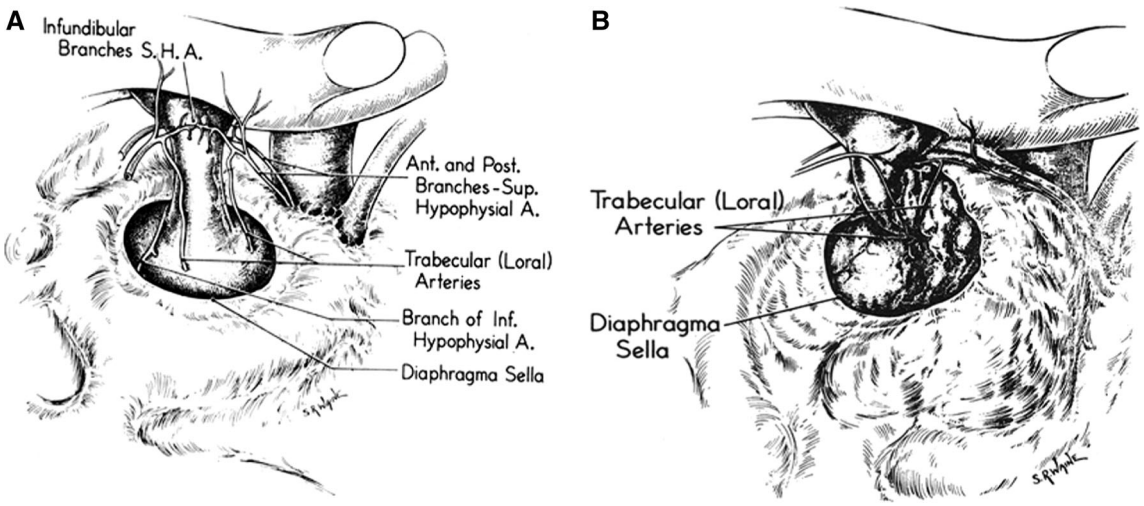

Fig. 1 Illustration of the vascular compression theory of pituitary tumor apoplexy. **a** Arterial supply to the normal pituitary gland. **b** Illustration of an enlarging pituitary adenoma stretching the diaphragma sella with compression of the trabecular arteries at the diaphragmatic notch. (Adapted from Rovit RL and Fein JM, Pituitary apoplexy: a review and reappraisal, *J Neurosurg*, 37:280–288)

rationale also applies to patients with prior pituitary radiation and chronic hypoperfusion, who may be more susceptible to infarction and hemorrhage. Hormonal surges can result from endogenous sources, such as pregnancy, the stress response, or exogenous administration of hormones or hormone altering drugs. Lastly, anticoagulation through drugs or immunodeficiency may exacerbate underlying vascular fragility in some cases of apoplexy. Notwithstanding the above risk factors, a majority of pituitary apoplexy cases have no clearly identifiable precipitants [31].

Null-cell adenomas comprise the most frequent histologic subtype associated with pituitary tumor apoplexy, in proportion to their usual incidence among pituitary tumors [1, 2, 18]. Although earlier work questioned a hemorrhagic proclivity in acromegaly and Cushing's disease cases, subsequent series have not demonstrated any clear evidence for subtype specificity among functional adenomas [17, 18]. Apoplexy has been reported in all age ranges, with a lower incidence among children than adults. A predilection for males is reported in some studies [1, 39], but not others.

Diagnosis and evaluation

The most critical differential diagnosis in pituitary tumor apoplexy is aneurysmal subarachnoid hemorrhage, although meningitis [40], pituitary abscess [41], complex migraine, stroke, optic neuritis, encephalitis, sinusitis [42], cavernous sinus thrombosis [43], pseudotumorcerebri, myocardial infarction, and syncope have also been reported [2, 11]. Although approximately 20–30 % of patients may have prior endocrine-related symptoms, 80 % of patients have no known prior history of pituitary lesions prior to the onset of apoplexy [1, 2, 17].

