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Chapter 97

Paroxysmal Hemicrania

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PAROXYSMAL HEMICRANIA

International Headache Society (IHS) code and diagnosis:
3.2 Paroxysmal hemicrania
3.2.1 Episodic paroxysmal hemicrania
3.2.2 Chronic paroxysmal hemicrania
World Health Organization (WHO) code and diagnosis:
G44.03 Chronic paroxysmal hemicrania
Short description: Paroxysmal hemicrania (PH) sufferers have attacks with similar characteristics of pain and associated symptoms and signs to those of cluster headache (CH), but they are shorter lasting, are more frequent, occur more commonly in females, and respond absolutely to indomethacin. In episodic paroxysmal hemicrania (EPH), attacks occur in periods lasting 7 days to 1 year separated by pain-free periods lasting 1 month or longer. In chronic paroxysmal hemicrania (CPH), attacks occur for more than 1 year without remission or with remissions lasting less than 1 month (21).
Other terms: Sjaastad syndrome

EPIDEMIOLOGY

PH is a relatively rare disorder. Data on PH epidemiology are scarce, and many cases are probably still overlooked. Following the original description (58), new patients have been identified in several countries (1,25,57) and isolated PH cases are no longer reported. The incidence and prevalence of PH are not known, but the relative frequency compared to CH is reported to be approximately 1 to 3% (1). Prevalence estimates in CH vary from 56 per 100,000 to 381 per 100,000 (51,61,69). It has been reported that the prevalence of CH in the United States, based on one large study, was 401 per 100,000 (51). However, this was a U.S. study of CH incidence, not prevalence, and converting incidence to prevalence estimates is naturally combined with uncertainties because survival time needs to be conjectured (61,68).

Sex Distribution

PH was originally considered to be a female disease. Male cases, however, clearly occur (46,48). In initial series there was a female:male ratio of 7:1, but a 1989 review reported a female:male ratio of 2.36:1 (1). Comprehensive and methodologically well-designed epidemiologic studies are required to establish the actual extent of the female preponderance in PH.

Age of Onset

PH may begin at any time, but its onset usually occurs during adulthood at the mean age of 34 years. The youngest age at onset was 1 year and the oldest 81 years (1,12). In the reviewed material from 1989, the mean age at diagnosis was 47 and the mean illness duration 13 years. As far as the subtypes are concerned, EPH seems to begin earlier (mean 27 years) than CPH (mean 37 years) (1).

GENETICS

There is no evidence of a genetic etiology in PH. Parents or siblings do not have an increased incidence of CH or migraine compared with the general population (1).

ANATOMY, PATHOLOGY, AND PATHOPHYSIOLOGY

The pathogenesis of PH remains unknown. The unilaterality and pain intensity, as well as the autonomic symptoms and signs, suggest that some mechanisms may be shared with the other trigeminal autonomic cephalalgias (TACs) listed in group 3 of the 2004 IHS headache classification. The absolute indomethacin effect, however, indicates that PH has a distinct pathophysiology. In most of the cases no underlying pathology is detected by any supplementary investigation. Several secondary cases, however, have been described (70) (Table 97-1).

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TABLE 97-1 Secondary Paroxysmal Hemicrania

- Vascular
  - Circle of Willis aneurysm
  - Occipital, middle cerebral artery infarctions
  - Parietal arteriovenous malformation
- Tumor
  - Malignant frontal tumor
  - Cavernous sinus meningioma
  - Petrous ridge meningioma
  - Gangliocytoma of the sella turcica
  - Pituitary adenoma
  - Parotid epidermoid metastases
  - Pancoast tumor
- Miscellaneous
  - Collagen vascular disease
  - Intracranial hypertension
  - Maxillary cyst
  - Ophthalmic herpes zoster
  - Essential thrombocythemia
  - Posttraumatic

From refs. 5, 33, 70.

