Cluster headache: Clinical aspects and therapy with neurostimulation

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Cluster Headache – Clinical Aspects and Therapy with Neurostimulation

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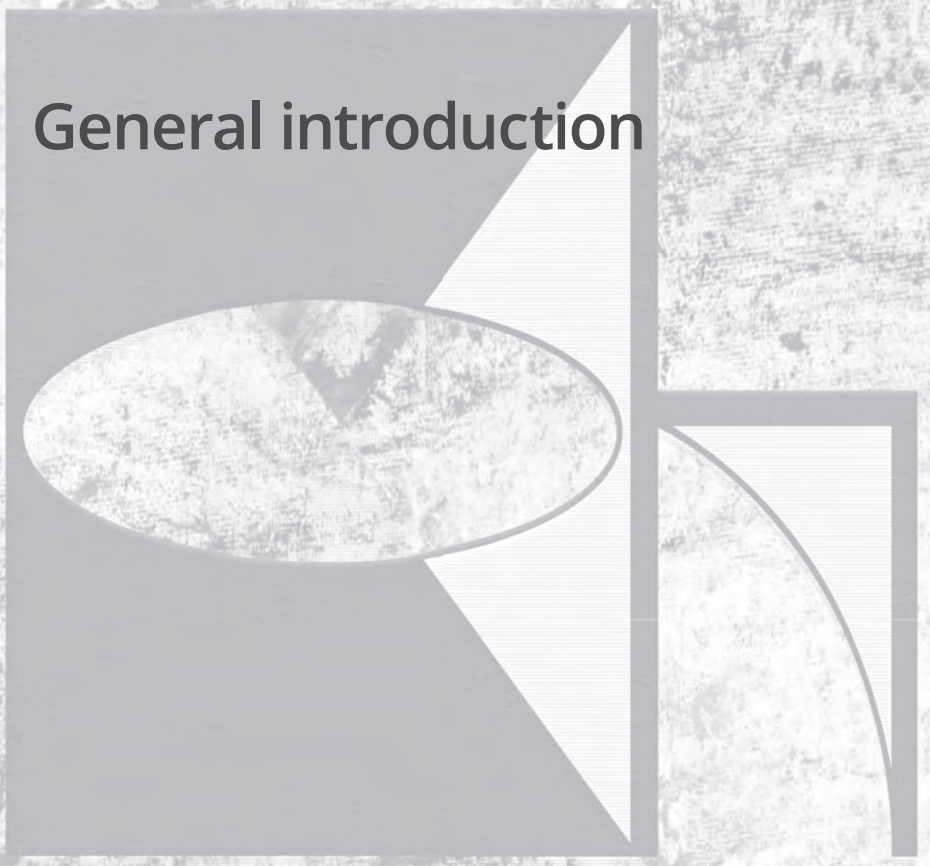
Voor mijn ouders

Contents

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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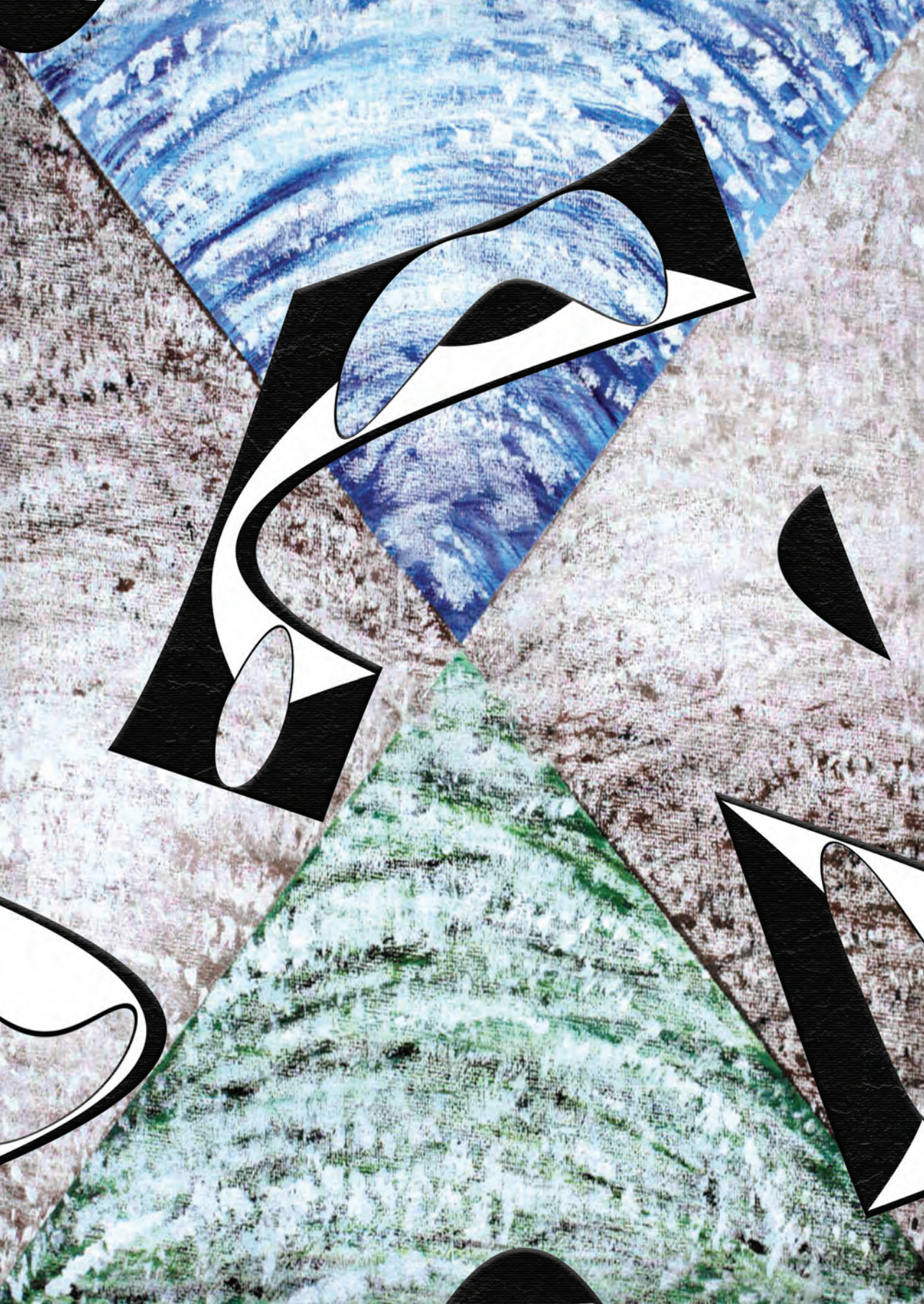

