Cluster headache: Clinical aspects and therapy with neurostimulation

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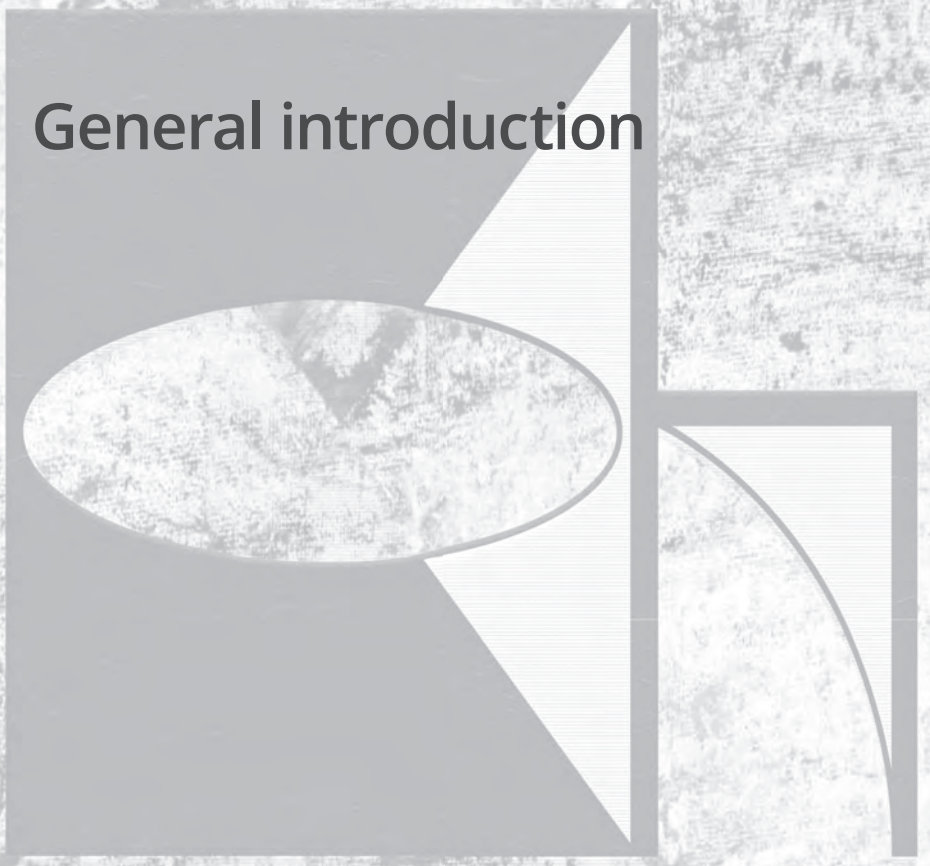
CHAPTER 1

General introduction



Cluster headache

The famous Dutch physician, anatomist and mayor of Amsterdam Nicolaes Tulp (1593-1674) was probably the first to describe the headache syndrome we now call cluster headache.[1] Over the years the syndrome was given many names (e.g. Horton's disease, migrainous neuralgia and hemicrania neuralgiformis chronica), finally resulting in the current name, which was given in 1952 by referring to the typical episodic character of the syndrome as it occurs in the majority of patients.[2,3]

Clinical presentation

Cluster headache is one of the primary headache syndromes categorized as a Trigeminal Autonomic Cephalgia, defined according to the trigeminal distribution of the pain and accompanying ipsilateral autonomic symptoms.[2] Cluster headache is characterized by unilateral short attacks of excruciating pain located in the (supra) orbital or temporal regions with simultaneously ipsilateral cranial autonomic features such as lacrimation (91%), conjunctival injection (77%) and nasal congestion (75%).[2,4,5] Most of these symptoms disappear after the attack, though ptosis and/or miosis may persist. Cluster headache attacks last between 15 and 180 minutes and can occur from once every other day to eight per day.[2]

There are two forms of cluster headache: episodic and chronic. Approximately 80% of the patients have the episodic form, which is defined as a life-time occurrence of at least two cluster periods lasting more than seven days, separated by pain-free remissions periods of more than one month. The remaining 20% have the chronic form, which is defined as having attacks for more than one year without remissions that last longer than 30 days.[2] Both varieties of cluster headache are associated with a lower quality of life and have considerable social impact.[6-8] Approximately 10% of chronic cluster headache patients is or becomes intractable or intolerant to regular medical treatment.[9]

