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Chronic paroxysmal hemicrania, hemicrania continua and SUNCT: the fate of the three first described cases

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Abstract The first patient with chronic paroxysmal hemicrania has been followed for 45 years, and for 33 years with indomethacin treatment. The headache became less severe with time; there was no indomethacin tachyphylaxis. The first patient with SUNCT was followed for 28 years, until his demise at 89. Pain became worse with time. No adequate therapy was found. The first patient with Hemicrania continua was followed for 19 years, until her demise at 81. She was treated with indomethacin during the whole observation time. There was no tachyphylaxis. Both patients treated with indomethacin developed gastric ulcer. And both had gastric surgery. Indomethacin

therapy may be a life-long affair. The risk of gastric complications may be substantial.

Key words Chronic paroxysmal hemicrania • SUNCT syndrome • Hemicrania continua • Indomethacin • Horner's syndrome

Introduction

Chronic paroxysmal hemicrania (CPH) was first described in 1974 [1, 2], and SUNCT syndrome in 1977 [3, 4], whereas hemicrania continua was described in 1984 [5]. The first CPH patient was observed 13 years prior to the description. The total time of observation for the first patient with each of these headaches has been considerable (Table 1).

Contact has been kept with these patients, also in recent years, although generally on a more sporadic and distant basis. The development of their headaches is,

therefore, generally known. Two of these patients have died (SUNCT and hemicrania continua, see Table 1), while the CPH patient is still alive at 89 years of age.

It is time to try to sum up what lessons may be learned from these long-lasting observations.

Chronic paroxysmal hemicrania (CPH)

The CPH patient was a female, born in 1917. Attacks started at 35, just after delivery (Table 1). We were con-

Table 1 CPH, SUNCT, HC. Gross development

	CPH	SUNCT	Hemicrania continua
Birth	1917	1916	1920
Onset headache	1952	1946	1945
Age, onset	35	30	25
First consultation with us, age	44	61	62
Indomethacin from, age	56	–	62
Present age*/demise**, age	89*	89**	81**
Observation time, years	45	28	19
Total duration of headache, years	54	≤60	56

sulted in 1961 – at 44. There were up to ≥ 20 attacks per day of about 20 min duration at the peak of complaint. The complaints fluctuated markedly, but there was never a headache-free day. Attacks were always right-sided, and they were accompanied by local, autonomic phenomena (lacrimation etc.). She had herself, years prior to the first consultation with us, found that acetylsalicylic acid was of some use, and she took up to 6–8 g/day. During the period of acetylsalicylic acid consumption, she developed a gastric ulcer along the lesser curvature several times, and a Billroth II operation was carried out in 1968 for this reason.

It is striking how many surgical operations she has undergone. She was particularly interested in having assessed whether there were any organs on the right (symptomatic) side that ought to be dealt with, surgically. Molars in the upper jaw, symptomatic side, were removed. A benign tumour was removed from the right kidney. An artificial hip joint was implanted on the symptomatic side. And she, finally, had the gallbladder removed. But also midline organs were removed: a hysterectomy was carried out. And even organs on the non-symptomatic side were removed: bilateral ovariectomy was carried out, in a separate operation. Moreover, there is a renal cyst (hydronephrosis?; present for >40 years?) on the non-symptomatic side, for which surgery has been considered.

It is also worthy of note that originally minor ptosis/miosis seemed to be present, on the symptomatic side. Horner's syndrome was, therefore, suspected (also in other early patients). This suspicion was later annulled. In a collaboration with Professor Stephen Smith in London, a world authority on pupillometry, it was demonstrated that there is no Horner's syndrome in CPH (patient no. 1 was included in the study [6]).

The latter study should be noted, as there are many cases of a so-called Horner's syndrome in unilateral

headaches reported in the literature, without even an attempt to verify it. All such communications should be regarded with due suspicion.

Recent years

She has been medicated with indomethacin since 1973 – a period of 33 years. Indomethacin immediately removed her pain attacks entirely and permanently, provided the dosage was correct. She became a master in titrating the dosage according to the varying extent of her complaints. The indomethacin dosage usually varied between 25 and 50 mg/day; a 75 mg dosage was necessary to keep the pain at bay during the worst periods. During troughs, 25 mg every second day might do.