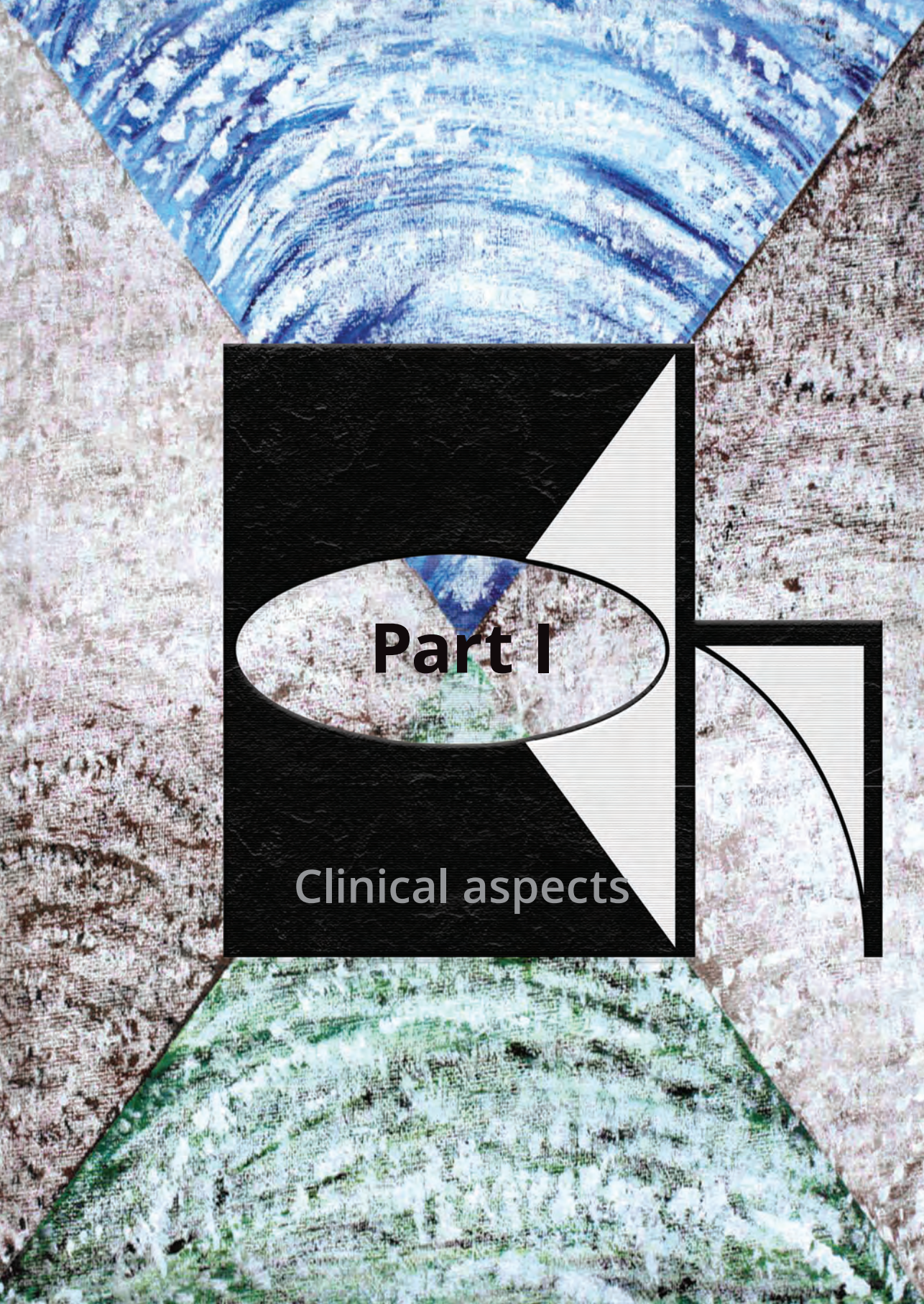
Part I
Clinical aspects

CHAPTER 2

Symptomatic trigeminal autonomic cephalalgias

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Abstract

Trigeminal autonomic cephalalgias (TACs) are primary headache syndromes that share some clinical features such as a trigeminal distribution of the pain and accompanying ipsilateral autonomic symptoms. By definition, no underlying structural lesion for the phenotype is found. There are, however, many descriptions in the literature of patients with structural lesions causing symptoms that are indistinguishable from those of idiopathic TACs.

In this article we review the recent insights in symptomatic TACs by comparing and categorizing newly published cases. We confirm that symptomatic TACs can have typical phenotypes. It is of crucial importance to identify symptomatic TACs, as the underlying cause will influence treatment and outcome. Our update focusses on when a structural lesion should be sought for.

Introduction

Trigeminal autonomic cephalalgias (TACs) are primary headache syndromes that own their name to the trigeminal distribution of the pain and the accompanying ipsilateral autonomic symptoms, as defined by the International Classification of Headache disorders (ICHD) III beta criteria[1] The most prevalent TAC is cluster headache, but the category also includes rare diseases such as paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and hemicrania continua.

It is well known that an underlying structural lesion can lead to TAC symptoms, which cannot easily be differentiated from those of idiopathic TACs.[2,3]• Recognizing these underlying pathologies is of crucial importance, as they can influence treatment and outcome. Here, we will give an update of recently published cases with an underlying structural lesion and a TAC phenotype.