Up to 23% of the patients can also experience aura symptoms preceding their attacks, which can exist of fully reversible visual, sensory, aphasic and/or dysarthric symptoms[4,5,10-12], but motor, brainstem or retinal symptoms are very rare.[12,13]

Epidemiology

The prevalence of cluster headache is about 1 in 1000 persons and the male to female ratio is 4.3:1.[14] Cluster headache can start at any age. There are several triggers for individual attacks such as alcohol, vasodilators, daytime naps, changes in air pressure, weather changes and certain odours.[5,10,15-18] Remarkably, these triggers do not cause cluster headache outside an episode.

Pathophysiology

The pathophysiological pathways of cluster headache are not known, although there are several hypotheses. In most of these, cluster headache is seen as a neurovascular disease[19], but a proposed pathophysiology must also include the trigeminal pain distribution, the accompanying autonomic and the circadian and seasonal features of the headache attacks.

The pain of a cluster headache attack is almost always located in the first division of the trigeminal nerve. The neurons of this part of the trigeminal nerve project to second-order neurons in the trigeminocervical complex. Pain signals from the trigeminocervical complex project to higher centers (the hypothalamus, thalamus, and cortex) via pain processing pathways.[20-22] The trigeminocervical complex activates also the parasympathetic autonomic outflow.[21] It has been suggested that involvement of this pathway can, at least partially, explain the ipsilateral autonomic symptoms.

The hypothalamus is suggested to play an important role in cluster headache, as increased activation of the hypothalamic grey matter could be visualized during attacks.[19,23-26] It has been hypothesized that these hypothalamic abnormalities reflect a dynamic process, which might tend to reverse outside the attack phase. The striking diurnal and seasonal pattern in cluster headache suggest a dysfunction of the suprachiasmatic nucleus of the posterior hypothalamus (also called "the biological clock").[27] Irregular sleep-wake patterns, longer REM-latencies and a decreased total amount and proportion of REM-sleep is reported in cluster headache patients during, but not outside, an episode.[28,29] It is likely that these sleep abnormalities might also be related to dysfunction of the biological clock. Deep brain stimulation of this part of the hypothalamus resulted in a decrease in nocturnal cluster headache attacks, improved sleep quality and sleep structure in chronic cluster headache patients.[30] The suprachiasmatic nucleus projects to the hypocretin system, which has influence on functions such as the sleep-wake cycle and the ability to modulate trigeminal nociceptive processing. Genetic association studies in cluster headache have suggested a role of the hypocretin system, as a polymorphism in the OX_2R receptor (*HCRTR2*) was repeatedly found to be associated with cluster headache.[31-34] Altogether, these findings strongly suggest a role for the hypothalamus in the pathophysiology of cluster headache.

Diagnosis and differential diagnosis

A diagnosis of cluster headache is based on the history of the patient and physical examination, by applying the criteria of the International Criteria of Headache Disorder-III beta version.[2] Although the diagnosis should not pose great problems because of the explicit phenotype and the typical seasonal and circadian pattern, in daily practice, a delay of 3-5 years in diagnosing cluster headache is not uncommon due to misdiagnosing and lack of recognition of the disease.[17, 35]

A contrast-enhanced cerebral MRI should be considered once in every suspected patient to exclude an underlying causal pathology as a variety

of intracranial underlying causal pathologies have been reported in patients with typical cluster headache symptoms.[36-38]

Cluster headache can be mistaken for one of the other Trigeminal Autonomic Cephalalgias. In general, attacks of paroxysmal hemicrania are shorter and should respond by definition to preventive treatment with indomethacin. Short-lasting Unilateral Neuralgiform headache with Conjunctival Tearing (SUNCT) and Short lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms (SUNA) can be differentiated from cluster headache by their shorter duration of attacks. Hemicrania continua does not occur in attacks, but the exacerbations of this syndrome resemble cluster headache attacks and in cluster headache also interictal pain is described.

Differentiating between cluster headache and migraine might be difficult in some patients. There are, however, several clear differences. The duration of migraine attacks is longer and migraine patients often seek rest during an attack, whereas cluster headache patients often are restless.[2] In addition, the accompanying symptoms of migraine are nausea and sensitivity to light, sound and smell, whereas in cluster headache these are not prominent.

