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EPISODIC PAROXYSMAL HEMICRANIA WITH SEASONAL VARIATION

Case report and the EPH-cluster headache continuum hypothesis

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ABSTRACT - Episodic paroxysmal hemicrania (EPH) is a rare disorder characterized by frequent, daily attacks of short-lived, unilateral headache with accompanying ipsilateral autonomic features. EPH has attack periods which last weeks to months separated by remission intervals lasting months to years, however, a seasonal variation has never been reported in EPH. We report a new case of EPH with a clear seasonal pattern: a 32-year-old woman with a right-sided headache for 17 years. Pain occurred with a seasonal variation, with bouts lasting one month (usually in the first months of the year) and remission periods lasting around 11 months. During these periods she had headache from three to five times per day, lasting from 15 to 30 minutes, without any particular period preference. There were no precipitating or aggravating factors. Tearing and conjunctival injection accompanied ipsilaterally the pain. Previous treatments provided no pain relief. She completely responded to indomethacin 75 mg daily. After three years, the pain recurred with longer attack duration and was just relieved with prednisone. We also propose a new hypothesis: the EPH-cluster headache continuum.

KEY WORDS: episodic paroxysmal hemicrania, chronobiological dysfunction, EPH-cluster headache continuum.

Hemicrânia paroxística episódica com variação sazonal: relato de caso e hipótese do continuum HPE-cefaléia em salvas

RESUMO - A hemicrânia paroxística episódica (HPE) é um tipo raro de cefaléia em que ocorrem breves episódios de intensa cefaléia hemicrânica, recorrendo várias vezes por dia e acompanhada de sinais autonômicos ipsilaterais. Estas dores se repetem, em geral, por períodos sintomáticos que duram de semanas a meses, separados por intervalos assintomáticos de meses a anos; no entanto, uma variação sazonal nunca foi relatada nesses casos. Descreveremos um caso de HPE com um nítido padrão sazonal. Trata-se de mulher de 32 anos, que referia dor hemicrânica à direita, mas principalmente periorbitária, em queimação, há 17 anos. A dor sempre ocorria durante 1 mês e com intervalos assintomáticos de 11 meses. Durante períodos sintomáticos a dor ocorria de 3 a 5 vezes por dia, com duração de 15 a 30 minutos, sem horário preferencial. Em 30% dos ataques apresentava lacrimejamento e congestão conjuntival. Não havia fatores desencadeantes ou de piora. No momento do exame, a paciente queixava-se da dor há 20 dias. O exame neurológico era normal. A tomografia de crânio, normal. Após a introdução de indometacina a paciente referiu desaparecimento da dor em 48 horas. Após três anos, a dor recorreu com duração mais longa e foi aliviada apenas com prednisona. Também propomos uma hipótese: o continuum EPH-cefaléia em salvas.

PALAVRAS-CHAVE: hemicrania paroxística episódica, disfunção cronobiológica, continuum HPE-cefaléia em salvas.

Episodic paroxysmal hemicrania (EPH) is a rare disorder characterized by frequent, daily attacks of short-lived, unilateral headache with accompanying ipsilateral autonomic features. These headaches occur, in general, for many years until they are diagnosed and treated. EPH distinguishes from chronic paroxysmal hemicrania (CPH) by its temporal profile: EPH has attack periods, which last weeks to months separated, by remission intervals lasting months to years whereas CPH occurs without remission periods.

We report a new case of EPH with a clear seasonal pattern and propose a new hypothesis: the EPH-cluster headache continuum.

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CASE

A 32-year-old woman complained of a strictly right-sided headache, mainly periorbital, burning type, for 17 years. Pain occurred with a seasonal variation, with bouts lasting one month (usually in the first months of the year) and remission periods lasting around 11 months. During these periods she had headache from three to five times per day, lasting from 15 to 30 minutes, without any particular period preference. There were no precipitating or aggravating factors. In one third of the attacks she had tearing and conjunctival injection ipsilaterally to the pain. Previous treatments with ergotamine, diazepam, flunarizine and carbamazepine provided no relief. Her neurological examination and CT scan of the brain were normal. After she started Indomethacin 75 mg daily she had complete remission in 48 hours. After three years, the pain recurred. At this time, it lasted around 30 minutes, occurring three times a day. No relief was experienced with indomethacin but treatment with prednisone resulted in an improvement.

