Paroxysmal hemicrania (PH) was first described by Sjaastad and Dale and called ‘chronic PH’ 2 years later. The current International Classification of Headache Disorders (ICHD-II) classification criteria requires at least 20 attacks of severe unilateral orbital, supraorbital, or temporal pain, lasting 2–30 min, accompanied by ipsilateral cranial autonomic features such as ptosis, eyelid edema, conjunctival injection, lacrimation, nasal blockage, or rhinorrhea. Attacks usually have a frequency of above five a day, and respond completely to indomethacin. Since the initial description, more than 100 cases have been reported. It would be useful to study a large group of PH patients to establish a genetic component of this disorder, but its rarity will make this a challenge.

As the initial description, more than 100 cases have been described in the literature.

Epidemiology and Sex Distribution

PH is a rare syndrome and patients have been described in several countries. The incidence and prevalence of PH has been reported to be approximately 1–3% that of the cluster headache (CH), or approximately 1 in 50 000, although it may be even rarer. PH can begin at any age, but the mean age at onset is in the 30s.

PH has been considered to be predominantly a problem of females. Initially, the reported female: male ratio was 7:1, but in a subsequent review of 84 patients the female: male ratio was 2.36:1. The recent case series of 31 patients has not shown a female preponderance (M:F ratio ~ 1:1). This contrasts with CH where there is a clear male preponderance and is more similar to short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). The predominant view of PH as a female condition may arise from misdiagnosis of males with PH as CH.

Family History and Genetics

Migraine is typically described as a genetic headache disorder and mutations have been discovered in patients with familial hemiplegic migraine. A family history of CH and SUNCT has been reported. It would be useful to study a large group of PH patients to establish a genetic component of this disorder, but its rarity will make this a challenge.

Pathophysiology

The pathogenesis of PH is poorly understood in relation to other primary headaches, such as migraine. During acute attacks of PH, calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) are elevated. This release is likely to mark trigeminovascular and cranial parasympathetic activation, and is similar to that observed in CH. Trigeminal and autonomic activation seems a marker of trigeminal autonomic cephalalgias (TACs). The physiology of this system is relatively well described and a degree of cranial autonomic activation is a normal response to a cranial nociceptive input. Important information to understanding the TACs, and PH in particular comes with the application of functional imaging techniques to these conditions. In PH, posterior hypothalamic activation contralateral to the pain has been observed, in addition to the contralateral ventral midbrain, red nucleus, and the substantia nigra. Hypothalamic region activation has been also reported in CH, SUNCT and hemicrania continua (HC).

In the latter, the ventrolateral midbrain area is also activated. Whether this latter area holds the key to understanding the indomethacin effect in these syndromes remains one of the important questions for the next few years.

Indomethacin inhibits the production of nitric oxide (NO) by endothelial and inducible NO synthase. A recent animal study also shows that indomethacin inhibits NO-induced dural vasodilation, whereas other cyclooxygenase (COX) inhibitors, such as naproxen and ibuprofen, do not. The role of NO in PH is yet to be fully elucidated.

Clinical Features

Typically, the pain is in the ophthalmic division of the trigeminal nerve, but it can widely occur in the head. The pain is strictly unilateral, although side shift may occur. Lacrimation, nasal congestion, conjunctival injection, and rhinorrhea are the most frequent symptoms and signs accompanying the attack. Yet, a wider range of autonomic features have been reported. Attacks occur several times per day, with a mean of 11 and median duration of 19 min in one large case series.

In one study, 65% of patients had phonophobia and photophobia, and 39% patients had nausea or vomiting during the attacks, or both; phonophobia was unilateral in 25% of patients and photophobia was unilateral in 40%. In addition, 80% of patients were agitated or restless, or both during the attack.

Triggers

The majority of attacks are spontaneous, and just 10% may be precipitated mechanically, either by bending or by rotating the head. An external pressure against the transverse processes of C4–5, C2 root, or the greater occipital nerve are said to trigger the attacks. Alcohol intake triggers pain in approximately one-fifth of patients, whereas menstruation does not seem to be an important and consistent trigger and the possible role of pregnancy has not been documented.
Subtypes

PH exists in episodic and chronic forms. In the episodic form attacks occur in periods lasting from 7 days to 1 year, separated by free periods lasting 1 month or longer. In the chronic form, attacks occur for more than 1 year without remission or with remission lasting less than 1 month. Approximately 20% of the patients have episodic form and the remaining 80% have chronic form. This is in clear contrast with CH where the pattern is reversed. The reason for this different pattern is not understood.