Treatment

Treatment of cluster headache consists in the majority of patients in a combination of acute and prophylactic treatment. Acute treatment aims at rapidly reducing the pain of individual headache attacks. First choices are inhalation of 100% oxygen and/or the 5-HT 1B/1D agonist sumatriptan administered subcutaneous or intranasal.[39-42] Prophylactic treatment aims at reducing the number of attacks and verapamil is the drug of first choice both in episodic and chronic cluster headache.[43] Unfortunately, not all patients benefit from the regular available medical treatment options. For those patients, a range of more experimental therapies may offer possible alternatives.

Neurostimulation

Hypothalamic deep brain stimulation was shown to be effective in some patients with medically intractable chronic cluster headache in small open studies, but was associated with morbidity (as diplopia and dizziness) and even fatality.[44-46] The risk and sometimes lack of effectiveness of deep brain stimulation has led several research groups to investigate extracranial neurostimulation treatments.

Recent pilot studies suggests that occipital nerve stimulation in patients with medically intractable chronic cluster headache might offer an effective alternative to conventional headache treatments.[47-50] Taken together, a reduction in attack frequency of ≥50% was seen in more than half of these selected patients and there was a patient satisfaction rate of 80%.[47-50] Follow up studies have shown long term efficacy of occipital nerve stimulation.[51,52] These encouraging results led to an European randomized, double blinded, investigator initiated clinical trial to investigate the effect and safety of occipital nerve stimulation as preventive treatment in medically intractable chronic cluster headache.[53]

The sphenopalatine ganglion is presumed to be involved in the cranial autonomic symptoms during attacks. A small prospective randomized sham controlled pilot study in 28 chronic cluster headache patients showed a reduction of ≥50% of pain intensity in about 25% of their patients after invasive sphenopalatine ganglion stimulation.[54]

One presumed mechanism for why occipital stimulation may be effective in cluster headache patients is that through the natural wiring in the nervous system electrical impulses captured in the peripheral nerve field of the occipital nerves exert modulating effects on the origin of the trigeminal nerve in the brainstem. Via which the second branch, the maxillary nerve has modulation effects on the sphenopalatine ganglion and indirectly on the function of the hypothalamus.

Recent case series reported a decreased frequency and severity of cluster headache after non-invasive vagal nerve stimulation.[55] Moreover, an open-label study with this neurostimulator showed a subjective

improvement in 13 out of 14 patients and a reduction in prophylactic treatment in seven patients.[56] Recently, this non-invasive vagal nerve stimulator was evaluated as adjunctive prophylactic therapy for cluster headache attacks in almost 100 chronic cluster headache patients.[57] A reduction in attack frequency of ≥50% was seen in 40% of those treated with standard of care plus vagal nerve stimulation versus 8.3% treated with standard of care.

Aims of this thesis

In this thesis different studies of clinical aspects of cluster headache and cluster headache treatment, especially neurostimulation therapies, are reported. The aims of this thesis are to gain a better understanding of clinical aspects of cluster headache and some of other TACs (chapter 2 – 8) and to evaluate various aspects of neurostimulation therapies in cluster headache (chapter 9 – 10).

Part I - Clinical aspects

Cluster headache and other Trigeminal Autonomic Cephalgias can have an underlying structural pathology as described in various case reports in the literature. In chapter 2 an overview of published symptomatic Trigeminal Autonomic Cephalgias is given. In chapter 3 a case of the so-called Cluster –Tic syndrome, of which cluster headache is a part, is reported. Both chapters might give some insight in how structural pathology can be involved in the phenotype of cluster headache. Chapter 4 describes a survey that explores the consequences of recently proposed changes in the ICHD-III beta version of the International Classification of Headache Disorders for diagnosing cluster headache. Aura symptoms as they can occur in cluster headache are described in chapter 5. The association between cluster headache and sleep rhythm is explored in chapter 6, and in chapter 7 a rare side effect of lithium carbonate given als preventive cluster headache treatment is described. The use and effects of illicit drugs in a Dutch cluster headache population is reported in chapter 8.

Part II - Therapy with neurostimulation

Chapter 9 descibes a patient in whom occipital nerve stimulation was effective during pregnancy. The acute effect of vagal nerve stimulation in episodic and chronic cluster headache in a meta-analysis of two randomized controled trials is described in chapter 10.

The general discussion in chapter 11 focuses on future perspectives based on the results of the present study.

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