DISCUSSION

EPH is a rare primary headache, described first by Kudrow, Esperanza and Vijayan in 1987[1], who also have named it. It is characterized by unilateral pain attacks in the orbital, supra-orbital or temporal region, between 1 to 30 minutes duration and severe intensity. It is accompanied by the ipsilateral autonomic symptoms such as conjunctival injection, tearing, nasal congestion, rhinorrhea, ptosis and palpebral edema. The pain occurs in a frequency of over 3 times a day (in general, 3 to 30 episodes). These periods last from some weeks to months and between them there are asymptomatic intervals lasting from months to years, in a similar pattern to episodic cluster headache[2]. The pain is described as throbbing or stabbing. It occurs in both sex, with a slight female preponderance (1,3:1), different from the female predominance seen in CPH cases (3:1)[3]. The age of onset varies from 12 to 51 years[4]. There were 23 cases reported of EPH at the time of writing (Table 1).

Our patient had a clear seasonal variation; her headache bouts lasted for one month, and usually occurred in January, February or March, consistently for 17 years. This is the first EPH case with a clear seasonal variation.

Table 1. Summary of EPH reported cases.

Case	Reference	Sex	Age	Age at onset	Daily attack frequency	Duration of individual attacks (min)	Duration of headache phase (months)	Duration of remission phase (months)
1	(1)	F	38	12	8-20	10-15	1	4-6
2		F	84	51	3-6	15-20	3-4	3-6
3		F	30	21	14-15	5-15	2-4	24
4		M	49	14	6-8	20-30	1	3-5
5		M	45	27	4-9	1-20	2	11
6		M	56	37	30	15	3-4	2-3
7	(17)	M	52	18	20	10-30	1-2	1,5-5
8	(18)	M	29	26	30	20	1-3	1-3
9	(19)	M	59	42	10	5-10	1	1-4
10	(20)	F	40	16	20	10-20	3-3,5	3-36
11	(2)	F	54	48	10-20	2-3	1	3-4
12		F	28	25	15-20	15-30	1	3
13	(15)	F	48	44	5-10	15	0,75	0,75
14		F	23	19	5-10	3	0,25	0,75
15		F	35	33	5-15	10	0,75	5,5
16		M	37	25	3-6	15	0,50	3
17		F	25	23	2-6	5	0,25	0,50
18		M	42	20	15-20	15	0,50	2
19	(6)	M	63	34	4-12	10-15	2	4
20		F	58	54	7-20	10	0,75	2
21		M	39	10	5	15	4,5	0,75
22		F	35	27	3-5	1-2	6	10-12
23	Veloso et al.	F	32	15	3-5	15-30	1	11

Table 2. Criteria proposed to paroxysmal hemicrania.

Chronic Paroxysmal Hemicrania

Diagnostic criteria:

A. At least 30 attacks fulfilling B-E
B. Attacks of severe unilateral orbital, supraorbital and/or temporal pain always on the same side lasting 2-45 min
C. Attack frequency above 5 a day for more than half the time (periods with lower frequency may occur)
D. Pain is associated with at least one of the following sign/symptoms on the pain side:
   1. Conjunctival injection
   2. Lacrimation
   3. Nasal congestion
   4. Rhinorrhea
   5. Ptosis
   6. Eyelid oedema
E. At least one of the following:
   1. There is no suggestion of one the disorders listed in groups 5-11
   2. Such a disorder is suggested but excluded by appropriate investigations
   3. Such a disorder is present, but the first headache attacks do not occur in close temporal relation to the disorder.

Note: most cases respond rapidly and absolutely to indomethacin (usually in doses of 150mg/day or less)

Episodic Paroxysmal Hemicrania

Diagnostic criteria:

A. At least 30 attacks fulfilling B-F
B. Attacks of severe unilateral orbital or temporal, or both, that is always unilateral and last 1-30 min
C. Attack frequency of 3 or more a day
D. Clear intervals between bouts of attacks that may last from months to years
E. Pain is associated with at least one of the following sign or symptoms on the painful side
   1. Conjunctival injection
   2. Lacrimation
   3. Nasal congestion
   4. Rhinorrhea
   5. Ptosis
   6. Eyelid oedema
F. At least one of the following:
   1. There is no suggestion of one the disorders listed in groups 5-11
   2. Such a disorder is suggested but excluded by appropriate investigations
   3. Such a disorder is present, but the first headache attacks do not occur in close temporal relation to the disorder.