Material and methods

In 2009, our group published a comprehensive update of symptomatic TACs reported until mid-February 2009.[4] With the this report as starting point, we conducted a Pubmed search from February 2009 to January 2015 with the following key words: Trigeminal autonomic cephalalgia, cluster headache, hemicrania continua, SUNCT, SUNA, paroxysmal hemicrania, secondary and symptomatic. Only articles written in English were included of which the full text was available. Cases were divided in three categories: "*probably secondary"*, "*possibly secondary"* and "*unknown*". Cases were defined as "*probably secondary*" when there was a dramatic improvement of the headache after treatment of the underlying lesion. Cases were defined as "*possibly secondary"*, when the patient was treated but did not become headache-free, or was not treated, but when a causal relation was possible based on previous experience with other patients. Efficacy of indomethacin was not considered as treatment response in paroxysmal hemicrania and hemicrania continua, as this is one of the diagnostic criteria and not specifically aiming at an underling lesion. The category "*unknown"* was used for patients in which a causal relation

between the phenotype and the lesion was less likely or at least unclear: in most cases the patient was not treated and a causal relation between the lesion and the TAC was unlikely on anatomical grounds, and/or a probable incidental finding.

Results

Cluster headache

We found 23 cases with a cluster headache-like phenotype in 23 articles.[2,5-26] We excluded 3 patients, as they did not fulfil the ICHD-III criteria beta version, all having an attack duration of more than 3 hours.[18,23,25] We excluded also another patient who did not have a structural lesion.[16] This resulted in 19 patients of whom 12 could be categorized as *probably secondary* and 7 as *possibly secondary* (Table 1).

Of the 12 cases in the *probably secondary* category, 5 had a neoplasm[15,19,21,29,31]: a non-functioning pituitary adenoma, an ipsilateral carotid paraganglioma, an ipsilateral prolactinoma, an ipsilateral glioblastoma multiforme, and an ipsilateral hemangiopericytoma. A vascular cause, a stroke secondary to moyamoya disease, was found in 1 patient.[36] Other patients had an intrasellar arachnoid cyst, maxillary sinusitis (n=2), compression of the right vertebral artery by fibrosis, sarcoidosis (with a hypothalamic lesion), and obstructive sleep apnoea.[8,10-12,22,26]

There were 7 cases defined as *possibly secondary*. Multiple sclerosis was found in 2, of whom both became pain free under verapamil or prednisone, which are used as prophylactic cluster headache medication and therefore are not strictly aiming at the "underlying lesion".[2,21] Another patient had an internal carotid artery dissection, but the outcome after treatment remained unclear.[6]• Other diagnoses in this category: recurrent posterior scleritis and aspecific meningitis (treated with prednisone), post-operative cluster headache (lens phacoemulsification and intraocular lens implant) , an angiomyolipoma, and an ipsilateral macroprolactinoma.[5,7,15,20] The latter 2 patients responded completely or partly to treatment of the underlying lesion, but only in combination with preventive cluster headache treatment.

Table 1. Symptomatic Cases of Cluster headache

Authors	Publication year	Age (year)	Sex	Headache phenotype	Duration of CH symptoms	Atypical features	Underlying lesion	Treatment	Follow up	Outcome
Probably symptomatic cluster headache										
Edvardsson [13]	2014	49	M	Cluster headache	1 month	Nausea, photophobia and phonophobia	Non-functioning pituitary adenoma (chromophobe adenoma)	Sumatriptan SC, oxygen, verapamil, surgery	17 months	Pain free
Malissart et al. [19]	2014	60	F	Cluster headache	3 days	-	Ipsilateral carotid paraganglioma	Surgery	Unknown	Pain free
Edvardsson et al. [10]	2013	43	M	Cluster headache	2 months	Nausea and photophobia/ phonophobia	Intrasellar arachnoid cyst	Craniotomy with cyst fenestration	4 months	Pain free
Edvardsson et al. [12]	2013	21	M	Cluster headache	3 weeks	-	Maxillary sinusitis	Antibiotics and sinus puncture	4 years	Pain free
Levy et al. [17]	2012	25	M	Cluster headache	3 months	-	Ipsilateral pituitary macroprolactinoma	Cabergoline	Unknown	Pain free
Edvardssonet al. [9]	2012	41	M	Cluster headache	3 months	Nausea and photophobia/ phonophobia	Ipsilateral glioblastoma multiforme	Surgery	12 months	Pain free
Ranieri et al. [22]	2009	39	M	Cluster headache	14 years	Maxillary pain next to perorbital pain, continues daily pain during last 7 months, tooth grinding and frequently waking up at night	Obstrubctive Sleep Apnoea diagnosis 14 years after cluster headache diagnosis	Intra-oral device	12 months	Pain free

Table 1. Symptomatic Cases of Cluster headache

Authors	Publication year	Age (year)	Sex	Headache phenotype	Duration of CH symptoms	Atypical features	Underlying lesion	Treatment	Follow up	Outcome
Sewell et al. [24]	2009	34	M	Cluster headache	17 years	At moment of consultation restless legs syndrome and numbness in fingers	Stroke caused by moyamoya	Two cranial bypasses	6 years	Pain free
Edvardsson [11•]	2013	24	M	Cluster headache	4 weeks	-	Acute maxillaris sinusitis	Antibiotics and sinus puncture	Several years	Pain free
Fontaine et al. [14]	2013	27	M	Cluster headache	4 months	-	Ipsilateral he-mangiopericy-toma	Surgery	9 months	Pain free
Van der Vlist et al. [26]	2013	31	M	Cluster headache	2 months	Diffuse headache next to the attacks	Sarcoidosis (also hypothalamic lesion)	Prednisone course	7 months	Pain free
Créac'h et al. [8]	2010	44	F	Cluster headache	7 months	Trigger factor: rotation of head to the right	Neurovascular compression caused by fibrosis surrounding both C3 and right vertebral artery	Verapamil for 6 months, microvascular dissection	2,5 years	Pain free
Possibly symptomatic cluster headache										
Candeloro et al. [6•]	2013	39	M	Cluster headache	21 years	Once attack duration of > 3 hours	Dissection of the right distal internal carotid artery	Heparin	6 months	Unknown
Mijajlović et al. [21]	2014	45	M	Cluster headache	7 days	-	Multiple Sclerosis	Brief course of methylprednis-olone with afterwards verapamil for 1 year.	3 year	Pain free

