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Hemicrania continua: a clinical study of 39 patients with diagnostic implications

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Hemicrania continua is an uncommon primary headache disorder, characterized by continuous unilateral pain, where pain exacerbations are associated with cranial autonomic features. The hallmark of this condition is the absolute response to indometacin. We describe the phenotype of this condition in a large series of patients. Thirty-six (92%) patients had side-locked pain and 3 (8%) had side-alternating pain. The majority (82%) of the patients had the chronic (unremitting) form and the severity range of background pain was 1–10 out of 10 on verbal rating scale, with a mean of 6.5. Thirty-eight (97%) of the patients rated the painful exacerbations between 6.5 and 10 with a mean of 9 and 28 (71%) described their severe pain as excruciating. Of the cohort, 97% had at least one cranial autonomic feature during exacerbations: 73% had lacrimation, 51% nasal congestion, 46% conjunctival injection and 40% ptosis and facial flushing. Other cranial autonomic features included rhinorrhoea, forehead/facial sweating, itching eye, eyelid oedema, sense of aural fullness and periaural swelling, miosis, mydriasis and swelling of the cheek and face. Thirty-one (79%) had phonophobia, which was unilateral in 14 (48%); 29 (74%) had photophobia, which was unilateral in 14 (48%); and 27 (69%) had motion sensitivity. In addition, about two-thirds were agitated or restless, or both, and about one-quarter were aggressive, mainly verbally, with severe pain. All patients had a positive placebo-controlled indometacin test (100–200 mg intramuscularly) or a positive oral indometacin trial, or both. We suggest the International Headache Society criteria be revised to remove the absence of side-shift pain as a criterion. Furthermore, revised criteria should encompass a more extensive range of cranial autonomic features and consider pain as fluctuating with moderate, severe and very severe intensity. Currently the *sine qua non* for hemicrania continua is a response to indometacin. Since there is no reliable clinical marker of that response, we recommend an indometacin test, either orally or by injection, for any patient with unilateral pain, with or without cranial autonomic symptoms.

Keywords: hemicrania continua; primary headache; indometacin

Abbreviations: ICHD-II = the second edition of International Classification of Headache Disorders; SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

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Introduction

A response to indometacin was reported in a subset of 54 patients who were described as having cluster headache variants with strictly unilateral, continuous headache (Medina and Diamond, 1981). The disorder was subsequently named hemicrania continua (Sjaastad and Spierings, 1984) in a description of two patients: a female aged 63 years and a male aged 53 years, who developed a strictly unilateral pain that was continuous and completely responsive to indometacin. One year earlier a male, aged 49 years, was described with a history of over 20 years of unilateral pain, mainly localized on the left side, who had a dramatic response to indometacin (Boghen and Desaulniers, 1983).

Following the description by Sjaastad and Spierings (1984), over 100 cases of hemicrania continua have been described (Bordini *et al*., 1991; Newman *et al*., 1994; Pareja *et al*., 2001; Peres *et al*., 2001; Bigal *et al*., 2002; Wheeler, 2002; Klein *et al*., 2006; Marmura *et al*., 2009) and reported in different countries and races (Ishizaki *et al*., 2002; Wheeler, 2002). The relative rarity of the syndrome has prevented substantial cohorts being collected by one group over a period short enough to provide a broadly based prospective description of the syndrome. Moreover, the systematic requirement for an indometacin response is desirable in order to concentrate the biology of the cohort. Hemicrania continua was thus not included in the first International Headache Classification (Headache Classification Committee of The International Headache Society, 1988).

Hemicrania continua has been considered as one of the trigeminal autonomic cephalalgias because its phenotype, including the presence of prominent cranial autonomic features with worsenings of headache, seemed somewhat comparable to cluster headache and paroxysmal hemicrania (Goadsby and Lipton, 1997). The second edition of International Classification of Headache Disorders (ICHD-II) (Headache Classification Committee of The International Headache Society, 2004) includes hemicrania continua within the 'Other Primary Headache' disorders, defining it by the presence of unilateral continuous daily headache without side shift. The background pain is considered to be moderate in intensity, although there may be exacerbations of severe pain. During exacerbations there is at least one ipsilateral cranial autonomic symptom, such as conjunctival injection, lacrimation, nasal blockage, rhinorrhoea, ptosis or miosis.

The aim of this study was to describe, in detail, the clinical picture of hemicrania continua by systematically and prospectively assessing a substantial cohort. The paper presents the hitherto largest cohort of patients that shows clear indometacin effect and compares the patients to the current gold standard i.e. the second edition of the International Classification of Headache Disorders. The work has been reported in preliminary form at the 60th American Academy of Neurology (Chicago, USA, 12–19 April 2008, Cittadini *et al*., 2008*a*) and at the European Headache and Migraine Trust International Congress 2008 (London, UK, September 4–7, 2008, Cittadini *et al*., 2009).

Methods

Thirty-nine patients (mean age 51 years, range 31–79) with possible hemicrania continua were identified at the National Hospital for Neurology and Neurosurgery from 1995 to 2008 and attended the out-patients clinic between 2004 and 2008. The data used for this study were obtained from the clinical notes and information received on the telephone or by direct interview, or both. Patients were seen by at least two specialists in the out-patient clinic. In order to have a consistent basis for the clinical comparison, we ensured that, where possible, one researcher (E.C.) conducted a structured interview with every patient for data collection. Thirty-eight patients were interviewed; we used the medical notes for one case as it was not possible to contact the patient by telephone; this patient's history had been taken directly by one of the authors (P.J.G.).

Patients gave written consent for the telephone interview or oral consent during the clinical visit, or both. The study was approved by the National Hospital for Neurology and Neurosurgery Joint Research Ethics Committee.

Standard questions including side, site, type of pain, severity, duration, frequency and periodicity of exacerbations; presence or absence of autonomic features; possible factors that make the pain worse; possible factors that make the pain better and behaviour during severe pain were answered for each patient. The patients were asked to grade their pain on a numerical verbal rating scale from 0 to 10, where 0 represented no pain and 10 the most severe pain imaginable. The response to oral indometacin and the placebo-controlled indometacin test (Cittadini *et al*., 2008*b*) was assessed. Our standard oral trial consisted of 25 mg indometacin three times a day for 5–7 days, subsequently increasing, if ineffective, to 50 mg three times a day for a further 5–7 days and then, if ineffective, to 75 mg three times per day for 2 weeks. The parenteral administration of indometacin is consistent with single blind injection of 100 or 200 mg. Further, the glyceryl trinitrate challenge, evaluated in some patients as part of the diagnostic work-up, consisted of administration of 1.2 mg sublingually. In addition, the patients response to other medications, and personal and family history for headache were recorded. Neurological examination findings and neuroimaging reports were collected from the clinical notes.

The results were collected and summarized using Excel (Microsoft).

Results

Of 39 patients, 33 had hemicrania continua as defined by the International Headache Society (ICHD-II) (Headache Classification Committee of The International Headache Society, 2004), six patients had unilateral head pain responding absolutely to indometacin but not fulfilling the ICHD-II criteria. In detail, two patients (Patients 31 and 34) had side-alternating pain, one patient (Patient 18) had side-alternating pain with an itchy eye as cranial autonomic features, two patients (Patients 13 and 27) did not have cranial autonomic features with exacerbations of the pain and one patient (Patient 36) had moderate rather than severe pain with exacerbations. Based on the criteria of strictly unilateral pain and an indometacin response, these patients are included in the analysis and the case for widening the diagnostic criteria is made.