On initial presentation in an emergency setting, CT scan of the head is often obtained first to rule out subarachnoid or intraparenchymal hemorrhage due to a vascular etiology. Hyperdense blood, with or without a fluid level suggestive of differing ages of hemorrhage onset, in the setting of a heterogeneous mass and occasional expansion of the sella turcica are often seen. However, absence of hemorrhage on CT does not preclude pituitary apoplexy. In one series, CT scans identified only 21 % of pituitary tumor hemorrhages, compared to an 88 % detection rate by MRI [1]. Therefore, clinical suspicion of pituitary apoplexy should prompt MRI, after ensuring hemodynamic stabilization of the patient and administration of corticosteroids, if indicated. Pituitary hemorrhage manifests with mixed intensity sellar attenuation on T1- and T2-weighted sequences, consistent with the usual pattern of blood degradation (Fig. 2) [44, 45]. MRI also elucidates anatomic detail of the underlying tumor, sellar expansion, suprasellar and parasellar extension, optic chiasm compression, and cavernous sinus involvement (Fig. 3) [46]. Apoplexy can be associated with antecedent sphenoid sinus mucosa thickening on MRI during the acute phase of symptomology in close to 80 % of cases [47–49]. Sphenoid sinus mucosa thickening also appears to correlate with more severe neurologic and endocrinologic compromise on presentation as well as on long-term follow-up, signifying greater compression of neurovascular structures (probably venous) by larger tumors [49]. Extrasellar findings in pituitary apoplexy include subarachnoid hemorrhage and unilateral or bilateral stroke from thrombosis, direct vascular compression,

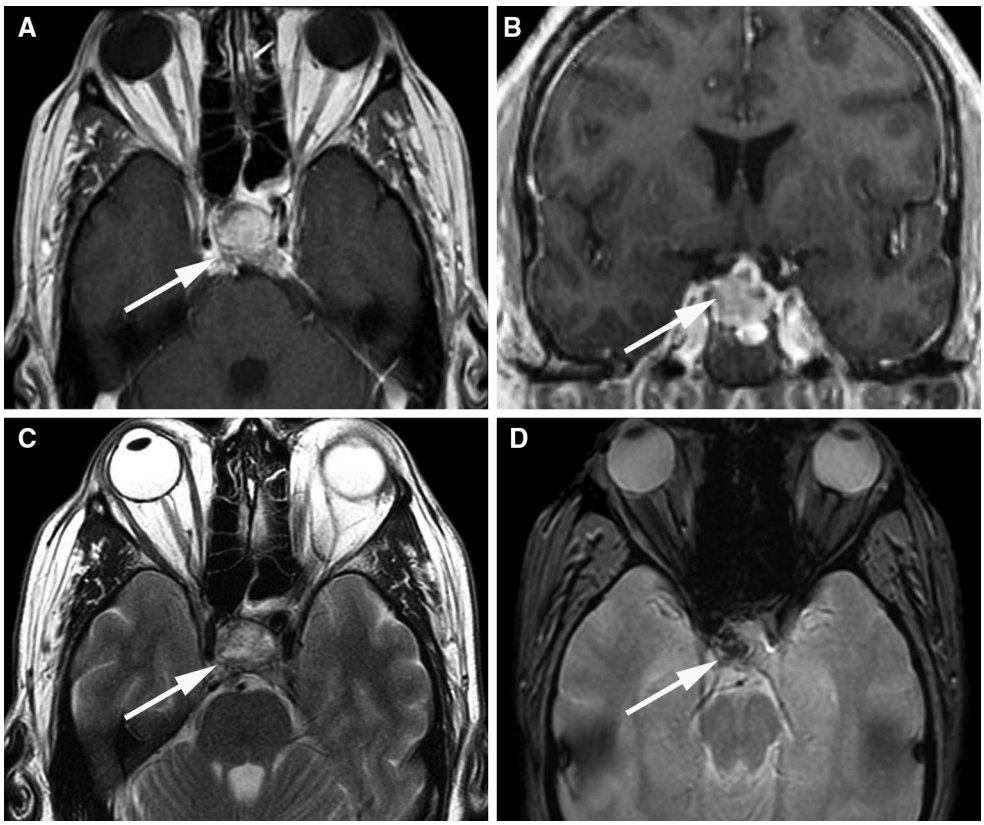

Fig. 2 Acute on subacute pituitary apoplexy in a 42-year-old man presented with a week of progressive headache, followed by acute onset right-sided double vision, ptosis, and partial ophthalmoplegia. MRI revealed a hyperintense heterogeneous sellar lesion (*arrow*) on **a** axial T1-weighted, **b** coronal T1-weighted, and **c** axial T2-weighted images. **d** Gradient echo images also demonstrated signal shortening, consistent with intratumoral hemorrhage

or vasospasm [50, 51]. Infarction of a pituitary adenoma with ischemic necrosis can also produce the clinical syndrome of pituitary tumor apoplexy as a result of acute swelling of the ischemic tumor.