Table 1. Symptomatic Cases of Cluster headache

Authors	Publication year	Age (year)	Sex	Headache phenotype	Duration of CH symptoms	Atypical features	Underlying lesion	Treatment	Follow up	Outcome
Gil-Gouveia et al. [15]	2013	79	F	Cluster headache	-	-	48 hours after lens phacoemulsification and intraocular lens implant	Verapamil, Sodium valproate, oxygen	9 months	Decrease in attack frequency
Messina et al. [20]	2013	27	M	Cluster headache	-	-	Angiomyolipoma	Hypothalamic deep brain stimulation	Unknown	Decrease in attack frequency
Donat [2]	2011	33	M	Cluster headache	-	-	Multiple Sclerosis	Verapamil	10 months	Pain free
Choi et al. [7]	2009	52	F	Cluster headache	10 years	Attacks sometimes on both sides. This time also blurred vison and central horizontal scotoma	Recurrent posterior scleritis and aseptic meningitis	Prednisone course	2 months	Unknown
Benitez-Rosario et al. [5]	2009	41	M	Cluster headache	12 months	Depressive symptoms	Ipsilateral macro-prolactinoma	Cabergoline, hormonal replacement, prednisone course, verapamil	About 1-2 month	Pain free

Paroxysmal hemicrania

We identified 3 cases of paroxysmal hemicrania, of whom all were excluded as they did not fulfil the ICHD-III criteria beta version.[27-29] The missing criterion in two patients was an unknown response to indomethacin[27,28] and the third reported bilateral instead of unilateral facial pain.[29]

Hemicrania Continua

We identified 7 cases[30-34] of symptomatic hemicrania continua of whom one was excluded as the patient did not receive indomethacin.[31] We categorized 2 cases as *probably symptomatic*, 3 as *possibly symptomatic* and 1 as *unknown* (Table 2).

The underlying lesion in the cases defined as *probably symptomatic* were a cerebral venous thrombosis and brain metastases of a primary lung adenocarcinoma.[32,34] Both patients responded to treatment of the underlying cause and indomethacin could be withdrawn.

In patients defined as *possibly symptomatic* the possible causes were post-traumatic and twice post-operative.[33] All received indomethacin as treatment for their hemicrania continua.

One case was classified as *unknown.* This patient was diagnosed with an orbital pseudotumour, treated with prednisone and indomethacin.[30]

Table 2. Symptomatic Cases of Hemicrania Continua

Authors	Publication (year)	Age (year)	Sex	Headache phenotype	Duration symptoms	Indomethacin response	Atypical features	Underlying lesion	Treatment	Follow up	Outcome
Probably symptomatic hemicrania continua											
Mathew et al.[32]	2014	42	M	Hemicrania Continua	1 month	Completely	Duration < 3 months	Cerebral venous thrombosis	Anticoagulation and antiedema therapy	3 days	Pain free
Robbins et al.[34]	2010	55	F	Hemicrania Continua	7 months	Completely	Ocular foreign body sensation	Brain metastases of primary lung adenocarcinoma	Indomethacin for 3 days, dexamethasone, chemotherapy and whole brain radiation	6 months	Pain free
Possibly symptomatic hemicrania continua											
Prakash et al.[33]	2009	52	M	Hemicrania Continua	10 years	Completely	-	Post-traumatic	Indomethacin	15 months	Pain free
Prakash et al.[33]	2009	36	F	Hemicrania Continua	2 years	Completely	-	Post-operative (tubectomy)	Indomethacin	5 months	Pain free
Prakash et al.[33]	2009	44	F	Hemicrania Continua	1 year	Completely	-	Post-operative (left parietal craniotomy for evacuation of haematoma and repair of the fracture after trauma)	Indomethacin	10 months	Pain free
Unknown: symptomatic hemicrania continua or incidental co-finding											
DeLange et al.[30]	2014	55	F	Hemicrania Continua	4 months	Completely	Disc edema, visual symptoms	Orbital pseudotumour	Prednisone, indomethacin	Unknown	Pain free

SUNCT and SUNA

We found 29 cases of SUNCT and SUNA[3•,35-48] of whom 1 was excluded because of bilateral pain during the attacks.[48] There were 14 cases defined as *probably symptomatic*, 12 as *possibly symptomatic* and 2 as *unknown* (Table 3).

Most cases were defined as *probably symptomatic* SUNCT/ SUNA. The cause found in patients with *probably symptomatic* SUNCT was most often compression of the trigeminal nerve by an artery (8 out of 14), followed by malignancies as a mixed gangliocytoma, an epidermoid tumour, and prolactinomas.[3•,37,39,42,46,49] Furthermore an aneurysm, and cavernous sinus dural fistula was found.[38;40] All patients responded completely to treatment of the underlying cause, which was most often surgery.

