Cluster headache: the history of the Cluster Club and a review of recent clinical research

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Summary

In September 2003, a scientific meeting was held in Rome to revive the tradition of the International Cluster Headache Research Group (or “Cluster Club”) meetings. Held in September 2003, in conjunction with the 11th International Headache Congress of the International Headache Society (IHS), this half-day satellite meeting consisted of lectures and discussions that covered current topics (taxonomy, pathophysiology and therapy) related to cluster headache (CH). The growing importance of international scientific collaboration in the field of CH, particularly in areas such as epidemiology, genetics and therapy, means that there is a definite need for more meetings of this kind in the future. We would like briefly to look back at some of the activities of the Cluster Club (started by Ottar Sjaastad) in its early years and to draw attention to some of the major clinical investigations performed during the last decade, notably in the areas mentioned above.

Introduction

Upon the initiative of Giuseppe Nappi and Gian Camillo Manzoni, a scientific meeting was recently organised in Rome to revive the tradition of the International Cluster Headache Research Group (or “Cluster Club”) meetings. Held in September 2003, in conjunction with the 11th International Headache Congress of the International Headache Society (IHS), this half-day satellite meeting consisted of lectures and discussions that covered current topics (taxonomy, pathophysiology and therapy) related to cluster headache (CH). The growing importance of international scientific collaboration in the field of CH, particularly in areas such as epidemiology, genetics and therapy, means that there is a definite need for more meetings of this kind in the future.

Early descriptions

Dutch physician and anatomist Nicolaas Tulp seems to have provided the first description of CH as long ago as 1641. Some hundred years later, Gerhard van Swieten, in his textbook of 1745, gave an even clearer report of a patient evidently affected by episodic CH. However, other authors often cited in the literature (Willis, Möllendorff, Bing) tended to present descriptions too short to allow a definite diagnosis, or case histories that had very little to do with the syndrome as we know it today (1). A more extensive account of so-called migrainous neuralgia was provided by Harris (2), although he did not differentiate clearly between this ailment and attacks of pain that were characterised by long duration and alternation from one side of the head to the other. Only when Horton (3) detailed the pain and its associated symptoms did the syndrome become generally known. The periodicity of the headaches was described by Ekbom (4) and by Kunkle et al. (5), who introduced the term “cluster headache”. Since our knowledge of the aetiopathogenesis of CH is still incomplete, the descriptive term cluster headache, also adopted in the first edition of the IHS headache classification (6), must, for the time being, suffice.

The Cluster Club

In the mid 1960s, only three or four papers on the subject of CH were appearing each year. However, during the 1970s several investigators be-
came interested in the topic, and in order to promote re-search ideas, to generate papers, editorial and other information, a research group was set up through the ef-forts of Ottar Sjaastad. It was called the “International Cluster Headache Research Group”, but for practical reasons this name was abbreviated to the “Cluster Club”. Sjaastad was its president, David Russell its treasurer and Lee Kudrow its secretary. The group decided to meet annually, rotating the venue between London, Scandinavia and the United States. Founding members were selected on the basis of their active involvement and interest in CH research. The very first meeting of the Cluster Club was held in Uppsala, Sweden, in 1979, in conjunction with the 10th Annual Meeting of the Scandinavian Migraine Society. Those present were: Karl Ekbom, John Graham, Mark Green, Ivar Hörven, Lee Kudrow, Ninan Mathew, Bent de Fine Olvarius, David Russell, and Ottar Sjaastad. Absent were Hartwig Heyck, Bayard T. Horton, Charles Kunkle and Nazhiyath Vijayan. Topics discussed at the first meeting included: lithium as a prophylactic treatment; infections, notably herpes simplex virus; patients manifesting symptoms of both CH and tic douloureux; intraocular pulse changes in CH; association of malignancy with CH.