Diagnosis of apoplexy merits a full evaluation of the endocrinologic status. A typical laboratory panel measures prolactin, fasting cortisol, adrenocorticotrophic hormone, thyroid stimulating hormone, thyroxine (T4), free T4, triiodothyronine (T3), growth hormone, insulin-like growth factor-1, follicle-stimulating hormone, luteinizing hormone, estrogen in females, and testosterone in males. Stress dose steroids should be given with either clinical or laboratory evidence of adrenal insufficiency. Concurrent thyroid hormone deficiencies should be repleted after correction of hypocortisolemia to prevent excess stimulation of metabolism in an adrenally insufficient patient. Electrolyte imbalance, especially hyponatremia, should also be investigated and anticipated in the acute setting and repleted cautiously as indicated [2, 52].

Patients should undergo full ophthalmologic examination on presentation, and following surgical resection. Deficits in visual acuity, visual field, or impairment of ocular motility may prompt more urgent intervention, especially among patients undergoing initial conservative management. Although bitemporal hemianopsia is classically associated with pituitary masses, central scotoma is the most frequently encountered visual deficit in one series of apoplexy patients, along with a significant preponderance of isolated nasal defects or generalized constriction of vision [19]. Therefore, pituitary tumor apoplexy should be suspected for acute onset headache with any constellation of visual impairment.

Management

The majority of pituitary tumor apoplexy cases appropriately result in surgical intervention, usually in a prompt manner via a transsphenoidal approach [11, 31], although some guidelines exist for conservative management in select cases [13, 29, 53]. The precise timing of surgical decompression is subject to debate. We favor the following strategy in the management of clinical pituitary apoplexy.

The most important initial intervention is repletion of corticosteroids, hemodynamic stabilization, and correction of electrolyte imbalance. Patients with impaired consciousness or actively deteriorating vision merit emergent