Tumours were most often the underlying cause in the category *possibly symptomatic* SUNCT/ SUNA: an ipsilateral prolactinoma (n=2), an ipsilateral pituitary tumour, a lung adenocarcinoma, and an ipsilateral meningioma.[36,37,44] Furthermore trigeminal nerve compression (n=4), multiple sclerosis, a mild hypothalamic-pituitary dysfunction by optical nerve hypoplasia, and a viral meningitis was reported. Five patients became pain free under preventive SUNCT treatment.[3•,35,43,47,49]

There were 2 cases categorized as *unknown*. One patient developed a varicella zoster virus meningoencephalitis 1 week after the SUNCT attacks and died within several weeks from arrhythmia secondary to myocarditis, likely as consequence of the viremia.[41] In the other patient a small posterior skull and cerebellar hypoplasia, without dysplasia, was found. A causal relation between the development of SUNCT and this anomaly is uncertain.[45]

Table 3. Symptomatic Cases of SUNCT/ SUNA

Authors	Publication (year)	Age (year)	Sex	Headache phenotype	Duration symptoms	Atypical features	Underlying lesion	Treatment	Follow up	Outcome
Probably symptomatic SUNCT/ SUNA										
Favoni et al.[49]	2013	53	F	SUNCT	3 years	-	Compression of trigeminal nerve by right superior cerebellar artery	Microvascular decompression trigeminal nerve	11 months	Pain free
Chitsanikul et al. [37]	2013	45	M	SUNCT	3 years	Improvement by vigorous activity	Ipsilateral mixed gangliocytoma and pituitary adenoma	Surgery	4 years	Pain free
Chitsanikul et al. [37]	2013	51	F	SUNCT	4 years	Right arm and facial numbness during attacks, irregular menstruation, decrease in libido, galactorrhoea	Ipsilateral prolactinoma	Surgery	18 months	Improvement in frequency and intensity
Cöven et al. [38]	2013	57	F	SUNCT	3 years	-	Aneurysm	Surgery	Unknown	Pain free
Domingos et al. [40]	2012	46	M	SUNCT	3 months	Blurred vision outside attack	Cavernous sinus dural fistula	Surgery	1 year	Pain free
Guerreiro et al. [42]	2009	57	M	SUNCT	3 months		Compression trigeminal nerve by superior cerebellar artery	Microvascular decompression	Unknown	Pain free
De Lourdes et al. [39]	2009	50	M	SUNCT	4 years	-	Ipsilateral macroprolactinoma	Cabergoline	7 months	Pain free

Table 3. Symptomatic Cases of SUNCT/ SUNA

Authors	Publication (year)	Age (year)	Sex	Headache phenotype	Duration symptoms	Atypical features	Underlying lesion	Treatment	Follow up	Outcome
Rodgers et al. [46]	2013	33	M	SUNCT	6-8 months	Triggered by head movements, chewing, jaw opening	Ipsilateral epidermoid tumour in cerebellopontine angle	Gabapentin, duloxetine, pregabalin, oxcarapene, phenobarbita, morphine, steroids, carbamazepine all ineffective, afterwards surgery.	6 months	Pain free
Williams et al. [3•]	2010	71	M	SUNCT	6 years		Compression trigeminal nerve by superior cerebellar artery	Lamotrigine, carbamazepine, gabapentin, baclofen, and prednisolone without benefit, surgery	32 months	Pain free
Williams et al. [3•]	2010	54	M	SUNCT/ SUNA	1-2 months		Compression trigeminal nerve by superior cerebellar artery	Carbamaze-pine, phenytoin, gabapentin, and baclofen without benefit. Surgery	32 months	Pain free
Williams et al. [3•]	2010	46	M	SUNCT	3 years		Compression trigeminal nerve by anterior inferior cerebellar artery, vein, adhesions	Lamotrigine, valproic acid, and topiramate without benefit, surgery	30 months	Pain free
Williams et al. [3•]	2010	56	M	SUNA	1 year		Compression trigeminal nerve by superior cerebellar artery	Lamotrigine and carbamazepine without benefit, surgery	20 months	Pain free

Table 3. Symptomatic Cases of SUNCT/ SUNA

Authors	Publication (year)	Age (year)	Sex	Headache phenotype	Duration symptoms	Atypical features	Underlying lesion	Treatment	Follow up	Outcome
Williams et al. [3•]	2010	51	F	SUNCT	5 years		Compression trigeminal nerve by superior cerebellar artery	Lamotrigine, prednisolone, and morphine without benefit, surgery	10 months	Pain free
Williams et al. [3•]	2010	49	M	SUNCT	26 years	-	Compression trigeminal nerve by superior cerebellar artery	Lamotrigine and topiramate without benefit, surgery	9 months	Pain free
Possibly symptomatic SUNCT/ SUNA										
Favoni et al. [49]	2013	55	M	SUNCT	9 years	-	Compression trigeminal nerve by superior cerebellar artery	Gabapentin, verapamil, pregabapentin and iv corticosteroids course, indomethacin for 1 month without effect, response on carbamazepine	Unknown	Pain free
Chitsanikul et al. [37]	2013	25	F	SUNCT	6 years	-	Ipsilateral prolactinoma	Indomethacin, lamotrigine, topiramate, carbamazepine, gabapentin, oxycodone and greater occipital nerve block all without effect, surgery	1 year	No improvement
Chitsanikul et al. [37]	2013	56	F	SUNCT	-	-	Ipsilateral pituitary tumour	Surgery	6 months	No improvement

Table 3. Symptomatic Cases of SUNCT/ SUNA

Authors	Publication (year)	Age (year)	Sex	Headache phenotype	Duration symptoms	Atypical features	Underlying lesion	Treatment	Follow up	Outcome
Chitsanikul et al. [37]	2013	30	F	SUNCT	12 years	-	Ipsilateral prolactinoma	Surgery	20 years	No improvement
Cascella et al.[36]	2011	57	F	SUNCT	1 month	-	Lung adenocarcinoma	Greater occipital nerve block and indomethacin without effect, valacyclovir and prednisone course, chemotherapy, gabapentin	5 months	Pain free
Kutschenko et al. [44]	2010	81	F	SUNCT	5 months	-	Ipsilateral meningioma	Gabapentin	Unknown	Pain free
Bogorad et al. [35]	2010	61	F	SUNCT	2 years	-	Multiple sclerosis	Carbamaze-pine, steroids, and indometh-acin	1 day	Pain free
Theeler et al. [47]	2009	27	F	SUNCT	14 years	Abnormal menstrual cycles and galactorrhea	History of left optical nerve hypoplasia since 2 years, mild hypothalamic-pituitary dysfunction	Observation	8 months	No change in attack frequency
Ito et al. [43]	2009	49	M	SUNCT	Several days	Fever	Viral meningitis	Sumatriptan SC for 3 days	Unknown, at least 4 days	Pain free
Williams et al. [3•]	2010	61	M	SUNCT/ SUNA	3 years		Compression trigeminal nerve by superior cerebellar artery and vein	Lamotrigine and phenytoin without benefit, surgery	22 months	Persistent attacks