Note: most cases respond rapidly and absolutely to indomethacin (usually 150mg/day or less)

Sjaastad suggested EPH could be a remittent form of CPH, but not a separate clinical entity[5]. It is likely that EPH and CPH are ends of a spectrum just as episodic and chronic cluster headache[4]. It would range from a form with alternating active and inactive periods (EPH), to another without asymptomatic periods (CPH) A continuous form evolving from the remitting course could also occur[6].

The International Headache Society (IHS) classification does not include EPH, but CPH is mentioned as a variant of cluster headache. Goadsby and Lipton[4] proposed diagnostic criteria (Table 2) for chronic and episodic paroxysmal hemicrania using the structure of the cluster headache criteria as a model[4]. Our patient met those criteria.

EPH could be considered as one of the trigemino autonomic cephalgias, therefore it could share the same mechanisms[4]. In this particular case, the seasonal variation presented by the patient suggests the role of hypothalamus in the pathophysiology of EPH, particularly the biological clock (suprachiasmatic nuclei) and the involvement of melatonin secretion.

Melatonin is the most sensitive surrogate marker of circadian function in humans, and its rhythmic secretion is under the control of the hypothalamus[7]. Melatonin secretion is marked influenced by seasonal changes in the light-dark cycle and plays a role in the effects of season on animal physiology and behavior[8]. Decreased melatonin levels have been reported in cluster headache patients (9,10) and me-

latonin has been used for the prophylactic treatment of cluster headache[11]. Melatonin has been shown to play a role in cluster headache circannual variation[12] and it may play a role in EPH seasonal variation as well. Indomethacin and melatonin have a similar structural formula[13], so indomethacin responsiveness could be related to melatonin's biological activity.

The circannual variation of the attacks in EPH has to be studied prospectively in order to support a possible chronobiological dysfunction in this type of headache. Further functional neuroimaging studies could also support a hypothalamic involvement in EPH. Indomethacin is the first choice treatment for cases of EPH. The initial dosage recommended is 75 mg per day. This dosage should be kept for 2 days. If there is no response, the dose has to be increased up to 250 mg a day. The medication brings often a fast response, occurring generally in the first 48 hours. The absence of response after 3 days of this treatment weakens the diagnosis of EPH. In a study by Pareja and Sjaastad, indomethacin produced a total relief of pain in the first 24 hours in almost all patients[14]. In general, the treatment is kept for a time that is slightly over the symptomatic periods of patient, and then it starts a gradual withdrawal[6].

Other drugs such as aspirin, naproxen, ibuprofen, paracetamol, mefenamic acid and corticosteroids were tested without success[2]. There are reports of improvement with calcium channel blockers, mainly with flunarizine and nicardipine[15]. A CPH case responsive to celecoxib was recently reported[16]. This new nonsteroidal anti-inflammatory drug could be an alternative treatment, although it has never been proved to be effective in EPH. The IHS considers the response to indomethacin as a criterion for the diagnosis of CPH but there is no mention to EPH. Definitive classification and diagnostic criteria is still lacking for EPH.

The main differential diagnosis of EPH is episodic cluster headache, although rare intracranial lesions that can simulate EPH have to be excluded[6]. Cluster headache differs from EPH because the shorter duration, higher daily frequency and an absolute response to indomethacin in EPH (although, the latter is not considered as a good criterion for some authors[4]. Besides that, cluster headache has a remarkable predominance in men, something that does not occur in EPH. Both present the same temporal profile with symptomatic periods of multiple attacks of strictly unilateral headaches of short duration with ipsilateral autonomic symptoms, separated by asymptomatic periods. In general, as the attack frequency increases above 4 to 5 painful episodes per day and the duration of these decreases below 30 minutes, the diagnosis of EPH becomes more likely[6]. There is an overlap between EPH and cluster headache diagnostic criteria: the range from 15 to 30 minutes in the headache duration and the range from 3 to 8 attacks a day in headache frequency. Our patient latest symptomatic period had pains with duration around 30 minutes and frequency of 3 attacks a day, which is into these ranges. And as EPH and episodic cluster headache have many similar features, we hypothesized the existence of an EPH-cluster headache continuum. Further clinical studies and larger case series are necessary to support this hypothesis.

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