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Cluster Headache

Aetiology, Diagnosis and Management

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Abstract

Cluster headache is characterised by repeated attacks of strictly unilateral pain in the orbital region associated with local autonomic symptoms or signs. The attacks are brief but of a very severe, almost excruciating intensity. For unknown reasons males are affected more often than females. Recent studies suggest that an autosomal dominant gene has a role in some families with cluster headache. Hormonal studies indicate a dysfunction in the central nervous system. Neuroimaging has revealed primary defects in the hypothalamic grey matter. Local homolateral dilatation in the intracranial segment of the internal carotid and ophthalmic arteries during attacks is the result of a generic neurovascular activation, probably mediated by trigeminal parasympathetic reflexes.

Sumatriptan 6mg subcutaneously is the drug of choice in the treatment of acute attacks. Inhalation of 100% oxygen can also be recommended. In the prophylactic treatment, verapamil is the first option. Other drugs that can be considered are

corticosteroids, which may induce a remission of frequent, severe attacks, and lithium. Oral ergotamine tartrate may be sufficient for patients with night attacks and/or short, rather mild to moderately severe cluster headache periods. Third line drugs are serotonin inhibitors (methysergide and pizotifen) and valproic acid. Patients should be encouraged to keep headache diaries and be carefully instructed about the nature and treatment of the headaches. Alcohol can bring on extra attacks and should not be consumed during active periods of cluster headache.

Cluster headache occurs in one per thousand in the population, with a clear male preponderance. Despite being relatively uncommon, the disease is well known to headache specialists, because of the high intensity of pain and the precise characteristics in pain location, accompanying local symptoms, and timing of attacks.[1-3]

According to the International Headache Society[4] attacks last for 15 to 180 minutes and occur from once every other day to 8 times a day. Pain is very severe, of a boring, bursting or piercing quality. It is strictly unilateral and recurs on the same side of the head in repeated attacks. It is located behind and around the eye and spreads to ipsilateral parts of the head or face. Headache attacks are associated with symptoms or signs indicating a local autonomic dysfunction.

Attacks occur in series (so called cluster periods) that are separated by headache-free interval remission periods that usually last for months or years (so-called episodic cluster headache). A minority of patients have attacks for >1 year without remission or with remissions lasting <14 days; they are diagnosed as having chronic cluster headache. Patients with chronic cluster headache are commonly divided into two subgroups: either unremitting from onset (primary chronic) or evolving from episodic (secondary chronic).

1. Aetiology and Pathophysiology

For unknown reasons cluster headache is much more common in males (80 to 85%) than in females. Cluster periods characteristically start in the third decade of life, and very seldom before the age of 20. In our experience few patients continue to get cluster headache beyond the age of 65 to 70, and the remission periods tend to become longer during the last decade. Chronic cluster headache may become episodic before ending.

In recent years the importance of heredity in cluster headache has become increasingly recognised. First-degree relatives of probands with cluster headache have been shown to have a 14-fold increased risk of getting cluster headache compared with the general population.[5] Second-degree relatives had a corresponding 2-fold risk. Similar results have been reported by Kudrow and Kudrow,[6] and recently by Leone et al.[7] Complex segregation analysis suggests that an autosomal dominant gene has a role in some families.[8] The responsible gene occurs in 3 to 4% of men and 7 to 10% of women with cluster headache. Cluster headache has been reported in five pairs of monozygotic twins, and, interestingly, all twin pairs were concordant for the disease, this being further support of a genetic background, at least in some patients. However, there may be selection bias here as these rare patients are more likely to be published than if the disease appeared in one of the twins only. Nevertheless, further genetic studies are of definite interest in cluster headache.