Although the pain in PH is strictly unilateral, autonomic involvement and ocular signs may be bilateral, albeit more pronounced on the symptomatic side. The existence of bilateral ocular signs seems to exclude the possibility of a single lesion of the peripheral nervous system being the cause of PH. A central lesion involving midline structures seems therefore more probable (e.g., hypothalamus, cavernous sinus) (40,56). Functional neuroimaging studies have shown specific activation of hypothalamic areas in some TACs, including CH and SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) syndrome (35,36,67). Similar neuroimaging findings in PH are not available.

The pain in PH cannot be explained by a disturbance in the autonomic nervous system alone. This is based on the observation that autonomic signs may precede the development of pain in precipitated attacks and that the pharmacologic suppression of autonomic signs does not influence the pain pattern during attacks (66). Besides, the clinical picture does not fit with any classic sympathetic or parasympathetic syndrome. The pathophysiologic mechanisms responsible for the pain in PH remain unknown. It has been suggested that the ipsilateral distribution of trigeminal fibers in the trigeminovascular system may explain the unilaterality of the pain, and evidence of trigeminal–parasympathetic activation during PH attacks has emerged (18).

The ocular findings in PH patients have been studied in detail with dynamic tonometry (22,23). Pulse synchronous changes in intraocular pressure (IOP) may be recorded. They depend on the volume of the pulsatile part of ocular blood flow (23). The pulse synchronous changes in IOP are reflected by the corneal indentation pulse (CIP) amplitudes, which may be measured in micrometers by dynamic tonometry (22). The corresponding changes in intraocular volume in cubic milliliters can be estimated using conversion tables. In PH there is a significant attack-related increase in CIP amplitudes, ocular blood flow, and IOP that is bilateral but more pronounced on the symptomatic side (55). The attack-related increase in IOP cannot be solely explained by changes in aqueous humor dynamics because the increased volume exceeds turnover of aqueous humor and the IOP changes occur so rapidly (<30 seconds). Therefore, these findings are probably the result of an acute vasodilation that increases intraocular volume due to a neurogenic impulse and vasoactive neuropeptide release (55).

Since changes in IOP and CIP may indicate local abnormal hemodynamics, spontaneous PH attacks were studied with transcranial Doppler (54). During attacks, there was hyperventilation, reduction of the end-tidal PCO2, and decrease in blood flow velocity in all insonated arteries, on both symptomatic and nonsymptomatic sides. In the anterior cerebral artery, the reduction was significantly smaller on the symptomatic side. There was no major difference between patients and controls considering reduction of flow during hypocapnia, indicating that vascular reactivity in PH is normal.

Corneal temperature has been found to be increased on the symptomatic side during attacks, a finding that may also be due to increased ocular blood flow following vasodilation (13).

The abruptness with which the accompanying autonomic signs occur in mechanically precipitated attacks suggests that they may be mediated by neurogenic impulses. This would involve neuropeptide-containing perivascular fibers of the trigeminovascular system with its connections to the cavernous sinus plexus and brainstem. The release of vasoactive peptides from sensory fibers, which run in close relationship to other autonomic fibers, may also lead to miosis, increased IOP, and other autonomic disturbances observed in PH (14,37). Calcitonin gene–related peptide (CGRP), a peptide released from trigeminal fibers, and vasoactive intestinal polypeptide (VIP), a parasympathetic peptide, have been found to be abnormally high during a PH attack (18). Values returned to basal levels following indomethacin treatment. This is similar to the peptides' profile found in CH (17), suggesting that this disorder and PH may share pathophysiologic traits to a certain extent. It is possible that the clinical picture in PH results from the interaction between neurotransmitters and neuromodulators released from sympathetic, parasympathetic, and sensory fibers at the frontal area and local autonomic and vascular mediators.

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The ocular vascular findings (increased IOP, conjunctival injection) may also be explained by autonomic changes. The situation seems to be more intricate since experiments show that the IOP increase is inhibited by an α-blocking agent (thymoxamine) as well as satellite ganglion blockade (66). This observation, together with increased sweating and decreased salivation on the symptomatic side during PH attacks, suggests sympathetic stimulation (52,53). The sweat abnormality observed in some patients (53,64,65) suggests a direct sympathetic stimulation rather than a supersensitivity reaction, which has been found in CH (64). Increased tearing, nasal secretion, and miosis may, on the other hand, be due to a parasympathetic stimulation during attacks (52).