Clinical characteristics used by the ICHD-II to define hemicrania continua

Pain

Laterality

Eighteen patients (46%) had exclusively right-sided pain and 18 (46%) had exclusively left-sided pain. Three (8%) patients had side-alternating attacks and the frequency was as follows: in two patients (Patients 18 and 31) the pain was more frequent on the right side, whereas in the third patient (Patient 34) the pain was more frequent on the left side.

Duration of the pain

According to ICHD-II, patients need to have daily and continuous pain, without pain-free periods for >3 months. In our cohort, 38 (97%) patients met these criteria. One patient did not have daily and continuous pain for >3 months, reporting daily pain initially for 3 months, followed by pain 5 days/week, followed by either no pain or pain for 2 days/month.

Severity of the pain

The range of severity of background pain was between 1 and 10 out of 10 on the verbal rating scale with a mean of 5.8. One patient (Patient 36), had continuous pain, rated 3–4 out of 10 on the verbal rating scale without exacerbations of severe pain. Thirty-eight (97%) of the patients rated the exacerbations of severe pain between 6.5 and 10 out of 10 on the verbal rating scale with a mean of 9. Two patients (5%) had continuous pain with severity of 10. Sixteen patients (42%) rated the severe pain at 10. Three patients (8%) rated severe pain at 9. Six patients (16%) rated the severe pain between 9 and 10. Two patients (5%) rated the severe pain between 8 and 10. Two patients (5%) rated the severe pain between 8 and 9. One patient (3%) rated the severe pain at 8. Two patients (5%) rated the severe pain between 7 and 8. One patient rated the severe pain between 6 and 9. Three patients (8%) rated the severe pain between 6 and 7. Twenty-eight (71%) patients described their severe pain as excruciating and 19 (49%) patients said that this was the most painful condition they had ever experienced comparing it to childbirth, a broken bone, toothache and burned hands.

Cranial autonomic features

According to ICHD-II, patients with hemicrania continua are required to have at least one cranial autonomic feature during the exacerbations of the pain and a limited list of features has been suggested. Here, 37 (95%) of the patients had at least one autonomic feature during exacerbations of the pain. Some patients had bilateral cranial autonomic symptoms (Table 1), while some features found in the cohort are not in the current diagnostic criteria, including forehead/facial flushing, itching of the eye, eyelid oedema and a sense of aural fullness or swelling (Table 1).

Table 1 Associated cranial autonomic symptoms

Autonomic feature	*n* (%)
Lacrimation	27 (73)
Nasal congestion	19 (51)
Conjunctival injection	17 (46)
Ptosis	15 (40)
Forehead/facial flushing	15 (40)
Rhinorrhoea	14 (38)
Forehead/facial sweating	13 (35)
Itching eye	12 (32)
Eyelid oedema	7 (19)
Aural fullness	7 (19)
Aural swelling	6 (16)
Miosis	3 (8)
Mydriasis	2 (5)
Swelling of the cheek	2 (5)
Swelling of the face	1 (3)
Dripping sensation at the back of the throat	1 (3)

Indometacin response

The ICHD-II requires an absolute response to indometacin. In our cohort, 36 (92%) patients had a placebo-controlled indometacin test (Cittadini *et al*., 2008*b*). Out of these 36 patients, 32 (89%) had a positive response, which is defined as becoming pain free on active treatment, but not on the placebo. Of this group, 27 (84%) underwent a trial of oral indometacin that was positive, two cases had indometacin intolerance and therefore did not have an assessable response, and in three patients the trial was not initiated for the following reasons: one case had side-effects during indometacin test that included nausea, abdominal pain and feeling cold and two had gastrointestinal problems. Three (8%) patients only had the oral trial with indometacin, which was positive i.e. an absence of headache on indometacin (Fig. 1). The mean daily dose of indometacin used in the oral trial based on 32 patients was 176 mg (range 50–500 mg). The median dose was 175 mg/day. Of the remaining two patients: one patient (Patient 9) found 25–50 mg/month useful, after an initial period of 100 mg/day and then 25 mg/day every 2 days, the other case (Patient 23) found 100–150/day useful, taken not on a daily basis. Table 2 shows the daily effective dose for each patient.

Indometacin and side-effects

Side-effects during the indometacin test were documented in nine (25%) of the patients, including dizziness in six (66%) and nausea and/or vomiting in 5 (55%). Other side-effects, reported by one patient only for each, were: abdominal pain, paraesthesia, feeling cold, headache, tachycardia and breathlessness, light headedness, felling 'spaced-out' and feeling ill.

Side-effects during the oral trial were documented in 27 (75%) patients out of 36 who had the oral trial including. The side-effects included abdominal pain in 18 (66%), dizziness in 9 (33%), nausea and/or vomiting with diarrhoea in 3 (11%) and abdominal bloating in two patients (7%). Other side-effects reported by one patient only were: paraesthesia, a sedated feeling, gastric ulcer, headache, feeling strange, 'spaced out' and lightheaded, breast swelling and mastalgia, feeling unwell, lightheadedness, drowsiness and lightheaded, tiredness and lightheaded.

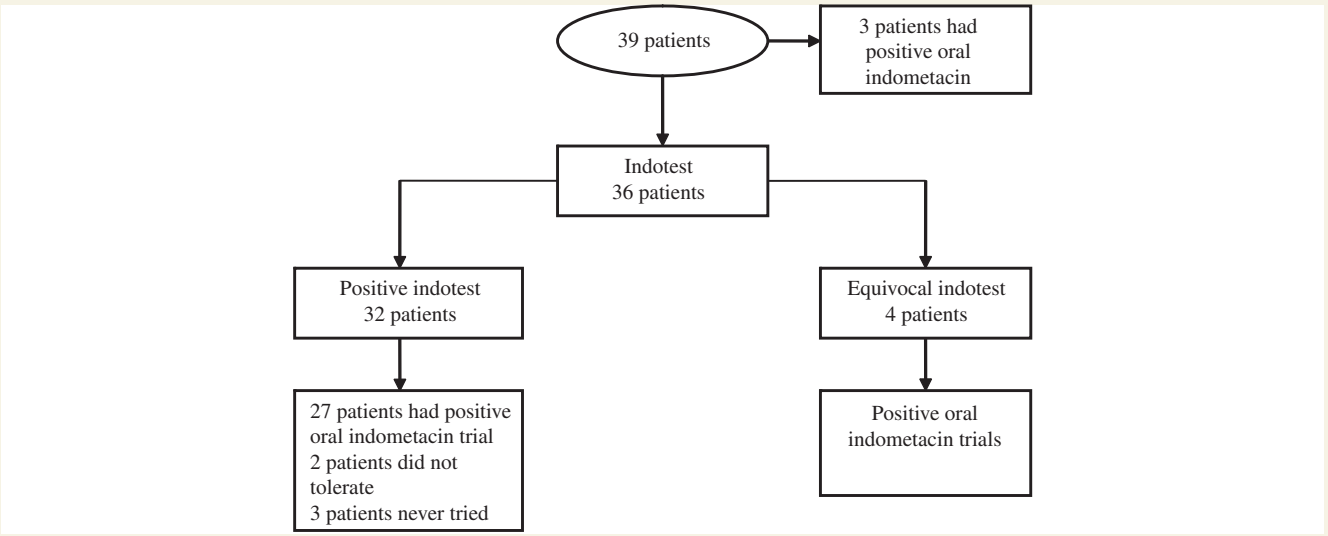

Figure 1 Flow chart of patients who had the placebo-controlled indometacin test (Cittadini *et al*., 2008*b*) and open label oral trials with indometacin.

