Indomethacin responsive headache syndromes: chronic paroxysmal hemicrania and Hemicrania continua. How they were discovered and what we have learned since

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Summary

In the indomethacin responsive headaches (IRHs), chronic paroxysmal hemicrania (CPH) and Hemicrania continua (HC), the indomethacin (INDO) response is swift, absolute, and permanent, with moderate doses. Traditionally, CPH has been linked to cluster headache (CH) due to clinical similarities: unilaterality, intensity, and some autonomic phenomena. However, other clinical features differ essentially between these two headaches: sex ratio, mean attack frequency (CPH: 13.6 versus CH: 1.7 attacks/day), and duration of attacks. The therapeutic profile in CPH (indomethacin effect: ++; triptan effect: generally non-existent) is reversed in CH. The autonomic phenomena also differ clearly, a forehead supersensitivity sweating pattern and Horner-like pupil being present only in CH. The chronic/non-chronic stage ratio is 3.9 in CPH, against 0.14 in CH, a >25 times difference. Conversely, CPH and HC are very similar, clinically speaking. Accordingly, we should probably sever the link between CH and CPH and favour, instead, a linking together of CPH and HC, the two principal IRHs.

KEY WORDS: chronic paroxysmal hemicrania, headache classification, Hemicrania continua, indomethacin, indomethacin responsive headaches

Introduction

Indomethacin responsive headache (IRH) patients exhibit an absolute/close-to-absolute response to indomethacin (INDO). The two first discovered IRHs – and still the principal ones – are chronic paroxysmal hemicrania (CPH) (1) and Hemicrania continua (HC). Since INDO has no curative properties, it must be administered continuously in these two chronic disorders. This discussion of these syndromes will focus mainly on purely clinical aspects and in addressing the issues raised in the title will be restricted principally, but not entirely, to our own experience. In recent years, the term “paroxysmal hemicrania” has been used in place of CPH in many circles.

The discovery of chronic paroxysmal hemicrania

In 1961, a 44-year-old female, with an eight-year-long history of headache, came to our attention (O.S.). She complained of frequent, extremely severe and relatively short-lasting unilateral head pain attacks, mainly around the eye/temporal area/forehead, but also involving the upper facial area and even, to a considerably lesser degree, the neck and shoulder area. The attacks were accompanied by marked cranial autonomic phenomena, ipsilaterally. At pain maximum, the patient’s attacks could recur at intervals of one hour or less; at other times, they were few and barely noticeable. The fierceness of the attacks at maximum pain and the autonomic involvement were reminiscent of cluster headache (CH) attacks, but the frequency and brevity of the attacks forced us to consider other diagnostic possibilities. The patient warned us that her condition was unsustainable and that we had limited time. She had already had upper jaw, symptomatic side teeth removed in a vain attempt to combat the pain, and now she wanted her symptomatic side eye removed. A multitude of investigations were carried out at that time. As regards treatment, we started out with CH drugs and continued with the then available analgesics and head pain drugs, all of no avail. Each intramural drug trial was followed by a marked deterioration. She then went home to recuperate, but knocked on our door again after a couple of months. She had, in the past, noticed some effect of acetylsalicylic acid. For this reason, in 1973, more than 12 years after first coming to our attention, INDO was finally tried. For the first time in approximately 20 years, the patient abruptly felt what freedom from pain was like; and it was continuous. In the meantime, a second patient, with a similar symptomatology, had appeared. A new headache could be coined (2).

How was Hemicrania continua discovered?

After the discovery of CPH, we systematically tried out INDO in all unclear, unilateral headache cases, in order to find out how specific the INDO response was. After 9-10 years, a 63-year-old female patient came along with...
an anteriorly located, unilateral headache of 38 years’ duration. Since onset, the pattern of the pain had been continuous, i.e. characterised by only slight fluctuation and without the pain peaks of CPH. Still, an absolute and lasting INDO effect was observed. Minimal, ipsilateral, cranial autonomic phenomena were present. It so happened that Giel Spierings had been adopting the same policy as us, i.e. trying INDO in various types of unilateral headache. During a walk one night in a street somewhere in Poland, we told each other about our patients. His Dutch patient was investigated in Trondheim, and soon afterwards these two cases, the first cases of HC, were reported (3), as were related laboratory findings (4).

What have we learned since?

The prevalence of indomethacin responsive headaches

Most workers in the field would agree that CPH is a rare disease. In the Vågå series of 1838 individuals, we found no definite cases. Unfortunately, the huge headache questionnaire studies tell us nothing in this context. The total number of published and recognised cases, during the first 12 years or so after the discovery of CPH, amounted to 84, with 12 cases being observed during the first six years (5).