It has been suggested that the primary defects in cluster headache are located in regulating centres in the anterior hypothalamus. There are several observations to support such a hypothesis. Alterations in biological rhythms of hormone secretion have been recorded, notably regarding cortisol, prolactin and testosterone, both during active periods and in clinical remission.[9] The pineal sleep hormone melatonin is a biological marker of hypothalamic function and the circadian system, and its secretion has also been shown to be altered in cluster headache. Nocturnal serum melatonin levels were lower

during the active cluster headache period than during the remission state[10] and the 24-hour urinary excretory pattern of its main metabolite 6-sulphatoxymelatonin was abnormal in both phases of the disease.[11] Plasma peak melatonin levels shifted (anticipated or delayed) both in remission and in the active phase of cluster headache suggesting a derangement of internal biological clocks in the suprachiasmatic nuclei.[11] Oral melatonin has consequently been tried in patients with cluster headache with some positive effects, at least in the short-term.[12] The therapeutic actions of lithium (*vide infra*) also seem to indicate a dysfunction of pacemaker or circadian regions in the hypothalamus.

Recent findings by positron emission tomography (PET) of an increased blood flow during attacks in the hypothalamic grey area on the painful side[13] and structural changes in the same area[14] lend further support to a central, hypothalamic, origin of the disease. Magnetic resonance imaging (MRI) angiographic studies and conventional carotid angiography have demonstrated a dilated intracranial segment of the internal carotid and ophthalmic arteries on the painful side during or outside attacks. This loss of vascular tone is believed to result from a defect in sympathetic perivascular innervation; the same nerves run to the eye, giving rise to the miosis and ptosis seen during attacks.

The loss of tone in ipsilateral retro-orbital arteries is in line with other clinical observations: during periods with cluster headache an increased sensitivity to vasodilator stimuli is seen; and attacks may be triggered by alcohol, histamine or nitroglycerin with onset occurring after an interval of 30 to 50 minutes after intake. This time latency before an expected attack is of great interest as regards the underlying mechanisms. Nitroglycerin is a donor of nitric oxide (NO) and it is tempting to believe that a local hypersensitivity to vascular effects of NO[15] is one part of a chain of events that leads to an attack following critical disturbances of the autonomic balance. Activation of the trigeminovascular system and cranial autonomic parasympathetic reflexes may explain the pain and the autonomic features of cluster headache.[16]

2. Diagnosis

The diagnosis is based mainly on the history of the patient. The patients should first be allowed to describe their symptoms spontaneously and to give the reason for the present consultation. They should then be questioned more systematically so that a clear structural picture of the pain is obtained. Cardinal features of the pain are: (i) extreme severity; (ii) strictly unilateral, orbital, supraorbital and/or temporal location; (iii) recurring brief attacks; (iv) a particular timing of attacks that not uncommonly appear with a 'clockwise' regularity; (v) local autonomic symptoms or signs such as conjunctival injection, lacrimation, rhinorrhoea, miosis, ptosis. In most instances the clinical picture is so clear-cut that there are really no diagnostic difficulties. There is generally no indication for a radiological investigation if the history and the clinical examinations are unremarkable.

However, in the very beginning of the course of disease a definite diagnosis may be somewhat difficult. Some patients may only vaguely describe their pain, and the duration of attacks may not be clearly stated. In such instances it may be helpful to elicit an extra attack by nitroglycerin in order to make direct clinical observations possible. Valuable information on the attacks and their time pattern may also be obtained if the patient keeps a diary record during one or more cluster periods.

2.1 Differential Diagnosis

Cluster headache should be separated from other headache disorders, such as migraine or trigeminal neuralgia. Migraine pain often starts on one side of the head but may spread to the greater part of the head. Characteristically, pain switches from one side to the other in successive attacks. This does not occur in cluster headache. Neither are visual or other focal aura symptoms associated with attacks of cluster headache. In contrast, aura symptoms are classic features in many patients with migraine. Since migraine is very common,

one may expect to find some patients who get both migraine and cluster headache. Such a combination may in our view solely be a question of coincidence.

Trigeminal neuralgia (tic douloureux) is characterised by paroxysmal attacks of unilateral facial or frontal pain, lasting for a few seconds and up to 2 minutes. Pain is sharp, electric-like and in most instances distributed along the second and/or third divisions of the trigeminal nerve. Pain can be precipitated from trigger areas in the facial skin or the oral mucosa. Carbamazepine and gabapentin are effective for trigeminal neuralgia but not in cluster headache.