Table 2 Effective dose of indometacin per day

Patient	Daily dose of indometacin (mg)	Patient	Daily dose of indometacin (mg)
1	225[a]	21	75
2	75	22	150
3	225	23	100–150[c]
4	Never taken	24	75[a]
5	150	25	225
6	Never taken	26	225
7	75	27	300–500
8	225	28	75–100
9	25–50[b]	29	225
10	150 per 3 days/week 300 per 4 days/week	30	150–200
11	150–200	31	150
12	150–300	32	225
13	225	33	300
14	225	34	225
15	100	35	75
16	225	36	75
17	150	37	Never taken
18	225	38	50–100–150–200
19	100	39	175
20	75		

a Indometacin stopped because of intolerance.
b Dose taken once per month.
c Dose taken less than daily.

Clinical features not currently used by the ICHD-II to define hemicrania continua

Age and gender of patients and duration of symptoms

Twenty-four were females and 15 were males (F:M ratio of ~1.6:1). The mean age at the onset of the symptoms was 38.7 years (range 10–67).

Site of the pain

In the cohort, the majority of the patients complained about pain over the temporal region 32 (82%), orbital region 26 (67%), frontal region 25 (64%), retro-orbital region 23 (59%), occipital region and parietal region 21 (54%), vertex and periorbital region 20 (51%), neck region 13 (33%) and the maxillary (second) division and ear in 12 (30%). Other areas affected are noted in Table 3.

Duration and frequency of exacerbations

Frequency of exacerbations

Exacerbations of severe pain were daily in 19 (49%) patients and anything between one and five times per week in 12 (31%). In the remaining group the exacerbations were reported as follows: in one case (Patient 1) the exacerbations were related to low atmospheric pressure; Patient 21 had 1–3 exacerbations per day; Patient 22 had one exacerbation per month; Patient 23 had between one exacerbation per week and one every 2–4 months; Patient 31 had one every 2 weeks; Patient 38 reported two patterns of exacerbations: a cycle lasting about 5 weeks during, which he had severe pain for 1 week and a second pattern during, which he could have several exacerbations (maximum 10) during the same day; and Patient 39 experienced between one exacerbation per week and one every 2 weeks. Patient 36 did not have exacerbations.

Length of exacerbation

There was a considerable variability in the length of exacerbations; between hours and days for the severe pain, which we have grouped as short, medium and prolonged. For shorter exacerbations, one patient each had exacerbations lasting between 30 and 60 min, 30 min to 3 h, 30 min to 4.5 h and 30 min to 48 h, respectively. Seven patients had medium length exacerbations: one patient between 1 and 9 h, three patients between 2 and 3 h, one between 2 and 5 h, one between 2 and 7 h and one between 3 and 4 h. For prolonged exacerbations, one patient had

Table 3 Site of attacks

Site	*n* (%)
Temporal region	32 (82)
Orbital region	26 (67)
Frontal region	25 (64)
Retro-orbital region	23 (59)
Occipital and parietal region	21 (54)
Vertex and periorbital region	20 (51)
Neck	13 (33)
V2 and ear	12 (30)
Upper teeth	8 (20)
Shoulder	7 (18)
Nose	6 (15)
Jaw	5 (13)
Eyebrow and lower teeth	4 (10)
Retro-auricular region	3 (8)
V3	2 (5)
Upper and lower gum	1 (2)
Nasal bridge	1 (2)
Below the jaw	1 (2)
Arm	1 (2)

Table 4 Characteristics of the pain

Characteristics	*n* (%)
Throbbing	27 (69)
Sharp	17 (43)
Constant/continuous	16 (41)
Pressure	12 (30)
Dull	10 (26)
Burning sensation	6 (15)
Aching	6 (15)
Stabbing	5 (13)
Boring	4 (10)
Toothache pain	2 (5)
Tearing	2 (5)
Stinging	2 (5)
Heavy sensation	2 (5)
Screaming	1 (2)
Tightening	1 (2)
Swelling sensation	1 (2)
Squeezing	1 (2)
Piercing	1 (2)
Hot sensation	1 (2)
Fluid sensation in the head	1 (2)
Electroshock sensation	1 (2)
Explosion sensation	1 (2)
Horrible/ferocious pain	1 (2)

exacerbations lasting between 3 and 24 h, one between 5 and 24 h, one between 10 and 24 h, one between 6 and 72 h, one between 24 h and 72 days, one between 24 h and 7 days, one between 48 and 72 h, one up to 48 h, four (10%) patients 24 h, and continuous daily severe pain in two (5%) patients. Patient 38 had a pattern of two headaches: one cycle lasting about 5 weeks during which he had severe pain for 1 week and a second pattern during which he could have several exacerbations (maximum 10) during the same day, each lasting 20 min. In Patient 36, there were no exacerbations of severe pain, six (15%) patients were unable to quantify the duration of severe pain and in Patient 8 the duration of severity was not quantified, although a clear diurnal variation was present during the day. In five patients the duration of severe pain was masked by the treatments.

Type of pain

The majority of the patients ($n = 27$, 69%) described their pain as throbbing and 17 (43%) referred to it as sharp. In 16 (41%) patients, the pain was reported as constant and continuous. Other types of pain are noted in Table 4.

Factors making the pain worse

Exacerbations of the pain could be either triggered or spontaneous. Commonly reported triggers were stress or relaxation after stress in 20 (51%) patients, and alcohol and irregular sleep in 15 (38%) patients. Data were available for 12 patients regarding the timing of worsening after the intake of alcohol: (i) within 10 min for one case; (ii) within 20–30 min for one case; (iii) within 30 min for four patients; (iv) within minutes for one case; (v) within 1 h for two cases; (vi) within 2–3 h for two cases; and (vii) within 10–20 min or 24 h later for one case, depending on the type of alcoholic beverage taken. Glyceryl trinitrate was evaluated in five patients and this triggered a typical exacerbation of severe pain for three patients in the following way: a typical exacerbation was reported in two cases and a typical exacerbation and migraine with mild severity was experienced in one patient. Interestingly, in the latter patient, the glyceryl trinitrate was administered again 90 min after the indometacin injection with no recurrence of pain. Furthermore, in the other two patients a different type of pain and no pain was reported, respectively. The range of triggers is noted in Table 5.