In recent years, she has only used indomethacin on attack days. When trying to adjust the dosage at the onset of an exacerbation, she could have more than just a hunch as regards the attack frequency. From such experiences, she has the clear impression that an improvement has taken place over the years, as regards the temporal pattern: the attacks became shorter, and there was a longer interval between attacks; there were rarely more than 1–2 attacks per day, and in recent months there have been up to three weeks between attacks. The attacks have become less severe. Nevertheless, attacks may still wake her up at night. She has not had a single “big attack” for more than a year and a half.

Attacks as such are still accompanied by lacrimation, conjunctival injection and rhinorrhoea. During all these years of pain freedom, she never noticed episodes of only autonomic features, i.e., solitary lacrimation, rhinorrhoea or conjunctival injection. We did not check for forehead sweating and arrhythmia on a subclinical scale during recent years. The pain was located in the same area, cen-

tring on the eye, but it was also felt in the forehead, temporal area, cheek and throat and down to the breast, all on the symptomatic side.

She has had three coronary infarctions in recent years. Blood pressure was 115/55. She presently suffers from heart disease and dyspepsia, in spite of taking drugs to reduce acid production. Dyspepsia is in all likelihood secondary to indomethacin medication.

She is nevertheless absolutely clear on two points: indomethacin has “saved her life”, and, there would be “no way” that she at any time would have relinquished indomethacin. Indomethacin has retained its effect after 33 years. There has been no tachyphylaxis. The intensity and duration of attacks in this patient have been reduced with time, and the interval between attacks has been drastically changed. But the disorder still persists after 54 years (Table 1). Dyspepsia and gastric ulcer have followed in the wake of acetylsalicylic acid and indomethacin medication. In spite of these setbacks, the medication could be continued until now.

SUNCT syndrome

The first patient (i.e., no. I [3]) was a male, born in 1916 (Table 1). Right-sided ocular/periorcular pain in 1–3-week long, biannual bouts started at around 30 years of age. In the early phase, there was usually a continuous, low-grade discomfort, with occasional minor exacerbation during the bouts. A decade or more later there was a transformation from the more continuous pain to paroxysms. This development seemed to have reached a plateau at the age of 58. There were then periods with attacks 6–9 months per year. The attack frequency ranged from 5 to 30 per hour, and the mean duration was

Table 2 Ocular variables in SUNCT and other unilateral headaches

Type of headache	Increment, symptomatic side, during attacks (%)	
	CIP ^a	Intraocular pressure
SUNCT ^b	138	60
CPH (<i>n</i> =7)	63	28
Cluster headache (<i>n</i> =18)	48	12
Hemicrania continua (<i>n</i> =2)	^c	No changes

^aCorneal indentation pulse amplitudes, see Refs [8, 10]

^bPresent patient: no. of solitary observations: 7

^cA questionable increase on the symptomatic side in one of the patients

15 s (range 10–60 s). During the worst periods, the pain was fairly intense, with nocturnal awakenings; otherwise, the pain seemed to be moderately intense. There was no restlessness during attacks. Attacks were accompanied by conjunctival injection, lacrimation and rhinorrhoea (and sub-clinical forehead sweating), all on the symptomatic side. Moreover, corneal indentation pulse (CIP) amplitudes and intraocular pressure increased markedly on the symptomatic side during attacks [8] (Table 2). There was also a clear asymmetry of forehead sweating during attacks (most marked on symptomatic side) [9]. Attacks could be precipitated by blowing the nose, extension and rotation of the head, brushing teeth, chewing (in particular sour apples) etc. No drugs, including those for trigeminal neuralgia, were found to be of any use.

The last years

General health

At 75, cancer of the prostate was detected. Its growth seems to have been slowed down by medication (Zoladux), but at 88, a spreading to the skeleton was verified, and – 4 months later – local pain started. At 87, a coronary by-pass operation was carried out. He recovered quickly from that. His demise at 89 years of age was due to an acute heart attack.

The headache

He always accepted, willingly, new investigations and new trials, his attitude being: this will probably not help me, but – maybe – those that come after me.