The second meeting (in 1980) was arranged by Marcello Fanciullacci. The next meeting, arranged by Marcia Wilkinson and Nat Blau, was held at the City of London Migraine Clinic in September 1982. Topics discussed were: bioavailability of ergotamine; pupillometric and pupillographic findings in CH; pupillary responses to nociceptive stimuli; the hypothalamus and the carotid body; pulse rate changes during attacks; surgical treatment; and chronic paroxysmal hemicrania, which at that time had been found in 40 cases worldwide. The fifth meeting was held in Munich (1983) to coincide with the birth of the IHS, and Annette Krabbe, Marcia Wilkinson and Carsten Saunte were elected as new members of the Cluster Club. Meetings were generally arranged in conjunction with congresses of the IHS and the Migraine Trust. They were rather informal events at which short presenta-tions were followed by ample time for discussion, and had great appeal due to the creative atmosphere they fostered. Researchers and clinicians learned from each other while exchanging ideas for further research and collaboration. The last meeting (prior to the above-mentioned Rome symposium in 2003) was held in 1994.

Clinical research in the past

At the time the Cluster Club was set up, a diagnosis of CH was commonly based upon the 1962 criteria of the American Ad Hoc Committee. Heredity and genetic fac-tors were thought to be of little aetiological importance. CH was still regarded in many quarters as a variant of migraine, one main reason being the presumed exis-tence of intermediate forms presenting features of both syndromes. However, detailed clinical analysis (1) dis-closed many striking differences between CH and mi-graine, and the former has now long been considered a separate entity, distinct from migraine.

In the past, theories on the pathogenesis of CH re-volved around the peripheral cranial arterial circulation and notably clinical evidence of a dilatation of the exter-nal carotid artery. Friedman and Mikropoulos, in their classic report (7), listed the following observations during CH attacks:

- a distended temporal artery in some cases;
- injection or even bloodshot appearance of the eye;
- nasal congestion;
- local increase of skin temperature;
- relief upon compression of the temporal or the carotid artery;
- good response to vasoconstrictors.

In one particular case we observed (1), performing carotid angiography during a headache attack, marked dilatation of the ophthalmic artery and a localised nar-rowing of the internal carotid artery distal to its exit from the carotid canal. Hörven, Nornes and Sjaastad (8) re-port ed vasodilatation in the region of the eye, as indi-cated by increased corneal temperature and increased pulse-synchronous, intraocular pressure variations measured by means of dynamic tonometry. Thus CH was regarded as a cranial vascular disorder, and pos-i-tive results of treatment with vasoconstrictors (ergota-mine tartrate) became further evidence in support of this.

A great deal of the early clinical research also dealt with personality characteristics (9), and it was stated by Gra-ham that CH patients are often heavy smokers and “a harder-drinking lot than comparable groups of migraine sufferers and controls”.

Recent progress in CH research

Recent decades have brought a considerable increase in clinical and experimental research. This has been
catalysed by the introduction of headache journals, national and international headache societies, headache symposia and meetings, and not least by the continued efforts of the Cluster Club. Table I lists some of the areas in which there have recently been advances in CH research.

Table I - Some areas in which there have been recent advances in CH research.

<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>Genetics</th>
<th>Neuropeptides, trigeminovascular activation, nitric oxide</th>
<th>Endocrinology</th>
<th>Neuroimaging procedures</th>
<th>Acute symptomatic treatment (sumatriptan)</th>
<th>Deep brain stimulation</th>
</tr>
</thead>
</table>

Diagnostic aspects

Horton and other workers had already demonstrated that the clinical features of CH attacks in most cases are so clear-cut that there are really no diagnostic difficulties. However, a recent nationwide survey of Dutch CH patients (10) indicates that the disorder did, in fact, continue to remain unrecognised or misdiagnosed in many cases for many years. In some less typical cases pain may be only vaguely described, it may have a long duration, or it may alternate between both sides of the head. Some patients at times suffer from sporadic attacks, presenting neither typical cluster nor chronic patterns, and in all these situations it can be helpful to observe the patient directly in the hospital ward. The intensity, duration, and time of day of the attacks should be recorded, along with the effects of any medication. An additional diagnostic test proposed by Blau (11) is to invite patients to demonstrate how they behave during severe attacks. The intense pain is known to give rise to extreme restlessness (11) or agitation, a clinical sign that has now been included in the revised IHS classification of CH (12).