Factors making the pain better

We assessed possible factors, apart from indometacin, that could reduce the pain. Twenty-one patients (54%) reported pain-relief with the following measures: eight patients reported a partial benefit mainly with heat around the head and/or neck and/or by staying in a warm environment and (i) having a hot pad around the head; (ii) having heat on the neck and possibly the back; (iii) having a warm pad or fur scarf around the head; (iv) having heat over the forehead and/or head; (v) staying in a warm environment or neck massage; (vi) staying in a warm environment; (vii) staying in a warm environment or having a hot bath or neck movement; or (viii) staying in a warm environment or having a scarf around the face or putting some pressure over the ear. Two patients reported partial benefit by putting an ice pack on the head and a cold flannel over the top of the head, respectively. Two patients reported partial benefit putting pressure with their hands over their eyes and head, respectively. Seven patients reported partial benefit in the following positions: (i) lying down in two patients; (ii) lying down or sleeping in one patient; (iii) lying down, holding the head, having a hot pad on the head or drinking

Table 5 Factors making the pain worse

Characteristics	*n* (%)
Stress	20 (51)
Alcohol	15 (38)
Irregular sleep	15 (38)
Bright lights	14 (36)
Exercise	12 (31)
Warm environment	11 (28)
Neck movement	9 (23)
Skipping meal	9 (23)
Strong smell	6 (15)
Coughing	6 (15)
Sneezing	6 (15)
Weather change	5 (13)
Tiredness	5 (13)
Smoking environment	4 (10)
Period	4 (10)
Nitroglycerine	3[a] (60)
Bending down	3 (8)
Dehydration	3 (8)
Relaxation after stress	2 (5)
Straining	2 (5)
Bending forward	2 (5)
Cold wind	2 (5)
Cold weather	2 (5)
Chocolates	2 (5)
Low atmosphere pressure	1 (2)
Wind	1 (2)
Clearing throat	1 (2)
Look up	1 (2)
Straining eye	1 (2)
Lifting	1 (2)
Fluorescent lights	1 (2)
Talking to people (social events)	1 (2)
Long hours in front of personal computer	1 (2)
Orange juice	1 (2)
White spirit	1 (2)
Cheese	1 (2)

a Nitroglycerine used only in five patients.

an energy drink in another case; (iv) massaging or leaning the head on the same side of the pain in one case; (v) sitting down in a quiet environment in one case; and (vi) staying in an upright position in another. Two patients found partial benefit with relaxation and another found it useful to be physically and mentally active. Although a number of different procedures, manoeuvres and positions were tried by the patients none had a significant effect on the headache.

Agitation

Twenty-seven (69%) patients were agitated and/or restless and 11 (28%) were aggressive, mainly verbally rather than physically, with severe pain.

Migrainous symptoms

Thirty-one (79%) of our patients had phonophobia, which was unilateral in 15 (48%) patients. Out of these 31, 28 (90%) had personal history of migraine, family history for migraine, headache not otherwise specified, or both. Twenty-nine (74%) patients had photophobia, which was unilateral in 14 (48%) cases. Out of these 29 patients, 23 (79%) had a personal history of migraine, family history for migraine, headache not otherwise specified, or both. Motion sensitivity is a common symptom in migraine. We found 27 (69%) patients had motion sensitivity and 24 (88%) of these had a personal history of migraine, family history for migraine, headache not otherwise specified, or both. Nine (23%) patients had osmophobia and eight (88%) of them had a personal history of migraine, family history for migraine, headache not otherwise specified or both. Twenty-one (53%) patients in our cohort had nausea or vomiting during the attacks, or both. Eighteen (85%) of these patients also had a personal history of migraine, family history for migraine, headache not otherwise specified, or both. It seems likely, given the high population prevalence of migraine (Steiner *et al*., 2003) and data on the family history of migraine and headache severity (Stewart et al., 2006), that the most severe headache reported here in families was migraine, although familial hemicrania continua is an interesting alternative possibility.

Primary stabbing headache

Stabbing headache was present in 14 (36%) patients.

Circadian and circannual periodicity

There was no clear preponderance of nocturnal attacks, however, 21 (53%) patients reported exacerbations during the night time with a variable frequency and without a predictable occurrence. We did not find a strictly circadian periodicity, but a considerable individual variation in exacerbation periodicity. Sixteen patients (41%) experienced worsening of the pain during the day as follows: in the morning in six patients (37%), morning and evening in four patients (25%), early evening in one patient (6%) and evening in another patient (6%), afternoon in three patients (18%) (although in one of them the worsening was described as slight) and between late afternoon and early evening in another patient (6%). Patient 37 reported exacerbations that tended to occur not on a daily basis but more frequently at certain times of the day such as 6 a.m., 11 a.m. and 9 p.m. Patient 28 reported a clear circadian pattern during the chronic period of her hemicrania continua characterized by exacerbations that occurred every 3 h, notably at 9 a.m., 12 p.m., 3 p.m., 6 p.m. and occasionally at 9 p.m.

With regard to the circannual periodicity, we did not find a clear circannual pattern; however, Patient 25 experienced a worsening of his pain during the months of April and May. The patient had a headache history of 3 years and noted this trend in the last 2 years. Patient 34 reported worsening of pain during January, May, June, July, August, October, November and December. Patient 7 noted that his pain possibly worsened during the months of July and August.

Migraine and analgesic overuse

We assessed the relationship between the presence of migrainous biology and hemicrania continua and found that migraine or headache not otherwise specified, was present in the personal

history of 26 (66%) patients and in the family history of 24 (61%) patients.

We assessed the presence of medication overuse, defined by the use of analgesic on ≥15 days/month, and found that it was present at some point in 28 (72%) patients. The analgesics used were codeine and paracetamol (acetaminophen) combinations, dihydrocodeine and paracetamol combinations, aspirin–paracetamol–caffeine combinations, paracetamol–codeine–doxylamine–caffeine combinations, paracetamol–codeine–caffeine combinations, ibuprofen, diclofenac, meloxicam, paracetamol, dihydrocodeine, codeine, nefopam, caffeine, tramadol, pethidine, morphine and triptans, such as sumatriptan, rizatriptan, eletriptan and zolmitriptan. Of this group, 24 (86%) patients had positive personal history for headache not otherwise specified or migraine, or positive family history for headache not otherwise specified or migraine, or both.

At one point, medication withdrawal was attempted in 21 (75%) patients without any important change in the headache phenotype. Patient 27, who used the highest daily dose of indometacin, at one point developed bilateral pain that settled once indometacin was stopped. The patient had positive personal history for migraine.

Periodicity and chronicity of hemicrania continua

At present the ICHD-II does not provide criteria for the chronic and episodic forms of hemicrania continua. In general, hemicrania continua can be classified as episodic (remitting) or chronic (unremitting) depending on the presence of daily and continuous pain without pain-free periods. We labelled hemicrania continua as chronic when the pain was daily and continuous without pain-free periods for minimum of 1 year, and episodic when there were pain-free periods of at least a day without treatment.

Chronic form

Thirty-two patients (82%) had chronic (unremitting) hemicrania continua, which was chronic from the onset in 21 (69%) patients and evolved from episodic in nine (28%) patients. In the latter group, the interval from the onset of the disease to the chronic form was 7.9 years (range 2 weeks to 26 years). In the nine patients with an initial episodic form, the frequency of the pain was not daily in eight patients and ~10 days/month in one case. One patient with a current chronic form had an initial chronic phase lasting about 2 years followed by a remission period lasting a further 2 years. In the whole group, the mean duration of the chronic phase was 12.3 years (range 3–49 years). One patient (3%) was in remission for about 3 years at interview: he had an unremitting form at onset lasting 2 years.