Differential Diagnosis of Paroxysmal Hemicrania

Secondary Paroxysmal Hemicrania

Probably as a result of publication bias, there are a number of case reports of symptomatic cases in the literature, though a causal relationship with the underlying structural lesion is uncertain in many cases. A diverse set of pathological processes has been suggested to cause symptomatic PH.

Headache is a frequent symptom of pituitary disease. In the largest clinicopathological study of pituitary tumors and headache in 84 patients, 5% had SUNCT whereas 4% had CH. Functioning rather than nonfunctioning adenomas were more likely to be associated with TACs. However, it is unknown whether the prevalence of pituitary tumors is higher in TACs patients, as no prospective community-based study has been performed to address this issue.

Several hypotheses have been put forward to explain the association between pituitary adenomas and TACs syndromes. First, these tumors may have a mechanical effect. Second, an increased intrasellar pressure may play a role in the genesis of the pain.

Finally, it has been suggested that the pathogenesis of the attacks is mainly neurohormonally mediated rather than by the size or invasiveness of the tumor. A volume effect seems unlikely as the presentation and disability associated with pituitary tumor-related headaches is unrelated to their size.

Differential Diagnosis between Paroxysmal Hemicrania and Other Primary Headaches

The main differential diagnoses include: (1) CH, (2) SUNCT syndrome, (3) trigeminal neuralgia (first division), and (4) HC when PH occurs with interictal pain.

Differential diagnosis between paroxysmal hemicrania and cluster headache

There is an important overlap in the clinical phenotype of PH and CH. Both conditions are strictly unilateral, relatively brief, frequent headaches that occur in association with ipsilateral cranial autonomic features. Mistaking PH for CH is problematic as, normally, treatments for CH are not very effective in PH. At present, the absolute response to indomethacin is the only crucial factor that permits a distinction between these two conditions. Nevertheless, there are useful clinical characteristics that help during the differential diagnosis between PH and CH. In contrast to CH, PH is typically characterized by (1) shorter duration and (2) a high frequency of attacks. In contrast to PH, CH is characterized by the presence of (1) often strictly circadian and circannual periodicity and (2) alcohol as the typical precipitating factor within 1 h in 90% of patients during their cluster bouts.

Differential diagnosis between paroxysmal hemicrania and SUNCT

PH differs from SUNCT syndrome in (1) attack duration, (2) temporal distribution of the attacks, and (3) precipitating factors. SUNCT attacks are typically shorter with a range between 5 s and 240 s. However, longer attacks can occur, with 600 s of the so-called saw-tooth pattern having been recorded in the largest case series reported. Additionally, in SUNCT the attacks are described as single stabs, a group of stabs, or long attacks with a ‘saw-tooth’ pattern of stabs between which the pain would not return to the baseline. Most SUNCT attacks have cutaneous triggers such as touching the face or scalp, washing, shaving, eating, brushing the teeth, talking, and coughing. In contrast, most PH attacks are spontaneous, and are longer than the stabs of SUNCT.

Differential diagnosis between paroxysmal hemicrania and trigeminal neuralgia

First division of trigeminal neuralgia attacks last for 5–10 s, with durations longer than 30 s being very rare. The attacks are never accompanied by prominent conjunctival injection, although slight lacrimation may infrequently be noted. Trigeminal neuralgia attacks are typically precipitated by trivial cutaneous stimuli on the trigeminal territory, whereas this does not occur in PH.

Differential diagnosis between paroxysmal hemicrania with interictal pain and hemicrania continua

The differential diagnosis between PH with interictal pain and HC can be difficult and a headache diary is very useful during the diagnostic workup, as it can provide important information regarding the temporal aspects of the pain. Some clinical features can help. First, the background pain in HC is typically moderate, although severe and very severe pain can also occur, whereas interictal pain in PH is generally less severe. Second, painful exacerbations in HC are long lasting, usually several hours, whereas those in PH are short lasting, typically a few minutes to 1 h. Third, the severity of pain during exacerbations is often moderate or severe in HC, whereas in PH it is excruciating. In general, a careful history supplemented with a headache diary help to differentiate one from the other (Table 1).