Various drugs were tried, none of them being effective [7]. At 75 years of age, he had amalgam totally removed from his teeth, and, simultaneously, two upper jaw molars (root-filled ones) were removed. He apparently felt better for the next two years, with more moderate pain and longer pain-free intervals. Thereafter, the pain attacks recurred with the same intensity as before. The last molar on the symptomatic side was removed at 87; and again there seemed to be a transitory improvement. The precipitation mechanisms in recent years were mainly neck movements, and the “beginning of chewing”. All in all, during the last 8–9 years, the attacks were severe, possibly even more so than previously. And “they were of longer duration than before”. Carbamazepine was continued until the end, in spite of the tendency to worsening of attacks. Attacks thus persisted until the end. There was thus no trend towards a late-stage amelioration. On the contrary, there seems to have been a deterioration. The case history probably

lasted close to 60 years and the prospective study 28 years (Table 1).

Hemicrania continua (HC)

The first patient (no. I [5]) was born in 1920. The strictly left-sided headache apparently started in 1945, at 25 years of age (Table 1). When first seen by us in 1983, she was 62 years old. The headache was continuous from the outset, and it was localised in the oculo-frontal and temporal areas. It was moderately intense, and there were only moderate fluctuations in the intensity. There were occasional, 1–3-s long jabs in the painful area. But there were no visible, localised, autonomic phenomena; the ocular variables showed no clear-cut abnormalities (Table 2).

For more than 30 years, she used up to 6 g acetylsalicylic acid per day, and that had taken away the top of the pain. Indomethacin was instituted in 1983 and took away the pain after 4–6 h, the effect being both complete and durable. The correct dosage seemed to be 75 mg; 50 mg did not quite suffice.

The last years

There had been mild, periodic, gastric distress through the years, on both acetylsalicylic acid and indomethacin medication. During a cold-season, durable stay in one of the southern European islands, at 66, she fainted in the bathroom during the night, due to a massive bleeding from a 2.5–3 cm wide ventricular ulcer. She was operated upon immediately to stop the bleeding (on a close to vital indication). It is worth mentioning that this happened the last night before a friend in the same flat was going to leave her alone.

The gastric distress, nevertheless, continued and later increased; it was only partially counteracted by cimetidine. The risk of continued indomethacin medication under these circumstances was carefully explained to her, but a certain stubbornness came to the fore: “if anyone dares to try to take away the indomethacin...” *She* was the one who had these pains and knew how they affected her. *No one* had the authority to give her absolute instructions. We felt that there were no means by which we could hinder her. The H₂ receptor antagonist, cimetidine, was replaced by omeprazol (Losec), 20 mg/day, as a safeguard, and gastroscopy was – according to plan – to be carried out every 6 months. As a consequence of the not quite so regular, but nevertheless mul-

tiple gastroscopies, a gastric ulcer was detected six years later; later a fibrin-covered ulcer was detected, and still later, diffuse gastritis, twice.

Because of these findings, a couple of times she agreed to reduce the indomethacin dosage (25 mg 1–2 times/day) and to live with a certain pain level (40%–60%). But, alas, she was back again on the regular dosage rather quickly. She had a short-lasting episode of transient global amnesia at 65.

During the period from 1995, at 75, until her demise in 2001, at 81, we mostly had indirect contact with her. The development from 1995 was as follows: the pain freedom on 75 mg indomethacin continued unabridged. There was no tachyphylaxis after 19 years of indomethacin usage.

She acquired (a) diffuse body pains (rheumatological expertise examination gave no indications for rheumatoid arthritis); (b) pyelonephritis (ESR:50 mm); (c) cancer cutis (basal cell carcinoma, left temporal region); (d) osteoporosis, with compression fracture at Th 12; (e) left-sided, marked hydronephrosis; (f) chronic, obstructive bronchitis and, finally (g) a low-grade, non-Hodgkin’s lymphoma with abdominal tumour and bone marrow infiltration. There was reduced general health condition, periodic fever (39°C) and anaemia (haemoglobin: 8.5 g/dl). During this last stage, she also had a left lower extremity vein thrombosis and was treated with warfarin (at 80). A cerebral CT from the last years was normal; X-ray of the cervical spine demonstrated uncovertebral arthrosis C5–7. Her physician had been deeply concerned about her NSAIDs usage – and cancelled it. Not long after, another prescription indicated that she – again – was on indomethacin, 50 mg/day. In other words, she used indomethacin to the end, although (possibly!) in a slightly reduced dosage. The headache was, as previously, always left-sided, and it had the same characteristics – and intensity – as before.