Episodic form

Six (15%) patients had the episodic (remitting) form, which was episodic from the onset in two patients (33%) and evolved from a chronic form in four patients (66%). In the latter group, the interval between the onset of the disease to the episodic form was 18 months, 22 months, 60 months (5 years) and 84 months (7 years), respectively. The mean duration of episodic phase was 47 months (3.9 years; range 13–72 months). In these six patients, the frequency of the pain was quantified as: (i) pain-free or seldom painful; (ii) daily pain that could last anything between 4 and 12 months; (iii) pain for 2–3 days/week; (iv) pain for 4–5 days in a month; (v) first bout with daily pain lasting 18 months consistent with a chronic form and second one with daily pain lasting 1 month; and (vi) daily pain initially lasting 3 months, followed by 5 days/week, followed by either no pain or pain for 2 days/month. Moreover, two patients had a remission period time lasting 11 months and 12 months, respectively, and one patient reported two remission periods lasting ~10–11 and 24 months each.

Medication responses

Abortive treatments

In our cohort, 12 (30%) patients had oxygen with none having a good response. Eleven (28%) patients tried subcutaneous sumatriptan (6 mg), nine (23%) had sumatriptan tablets, five (13%) had sumatriptan nasal spray with no response in each group and one patient that tried sumatriptan tablets had an allergic reaction. Thirty-four patients (87%) had a non-steroidal anti-inflammatory drug other than indometacin with a good response in five (15%) and no response in 29 (85%; Table 6).

Prophylactic treatments

In the cohort, 34 (87%) patients had a preventive treatment in addition to indometacin. A number of patients tried a short-term treatment such as greater occipital nerve block, intravenous dihydroergotamine, intravenous aspirin, intravenous lidocaine and

Table 6 Responses to abortive medicines

Treatment	Patients *n*	Effective (%)	Ineffective (%)
Oxygen	12	0 (0)	12 (100)
Sumatriptan s.c.	11	0 (0)	11 (100)
Sumatriptan oral	9	0 (0)	8 (89)[a]
Sumatriptan nasal spray	5	0 (0)	5 (100)
Naratriptan	3	0 (0)	3 (100)
Rizatriptan	2	0 (0)	2 (100)
Eletriptan	1	0 (0)	1 (100)
Zolmitriptan oral	1	1 (100)	0 (0)
Non-steroidal anti-inflammatories	34	5 (15)	29 (85)
COX-2 inhibitors	14	2 (14)	12 (100)
Dihydroergotamine nasal spray	1	0 (0)	1 (100)
Dihydroergotamine oral	1	0 (0)	1 (100)
Dihydroergotamine suppository	1	0 (0)	1 (100)
Paracetamol	16	0 (0)	16 (100)
Co-codamol	7	1 (14)	6 (86)
Co-dydramol	6	0 (0)	3 (50)
Codeine	5	0 (0)	5 (100)
Lidocaine intranasal	2	0 (0)	2 (100)

a One patient had an allergic reaction.

Table 7 Prophylactic treatment responses

Treatments	Patients *n*	Effective (%)	Ineffective (%)
Short term			
Greater occipital nerve block	23[a]	8 (35)	13 (56)
IV aspirin	4	2 (50)	2 (50)
IV dihydroergotamine	3	1 (33)	2 (66)
IV lidocaine	1	0 (0)	1 (100)
IV caffeine	1	0 (0)	1 (100)
Long term			
Topiramate	12[b]	5 (41)	6 (50)
Valproate	10	0 (0)	10 (100)
Gabapentin	13	0 (0)	10 (100)
Verapamil	9	0 (0)	9 (100)
Propranolol	12	0 (0)	12 (100)
Amitriptyline	26[c]	0 (0)	24 (92)
Dothiepin	4	0 (0)	4 (100)
Methysergide	6	1 (16)	5 (84)
Pizotifen	10	0 (0)	10 (100)
Glucocorticoteroids	5	3 (60)	2 (40)
Lithium	5	0 (0)	5 (100)
Occipital nerve stimulation[d]	8		

a The outcome was equivocal in two cases.
b One patient stopped the drug shortly after due to side-effects.
c Outcome unclear in two cases.
d These data are available elsewhere (Burns *et al*., 2008).

intravenous caffeine. About one-third responded to greater occipital nerve injection. Eight patients (20%) underwent occipital nerve stimulation. The outcome of six patients has been recently reported and promising results suggest that occipital nerve stimulation is effective in this condition (Burns *et al*., 2008). The other treatments tried are outlined in Table 7.

Co-morbidities, examination and MRI findings

Nine patients (23%) had abnormal findings on neurological examination. These were mainly ipsilateral sensory changes consistent with (i) reduction in sensation to pinprick on the right side of the body; (ii) reduction in sensation to light-touch, pinprick and temperature on the left V1–V2–V3 and C2–C3; (iii) mild reduction in sensation to light touch, pinprick and temperature on the right V1–V2–V3; (iv) left V1 division trigeminal allodynia with reduction in sensation on light touch and increase in sensation on pinprick, right pupil slightly smaller and irregular compared to left one; (v) patch of subjective sensory change on the right cheek; (vi) decrement in sensation on the right in V1 and V2; (vii) left-sided hemiparesis and bilateral neural deafness in a patient with a past medical history of sensorineural deafness and cerebrovascular event; (viii) mild left lower motor facial weakness, mild decrement in sensation to light touch, pinprick and temperature on the left V2, hearing reduction in the left ear in a patient with a past medical history of Ramsay-Hunt syndrome and (ix) decrement in sensation to the pinprick to the left upper face.

In nine (23%) patients, the headache was classified as chronic post-traumatic type by definition of the onset of the pain in close temporal relation to head injury. The injuries were as follows:

(i) Head trauma associated with loss of consciousness in three patients.
(ii) Head trauma not associated with loss of consciousness in two cases.
(iii) Sinus operations characterized by sinus washout and left turbinectomy in one case and straightened nasal septum in another case.
(iv) Pituitary infarct in one case.
(v) Vitreous haemorrhage in one.

Brain imaging

Thirty-five (90%) patients had brain imaging, which included MRI or CT scan. Twenty-one (60%) patients had a normal intracranial appearance, while in 14 (40%) cases, radiological abnormalities were found. The majority of the findings were considered incidental (Table 8).

Discussion

We describe a substantial series of patients affected by unilateral, fluctuating head pain, typically associated with cranial autonomic symptoms during exacerbations, who are absolutely responsive to indometacin i.e. hemicrania continua. In contrast to current diagnostic criteria, we report side-alternating pain and rarely an absence of cranial autonomic features. The data show a wider range of cranial autonomic features during the painful exacerbations including forehead/facial flushing and sweating, eyelid oedema, itching eye, aural fullness and peri-aural swelling that need consideration. The data confirm the existence of both episodic and chronic forms, with the latter being the most typical presentation. Taken together, the findings suggest some revisions to the current diagnostic criteria (Table 9) and serve to define more completely the condition for clinicians.