Other differential diagnoses may be dissection or occlusion, aneurysm, or aneurysmal dilatation of the internal carotid artery. Sinusitis, glaucoma, posterior scleritis and other ocular disorders should also be considered in patients presenting atypically.

In this context the rare disorder of chronic paroxysmal hemicrania (CPH) should be mentioned. CPH has a clinical picture that is similar to cluster headache. However, attacks are shorter in length, much more frequent, occur mostly in females, and there is an absolute response to indomethacin. The chronic stage of CPH may be preceded by an episodic stage, in analogy with what is seen in cluster headache.

3. Treatment

Treatment may be given against the acute attack (symptomatic treatment) or as a prophylaxis. Both options are to be recommended in most patients. Severity and duration of attacks may vary somewhat during an individual cluster headache period, and this should be considered when evaluating effects of acute treatment. Spontaneous remissions may also add to evaluation difficulties.

3.1 Acute Symptomatic Treatment

3.1.1 Triptans

Sumatriptan given subcutaneously is at present the drug of choice in the acute treatment of cluster headache. Sumatriptan is a selective serotonin (5-hydroxytryptamine; 5-HT) 1B/1D/1F receptor agonist and causes selective cranial vasoconstriction, via 5-HT_{1B} receptor activation, and inhibition of the trigeminal nerve.[17] Randomised, double-blind, placebo-controlled, crossover studies of sumatriptan have been carried out in 173 patients[18] and results from non-blind trials have been reported in >240 patients. The severity of headaches has been shown to decrease in 74% of attacks within 15 minutes after sumatriptan 6mg subcutaneously compared with 26% of the attacks following placebo.[19] Furthermore, at least one third of the patients became free of pain within 10 minutes compared with 3% after placebo. The severity of functional disability also decreased more in response to sumatriptan than placebo. Sumatriptan was well tolerated and there were no serious adverse events. Heart rate and blood pressure were unaffected, and no abnormalities were found in laboratory parameters or electrocardiograms during treatment with sumatriptan.

It is recommended that sumatriptan should not be used more than twice daily. However, this may give rise to some problems when the patient has frequent attacks (3 to 8 attacks per day). These unlucky patients should be provided with oxygen gas as a parallel acute treatment and/or given an adequate prophylaxis to reduce attack frequency. However, the occasional patient may possibly be allowed to treat >2 attacks per day with sumatriptan for short periods if everything else has failed. Sumatriptan is generally recommended in patients aged 18 to 65 years, and we have at present rather limited knowledge on its efficacy, safety and tolerability in patients with cluster headache outside these age limits. Sumatriptan is efficacious also in long-term treatment[20] and does not lose its potency on frequent use (tachyphylaxis).

Angina pectoris and uncontrolled arterial hypertension are the most important contraindications for sumatriptan. It is remarkable that severe adverse effects of sumatriptan are rare in cluster headache.[18] There is only one case report of a female patient aged 47 years with a myocardial infarction after a few subcutaneous injections of sumatriptan. She had no history of underlying ischaemic heart

disease.[21] Another two patients with cluster headache have been described as having transitory ischaemic electrocardiograph changes following subcutaneous sumatriptan. In both patients evident contraindications to the use of sumatriptan were not taken into consideration before treatment.[18] *In summary,* it is important to properly select those patients that may be candidates for sumatriptan treatment.

Oral sumatriptan has no evident prophylactic effect against acute attacks.[22]

Zolmitriptan provided a meaningful pain relief in several patients with episodic cluster headache, but not until 30 minutes after intake.[23] Patients with chronic cluster headache do not obtain relief. In the future, more rapidly absorbed formulations of orally or nasally administered triptans are needed to provide effective treatment for this disease.