An exact early diagnosis may be somewhat difficult to establish in patients who have suffered no headaches prior to the current pain episode. Recently, a follow-up study was performed of 60 patients after an assumed first period of CH (13). According to the IHS criteria of 1998 (6) they had on admission suffered from the "cluster headache periodicity undetermined" sub-form of the disorder. A subsequent follow-up (personal observation) showed that about a quarter of the patients had experienced only one headache period during a mean observation time of 9 years, which is of considerable interest given that two or more headache periods are commonly required for a definite diagnosis of episodic CH. More prospective studies on the prognosis of CH are obviously needed.

During recent years increased attention has been paid to some rare headache syndromes having certain clinical features in common with CH (Table II). They are all characterised by frequent short-lasting unilateral headaches associated with prominent local autonomic phenomena and represent, according to Goadsby and Lipton (14), a rare, yet important, spectrum of the primary headache syndromes. They are now classified together with CH as a group of trigeminal-autonomic cephalalgias and are included in the recent revised IHS classification system (12). An activation of trigeminal-facial parasympathetic reflexes via brainstem connections is proposed as the underlying pathophysiological mechanism.

Table II - Primary short-lasting headaches with prominent autonomic features. (After Goadsby and Lipton, ref. 14).

<table>
<thead>
<tr>
<th>Episodic cluster headache</th>
<th>Chronic cluster headache</th>
<th>Chronic paroxysmal hemicrania</th>
<th>Episodic paroxysmal hemicrania</th>
<th>SUNCT syndrome</th>
<th>Cluster-tic syndrome</th>
</tr>
</thead>
</table>

Epidemiology

There have been few epidemiological investigations. In 9,803 18-year-old Swedish army conscripts CH was found in 0.09% (15). A population study of 21,792 inhabitants of the Republic of San Marino (16) yielded an overall prevalence of 0.07%. Rasmussen et al. (17) found one single case of CH among 740 Danish adult subjects randomly selected from part of Copenhagen County, yielding a prevalence of 0.14%. A similar rate (2/2,008) was reported among inhabitants in the district of Porto (18). In Olmsted County, Minnesota the overall age-and sex-adjusted incidence was 9.8 per 100,000 person-years or approximately 1/25 that of migraine (19). This latter figure may, however, be somewhat controversial owing to the cluster diagnosis criteria applied in this study.

There have been two recent, careful epidemiological studies; the first one was carried out in the Republic of San Marino (20), as an update of the previous investigation conducted in the 1980s. The prevalence rate was 56/100,000 and the incidence rate 2.5/100,000/year, and in fact, this is the first prospective study ever on the incidence of CH. The other one is a Norwegian investigation (the Vågå study) conducted by Sjaastad and Bakkeiteig (21), who reported a rather high prevalence of 326/100,000 in the total population. Among other things they pointed out that direct questioning of headache victims is necessary, and that long remissions, relative mildness and brevity of attacks may contribute to a misdiagnosis of CH.

It is generally stated that CH is uncommon among children and adolescents. Hitherto no major epidemiological studies have been performed besides the one in Sweden mentioned above (15). However, through a recent collaboration between 27 headache centres in Italy (22), the one-year prevalence of CH was calculated to be 0.03% out of 6,629 subjects under 18 years of age who had attended the outpatient departments of the centres.

There is a tendency to a bimodal distribution of the
age at onset in women with a number of sufferers experiencing their first attacks after the menopause (23,24). In his monograph Kudrow (9) stated that “peculiar to the female distribution an increased frequency occurred between the ages of fifty and sixty years” referring to our series and his own series of 70 female patients.

Of considerable interest was Manzoni’s report that the male preponderance of CH has decreased progressively over the years (25,26). In a total of 482 patients, he demonstrated a clear change in gender ratio and suggested that this might be due to changes in lifestyle factors over the years, such as employment rate and smoking habits in both sexes. We have recently confirmed such a change in sex ratio over time in our series of 554 patients collected over more than three decades (27), and we have also tried to see whether there is any relation between sex ratio and age at onset. In summary, we found that the male to female ratio varied widely as a function of age at onset both in episodic and in chronic CH, although there was an overall male preponderance. Table III shows sex, age at onset and gender ratio in our patients with episodic and chronic CH. The male preponderance with regard to onset of CH was most pronounced between 30 and 49 years of age, while after 50 there were equal numbers of new male and female patients with chronic CH. In the latter variety, the females overall displayed a rather even distribution of age at onset. Chronic CH in women started later than in men and also later than episodic CH in women. The nature of the sex- and age-related pattern of headache onset remains to be elucidated but sex-dependent endocrine and/or genetic regulatory mechanisms, possibly of hypothalamic origin are likely to be involved. Since the mean age at onset had not changed over time and the number of postmenopausal new female patients with chronic CH was rather modest, there must be some specific explanation for the decreasing male preponderance, most likely environmental and related to changes in lifestyle, as suggested by Manzoni.