Epidemiology

The incidence and prevalence of hemicrania continua is unknown. It was initially considered to be a very rare syndrome; however, the increasing number of patients identified in the headache subspecialty clinic suggested that this condition may be under diagnosed (Peres *et al*., 2001). On the other hand, using strict diagnostic criteria, the relatively small number of patients diagnosed over a period of 13 years given our referral base and interests, suggests this is a rare condition. The number of patients with unilateral chronic daily headache that were evaluated over the same period is unknown as we did not specifically look for this, although the senior author's cluster headache cohort by comparison over the same duration was more than one thousand patients. Only a large population-based study will properly address this issue. In our group the range of headache onset was between 10 and 67 years. Our findings confirm the existing literature that states this condition can begin at any age (Fragoso and

Table 8 Hemicrania continua and abnormal intracranial imaging

Patients	Abnormal intracranial imaging
1	A few non-specific subcortical white matter lesions and evidence of the previous left mastoidectomy.
2	Non-specific white matter lesions within both frontal lobes.
3	A few subcortical and paraventricular white matter non-specific signal abnormalities (Patient 4).
4	A very few non-specific T_2/fluid attenuated inversion recovery signal hyperintensities, mostly subcortical.
5	Asymmetrical large Meckels' caves are noted (the right is larger). Multilevel non-compressive degenerative cervical and upper thoracic disc-osteophyte bars are shown with mild narrowing of the right C4, C7 and C8 intervertebtal foramina.
6	Some opacification in the sphenoid and frontal sinuses and ethmoidal air cells consistent with inflammatory change.
7	Volume loss of both cerebral hemispheres. Periventricular low density in keeping with small vessel disease.
8	One non-specific small subcortical signal abnormality in the right superior operculum. Partial empty sella. Mild inflammatory changes in both mastoid air cells more on the left.
9	Cerebellar tonsils just protrude through the foramen magnum. Minor paranasal inflammatory sinus disease noted.
10	Well defined, diffusely enhancing extra axial mass lesion arising from the right sphenoid wing lateral of the right cavernous sinus. The appearance is that of a meningioma.
11	Lobular mucosal thickening present in all paranasal sinuses.
12	Right transparietal with its tip lying close to the posterior body of the corpus callosum. Some signal change and old blood products along the shunt track. Cyst-like lesion in the adjacent region of the corpus callosum, in keeping with a long-standing injury. The right superior temporal gyrus has a high T_2 signal and severely atrophied. The appearance is in keeping with an old ischaemic insult. There is bilateral peritrigonal white matter confluent signal abnormality. The pituitary gland shows convex upper border.
13	Evidence of small vessel disease.
14	Focal abnormality of the right parietal bone. The appearance is most keeping with reticular cell histiocytosis. The lesion was diagnosed as eosinophilic granuloma on excision biopsy.

Machado, 1998; Peres *et al*., 2001; Newman *et al*., 2004; Baldacci *et al*., 2008) but the mean age at onset is in the thirties. In the Vaga study (Sjaastad and Bakketeig, 2007) one patient had a clinical picture that resembled hemicrania continua, but the indometacin trial was not attempted to confirm the diagnosis. These data suggest that the prevalence of hemicrania continua may be no more than one in 1838; in effect a rare condition.

Sex distribution

A clear preponderance of females (5:1) was initially reported in the first 18 cases reviewed by Bordini and colleagues (1991), however, the female preponderance has decreased with more reported cases to 1.8:1 (Newman *et al*., 1994). In a study of 34 patients the female:male ratio was 2.4:1 (Peres *et al*., 2001). In our case series we found a small female preponderance, in line with the literature, although interestingly clearly less than is seen for migraine.

Laterality and severity of the pain

The International Headache Society (Headache Classification Committee of The International Headache Society, 2004) criteria require unilateral pain without side shift, however, four patients with pain that alternated sides (Newman *et al*., 1992, 2004; Marano *et al*., 1994; Baldacci *et al*., 2008) have been described. In addition, the side-alternating attack is not uncommon in the trigeminal autonomic cephalalgias that typically are considered side-locked unilateral syndromes (Manzoni *et al*., 1983; Bahra *et al*., 2002; Cohen *et al*., 2006; Cittadini *et al*., 2008*b*). In our series, three patients had side-shifting pain and we propose in the next revision of the diagnostic criteria that pain side shifting be allowed.

Among the primary headache syndromes, typically cluster headache is described as an excruciating syndrome and is often called 'suicide headache' (Torelli and Manzoni, 2003), although it is now reasonably established that other trigeminal autonomic cephalalgias such as paroxysmal hemicrania (Cittadini *et al*., 2008*b*), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA) (Cohen *et al*., 2006) are indeed often excruciating conditions. Hemicrania continua has been considered a syndrome with moderate intensity but with exacerbations of severe pain according to the current criteria (Headache Classification Committee of The International Headache Society, 2004). We found, in the majority of our patients, the range of the continuous pain was anything between 1 and 10 out of 10 on a verbal rating scale. In addition, 70% of patients described their painful exacerbations as excruciating and almost half of the patients considered them as the worst pain they had ever experienced with a severity of anything between 8 and 10 out of 10 on a verbal rating scale. These findings suggest that the pain in this condition, although typically fluctuating, is indeed more severe than previously considered. The data reinforce the need for rapid diagnosis and effective treatment to minimize unnecessary suffering.

Periodicity and chronicity of the pain

Current criteria for the diagnosis of hemicrania continua mandate daily and continuous pain, without pain-free periods for more than 3 months. Typically hemicrania continua is chronic with the episodic form being less common. The current classification (Headache Classification Committee of The International

Table 9 Diagnostic criteria for hemicrania continua

Current

4.7 Diagnostic criteria:
- (A) Headache for >3 months fulfilling criteria B–D
- (B) All of the following characteristics:
  - (1) unilateral pain without side shift
  - (2) daily and continuous, without pain-free periods
  - (3) moderate intensity, but with exacerbations of severe pain
- (C) At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain:
  - (1) ipsilateral conjunctival injection and/or lacrimation
  - (2) ipsilateral nasal congestion and/or rhinorrhoea
  - (3) ipsilateral miosis and/or ptosis
- (D) Complete response to therapeutic doses of indomethacin
- (E) Not attributed to another disorder

Proposed

4.7 Revised diagnostic criteria:
- (A) Headache occurring for >3 months fulfilling criteria B–D
- (B) Unilateral headache with moderate or greater severity
- (C) Headache is accompanied by either one of:
  - (1) one or more of the following cranial autonomic features occurs during exacerbations:
    - (i) ipsilateral conjunctival injection or lacrimation, or both
    - (ii) ipsilateral nasal congestion or rhinorrhoea, or both
    - (iii) ipsilateral miosis or ptosis, or both
    - (iv) ipsilateral eyelid oedema
    - (v) ipsilateral forehead and facial sweating
    - (vi) ipsilatreal forehead and facial flushing
    - (vii) ipsilateral sense of aural fullness or peri-aural swelling, or both
    - (viii) ipsilateral itching eye; or
  - (2) sense of restlessness or agitation, or aggravation of the pain with movement
- (D) Complete response to adequate[a] trial of indometacin
- (E) Not attributed to another disorder

a Adequate trial is defined as a period of time during which an appropriate oral dose of indometacin is administered. One approach is for indometacin to start at 25 mg three times a day for 5–7 days and subsequently increasing, if ineffective, to 50 three times a day for other 5–7 days and then, if ineffective, to 75 three times per day for 14 days. An alternative is the parenteral administration of indometacin 100 or 200 mg preferably single blinded with a dose of placebo by injection.