Table 3. Symptomatic Cases of SUNCT/ SUNA

Authors	Publication (year)	Age (year)	Sex	Headache phenotype	Duration symptoms	Atypical features	Underlying lesion	Treatment	Follow up	Outcome
Williams et al. [3•]	2010	48	F	SUNA	2 years		Compression trigeminal nerve by anterior inferior cerebellar artery and vein	Lamotrigine and gabapentin without benefit, surgery	20 months	Persistent attacks
Williams et al. [3•]	2010	49	F	SUNCT	5 years		Compression trigeminal nerve by superior cerebellar artery	Lamotrigine, indomethacin, pethidine, and topiramate without benefit, surgery	10 months	Persistent attacks
Unknown: symptomatic SUNCT/ SUNA or incidental co-finding										
Granato et al. [41]	2014	72	M	SUNCT	-	Fever	Varicella zoster virus meningoencephalitis (after 1 week)	Gabapentin, acyclovir intravenous course, anti-platelet treatment	1 month	Died
Panconesi et al. [45]	2009	54	M	SUNCT or trigeminal neuralgia	14 years	-	Posterior fossa abnormality	Gabapentin together with carbamazepine	Unknown	Reduction in attacks

SUNCT Short-lasting Unilateral Neuralgiform headache attacks with Conjuctival injection and Tearing; SUNA Short lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms

Discussion

The goal of this review was to give an update on underlying structural lesions associated with TACs, published between February 2009 (since the last review) and January 2015. We identified 53 typical cases: 19 cases with cluster headache, no cases with paroxysmal hemicrania, 6 cases with hemicrania continua, and 28 cases with SUNCT/ SUNA.

Tumours were reported in 16 of the 53 cases diagnosed with a TAC, mainly pituitary tumours. Prolactinomas were found in 2 cluster headache and 4 SUNCT patients, followed by pituitary adenomas (n= 2). It has indeed been reported that pituitary tumours account for a large portion of the secondary causes of SUNCT.[50] The other way around, various types of headache including TACs have been reported as frequent symptom of pituitary tumours.[51] An association between the side of the tumour and side of the headache has been suggested.[52••] In most of the reported cases of secondary SUNCT and secondary cluster headache, surgery or medical treatment of the pituitary tumour resulted in improvement.

A vascular lesion as underlying cause was less often found. An intracranial or extracranial dissection was reported in only 1 of the 19 cluster headache patients. This patient was diagnosed with cluster headache several years before he experienced a cluster headache attack with prolonged duration, which was probably caused by a carotid dissection.[6•] Dissection as a cause for cluster headache is rare, but has been reported in earlier reviews.[4,50] Recognition is of crucial importance as it can have serious consequences for patients. Cases with carotid dissection have shown improvement of the headache after antiaggregant or anticoagulant therapy. Most patients did not even need preventive cluster headache treatment. Repeated contrast-enhanced magnetic resonance imaging (MRI) should be considered if the characteristics of the headache attacks change over time.

In 12 SUNCT patients a trigeminal nerve compression by vascular structures as possible cause of SUNCT was found. Eight of 11 surgical treated patients became headache free whereas only 3 patients had no

benefit of the procedure. This is an important finding as SUNCT is often considered medically intractable. Trigeminal nerve compression was found in 42.8% of this series.

A sinusitis was considered probably causal in 2 cluster headache patients. Sinusitis is a common misdiagnosis in cluster headache. Lainez et al showed that 14 of 75 cluster headache patients (18.7%) were initially misdiagnosed as having a sinusitis.[53••] It is sometimes very difficult to make a clear distinction between sinusitis and a TAC.[54]

In summary, we found 53 typical cases of secondary TACs in our literature study covering the period from February 2009 to January 2015. Secondary underlying lesions seem to be rare in TACS. However, physicians should be aware of possible underlying pathology, as, for example, prolactinomas or glioblastomas, arteriovenous malformations, dissections and various inflammations can cause a TAC like phenotype. In our opinion not only a contrast-enhanced cerebral MRI should be considered once in every patient to exclude a causal underlying pathology, but also imaging of cervical vascular structures.

Most of our findings are in accordance with those of Wilbrink et al.[4] Of additional importance, is the more recent observation that in more than 40% of patients with SUNCT/SUNA a trigeminal nerve compression by the superior or inferior cerebellar artery was present and that most of these patients experienced spectacular improvement of their headache after surgical decompression. In contrast to other reviews, we found less frequently an intracranial or extracranial dissection causing cluster headache.[4,50] This could be explained by the fact that there are already various case reports about intracranial and extracranial dissections causing cluster headache.[55-57] The importance of a cerebral MRI to exclude underlying lesions is shown in the current review, as cerebral lesions (e.g. pituitary tumors) were associated with TACs.

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CHAPTER 3

A case report about cluster-tic syndrome due to venous compression of the trigeminal nerve

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Abstract

Introduction

The term "cluster-tic syndrome" is used for the rare ipsilateral co-occurrence of attacks of cluster headache and trigeminal neuralgia. Medical treatment should combine treatment for cluster headache and trigeminal neuralgia, but is very often unsatisfactory.

Case description

Here, we describe a 41 year old woman diagnosed with cluster-tic syndrome who underwent microvascular decompression of the trigeminal nerve, primarily aimed at the "trigeminal neuralgia" part of her pain syndrome. After venous decompression of the trigeminal nerve both a decrease in trigeminal neuralgia and cluster headache attacks was seen. However the headache did not disappear completely. Furthermore she reported a decrease in pain intensity of the remaining cluster headache attacks

Discussion

This case description suggests that venous vascular decompression in cluster-tic syndrome can be remarkably effective, both for trigeminal neuralgia and cluster headache.