Hemicrania continua may at face value seem to outbalance CPH numerically, and this difference is probably real. However, the accuracy of diagnosis of this headache may vary. With the combination of a properly carried out, positive INDO test and the characteristic temporal profile, the chances of misdiagnosis in CPH would generally seem to be small. Conversely, in HC, wrongly conducted INDO tests, insufficient information concerning the tests carried out, as well as the propos- al to replace the INDO test with one solitary autonomic phenomenon (see later) may contribute to greater diagnostic uncertainty. Furthermore, prevalence figures depend heavily upon the types of cases included. Around 1990, six years after its description, no more than 18 cases of HC were known of (6) (corresponding figure for CPH: 12). It should be emphasised that HC is, first and foremost, an anteriorly located headache. HC is not a post-traumatic headache. Cases where a traumatic genesis cannot be excluded have been reported as HC.

The significance of indomethacin in indomethacin responsive headaches

The diagnosis of these disorders cannot, at present, be established without a positive INDO test. It is, therefore, of crucial importance that the test for INDO efficacy be conducted in an optimal way. The standard procedure is 25 mg three times a day, orally, for three days and, if the response is unsatisfactory, 50 mg three times a day for three days.

If pain freedom follows, this means that one may be faced with an IRH. However, a procedure every bit as important as the introduction of INDO itself is the discontinuation of it after a few days, to observe whether the headache reappears. Since INDO has no curative ef-
Can the headache alternate sides in indomethacin responsive headaches?

The problems with the Indotest in establishing the HC diagnosis will be accentuated when one of the hallmarks of HC, the side-locked hemicrania, is absent. In this special situation, it is all the more important that the drug withdrawal test be carried out in a proper manner. Involvement of the side opposite the usual headache side may occur in various ways. First, there may be a co-involvement of the opposite side of varying degree when the pain gets relatively intense (14), as occurs in other unilateral headaches, like cervicogenic headache (15-17). Second, on occasional days, head pain can be located solely on the non-dominant side, thus showing side alternation, like in migraine. This change of laterality may last a day, or longer. In our experience, this is a rare phenomenon. Whether permanent side-shifts can occur, as in CH, is an open question. Finally, bilateral HC has been described, albeit summarily (18). Bilateral HC as such is probably acceptable; it is likely to be a rare phenomenon.

In CPH, side alternation appears rarely, i.e. in ca 3.5% of cases (Table I).

Temporal patterns in indomethacin responsive headaches

Hemicrania continua. The first two patients showed a chronic pattern from the outset (3). The third patient, prior to the chronic stage, had experienced a remitting phase, with relatively short-lasting pain episodes (19). The remitting phase may be year-long. In a review of the first 18 patients, approximately half of them had experienced a remitting first phase (6). At the time of the review, 89% of the patients were in the chronic stage. The existence of a remitting stage is an incontrovertible observation. One of our patients has been followed from the remitting to the chronic phase, with complete INDO response in both phases (20).

In connection with HC chronicity, the claim that HC is a type of chronic daily headache (CDH) should be commented upon. CDH is a syndrome whose only common denominator is the chronicity. While generic terms of this kind should yield clear diagnostic advantages, the term CDH could, on the contrary, lead to a grouping together of headaches as diverse as, for example, HC and medication overuse headache. Clearly, this would not increase the understanding of these headaches, nor enhance diagnostic precision. CDH seems to be, if anything, an ill-defined, bilateral, rather symptom-poor, hard-to-classify and hard-to-treat headache. The features of HC, on the other hand, are practically the opposite of these and a unilateral headache that can be defined and treated, even efficiently, should be kept well out of the CDH orbit.

Chronic paroxysmal hemicrania. The standard work concerning the temporal characteristics of solitary CPH attacks is that of Russell (21) in which, to investigate heart rhythm disturbances, each CPH patient was required to carry a portable tape recorder and a marking system. In this way, chronometric data could be collected for 105 separate attacks in five inpatients. The small size of this sample does not in any way detract from the results obtained in this study: its accurate diagnoses and watertight methodology are what matters. Russell’s study was carried out in periods in which patients were experiencing both moderate (mean frequency: 6.5 attacks/24 h; range: 4-8) and severe attacks (mean frequency: 21.8 attacks/24 h; range: 13-38). On the basis of these figures, the arithmetic mean would be 14.2 attacks/24 hours. However, since there were more severe than mild attacks, a more correct mean might be around 15 attacks/24 hours.