Headache Society, 2004) does not include criteria that indicate how to classify the chronic and episodic forms based on duration and frequency of the pain. Our data confirm that chronic hemicrania continua can arise *de novo* (primary chronic hemicrania continua), or evolve from the episodic subtype (secondary chronic hemicrania continua). In addition, episodic hemicrania continua can arise *de novo* (primary episodic form) or some patients can switch from the chronic to episodic form (secondary episodic). The majority of our patients had the primary chronic form, which is in line with the current literature (Peres *et al*., 2001). Twenty-four years after the naming of this syndrome, a clear classification is desirable for the two sub-forms. The crucial question is how to differentiate between them?

Considering other unilateral primary headaches syndromes, such as migraine and the trigeminal autonomic cephalalgias, there are two substantial ways to classify chronic and the episode subtypes. ICHD-II considers migraine chronic when the pain occurs on ≥15 days/month for >3 months. Trigeminal autonomic cephalalgias are described as chronic when attacks occur for >1 year without remission or with remissions that last <1 month, and episodic when periods last 7 days to 1 year separated by pain-free periods lasting 1 month or longer. One way to define the temporal profile of hemicrania continua is to adopt the trigeminal autonomic cephalalgias convention and consider time-free periods >1 year or longer. The question then is what is the minimum pain-free period required to make the chronic/episodic distinction? From our data there are two groups of patients: one group that experiences pain-free periods lasting between 1 day and several months, and another group that never have pain free periods without treatment. We suggest that the term chronic should apply to patients without pain-free periods for at least 1 year, and the term episodic to patients who have any pain free period longer than a day without treatment. The fact that the latter group has spontaneous pain free periods suggests a biological distinction from those who never have a pain free day for years. Interestingly, patients with either the chronic or episodic forms can have remission periods. Out of 33 patients, two with chronic hemicrania continua experienced remission periods at one point, while 3 of the 6 patients with episodic disease had a pain-free period at one point that could last up to a year. This is important to consider in any treatment strategy and suggests the need for long follow-up periods, particularly for device-based interventions. Furthermore the term 'remitting' may be more attractive to describe pain free periods, and might be considered.

Autonomic symptoms

By the current definition, patients with hemicrania continua are required to have at least one cranial autonomic feature with exacerbation of severe pain. This was also the case for cluster headache in the first classification (Headache Classification Committee of The International Headache Society, 1988) and was revised in ICHD-II (Headache Classification Committee of The International Headache Society, 2004) due to clinical experience. Lacrimation, nasal congestion, ptosis, conjunctival injection and rhinorrhoea are the most frequent signs accompanying the severe pain (Peres *et al*., 2001). In 90% of our patients, at least one of the autonomic features currently mandated was present. However, our cohort also reported a wider range of cranial autonomic features including facial flushing, facial sweating, itching eye, eyelid oedema, sense of aural fullness or swelling. In particular, one patient had only an itching eye. Itching eye, also described as sensation of sand or eyelash in the affected eye or ocular discomfort has been described as a typical symptom in patients with hemicrania continua (Bordini *et al*., 1991; Newman *et al*., 1994). In our experience this symptom is not specific to hemicrania continua, rather it is simply another cranial autonomic feature. The presence of a full range of cranial autonomic features typically reported in trigeminal autonomic cephalalgias (Cittadini *et al*., 2008*b*) suggest the importance of asking about them during the clinical interview, as they can be troublesome for some patients and diagnostically helpful. Interestingly, cranial autonomic features were not present in two patients of our series, otherwise typically responsive to indometacin. Absence of cranial autonomic features is recognized in about 3% of patients with cluster headache (Nappi *et al*., 1992; Bahra *et al*., 2002). Our data suggest both the consideration of a

broader range of cranial autonomic symptoms in the next revision of the ICHD, and recognition that cranial autonomic symptoms are not a *sine qua non* of the condition.

Site of the pain

The ICHD-II does not suggest specific site of the pain. The pain may be reported over the forehead, temporal, orbit and occipital region, although any part of the head or neck can be affected (Bordini *et al*., 1991). In our cohort, we found a similar widespread distribution and in addition involvement of the face. These data show that the pain does not have a strict distribution. The facial distribution may result in mis-diagnosis as a facial pain syndrome and this needs to be more widely known in specialty pain clinics.

Differential diagnosis

The differential diagnosis of long-lasting unilateral headache includes hemicrania continua, unilateral chronic migraine and new daily persistent headache, probably largely its migrainous sub-type (Goadsby and Boes, 2002); and the other trigeminal autonomic cephalalgias when they occur with background pain, notably paroxysmal hemicrania. Hemicrania continua can be differentiated from chronic migraine and new daily persistent headache by the positive response to indometacin (Goadsby and Boes, 2002). In addition, it has also been suggested that unilateral photophobia or phonophobia, or both, are more frequent in hemicrania continua and trigeminal autonomic cephalalgias such as cluster headache (Vingen *et al*., 1998; Irimia *et al*., 2008), paroxysmal hemicrania (Cittadini *et al*., 2008*b*; Irimia *et al*., 2008) and SUNCT/SUNA (Cohen *et al*., 2006; Irimia *et al*., 2008), than in migraine and new daily persistent headache (Irimia *et al*., 2008). In our cohort, unilateral photophobia and phonophobia were common, inline with other trigeminal autonomic cephalalgias. The presence of these unilateral symptoms is a clinically useful feature; however, further comparison studies between hemicrania continua and unilateral chronic migraine are needed to confirm the clinical utility of this observation.

The differential diagnosis between hemicrania continua and paroxysmal hemicrania with interictal pain can be difficult and certainly a headache diary is very useful in the evaluation. In our experience, hemicrania continua typically has less prominent cranial autonomic features than paroxysmal hemicrania; also the background pain in hemicrania continua is typically more severe than the interictal pain in paroxysmal hemicrania. In addition, painful exacerbations in hemicrania continua are long lasting, usually several hours and less frequent whereas those in paroxysmal hemicrania are short lasting, typically <1 h and occur many times a day. In general a careful history supplemented with a headache diary allows these two headache types to be differentiated.

Concomitant headache, migraine and bilateral pain

About two-thirds of our cohort had a personal history of migraine or headache, a positive family history of migraine or headache or both. It is likely that as migraine is common (Steiner *et al*., 2003), headaches not otherwise specified, but bothersome enough to be noted, were migraine (Tepper *et al*., 2004). Migraine is commonly seen in patients with other trigeminal autonomic cephalalgias, such as cluster headache (Bahra *et al*., 2002), paroxysmal hemicrania (Cittadini *et al*., 2008*b*) and SUNCT/SUNA (Cohen *et al*., 2006). Indeed in both cluster headache and paroxysmal hemicrania, inter-paroxysmal pain is typically seen where there is an intercurrent personal or family history of migraine. The high prevalence of migraine in our group may suggest a predisposition for primary headaches, that patients with a disabling headache seeking medical advice more often or perhaps reveals that the biological predisposition to migraine is more common than we have hitherto considered. Furthermore, patients with migraine (Wilkinson *et al*., 2001; Bahra *et al*., 2003), cluster headache (Paemeleire *et al*., 2006), paroxysmal hemicrania (Cittadini *et al*., 2008*b*) or SUNCT/SUNA (Cohen *et al*., 2006), and with underlying migraine biology, tend to dominate cohorts who develop medication overuse headache.