Introduction

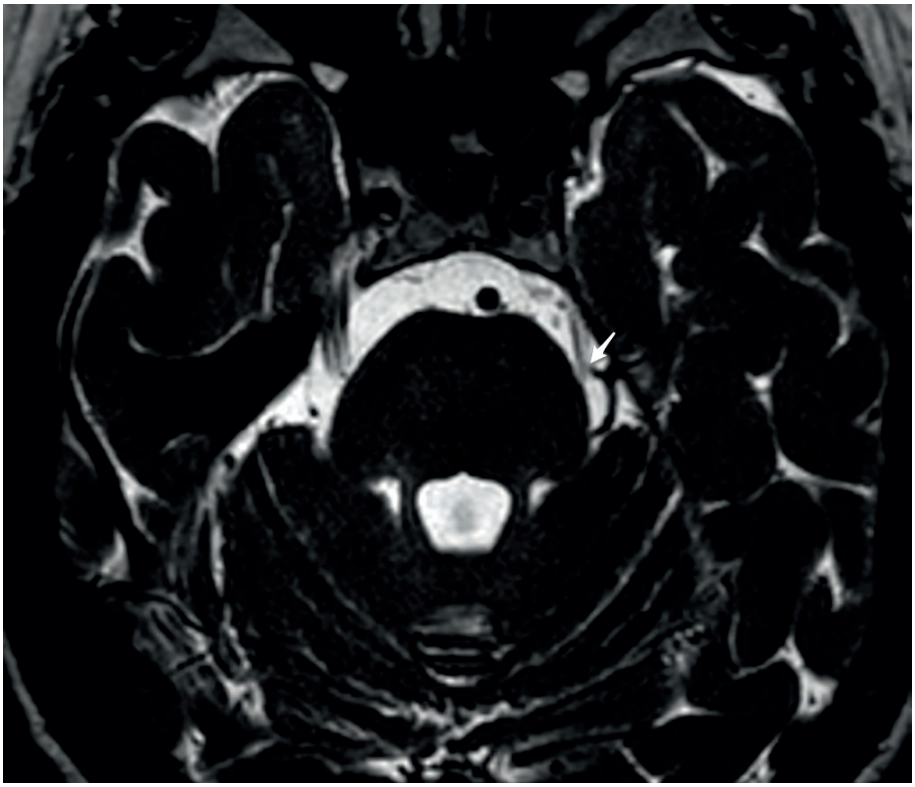
The term "cluster-tic syndrome" is used for the rare ipsilateral co-occurrence of attacks of cluster headache and trigeminal neuralgia within the same patient.[1] Since the first description in 1978[2], around 40 patients suffering from this combination of facial pain syndromes have been described. Medical treatment should combine treatment for cluster headache and trigeminal neuralgia, but is very often unsatisfactory. In the ICHD-3 beta criteria, the cluster-tic syndrome is mentioned in a remark under paragraph 3.1 Cluster Headache, but not listed as a separate entity.[3] It is emphasized that both headache syndromes should receive distinct diagnoses. Previously, some patients were described in whom medication was not effective and who underwent surgical treatment procedures (e.g. decompression, section or thermocoagulation of the trigeminal nerve or root), and these procedures were described to be often effective for both trigeminal neuralgia and cluster headache attacks.[1,4,5] Here, we describe a patient who underwent microvascular decompression of the trigeminal nerve, primarily aimed at the 'trigeminal neuralgia' part of her pain syndrome.

Case report

In 2009, a now 41 year old woman started to suffer from pain paroxysms lasting several seconds to 2 minutes around the left eye and on the left forehead without autonomic symptoms. After 6 months, she also developed redness and tearing of the eye during these attacks. At first, attacks were only provoked by rising after sitting, later they appeared spontaneously up to 30 times per day. The attacks were never provoked by touching the face, talking or swallowing. Because of the autonomic symptoms, she was first treated elsewhere with indomethacin (150 mg/day), without effect. One year later, next to the "original" attacks, she developed a second kind of attacks in the same facial region, which were very severe, occurred up to 4 per day, and lasted between 30 and 90 minutes. There were no attack-free periods of ≥ 1 month. During these attacks she had redness and tearing of the eye, a ptosis and