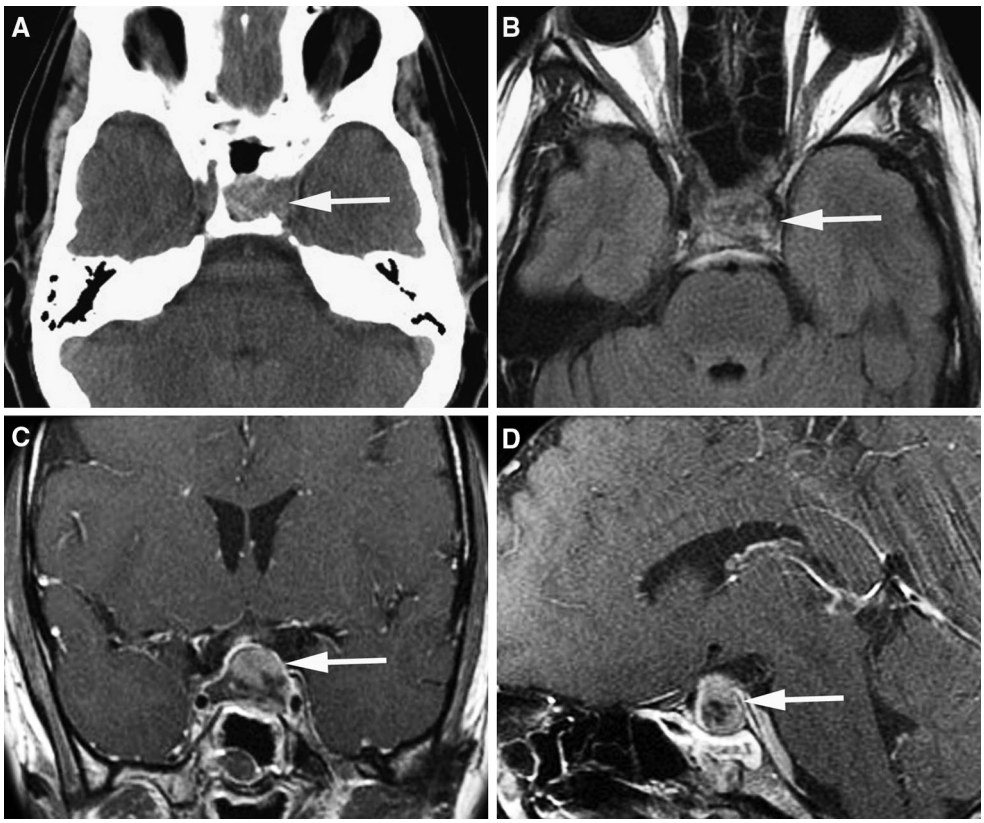

Fig. 3 Acute to early subacute pituitary apoplexy in a 42-year-old man who presented with 5 days of progressive headache and double vision, with a partial right oculomotor palsy. **a** Non-contrast CT revealed a relatively hyperdense sellar lesion (*arrow*) with compression of the left cavernous sinus. **b** Axial T2-weighted FLAIR, **c** coronal T1-weighted gadolinium-enhanced, and **d** sagittal T1-weighted gadolinium-enhanced MRI images demonstrated the evolving hemorrhagic pituitary lesion (*arrow*), with extension of blood into the prepontine space

surgical decompression. Surgery within the first week is preferred for patients with visual deficits or cranial neuropathies, without active decline in symptoms and signs. In fact, earlier intervention correlates with improved neurologic outcomes in several studies, as discussed below. Patients with stable or improving visual symptoms, especially related only to an isolated ocular palsy, may be conservatively managed, with elective surgery if any new deficits arise in follow-up. Biochemical evidence of a prolactinoma during the initial workup may encourage medical management alone, given excellent response rates to dopamine agonists. Even in the absence of neurologic or endocrinologic deficits, surgical decompression may relieve intractable headaches by diminishing the tension within and around the sella.

Outcome

Despite the foreboding name, a majority of pituitary tumor apoplexy patients experience significant improvement in symptoms with both surgical and expectant management. In apoplexy patients with visual deficit on presentation, 53–89 % experienced improvement after transsphenoidal surgery [1, 2, 16, 18, 19]. This range is slightly lower at 40–80 % following transcranial decompression of a pituitary mass [18, 54]. Visual recovery occurs in stages, suggestive of different mechanisms of response to injury [55]. Different opinions exist on the optimal time of surgical intervention for apoplexy and its impact on visual recovery. Several authors note that surgery within the first 8 days after presentation with apoplexy is more likely to improve visual deficits compared to delayed intervention [1, 9, 56]. However, others did not find any significant difference in degree of visual recovery between patients with less than versus greater than 7 days of visual loss before treatment [18, 19]. Across all pituitary adenomas, Cohen et al. [57] reported that duration of symptoms (less than 6 months) inversely correlated with recovery, and that preoperative visual acuity was predictive of visual outcome. The appearance of the optic disc was a strong predictor of visual outcome in some series but not others [18, 19].

Cranial neuropathies are more likely to improve in patients who underwent early surgical intervention, within

2–3 days of presentation, compared to later surgery [20, 21]. Oculomotor palsy, the most commonly encountered cranial nerve deficit in pituitary apoplexy, frequently develops in a defined sequence of mydriasis, gaze limitation, and lastly, ptosis, which usually improves in the reverse order following surgery [21]. Concurrent involvement of abducens, trochlear, and rarely trigeminal, palsies usually occurs after the onset of oculomotor deficits, and may recover faster than the third nerve palsy. MRI and histopathologic findings of pituitary tumor infarction attributed to ischemia, rather than hemorrhage, may further portend a more favorable neurologic and ophthalmologic outcome [58]. Notwithstanding these different observations, we favor prompt, but not necessarily emergent, transsphenoidal surgical decompression of apoplectic pituitary lesions.

Hypopituitarism, requiring long-term steroid placement, results in 58–83 % of apoplexy patients [1, 2]. Transsphenoidal resection of an apoplectic lesion can reverse preoperative hypopituitarism in about 25 % of patients [49]. Diabetes insipidus occurs less commonly, in approximately 6–8 % of patients [1, 2]. Although hemorrhagic infarction may result in partial obliteration of a pituitary lesion, long-term follow-up is still merited for residual tumor and late-onset recurrence [59]. Mortality in the acute setting is less than 2 % in the modern era of diagnostic and therapeutic armamentarium.

Conclusion

Pituitary tumor apoplexy is a clinical event, and occurs in a subset of pre-existing pituitary lesions that become hemorrhagic and/or ischemic. Hemodynamic stabilization, reversal of electrolyte imbalance, and correction of adrenocorticoid insufficiency are of utmost importance on initial encounter. Transsphenoidal surgical decompression improves outcome in a majority of cases, although conservative management may be appropriate in select scenarios.

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