Heart rate and electrocardiogram (ECG) changes during attacks show no typical pattern and differ therefore from those observed during CH attacks (50). There is, however, a tendency to marked variations in heart rate in association with attacks of PH. Attack-related heart rhythm disturbances have been observed in some patients: bradycardia and sinoatrial block, bundle branch block with episodes of atrial fibrillation, multiple extrasystoles, and bradycardia (50). These findings may indicate a dysfunction in the central control of the autonomic nervous system during PH attacks.

Pain pressure threshold (PPT), the nociceptive flexion reflex (RIII), corneal reflex, and blink reflex have been studied in a few PH cases (2). The PPT and the subjective pain perception following sural nerve stimulation were reduced in PH, as was the RIII reflex threshold on the symptomatic side as compared to controls. Blink reflexes were normal, and the corneal reflex thresholds were reduced bilaterally, irrespective of indomethacin intake. Interestingly, the RIII threshold was not affected by indomethacin, but the subjective pain perception was significantly more asymmetric in PH on the drug than in controls.

The Indomethacin Effect

The mechanism behind the absolute indomethacin effect and the reason why equipotent cyclooxygenase inhibitors are not as effective remain unknown. It does not seem to be due to its effect on prostaglandin synthesis, since other nonsteroidal antiinflammatory drugs (NSAIDs) with an even more potent antiprostaglandin action have little or no effect in PH. Both indomethacin and acetylsalicylic acid block neurogenic inflammation (9). Indomethacin reduces cerebral blood flow (71), but its effect on peptide-induced vasodilation of isolated ophthalmic arteries is no different than other NSAIDs. It is possible that indomethacin affects vessels via a nonprostaglandin-related phenomenon (16,47). The indomethacin effect seems to be symptomatic rather than curative, since symptoms recur after the discontinuation of the drug.

The mechanism behind precipitation of attacks may theoretically be due to reflex mechanisms involving connections between the trigeminovascular system and brainstem. However, local pathologic findings in the neck structures have not been found.

In conclusion, the pathologic mechanisms behind the PH syndrome are incompletely understood. However, based on the available information, the occurrence of both unilateral and bilateral symptoms may suggest a primary central triggering mechanism and a secondary involvement of peripheral factors probably mediated by neurogenic impulses.

CLINICAL FEATURES

IHS diagnostic criteria for PH (21):

A. At least 20 attacks fulfilling criteria B through D
B. Attacks of severe, unilateral orbital, supraorbital, or temporal pain lasting 2 to 30 minutes
C. Headache is accompanied by at least one of the following:
  1. Ipsilateral conjunctival injection and/or lacrimation
  2. Ipsilateral nasal congestion and/or rhinorrhea
  3. Ipsilateral eyelid edema
  4. Ipsilateral forehead and facial sweating
  5. Ipsilateral miosis and/or ptosis
D. Attacks have a frequency >5 per day for more than half of the time, although periods with lower frequency may occur.
E. Attacks are prevented completely by therapeutic doses of indomethacin (see Notes).
F. Not attributed to another disorder (see Notes)

Notes:

1. To rule out incomplete response, indomethacin should be used in a dose of at least 150 mg daily orally or rectally, or at least 100 mg by injection, but for maintenance smaller doses are often sufficient.
2. History and physical and neurologic examinations do not suggest any of the disorders listed in groups 5 to 12, or history and/or physical and/or neurologic examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

IHS diagnostic criteria for EPH (21):

A. Attacks fulfilling criteria A to F for 3.2 Paroxysmal hemicrania
B. At least two attack periods lasting 7 to 365 days and separated by pain-free remission periods of ≥ 1 month

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IHS diagnostic criteria for CPH (21):

A. Attacks fulfilling criteria A to F for 3.2 Paroxysmal hemicrania

B. Attacks recur for >1 year without remission periods or with remission periods lasting <1 month.

History

Sjaastad and Dale reported a new treatable headache entity in 1974 (58), and in 1976 they named the entity chronic paroxysmal hemicrania (59). The first case seen by Sjaastad was described in detail in his book *Cluster Headache Syndrome* and will be quoted extensively because of its importance (57).