Diagnosis and Investigations

A good clinical history with the employment of headache diary, a detailed neurological examination, and therapeutic trial of indomethacin are necessary to make a diagnosis of PH. A brain magnetic resonance imaging (MRI) scan is a sensible screening investigation to be performed routinely.
Table 1  Comparison based on large cohorts of PH, CH, SUNCT/SUNA, and HC described in the literature

<table>
<thead>
<tr>
<th>Sex</th>
<th>PH</th>
<th>CH</th>
<th>SUNCT/SUNA</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>M=F</td>
<td>3 M to 1 F</td>
<td>1.5 M to 1 F</td>
<td>11 M to 1.6 F</td>
<td></td>
</tr>
</tbody>
</table>

Pain
- Quality
  - Sharp/stab/throb
- Severity
  - Very severe
- Distribution
  - V1>C2>V2>V3

Attacks
- Frequency (days)
  - 11
- Length (min)
  - 2–50

Triggers
- Alcohol
  - +
- Nitroglycerin
  - +
- Cutaneous
  - –

Agitation/restlessness (%)
- 80:
- 90:

Episodic versus chronic
- 35:65
- 90:10

Treatment effects
- Oxygen
  - No effect
- Sumatriptan 6 mg
  - 20%
- Indomethacin
  - 100%


Abbreviations: C, cervical; CH, cluster headache; HC, hemicrania continua; PH, paroxysmal hemicranias; SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; V, trigeminal.


Natural History and Prognosis

As PH is a relatively recently described syndrome, there is a paucity of literature on its natural history and long-term prognosis. The available evidence suggests that it is a lifelong condition with a mean duration of illness of 13.3 ± 12.2 years, although episodic PH can transform into chronic PH and vice versa, and long-lasting remission can occur. Patients typically do not develop tachyphylaxis to indomethacin. Indomethacin does not seem to alter the condition in the long term, though a significant proportion of patients can decrease the dose of indomethacin required to maintain a pain-free state over time.

Treatment

The ICHD-II criteria require an absolute response to indomethacin. The indomethacin test can be performed in two different ways: the oral trial or a placebo-controlled indomethacin test. The mean daily dosage is 100 mg with a range of 25–300 mg. However, some patients need only 12.5 mg per day. Dosage adjustment may be necessary to address the clinical fluctuation seen in PH. Daily dosing of indomethacin for a long period may be troublesome mainly due to gastrointestinal adverse effects. The parenteral trial consists of single-blind administration of 100 or 200 mg, or both and placebo. It has been suggested that placebo-controlled may be the gold standard, when applied.

There are no controlled trial options for the management of PH when indomethacin cannot be tolerated. There has been limited success reported with the use COX-2 inhibitors. However, the prolonged use of these agents has been linked to an increased risk of myocardial infarction and strokes that led to the worldwide withdrawal of rofecoxib from the market. For that reason, the available COX-2 inhibitors should be prescribed with caution in this condition. Topiramate and verapamil have both been reported to be useful in several case reports.

Most PH attacks are short and therefore there is no indication for acute therapy. With longer attacks, both response and lack of response to sumatriptan have been reported. Greater occipital nerve block with lidocaine and methylprednisolone has a positive effect in some patients.

Conclusion

PH is a rare primary headache that belongs to the group of TACs, which are headaches characterized by unilateral headache associated with prominent cranial autonomic features such as lacrimation, conjunctival injection, or nasal symptoms. TACs include CH, PH, and SUNCT/short-lasting...
unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). PH has intermediate duration and intermediate attack frequency in comparison with other TAC headaches. PH is a treatable and severe primary condition that can be very rewarding to diagnose and treat.


Further Reading

Cohen AS, Matharu MS, and Goadsby PJ (2006b) Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA) – a prospective clinical study of SUNCT and SUNA. Brain 129: 2746–2760.


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