Further, medication overuse has been also reported in two patients with hemicrania continua (Young and Silberstein, 1993) and resolution of persistent, unilateral pain resembling hemicrania continua has been described following the cessation of medication overuse (Warner, 1997). Here 23 of 27 patients with medication overuse had migraine biology, although 21 of 27 patients who had once stopped medication overuse did not report any important change in the headache phenotype. In addition, it is worth noting that one patient on the highest indometacin dose developed bilateral pain that settled when the drug was withdrawn; the patient had positive history for migraine. These data suggest that high and daily use of indometacin can perhaps lead to medication overuse problems as already noted for other non-steroidal anti-inflammatories (Bigal *et al*., 2008*b*). It is unclear why in the group of patients with hemicrania continua, a subgroup is prone to develop bilateral headache typical of rebound headaches in a context of medication overuse problem, although this would be an interesting phenomenon to try and understand, and is likely to be genetically determined.

Behaviour

Typically patients with cluster headaches are agitated and restless (Torelli and Manzoni, 2003) and aggressive behaviour is often seen (Bahra *et al*., 2002). Recently, it has been reported that 62% of the patients with SUNCT were agitated during attacks (Cohen *et al*., 2006), 80% of the patients with paroxysmal hemicrania were agitated and/or restless and one-quarter were described as being aggressive during the pain (Cittadini *et al*., 2008*b*). Our findings here show that 69% of the patients were agitated or restless or both and that 28% were aggressive, mainly verbally, during the severe pain. However, the majority of the patients (69%) also reported exacerbation of the pain with motion during attacks. The prominent presence of these contrasting features seems quite unique to hemicrania continua. These data are consistent with the activations in the region of the posterior hypothalamic grey using functional imaging techniques in these conditions and add to the biological case for grouping

hemicrania continua with the trigeminal autonomic cephalalgias (Goadsby *et al*., 2008).

Family history and genetics

Family histories of hemicrania continua have not commonly been reported in the literature. Pareja and colleagues (1990) described a patient with episodic hemicrania continua who had a sister with hemicrania continua. Furthermore, in 1999 a case report describing occurrence of familial hemiplegic migraine and primary hemicrania continua, suggested a common pathophysiological link rather than chance, given the rarity of the conditions (Evers *et al*., 1999). Specific genetic studies have not been carried out in hemicrania continua and the rarity of this disorder will make this difficult.

Indometacin response

A response to indometacin is considered to be a *sine qua non* in hemicrania continua and we have adopted that position. We found that all patients (81%) who could tolerate oral indometacin had an absolute response to the oral trial. Interestingly, two patients found indometacin useful even when not taken daily. Some three-quarters of patients reported side-effects at some point, mainly gastrointestinal problems and dizziness, which may lead to a discontinuation of the medicine. In this context, where gastrointestinal side-effects have been a problem, employing a placebo-controlled indometacin test by injection was very helpful. In fact, only about a quarter of patients reported side-effects during the controlled indometacin test, mainly dizziness and nausea or vomiting, or both. A noteworthy limitation to the work here is that we have not systematically explored a dose–response relationship, particularly with lower doses. This would be an interesting question. In our cohort the majority of the patients (89%) had a positive test, which confirmed the diagnosis of hemicrania continua. We also assessed the response to high flow oxygen, which is typically positive in cluster headache (Cohen *et al*., 2009) and sumatriptan subcutaneously, which is usually positive in cluster headache and migraine (Lance and Goadsby, 2005). Open label use of subcutaneous sumatriptan (6 mg) has been reported to be ineffective in patients with hemicrania continua (Antonaci *et al*., 1998). In our cohort, all patients that underwent both oxygen and sumatriptan subcutaneously had a negative outcome. This would be consistent with hemicrania continua being a unique biological identity, and ideally, double-blind controlled studies would be undertaken to confirm our open label results.

Neurological examination and secondary headache

As a rule, patients with hemicrania continua tend to have normal neurological examinations. In our group, nine (23%) patients had abnormal findings on neurological examination, mainly with mild sensory changes. Two patients had an abnormal neurological examinations as well as a previous history of stroke, one had bilateral neural deafness and one had had Ramsay-Hunt syndrome. One patient had neuroimaging findings consistent with right sphenoid wing meningioma. The lesion was stable for several years and her pain switched from chronic pain to episodic at one point so we considered on balance that the lesion did not have a pathogenetic role. Probably as a result of publication bias, secondary hemicrania continua is relatively common in the literature in comparison to the primary variety, and can be caused by diverse pathological processes at various sites (Antonaci and Sjaastad, 1992; Rothbart, 1992; Brilla *et al*., 1998; D'Alessio *et al*., 2004; Levy *et al*., 2005; Rogalewski and Evers, 2005; Vikelis *et al*., 2005; Ashkenazi *et al*., 2007; Valenca *et al*., 2007; Prakash and Dholakia, 2008). Furthermore, four patients are described with post-traumatic hemicrania continua following head trauma (Lay and Newman, 1999). In our cohort, nine patients (23%) had post-traumatic hemicrania continua and in four (44%) of them there was sensory impairment possibly due to damage of the trigeminal nerve following the injury. These data highlight the importance of considering hemicrania continua in the differential of post-traumatic headache, as prompt treatment can relieve the problem.

Conclusions

We have described 39 patients affected by hemicrania continua characterizing the clinical picture of the disorder. Advantages of the study include that all patients have been seen by at least two clinicians with broad experience in headache, the cases have been seen contemporaneously and the clinical aspects have been described prospectively. A limitation of all hospital-based studies is the bias of referral; however, for such a rare condition there seems no other reasonable way to collect an appropriate cohort before a population-based study is executed. We have found the current International Headache Society classification overly restrictive (Headache Classification Committee of The International Headache Society, 2004), particularly the mandatory criteria of the absence of side-shifting pain and the occurrence of cranial autonomic features. Therefore, we propose changes based on this cohort and offer a nomenclature to classify the temporal pattern. We emphasize here the absolute response to indometacin as part of the diagnosis, and recommend the use of indometacin in all patients with unilateral pain syndromes either by injection or orally, providing there are no absolute contraindications. Furthermore, we suggest the placebo-controlled indometacin test to be the gold standard when applied, facilitating diagnosis and research. Interestingly, the majority of our cohort showed signs of agitation, or restlessness, or both, and nearly one-third were aggressive during severe pain, consistent with the neuroimaging findings of hemicrania continua, which suggest some important part of the pathophysiology occurs in the posterior region of the hypothalamus, as with the other trigeminal autonomic cephalalgias. Hemicrania continua is a treatable primary headache that, once diagnosed, responds well to management. Future studies may include a comparison between hemicrania continua and unilateral chronic migraine, to attempt to identify specific clinical markers that correlate with the response to indometacin.

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