> "The first case of chronic paroxysmal hemicrania (CPH), a female aged 44 years with a 9-year history of headache, was brought to our cognizance in 1961, with a diagnosis of 'typical cluster headache.' However, the patient was a female (which, of course, may be consistent with a diagnosis of ordinary cluster headache, although females are admittedly rarely affected). There was another trait that, upon scrutiny, did not seem to be quite typical: there was a multitude of attacks per 24h, i.e. up to 24 or more per day. Another remarkable feature was the intractability of the headache. . . .Over the course of the following years, every feasible drug was tried on her. Prior to each admission, she had discontinued her usual drug (mainly acetylsalicylic acid) which kept the attacks at a reasonable level. Each drug trial ended either with an absolutely negative response, or—more usually—with an adverse reaction. The latter response pattern was so typical that for almost every new drug that was tried she was brought from a stage of moderate or weak attacks to a stage of incapacitating and excruciatingly severe attacks. . . . But she would not give up the hope that there was a solution to her problem. And she was the one who motivated us to try new approaches, not the other way around. . . . To make matters even worse, she was diagnosed as being an hysterical person. . . despite the unilaterality of the pain, lacrimation, rhinorrhoea, etc. . . .
>
> "[T]he patient felt that everything centred on the eye. . . .[W]e had arrived at a point where we were running out of arguments when trying to reject the patient's contention that an enucleation of the right (symptomatic side) eye would perhaps solve her pain problem.
>
> "Fortunately, the following developments took place simultaneously. The patient had from the start claimed that salicylates seemed to give her some relief, not to the extent that the pain disappeared, but at times when they were not maximal the paroxysms could be modified by salicylates. Perhaps the paroxysms became even more rare during such medication. We thought that a lot of drugs would be more promising than salicylates as potential therapeutic agents. The anti-inflammatory agents were therefore put rather far down on our list of potentially effective drugs worthy of trial. . . .When in late 1972 we finally arrived at indomethacin on our list, the response was no less than miraculous" (57).

A remitting form of the disease was subsequently recognized and termed episodic paroxysmal hemicrania (28). The IHS gave diagnostic criteria for CPH in 1988 (20), and in 2004 the IHS classified CPH and EPH as subtypes of paroxysmal hemicrania (21).

Headache Phenotype

Patients with PH typically have unilateral, brief, severe attacks of pain associated with cranial autonomic features that recur several times per day. The pain is most often in a V_1 distribution, but it can be extratrigeminal. In Antonaci and Sjaastad's retrospective review of 84 CPH patients, the maximal pain was most often in the ocular, temporal, maxillary, or forehead areas (1). It was less often in the neck/shoulder, retroocular, or occipital regions (1). The quality of pain is usually clawlike or throbbing, but it can sometimes be described as dental, boring, or pressing (1). The pain has an abrupt onset and cessation. Roughly 50% of patients prefer to sit or curl up in bed during attacks (1). Photophobia (21%), nausea (14%), and vomiting (2%) may be present (1). In one study, 27 of 31 patients asked noted at least one migrainous feature of photophobia, nausea, or vomiting during an attack (5).

Ipsilateral autonomic features typically occur during attacks of pain. The most common symptoms are lacrimation and nasal congestion, but conjunctival injection, rhinorrhea, forehead and facial sweating, eyelid edema, ptosis, and miosis can also occur (1). Bilateral autonomic symptoms can occur (1). Dissociation between pain and autonomic features can be seen (40).

The headache usually lasts 10 to 30 minutes (mean 20.9 minutes), with a range from 2 to 120 minutes (1). The frequency ranges from 1 to 40 attacks per day, with a mean of 11 attacks per day (1). In 74 patients, the mean usual duration was 26 minutes and the mean usual attack frequency was six (5). In a prospective study of 105 attacks in five patients, the mean duration was 13.3 minutes and the mean frequency was 14 per day (49). Attacks often occur regularly throughout the 24-hour period, without the preponderance of nocturnal attacks typically seen in CH. Nocturnal attacks associated with rapid eye movement (REM) sleep have been reported (26). Interictal discomfort or pain is present in up to one-third of patients (1).