**Genetic status**

CH is a rare disorder, with a prevalence of about 1-2/100,000 individuals. Most cases are sporadic but during the past few decades a growing number of families with more than one affected member have been recognised. First-degree relatives of probands with CH have been shown to have a fourteen-fold increased risk of suffering from CH compared with the general population (28). Second-degree relatives had a corresponding two-fold risk, and hence the possibility of a genetic component in the aetiology has to be considered. Ideally a genetic model would explain all the clinical characteristics such as male preponderance, unilateral nature of headaches, autonomic features, attack pattern and periodicity. Familial aggregation in a few cases may be due to common environmental exposure or a genotypic heterogeneity. There may also be a complex pattern such as gene-gene interactions, gene-environmental interactions, sex- and age-dependent expression of genes to explain the apparent sporadic disorder. This may be exemplified by age-dependent male-to-female ratio and observations of a decreasing male preponderance over the last three decades.

CH has been observed in 7 monozygotic (MZ) pairs of twins (29-36) (Table IV) but these few selected reports of MZ twins concordant for CH may be biased as such rare sufferers are possibly more likely to be published than if the disease appeared in only one of the twins. We have recently studied the occurrence of CH in twins (36) utilising a cross-match of Swedish national registers of twin births and hospitalisations. Seventeen discordant twin pairs were found, in which CH status could be verified in 11 complete pairs. Our results differ in some respects from the case reports mentioned above, this possibly being due to differing selection procedures and recruiting of cases. To explain familial aggregation, a larger sample of affected twins is needed. An increased risk of CH in first and second degree relatives has been found in several clinical series (9, 33, 37-43) (Table V), which underlines the importance of considering genetic or common environmental factors in the aetiology. By means of segregation analysis and model fitting, Russell et al. (38) reported that a multifactor genetic model fitted the data better than a sporadic one. Their results suggest that an autosomal dominant gene with reduced penetrance might have a role in some families and that the gene would be present in twice as many women as men.

In Kudrow’s series (n=495) (9), 3.5% of males and 10% of females reported having close relatives with CH. Interestingly, familial CH was found to display a gender

<table>
<thead>
<tr>
<th>Age at onset (years)</th>
<th>Episodic cluster headache</th>
<th>M.F</th>
<th>Chronic cluster headache</th>
<th>M:F</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males (M)</td>
<td>Females (F)</td>
<td>3.2:1</td>
<td>Males (M)</td>
</tr>
<tr>
<td>10-19</td>
<td>82</td>
<td>26</td>
<td>6.5:1</td>
<td>9</td>
</tr>
<tr>
<td>20-29</td>
<td>156</td>
<td>34</td>
<td>4.5:1</td>
<td>15</td>
</tr>
<tr>
<td>30-39</td>
<td>78</td>
<td>12</td>
<td>6.5:1</td>
<td>14</td>
</tr>
<tr>
<td>40-49</td>
<td>59</td>
<td>7</td>
<td>4.8:1</td>
<td>8</td>
</tr>
<tr>
<td>50-59</td>
<td>23</td>
<td>10</td>
<td>2.3:1</td>
<td>3</td>
</tr>
<tr>
<td>60-69</td>
<td>5</td>
<td>2</td>
<td>2.5:1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>403</td>
<td>91</td>
<td>4.4:1</td>
<td>49</td>
</tr>
</tbody>
</table>
ratio, affecting relatively more women than the sporadic form (40-42). Differences in results may have methodological explanations including the method of recruiting familial cases and inclusion criteria. In two of the reports (40,43) patients with “CH periodicity undetermined” were included as well as patients with CH fulfilling IHS criteria minus one symptom, mostly the attack duration criterion.

Table IV - Cluster headache in twins.