The mean duration of the attacks was 13.3 min±7.6 (range 3-46 min). Only three lasted longer than 30 minutes, the longest being 46 minutes. In a recent, prospective study of 31 CPH cases, a mean frequency of 11 attacks per day was observed. Later, the frequency was stipulated at 20 per day (10). The mean duration was 17 minutes with a range of 10 seconds-4 hours. This range is somewhat surprising. In 55% of
these cases, attacks could last >30 minutes. These figures should be compared with the three out of 105 attacks with >30 minutes’ duration recorded in Russell’s series (21). These differences may be significant. Russell’s data should be taken as the standard, also in the future.

Chronic paroxysmal hemicrania: stages and INDO responsiveness

Of the two forms of CPH, the chronic (non-remitting) form dominates quantitatively, the chronic/non-chronic ratio being 3.9 (5) (Table I). Of the 42% of CPH cases experiencing a remitting (episodic) stage, approximately half go on to develop the chronic form. Absolute INDO effect has been demonstrated in both stages. There is evidently little reason to believe that in a patient in an INDO-responsive chronic stage, the early stage with remitting headache was INDO non-responsive. Until recently, no patient had been followed from the non-chronic through to the chronic stage. However, in one young female patient with a remitting course, the intracocular pressure was 12.2 mmHg on both sides, between attacks, as opposed to 13.4 (symptomatic side) and 11.2 during attacks. The corresponding values for ocular pulse (corneal indentation pulse, CIP) amplitudes were 24/23 µ vs 56/38 µ, respectively (22), both measurements in accordance with what is found during CPH attacks in the chronic stage (23) (Table I). At the time (1979), this patient seemed to be approaching a chronic stage, in that active periods seemed to be becoming steadily longer and remissions shorter. At follow-up in June 2009, this patient was indeed found to have had several year-long periods of chronic paroxysms over the years, the last one lasting 2-3 years and ending >1 year previously. INDO had been used constantly during exacerbations. This case is notable for two reasons: this patient is probably the first detected case of CPH with a remitting form (1979, when she was included in our autonomic function studies). She is also the first CPH case with a proven transition from the remitting to the chronic phase, showing the INDO response in both phases. The opposite evolution, i.e. from the chronic to the remitting stage, has also been observed, again with INDO response in both phases (20). These observations seem to show that temporal changes in individual patients are cosmetic more than reflecting a radical revolution of the basic structure of the headache. The non-chronic stage can be long-lasting in IRHs (up to 25 years). Putatively, it can persist all through life.

Hemicrania continua: developed from cluster headache?

This brings us to the notion that HC could represent a development from CH (24). Realistically, this idea would have to be supported by the presence of, at least, a positive triptan and a negative Indotest in the cluster stage and the reverse pattern in the fully developed stage. No one has yet come close to demonstrating this. Fully developed HC and CH are two essentially different disorders. Logically, it is highly unlikely that INDO sensitivity, which is a fundamental property, can be acquired in the course of CH evolution. It would also be desirable to demonstrate that CIP amplitudes (23) are increased in stage I, but not in stage II (Table I). The non-chronic, early stage of HC may be so atypical that it can be confused with various headaches. This seems to have been a trap for many clinicians (e.g. 25).

Hemicrania continua: with and without INDO response?

It has long been suggested – this is an idea probably promoted mostly by American investigators – that there exist HC cases that show no INDO sensitivity and that such cases are, otherwise, “pure” cases of HC. This is a challenging idea as it clashes with the viewpoint that, by definition, there is an absolute INDO response in HC. A recent study found that non-responders outnumbered responders by far (12), in accordance with the allusion: “HC is not that rare” (26). We, too, have observed a number of patients with unilateral headache and without an optimal INDO response. The headache has been partly severe, with regional allodynia and marked ipsilateral, cranial autonomic phenomena, the main zone of pain most frequently seeming to be in the temporal/vertex area and not located anteriorly. These patients are not examples of HC. They suffer from an entirely different headache, “non-indomethacin responsive chronic hemicrania”, or: "NIRCH", as recently described (11) and can, at least in solitary cases, be treated highly successfully by extra-cranial, electrical stimulation. There thus seem to be at least two types of continuous, unilateral headaches. Since we may be only at the beginning of the exploration of unilateral headaches, even "NIRCH" may prove to consist of various subgroups. The fundamental change in viewpoint is, therefore, that we are not faced with two types of HC, as previously believed: one type is HC; the other, without the indomethacin response, is far from being HC.