Most attacks are spontaneous, but 10% of patients can trigger attacks with neck movement (1). Alcohol ingestion triggers attacks in approximately 7% of patients (1).

PH has chronic and episodic patterns, similar to CH. In contrast to CH, however, the chronic form of paroxysmal PH is more common than the episodic form, occurring in 80% of patients (1). Approximately 20% of patients with PH have clear intervals between bouts of attacks (EPH).

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The duration of the headache phase in EPH ranges from 2 weeks to 4.5 months (39). Remissions in EPH range from 1 to 36 months (39). EPH has been reported to stay episodic for up to 35 years (1). EPH can evolve into typical CPH and vice versa.

PH has been observed in association with other primary headache disorders, including trigeminal neuralgia (paroxysmal hemicrania–tic syndrome) (7,10), CH (11), migraine (41), primary stabbing headache (62), and primary cough headache (31). Typically, each type of headache requires a separate treatment (except when PH is associated with primary cough headache or primary stabbing headache).

Unusual clinical features have been reported, including side-alternating attacks (19,40,44), bilateral or center of forehead pain (38,45), and absence of autonomic features (6,8,44). Cases presenting with primarily ear pain and a sensation of external acoustic meatus obstruction have been reported, and a case of CPH associated with the red ear syndrome has been described (6). CPH with aura has been reported (32).

DIFFERENTIAL DIAGNOSIS

Numerous cases of secondary PH have been reported, underlining the importance of magnetic resonance imaging (MRI) of the brain in every case. Even cases fitting all the criteria for CPH that respond completely to indomethacin can have a secondary etiology (5). Secondary causes of PH are listed in Table 97-1.

The number one differential diagnosis for CPH is chronic CH, while EPH is most likely to be confused with episodic CH. The female sex preponderance of PH is the opposite of CH, but this is not helpful information when confronted with the individual patient. PH differs from CH mainly in the higher frequency and shorter duration of individual attacks (Table 97-2). The mean usual attack

TABLE 97-2 Clinical Features of the Trigeminal Autonomic Cephalalgias and Hemicrania Continua

	Cluster Headache	*Paroxysmal Hemicrania*	*SUNCT Syndrome*	*Hemicrania Continua*
Sex F:M	1:2.5–7	2.36:1	1:1.3	2:1
Pain:				
Type	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, sharp	Background dull ache; throbbing/stabbing exacerbations
Severity	Excruciating	Excruciating	Severe	Moderate background pain; severe exacerbations
Site	Orbit, temple	Orbit, temple	Periorbital	Orbit, temple
Attack frequency	1/alternate day–8/day	1–40/day (>5/day for more than half the time)	3–200/day	Continuous
Duration of attack	15–180 min	2–30 min	5–240 sec	Continuous background pain; exacerbations variable, lasting minutes to days
Autonomic features	Yes	Yes	Yes (prominent conjunctival injection and lacrimation)	Yes (mainly with exacerbations; less prominent than in other trigeminal autonomic cephalalgias)
Migrainous features*	Yes (photophobia may be lateralized to pain side)	Yes (photophobia may be lateralized to pain side)	Very rarely (photophobia may be lateralized to pain side)	Yes (during exacerbations)
Alcohol trigger	Yes	Occasional	No	Rare
Indomethacin effect	—	++	—	++
Abortive treatment	Sumatriptan injection Oxygen	Nil	Nil	Nil
Prophylactic treatment	Verapamil Lithium	Indomethacin	Lamotrigine	Indomethacin

*Nausea, photophobia, or phonophobia; ++ indicates absolute response to indomethacin. From (33).