Comments

SUNCT continued its relentless course for close to 60 years and grossly kept its characteristics: the recurrent, long-term pattern was still present. The severity of the disorder tended to increase with age, both with regard to pain intensity, attack duration and frequency of attacks. No drugs of any use were found. It is worth noticing that the continuous course that prevailed during the bouts in the first decade or so never showed up again. This initial, temporal pattern distinguishes it from trigeminal neuralgia, which some clinicians still think of as a differential diagnostic alternative.

The following inferences can be made at the present time:

The marked increase in intraocular pressure and CIP amplitudes in this SUNCT patient (Table 2) could only be compared with cluster headache at the time; the difference as for both variables is a major one. In all probability, this indicates a difference in the pathogenesis of the two headaches. Later, we obtained the results of the corresponding studies in CPH (Table 2).

The difference between CPH and cluster headache is sizeable, but the differences between CPH and SUNCT are as marked for both variables. SUNCT, therefore, seems to be in a group of its own [8].

The sweating pattern in SUNCT syndrome seems most similar to that in CPH [9].

In HC [11] there were no definite abnormalities, as regards the ocular variables (Table 2); forehead sweat variables were also within the normal range [11].

HC lasted 56 years, and there were no signs of amelioration. One may speculate that the gravely reduced general health condition and the fever may have augmented the headache complaints during her last years.

In the CPH patient, with a case history of 54 years, there was, on the other hand, a clear tendency for the attacks to become more moderate. The efficacy of indomethacin was kept up both in CPH (33 years treatment) and in HC (19 years treatment) without any signs of tachyphylaxis.

Both patients with long-lasting indomethacin treatment reached an old age in spite of the complication risk. Their ages, 81 and 89 respectively, are at, respectively well above the mean lifespan in Norway at this time. And they have had a decent life in spite of the complications and constant risk of complications.

The potentially harmful effects of long-term indomethacin therapy make it imperative, not only in those with intermittent symptoms, but also in those with considerable fluctuation, to try to reduce/discontinue indomethacin at intervals. The lowest effective dosage should at all times be titrated.

An indomethacin test is a *must* in the diagnostic process in both CPH and HC. This is the foundation of the diagnosis, and it also represents the ethical basis for continued indomethacin therapy. To begin indomethacin ther-

apy, which in principle may be a lifelong treatment, is a serious matter. The risk of upper gastro-intestinal tract irritation/lesion seems in the long run to be considerable, as seen in both the present patients. The routine gastroscopy practice that we introduced in one of our patients represents a heavy load on the health system and may still not be an adequate safeguard. Although CPH and HC are two separate disorders, the problems connected with long-term indomethacin therapy create a common complex of problems. With long-term therapy, which in many cases certainly will be necessary at this stage of development, a strategy rendering the highest possible protection to the gastric mucosa should be followed.

The story, in particular that of the HC patient, brings up ethical considerations. Should indomethacin at one stage have been *forbidden*? The fact is that the HC patient could have expired during the one-time bleeding episode.

From the patients' point of view, the matter appeared quite differently. They were "in command of their own lives" and wanted no interference with the drug consumption. The conflict of interest was obvious and major. Besides prescriptions, they wanted one thing from us: protect us from the gastro-intestinal complications as well as you can, and we will take care of the rest – including the dosage level.

These patients were craving the drug, almost like drug addicts. They even warned us: the HC patient would do "drastic things" if not given access to the drug; the CPH patient time and again emphasised that the biggest river in Norway ran close to her home.

We reasoned this way: one cannot send the police to the domestic sphere to enforce a ban on indomethacin usage. To enforce the ban by allotting "police authority" to a family member would also create non-sustainable conditions within the family. A patient who is up and about will be able to provide the drug – and to hide it. The only way, as we saw it, would be to convince the patient of the real and great danger – the Damocles sword, so to speak. The patients understood – and accepted – the danger. They were prepared to meet whatever dangers there were, even exitus, if only they could have a decent life – as long as they lived.

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