3.1.2 Oxygen

Inhalation of 100% oxygen, usually at 6 to 7 L/min, has long been known to be rapidly effective in relieving pain during attacks in several, but far from all, patients (50 to 85%).[24,25] The mechanism of action is probably vasoconstriction. Those who respond best are patients under the age of 50 years with the episodic type of disease. If oxygen inhalation is started at the onset of the attack, it often aborts the attack entirely. The pain declines after 5 to 15 minutes of continuous breathing through a loosely applied facial mask. Oxygen should be discontinued if no effect occurs after 15 to 20 minutes. Oxygen can be given in addition to acute treatment (e.g. sumatriptan) and prophylactic treatment.

A great advantage is that oxygen causes no adverse effects. A drawback of oxygen inhalation treatment is that the patient must have continuous access to the oxygen supply, which for several reasons may be impractical. Oxygen tanks should be kept both at home and in the work place. Their use is restricted by precautions required by fire authorities, and the equipment is inconvenient since it cannot be carried around. Furthermore, it forces the patient to sit still during treatment, a behaviour that usually is incompatible with the intense pain. This may explain why only one third of the patients who benefit from oxygen continue its use.

Hyperbaric oxygen (2.5 ATA) has been tested as a prophylactic treatment in cluster headache. However, in a double-blind placebo-controlled crossover study in patients with episodic and chronic disease, no significant effect was obtained.[26]

3.1.3 Intranasal Lidocaine

Anaesthetics, applied deep in the nostril on the painful side, have been tried in attempts to block pain close to its anticipated origin (deep behind the eye). Lidocaine is currently preferred.[27] Lidocaine 20 to 60mg, given as nasal drops or spray, results in mild to moderate relief within 1 to 10 minutes in most patients, but only a few patients obtain complete pain relief.

3.1.4 Ergotamine Tartrate

Oral or rectal administration of ergotamine tartrate has a limited value only against acute attacks. Ergotamine inhalation may give some relief, but there are practical problems with inhaling ergotamine. One study reported relief from pain within half an hour in 71% of 114 attacks,[28] and in another trial 79 out of 100 patients obtained 'significant relief' from sublingual or inhalant ergotamine preparations.[29] However, there are no recent trials on inhaled ergotamine in patients with cluster headache. Ergotamine is a potent vasoconstrictor and the most serious adverse effect is arterial spasm. Ergotamine is contraindicated in, among others, patients with coronary or peripheral vascular disease, arterial hypertension, and severe diseases of the liver and kidney. Long-term use may lead to dependence.

Dihydroergotamine, inhaled or given subcutaneously, may be tried to terminate acute attacks[30] and has been said to give rise to fewer adverse effects than does ergotamine tartrate. Occasionally, mild leg pain may be experienced.

3.1.5 Analgesics

It is generally stated that analgesics are of limited value in the treatment of cluster headache. Because of a slow absorption they are not sufficiently

effective to counteract the rapidly increasing pain, and their maximum pharmacological activity coincides temporally with when the cluster attack is either spontaneously decreasing in severity or is resolved. Some problems with habituation and toxicity may appear on prolonged treatment with repeated high dosage. Frequent use of analgesics (notably opioids) is generally not to be recommended in cluster headache.

3.1.6 Conclusion

Patients want simple self-administered drugs with high efficacy and a tolerable, rapid and consistent action. In our experience there are no pharmacological agents at present that can compete with sumatriptan. Sumatriptan is given as a sole acute medication or added to prophylactic management. It is well tolerated and there is no evidence of any tachyphylaxis with long-term treatment. It should be remembered that sumatriptan is an expensive drug. Alternative acute treatments may be considered for: (i) patients with >2 attacks per day; (ii) patients with intolerable adverse effects or any contraindications to sumatriptan; (iii) patients with extended periods of headache or a chronic syndrome. Very young or very old patients should also receive an individually tailored acute treatment. There is at present only limited experience in the management of patients in the latter age groups. It appears rational that pregnant and nursing women with a period of cluster headache should not be given sumatriptan. In most of the patient groups mentioned, inhalation of 100% oxygen is recommended as the acute therapy of first choice.