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duration of PH is 26 minutes (5), while the mean usual attack duration of CH is approximately 60 minutes (27). The mean usual attack frequency of PH is six (5), while the usual attack frequency of CH is one (30). There is considerable overlap in these characteristics, however. For example, although the usual attack frequency in a series of 74 patients was six, 63% of patients had a usual attack frequency in 24 hours of less than six, and if one were only looking for PH in patients with a high frequency of daily attacks, some cases of PH would be missed (5). Sophisticated instrumental examinations such as evaporimetry, pupillometry, and dynamic tonometry can detect differences between PH and CH sufferers (57), but such investigations are not frequently available to most physicians. PH responds dramatically to indomethacin, while the evidence for the efficacy of indomethacin in CH is minimal and anecdotal (4). Since PH and CH can be clinically indistinguishable, any patient presenting with what appears to be CH should have an indomethacin trial, especially if attacks have been refractory to usual CH treatments.

Short-lasting paroxysmal hemicrania must also be differentiated from SUNCT syndrome (Table 97-2). In PH the attacks have a uniform distribution throughout the day and night and the triggers are different than those seen in SUNCT (33). PH attacks abate with indomethacin, which is not effective in SUNCT. Some patients with PH complain of a dull interictal pain in their usual attack location between attacks (33). These patients are usually differentiated clinically from hemicrania continua on the basis of the temporal profile of the attacks and the associated features (Table 97-2). The exacerbations in hemicrania continua are longer lasting and have less robust autonomic features than the attacks seen in CH, paroxysmal hemicrania, and SUNCT.

PROGNOSIS

The natural history of PH is largely unknown. In a review of all the reported cases in 1989, the mean duration of illness was 13.3 $\pm$ 12.2 years (1). It seems to be a lifelong condition, although EPH can transform into CPH and vice versa. Patients typically do not develop tachyphylaxis to indomethacin. Many patients can decrease the dose of indomethacin required to maintain a pain-free state over time (43).

MANAGEMENT

The treatment of PH is entirely prophylactic, as attacks are too short and intense for any acute oral treatment to be effective. Indomethacin is the drug of choice and must have an absolute effect on the symptoms, provided the dose is sufficient for that particular individual (4). When PH is suspected, an indomethacin trial should be performed. The trial dosage of indomethacin should be increased to at least 150 mg per 24 hr for 3 to 4 days. The beneficial effect is seen within 48 hours (a few hours to 5 days). Six out of 11 CPH patients became pain free within 7 hours after indomethacin, and in only one the time before relief was greater than 24 hours (42). The maintenance dosage is usually 25 to 100 mg per day but may vary inter- and intraindividually between 12.5 and 300 mg/day, depending on the fluctuation in attack severity (55). On discontinuation, symptoms usually reappear within 12 hours to a few days (1 to 14 days) (63). However, long-lasting remission periods up to years have been described (24). Indomethacin requirements usually vary with time, and many patients find that the minimum effective dose varies from one moment to the next.

In about 10% of cases indomethacin side effects are expected (1). The potentially most serious side effects of indomethacin are dyspepsia and the development of a bleeding peptic ulcer. Antacids, H2 blockers, or proton-pump inhibitors should be considered when indomethacin is being given over longer periods. Nausea, vomiting, vertigo, and purpura have also been reported during indomethacin use (1). Suppositories of indomethacin may help if gastric intolerance is a major problem, or when the dose eventually needs to be increased up to higher doses, such as 300 mg per day.

Other Drugs

Verapamil and acetylsalicylic acid may give partial relief, especially in the early stages of PH (15). Two out of six CPH patients obtained complete relief with piroxicam β-cyclodextrin, and one had moderate relief (60). There are reports on the effectiveness of celecoxib and rofecoxib in PH (29,34). Since PH attacks are relatively short, testing the effect of acute drugs may be particularly difficult. However, except in some reports (15,19), sumatriptan and oxygen are considered ineffective. The effect of prophylactic drugs is better tested in chronic cases, since an eventual "response" may correspond to the natural fluctuation of the disease. Anecdotal reports on the efficacy of various drugs may be related to inobservance of this fact. Lithium, carbamazepine, and other anticonvulsants are ineffective. Anesthetic blockades of the greater occipital nerve, supraorbital nerve, and minor occipital nerve are ineffective (3).

Surgical and Nonpharmacologic Treatment

There is no evidence of efficacy of surgical treatment, chiropractic manipulation, acupuncture, or other alternative options for the treatment of PH.

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P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
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