<table>
<thead>
<tr>
<th>Study</th>
<th>MZ concordant</th>
<th>Co-twin with “almost certain” CH, not interviewed by the authors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eadie and Sutherland, 1966</td>
<td>MZ concordant</td>
<td>42-year-old brothers with episodic CH since the ages of 9 and 12 yrs</td>
</tr>
</tbody>
</table>
| Couturier et al., 1991       | MZ concordant | 1) Two brothers born 1960 with onset of episodic CH at 16 and 22 yrs of age, one evolved into sec. chronic CH. The father had migraine.  
| (first reported 1987)        | 2 MZ concordant | 2) Two males born 1943 with CH onset at ages 18 and 20. |
| Roberge et al., 1992 (ref. 31)| MZ concordant | Brothers born 1944. Paroxysmal tachycardia. Episodic CH since ages 33 and around 25 yrs. Minibouts |
| Sjaastad et al., 1993 (ref. 32)| MZ concordant | Diff. sex twin pair discordant for CH found in pedigree tree. The female had CH |
| Kudrow and Kudrow, 1994 (ref. 33)| DZ discordant | Brothers. Migraine since childhood. Since 3 yrs episodic CH in both. |
| Lampl, 2002 (ref. 34)        | MZ concordant | Sisters age 38. Migraine without aura since childhood. Episodic left-sided CH since age 24 and 31. |
| Schuh-Hofer et al., 2003 (ref. 35)| MZ concordant | Five diff. sex pairs |

Table V - Familial cluster headache in clinical series.

<table>
<thead>
<tr>
<th>Study</th>
<th>Relatives with CH (%)</th>
<th>Population relative risk</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kudrow, 1980 (ref. 9)</td>
<td>3.5% M 10% F</td>
<td>11.3%</td>
<td>No adjustment for sex and age</td>
</tr>
<tr>
<td>Kudrow and Kudrow, 1994 (ref. 33)</td>
<td>10% M 12% F</td>
<td>3.5%</td>
<td>Autosomal dominant gene with reduced penetrance?</td>
</tr>
<tr>
<td>Manzoni, 1983 (ref. 37)</td>
<td>6.7% 12 M 11 M 1F</td>
<td>14.1 2.3</td>
<td>Autosomal dominant gene with reduced penetrance?</td>
</tr>
<tr>
<td>Russell et al., 1995 (ref. 38)</td>
<td>7% n=25 1.2% n=26 0.2% n=10</td>
<td>39.2 8.1</td>
<td>M:F=1.3:1 in all familial cases, 19% of relatives fulfilled IHS criteria minus one, 21% periodicity undetermined.</td>
</tr>
<tr>
<td>Montagna et al., 1998 (ref. 39)</td>
<td>2.3%</td>
<td></td>
<td>M:F=1.3:1 in all familial cases</td>
</tr>
<tr>
<td>Leone et al., 2001 (ref. 40)</td>
<td>20% n=44 3.3% n=39 0.6% n=18</td>
<td>39.2 8.1</td>
<td>M:F=1.4:1 Familial cases were younger</td>
</tr>
<tr>
<td>El Amrani et al., 2002 (ref. 41)</td>
<td>11% n=20 3.4% n=22</td>
<td></td>
<td>IHS criteria minus one accepted (n=24).</td>
</tr>
</tbody>
</table>
Taken together the patterns of inheritance may, as mentioned, indicate an autosomal dominant gene with reduced penetrance or no specific mode of inheritance. On the basis of current hypotheses regarding CH aetiology, several association studies of candidate genes have been carried out but so far giving negative or not significant results (44-49) (Table VI). For further progress family studies with genome scans are needed to identify regions of potential interest. This will require large samples of well-defined families, large pedigrees and increased collaboration between neurological centres and geneticists in several countries, which again underlines the importance of an international Cluster Club.

**Pathophysiology**

Periods with CH are associated with an increased sensitivity to various vasodilator stimuli. Attacks may be provoked by alcohol, histamine or nitroglycerin with onset occurring after an interval of 30-50 min after intake. The time period before an expected attack is of great interest as regards the pathophysiology of the disease. An initial sympathetic stimulation after nitroglycerin appears to be followed by rebound increase of parasympathetic and vagal tone in conjunction with the headache attack. Also, there is an increase of sympathetic activity during both spontaneous and induced cluster attacks, possibly secondary to the perception of pain.