3.2 Prophylactic Treatment

Before the successful introduction of sumatriptan injections for individual attacks, the lack of a reliable acute treatment usually resulted in the testing of a variety of more or less effective prophylactic treatments. Today, the effective acute handling of individual attacks by sumatriptan injection and/or oxygen inhalation has lowered the need for prophylactic treatment. Such drugs are usually tested as additional treatment for patients with >2 attacks per day, or when adverse effects or insufficient effect occurs with the acute treatment.

3.2.1 Calcium Channel Antagonists

By unknown mechanisms calcium channel antagonists are effective as prophylactic treatment of episodic and chronic cluster headache. Verapamil is now the preferred first choice in the prevention of cluster headache.[31,32] It has a high efficacy in many patients and gives few adverse effects, also in the high doses that are sometimes needed. Approximately two thirds of patients receiving verapamil improve by >50% at daily doses of 240 to 480mg or higher, patients with severe chronic cluster headache require from 720mg up to approximately 1200mg per day.[33,34] Verapamil may be combined with lithium in patients with chronic disease. Constipation, postural hypotension, water retention and fatigue are the most common adverse effects.

3.2.2 Ergotamine

Regular administration of ergotamine (ergotamine tartrate) 3 to 4 mg/day over a few weeks has been used as prophylaxis for a long time.[35] If the patient has nocturnal attacks, 1 to 2mg may be given at night in the form of tablets or suppositories. If the attack pattern is constant over the 24 hours, the doses should be taken 30 minutes to 1 hour before the expected attack. Ergotamine may be sufficient for patients with short, rather mild cluster headache periods. The medication should be carefully monitored so that the total weekly dose of ergotamine is not too large. A drawback is that ergotamine should not be combined with sumatriptan treatment. Ergotamine prophylaxis has consequently been replaced in recent years by the calcium channel antagonist verapamil.

3.2.3 Corticosteroids

The corticosteroids prednisone and dexamethasone are effective and rapid-acting prophylactic drugs in the treatment of episodic and also, but to a lesser extent, chronic cluster headache. The mechanism of action is uncertain. Prednisone, usually 40 to 60 mg/day but up to 80 mg/day, has been used. Alternatively, dexamethasone 8mg daily or

methylprednisolone 500 to 1000mg intravenously usually eliminates or strongly reduces the number of attacks within 1 to 2 days.[36,37] Since adverse effects of corticosteroids increase with long-term use, these agents are used only to induce remission in patients with severe attacks of high frequency and intensity, particularly in the mid-part of a period. The headache usually returns when the dose of prednisone or dexamethasone is reduced below 25mg or 4mg per day, respectively. Treatment should be stopped within about 3 weeks of starting.

3.2.4 Lithium

Ever since its introduction for the treatment of manic-depressive disorders and periodic depression, lithium has been tried in various psychiatric, neurological and medical diseases. Lithium has thus been shown to be effective in patients with chronic cluster headache and those with episodic cluster headache.[38-40] Most patients will benefit from a daily dose of 600 to 900mg of lithium carbonate and are helped even at rather low serum concentrations of between 0.3 and 0.8 mmol/L. Positive effects may be seen within only a few days of starting treatment. Long-term effects of lithium are, on the other hand, less well known and some patients may develop drug tolerance.

Lithium is now widely used in clinical practice in the treatment of cluster headache but it should be borne in mind that results have derived mainly from non-blind clinical trials. Lithium may be combined with corticosteroids in patients with severe disease.[41]

Lithium has a number of adverse effects, for example, tremor, polyuria and diarrhoea. Renal and thyroid functions should be checked before and during treatment. The therapeutic range is narrow and adverse effects may occur even at the higher upper range of the treatment window (0.8 to 1.2 mmol/L). Serum lithium concentrations should be measured in the morning, 12 hours after the last oral dose. Lithium interacts with such drugs as indomethacin, diclofenac, thiazides and thiazide-related diuretics. It displaces intracellular sodium. Dehydration may quickly raise lithium concentrations. Lithium affects internal biological rhythms but its exact mechanisms of action in cluster headache remain largely unknown.