Comment on some recent claims about chronic paroxysmal hemicrania

A recent study (10) lists among CPH provocative factors: “pressure over the greater occipital nerve”, observed in one patient. The structures from which CPH attacks can be provoked mechanically have previously been outlined in detail (27,28). In our series of 11 CPH patients, there were four (36%) in whom attacks could be precipitated from the neck/occipital area (28). This percentage should be compared with the 3% (one in 31 patients) recorded in the other series, a greater than tenfold difference. The remaining patients who did not exhibit mechanically precipitated attacks in all probability have not been investigated clinically with the distinct aim of detecting specific precipitation mechanisms. The recent investigation (10) is probably not an investigation of mechanically precipitated attacks in CPH at all. On this basis, it becomes hard to accept that the solitary positive case reflects the situation in the whole group. The authors of this study (10) also claim that “fullness in the ear” in addition to being an integral part of the CPH attack, deserves inclusion among the autonomic phenomena making up a part of the CPH criteria. In this case, however, unlike the autonomic phenomena in HC,
the autonomic phenomenon is not intended to be a substitute for INDO responsiveness. Eight patients (26%) apparently had “fullness in the ear”, one of whom had no other autonomic symptom. The specificity of this symptom has not been checked. The whole “ear fullness” argument in CPH leaves much to be desired. Only 82% (14 out of 17 patients) of those who were tested with an indomethacin dosage of 100-200 mg intramuscularly had a positive test. On the other hand, some of the non-responders to this test apparently responded favourably to oral INDO. This does not stand to reason. If comparable doses of INDO are given by these two routes of administration, the parenteral route should, if anything, give better, not poorer results. The problem here is not due to the drug: it derives, in all probability, from human error.

Also the INDO dosage in this series raises doubts, the mean being 137 mg, orally, and the range 30-300 mg/day; 300 mg/24 hours is certainly a high dosage, the upper recommended oral dosage being 200 mg; preferably the dosage should be >=150 mg/day. Eleven subjects (35%) had a daily dosage of >=200 mg. Whereas INDO therapy in IRHs is generally characterised by relatively low dosages, this recent series clearly takes us into the domain of high-dosage INDO. This allows the general, non-specific, analgesic effect of INDO to be brought into focus. This effect is characterised by relatively high INDO dosages, slower onset of effect and lack of complete effect. The relatively low-grade effect of INDO in CH may be explained on this basis.

Moreover, the authors found a barely noticeable sex difference, and certainly no female preponderance (F/M ratio of 0.8; later described as M=F). Antonaci (5) found a F/M ratio of 2.36. There thus emerges an almost threefold difference between the two series: a serious discrepancy.

While Antonaci (29) found absolutely no sumatriptan effect in CPH, this group found an effect in 20% of their cases.

There is a profound difference between this series and what we consider genuine CPH (1,2,5). The question is not so much whether or not, but rather to what extent there has been an admixture of CH cases: the duration of attacks, the lack of INDO effect, the partial effect of sumatriptan, the lack of occipital area precipitation sites, the high extent of restlessness during attack (80%), the grave lack of female preponderance etc.

**Chronic paroxysmal hemicrania as a REM sleep-locked headache**

Two different patterns have been identified with regard to the REM stage of sleep and the timing of nocturnal attacks in CPH. In one patient, 17 out of 18 attacks occurred during REM sleep (28,30). This prompted usage of the term “REM sleep-locked” to refer to such headache attacks which are coded at no. 346.2 in the International Classification of Sleep Disorders (31). This patient possesses the unique feature of mechanical attack precipitation. In two other CPH patients, none of the 14 nocturnal attacks appeared in REM sleep (28). A relationship between nocturnal attacks and REM stage, albeit less constant, has also been found in CH (32).

**Where should chronic paroxysmal hemicrania and Hemicrania continua be placed in the classification system?**

When CPH was first described, the role of INDO already seemed to be a decisive one. However, particularly in the beginning, there was some strong opposition to “linking a headache diagnosis to a drug”. Initially, we emphasised the similarity with CH. Outwardly, once attacks of these two types had started, they appeared similar. However, as we have stressed many times, similarity does not mean identity. At the time, wanting to avoid seeming provocative and ostentatious we opted not to accentuate the uniqueness of CPH, and instead linked it to CH. But, we were immediately heavily criticised by many of the leading headache experts: why did we not “dare” to state that CPH in principle was different from all headaches existing at the time? Our critics were probably right: CPH and CH do not have much in common, except for the unilaterality, the intensity, and some cranial autonomic abnormalities. In Table I, some of the important variables (also including some cranial, autonomic disturbances) that, grossly, contribute to separating these headaches have been summarised. The differences are fundamental: the female/male ratio; the chronic/non-chronic ratio; the number of attacks per day; the CIP amplitudes, and so on, show clear differences between CH and CPH (Tables I and II). It is thus not only the INDO sensitivity that divides the two headaches. Since its position is unique, CPH should not have been put under the umbrella of CH, originally. The link between CH and CPH should be undone.