Nitroglycerin is a donor of nitric oxide (NO) that has powerful vasodilator effects. Sustained therapy with long-acting organic nitrates may even induce extra periods of CH (50), this being in accordance with a recent hypothesis that CH is due to a hypersensitivity to NO (51). Many similarities exist between spontaneous and nitroglycerin-induced attacks and hence a single pathophysiological mechanism may be responsible. Goadsby and Edvinsson (52) have found evidence for trigemino-vascular activation during attacks, recording an increase of plasma calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) in the external jugular vein on the symptomatic side. Increase of CGRP during attacks provoked by nitroglycerin has also been reported (53). Sumatriptan rapidly aborts an attack of CH in close parallel to a decrease of plasma CGRP in the ipsilateral external jugular vein (52,53), and this provides additional support for activation of the trigeminovascular system during headache attacks. Endocrine regulation of melatonin, cortisol, prolactin and testosterone is altered both during active cluster periods and in clinical remission. Figure 2 illustrates a close collaboration in research on melatonin between our group and our Italian friends, professors Sicuteri, Fanciullacci, Marabini, Polleri and others. The circannual urinary excretion of melatonin was found to be lowered (54) and serum levels of melatonin to be reduced during the night in active periods of CH (55,56). Urinary excretion of the main metabolite of melatonin (6-sulphatoxymelatonin) was also reduced in CH patients in the cluster period (57). All these findings strongly point to a local dysfunction of the hypothalamus in CH.

![Figure 2 - Scientific cooperation between Stockholm, Sweden, and Italy on the neurohormone melatonin in cluster headache.](image-url)
Cluster headache: the Cluster Club and recent clinical research

Functional neuroimaging has greatly contributed to the understanding of the basic mechanisms in CH. By using PET, May et al. (58) demonstrated an activation of the ipsilateral inferior hypothalamus during attacks and suggested that CH should be regarded as a functional neurovascular disorder of pacemaker or circadian regions in the hypothalamic grey matter. Furthermore, structural changes of this particular region have been demonstrated for the very first time (59), and attacks of CH are most probably initiated and maintained via dysfunctions in the inferior posterior hypothalamus.

While a genetic background appears to be evident in some cases, the aetiology of CH is still largely unknown. A thorough case-control study has been performed (60,61) aiming at evaluating any associations between life habits and general risk factors for CH. However, it failed to disclose a significant association with factors often cited in previous literature (61), with the exception of cigarette smoking, head trauma, and a positive family history of headache. Other, similar investigations are needed with a focus on CH appearing in young or elderly sufferers, in twins and in families, in the chronic vs the episodic headache variety, and preferably also in representative general populations.

**Acute symptomatic treatment with sumatriptan**

Individual attacks are relatively brief, but they are usually of such severe intensity that treatment of symptoms may be difficult. The pattern of attacks varies from patient to patient, and treatment problems may arise when there are frequent attacks, extended periods of headaches, or even a chronic syndrome.

Subcutaneous sumatriptan is now regarded as the most effective acute treatment of attacks (for a review see 62). A randomised, double-blind, placebo-controlled and cross-over study in 39 evaluable patients showed that sumatriptan injection 6 mg gave highly significant relief of CH in 74% of patients within 15 minutes vs 26% of patients after placebo. A similar controlled study in 134 evaluable patients showed that a dose of 12 mg was not more effective than a sumatriptan injection (6 mg), but was associated with a higher incidence of adverse events.

Also of interest are the long-term effects of the drug, and two large clinical trials have been performed to date. In one open-label trial (62) subcutaneous sumatriptan (6 mg) was evaluated to assess the safety and efficacy in the first 3 months of a 24-month open study. A total of 138 patients each treated a maximum of two attacks daily, and the study recorded as many as 6,353 attacks. Adverse events were reported in 28% of attacks, being qualitatively similar to those seen in migraine long-term trials. The incidence did not increase with frequent use of sumatriptan. Headache relief was obtained at 15 minutes for a median of 96% of attacks treated. There was no indication of tachyphylaxis, decrease in the speed of response, or increased frequency of attacks with long-term treatment. In another trial (63) results of subcutaneous sumatriptan were investigated over a period of up to one year. A total of 2,031 attacks in 52 patients were evaluated. Good results were reported in 88% of all attacks, and no decline in efficacy occurred during the course of the study. Patients with chronic CH responded well to treatment, but to a lesser extent and more slowly than patients with episodic CH. The profile of adverse events was comparable with results from other studies.