3.2.5 Serotonin Receptor Antagonists and Valproic Acid

Methysergide is a semisynthetic ergot alkaloid which has been used for many years as a prophylactic treatment, in both patients with migraine and those with cluster headache.[42] It has many adverse effects, notably a risk of inducing retroperitoneal fibrosis, and treatment should therefore be interrupted every 4 months for a 2-week interval. It is available only on a licence basis and is now seldom used in patients with cluster headache.

Pizotifen is structurally closely related to cyproheptadine and tricyclic antidepressants. A number of trials have been performed, although admittedly in rather small non-blind series, where a 'definite improvement' has been obtained in about 50% of patients. There has been one single-blind trial of pizotifen against cluster headache[43] where results were compared with those of placebo. Of 28 patients, 16 (57%) either became free from attacks or improved by >50%. Results from a number of non-blind studies have been reviewed[44] and are approximately comparable with those of optimal ergotamine prophylaxis. The most common adverse effects of pizotifen are drowsiness, stimulation of appetite and a dose-dependent increase of bodyweight. Long-term effects of pizotifen are not sufficiently documented, but it seems that some patients with chronic cluster headache may benefit, at least for a few months. Pizotifen has been commonly used in Europe but is not available in, for instance, the United States.

Valproic acid (sodium valproate), a γ-aminobytyric acid (GABA)-mimetic agent, has been evaluated in small non-blind studies.[45] The dosage has ranged from 600 to 2000 mg/day. Adverse effects are similar to those of pizotifen.

In summary, these drugs may be seen as third line options but can be tried when patients do not respond to conventional treatment or when the latter is contraindicated.

Table I. Main guidelines for acute and prophylactic treatment of cluster headache

Acute treatment
Sumatriptan subcutaneous injection 6mg and/or oxygen 100% inhalation 7 L/min
Prophylactic treatment
Verapamil 360-720 mg/day
Prednisone, ergotamine or lithium (these first four agents may be used in combination)
Methysergide, pizotifen or valproic acid[a]

a Methysergide is available on a licence basis. Pizotifen is not available in some countries such as the US.

3.2.6 Other Medication

Leone et al.[12] compared melatonin 10mg orally with placebo in 20 patients for 2 weeks in a double-blind pilot study using parallel groups. Positive results were reported and no adverse effects occurred.

Other treatments have also shown some promise, for example; topiramate,[46] baclofen[47] and transdermal clonidine.[48] However, the results have been obtained in short-term, non-blind trials in a limited number of patients.

3.2.7 Surgical Treatment

Surgery may be considered in patients with intractable chronic cluster headache which is totally resistant to pharmacotherapy. Trigeminal lesions, produced mechanically or chemically, or by root section, may eliminate attacks in such patients, apparently by blocking nociceptive afferent input via trigeminal nerve pathways. The best results are obtained by thermocoagulation of the Gasserian ganglion.[49,50] Recently γ-knife radiosurgery has also been used in patients with cluster headache for lesioning the trigeminal nerve root.[51]

Surgical procedures should be reserved for consistently unilateral headaches in patients with a stable personality profile.[50] It is important to remember that a recurrence may be seen on the contralateral side, and the risk of keratitis must always be borne in mind.

4. Conclusion

Treatment recommendations for patients with cluster headache are shown in table I. The patient should be instructed about the nature and treatment of cluster headache, and also on the current knowledge of its underlying mechanisms. It is very important to relieve the fear and anxiety the patient may have of the repeating episodes of severe pain. Alcohol may elicit an attack and should not be consumed during cluster periods. Afternoon naps should be avoided as they too can trigger attacks. Patients should be encouraged to keep a headache diary and it is necessary to re-evaluate the treatment on every visit of the patient.

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