**Table II - Therapy effect in chronic paroxysmal hemicrania and cluster headache**

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<thead>
<tr>
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<th>CPH</th>
<th>CH</th>
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<tbody>
<tr>
<td>Triptan effect</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Indomethacin effect</td>
<td>++</td>
<td>-*</td>
</tr>
</tbody>
</table>

Abbreviations: CPH=chronic paroxysmal hemicrania; CH=cluster headache. *In usual dosages: 75-150 mg/day

Another important question comes up: what is the relationship between CPH and HC from a classification point of view? The fact that these two headaches – and these two alone – respond to INDO in an absolute manner brings them close together (Table III). There are only minor clinical differences between them. In Fabio Antonaci’s doctoral thesis (33), a thorough search was made for such differences: triptan response, cranial nerve blockades, and forehead sweating pattern (34) showed no gross differences. The sex ratio showed a clear female preponderance in both disorders, albeit more marked in HC (Table III). On pupillometric testing, there were no definite supersensitivity reactions to sympathicomimetics in either headache disorder.

Furthermore, the long-term pattern is characterised by remitting and non-remitting phases, the chronic phase...
Effects of cranial blockades - sweating pattern - forehead supersensitivity - Horner-like picture - anterior > posterior pain - absolute INDO effect - chronic and non-chronic pain patterns

between them knits them together (Table III). Classification-wise, this parity should be emphasised: these headaches belong together in the classification system. The superstructure would even have a natural designation: INDO responsive headaches with the emphasis on the plural: there is more than one.

Table III - Chronic paroxysmal hemicrania and hemicrania continua: similarities

<table>
<thead>
<tr>
<th></th>
<th>CPH</th>
<th>HC</th>
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</thead>
<tbody>
<tr>
<td>Female/male ratio</td>
<td>2.4</td>
<td>5.0</td>
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<tr>
<td>Chronic/non-chronic</td>
<td>3.9</td>
<td>8.0</td>
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<tr>
<td>Absolute INDO effect</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anterior &gt; posterior pain</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Horner-like picture</td>
<td>-</td>
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<tr>
<td>Forehead supersensitivity</td>
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<td>Sweating pattern</td>
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<td>Effect of cranial blockades</td>
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<td>Effect of triptans</td>
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</tbody>
</table>

Abbreviations and symbols: CPH=chronic paroxysmal hemicrania; HC=hemicrania continua; *see ref. 6; **ratio between chronic and non-chronic pain patterns

Nomenclature

All (?) unilateral headaches have a remitting and a non-remitting phase. In CH, the remitting (episodic) form clearly dominates, accounting for around 88% of the total (28). The characteristic temporal pattern of the, quantitatively speaking, dominant form (i.e. the clustering) has, naturally, given the name to the whole group. The term chronic CH, meaningless as it seems to be, with an inherent contradiction in adjecto, may, nevertheless, seem to be acceptable.

In CPH, the situation is the reverse: the chronic form dominates, accounting for around 80% of the total group (5). The appellation for this group should probably have followed the same rule as the one applied in CH.

“Paroxysmal hemicrania” nevertheless, presently, seems to be the preferred term for the temporal phases of CPH, as far as the International Headache Society is concerned. It is probably not a particularly well chosen term. With the word “chronic” added, the virtual number of headaches alluded to would be considerably downscaled. For these and other reasons, the designation for the entire group should be CPH.

References

7. Sjaastad O. Chronic paroxysmal hemicrania, hemicrania continua, and SUNCT: the fate of the three first described cases. J Headache Pain 2006;7:151-156
11. Sjaastad O, Fredriksen TA, Jorgensen JV. Electrical stimulation in headache treatment. For separate headache(s) or for headache generally? Funct Neurol 2009;24:53-59
20. Sjaastad O, Antonaci F. Chronic paroxysmal hemicrania (CPH) and hemicrania continua: transition from one stage to another. Headache 1993;33:551-554
33. Antonaci F. Chronic paroxysmal hemicrania and hemicrania continua. Two different entities? Trondheim; Tapir 1998: Thesis no. 139