Several patients report that pain relief starts as early as 5 minutes after injection of sumatriptan, and the great majority of patients become nearly or completely pain-free within 10-15 minutes. The clinical effect parallels the peak plasma concentration and occurs considerably faster than in migraine therapy, which may indicate that different mechanisms of action are operative in these two diseases. Interestingly, most of the accompanying symptoms from the eye and nostril disappear in parallel with pain, which could indicate that these symptoms are in some way related to activation of pain fibres.

Use of sumatriptan more than twice daily is usually not recommended but this might give rise to some problems when the patient has frequent attacks (3-8 attacks per day). These unlucky sufferers should be provided with oxygen gas as a parallel acute treatment or given an adequate prophylaxis to reduce attack frequency, where sumatriptan is added as a symptomatic agent for intolerable headaches. The occasional patient may possibly be allowed to treat more than two attacks per day with sumatriptan for short periods if all else has failed. Subcutaneous injection is more effective than nasal spray in the treatment of CH (64). Oral sumatriptan has no evident prophylactic effect against acute attacks, in contrast to the actions of ergotamine tartrate, for example. It should be emphasised that we have at present rather limited knowledge on the efficacy, safety and tolerability of sumatriptan in CH outside the age limits of 18-65 years. Any contraindications should of course be taken into account before the treatment is given, even though there have been only few instances of serious adverse events following sumatriptan in CH (62). One patient, a female of 47, suffered a myocardial infarction after only a few subcutaneous injections, despite having no history of underlying ischaemic heart disease. Another two patients with CH revealed transitory ischaemic ECG changes following subcutaneous sumatriptan. In both patients, however, evident contraindications to the use of sumatriptan were not taken into consideration before treatment.

**Recent alternative prophylactics**

In most quarters verapamil, steroids and lithium, alone or in different combinations, are used in the prophylaxis of CH. Other therapeutic options that have been tried recently are sodium valproate, topiramate, melatonin, capsaicin, naratriptan, tizanidine, clonidine transdermally and hyperbaric oxygen. The results are, however, mainly based upon rather small patient series. Resetting of internal pacemakers by shifting sleep-wake cycles and/or exposure to bright light may be another therapeutic option in some cases.

Surgical procedures may be considered in carefully selected sufferers if all else has failed. Thermo-coagulation of the Gasserian ganglion is at present the method of choice. Minimal requirements for achieving a lasting headache-free state are total analgesia of the first and second divisions of the trigeminal nerve and dense or complete corneal numbness. Therefore the risk of keratitis must always be borne in mind.
Deep brain stimulation

As previously mentioned it seems that the “generator” of CH is located in the inferior posterior hypothalamic grey matter ipsilateral to the pain. Recently Leone et al. (65-67) performed electrical stimulation of this particular area in 7 severe therapy resistant chronic CH patients their aim being to prevent the critical activation during headaches. Postoperative MRI verified the position of the permanent electrode. Nine hypothalamic implantation and stimulation procedures (67) were well tolerated and yielded most positive therapeutic results, also in the long-term; five of the patients became pain-free without any further medical treatment. Interestingly, pain attacks reappeared if patients switched off their stimulators. Deep brain stimulation seems to be very promising and should be tried in carefully selected chronic CH patients who are unresponsive to medical or other treatments.

Concluding remarks

In conclusion, cluster headache is one of the most severe pain conditions known to mankind. The suffering of the patient is enormous, which places special demands on the treating physician as regards his or her empathy and understanding of the patient’s whole situation. Sumatriptan provides the most effective principle of acute therapy but the main aim of treatment should, in our opinion, be to prevent the attacks. CH is now regarded as a neurovascular form of primary headache with its attack “generator” in the ipsilateral inferior posterior hypothalamicus. Deep brain stimulation of this particular region provides a novel treatment option that is directed against the presumed CNS origin of pain attacks.

References

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