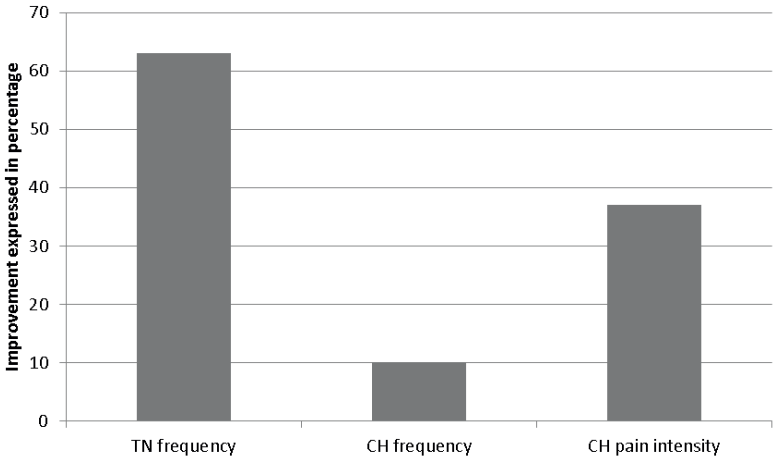
nasal congestion. A diagnosis of "cluster-tic syndrome" was made. Her previous medical history contained hypertension (for which she took verapamil 240 mg/day since many years), asthma, polycystic ovaria and a myeloproliferative disorder (JAK2, BCR ABL negative). Next to verapamil she used ferro fumarate, acetylsalicylic acid, ezetimibe, triamterene/hydrochlorothiazide and atorvastatin. She used oxygen as acute cluster headache treatment with good effect. She did not smoke or use alcohol. Neurological examination was normal and two cerebral MRIs (2009 and 2014) showed no abnormalities. There was no neurovascular "conflict" at the root-entry zone of the left trigeminal nerve seen. After the diagnosis "cluster-tic syndrome" was made, she was treated with a variety of combinations: verapamil (max 320 mg/day) and gabapentin (max 1200 mg/day), verapamil and pregabalin (max 225 mg/day) and finally verapamil, pregabalin and oxcarbazepine (450 mg/day). All combinations gave an insufficient effect. Because of side-effects, the doses of these medications could not be increased. After a carefully consideration, the patient did not want to use lamotrigine or lithium, also because the latter drug would have an interaction with hydrochlorothiazide, which she was using at that time. C1-C2 and sphenopalatine blocks were also not effective. After several greater occipital nerve blocks, the frequency of the "trigeminal" attacks decreased temporarily, while the frequency of the "cluster" attacks did not change. In 2015, a microvascular decompression of the left trigeminal nerve was performed. At revision of the last MRI, a compression of the trigeminal nerve by the petrosal vein was suspected (Figure 1). Indeed, during the operation, a compression of the trigeminal nerve by the petrosal vein was found. The vein was coagulated. There was no arterial compression of the trigeminal nerve. After the operation, the frequency of the attacks of trigeminal neuralgia decreased, the pregabalin could be stopped and the dose of oxcarbazepine could be lowered to 150 mg/day. Remarkably, also the cluster headache attacks became less frequent and the remaining attacks were less severe. Besides, she reported a shift of the pain from the left eye and forehead to the left temple. The improvement could also be seen in her careful registration of both headache types and the severity of the cluster headache attacks (Figure 2).

Figure 1. MRI brain before microvascular decompression of the left trigeminal nerve



The white arrow is pointing at the compression of the trigeminal nerve on the left side by the petrosal vein.

Figure 2. Improvement in trigeminal neuralgia and cluster headache attacks after microvascular decompression of the left trigeminal nerve compared to the situation before decompression



Discussion

Although it is always difficult to draw conclusions from the description of one patient, this case contains several remarkable aspects, in our opinion. First, the cluster-tic syndrome is very rare by itself, with only around 40 cases described in the literature. Second, the development of a phenotype starting with trigeminal neuralgia in the ophthalmic branch, then trigeminal neuralgia with autonomic symptoms (or SUNCT, see below), to be followed after one year by additional typical cluster headache attacks is – to say the least – very remarkable. In the literature, cases have been described in which trigeminal neuralgia was followed by the occurrence of cluster headache, vice versa, and in which both syndromes started simultaneously. Autonomic features can occur in patients with trigeminal neuralgia, leading to the suggestion that there might be an overlap between trigeminal neuralgia and SUNA/SUNCT.[6,7] However, a patient with a cluster-tic syndrome starting with trigeminal neuralgia without autonomic features, then developing trigeminal neuralgia with autonomic features (or SUNCT), to end with the "full" cluster-tic syndrome has not been described previously. As the intermediate part of the phenotype resembled SUNCT, the final part could also called "cluster-SUNCT syndrome". The third remarkable aspect was that the MRI did not show an arterial neurovascular conflict, as is established as a frequent cause of trigeminal neuralgia, but venous compression, confirmed during the operation. Venous compression as a cause of trigeminal neuralgia has been controversial, but recently in 38% of 326 consecutive patients who underwent microvascular decompression for trigeminal neuralgia a venous conflict was found, alone in 8.9% and in combination with arterial compression in 29.1%.[8] Next to venous compression[1,4,8], only a few other secondary causes for cluster-tic have been suggested before in case-reports. These include multiple sclerosis, pituitary adenoma, a dural carotid-cavernous fistula and vascular compression of the trigeminal root by basilar artery ectasia.[9-12]

Also, the response of the headache phenotype to the vascular decompression was remarkable, as there was not only a reduction in frequency of trigeminal neuralgia/SUNCT attacks, and a reduction of

frequency and severity of cluster headache attacks, but also a shift in pain location. The response in this patient resembles the recently described response after decompression in SUNCT/SUNA patients.[13,14]

Efficacy of surgical therapy for the cluster-tic syndrome has been described before. In the four cases described by Solomon et al. both the attacks of trigeminal neuralgia and those of cluster headache disappeared, but later returned.[4] In a patient described by Alberca and Ochoa, both headache syndromes disappeared after decompression, but after 20 years returned at the contralateral side of the face.[1] So far, in our case, the effects did not diminish over time. Whereas surgical decompression of trigeminal neuralgia is a well-established treatment, the efficacy of the same procedure in cluster headache is controversial. A long term success-rate, described as at least 50% relief, was achieved in 14 out of 30 initial procedures in 28 patients with chronic cluster headache.[15] Invasive or destructive treatment aimed at the trigeminal nerve, however, has not been an established treatment of cluster headache.[16]

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CHAPTER 4

Evaluation of the new ICHD-III beta cluster headache criteria

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Abstract

Introduction

In the revised criteria of the International Classification of Headache Disorders (ICHD-III beta) the following items are added to the diagnostic criteria of cluster headache: ipsilateral sensation of fullness in the ear and ipsilateral forehead/ facial flushing. We evaluated the possible additional value of these symptoms for diagnosing cluster headache.

Methods

In this cross-sectional cohort study of (potential) cluster headache patients we investigated these additional symptoms using a web-based questionnaire. Patients not fulfilling the ICHD-II criteria for cluster headache, but fulfilling the ICHD-III beta criteria were interviewed.

Results

Response rate was 916/1138 (80.5%). Of all 573 patients with cluster headache according to ICHD-II criteria, 192 (33.5%) reported ipsilateral ear fullness and 113 (19.7%) facial flushing during attacks. There was no difference in reporting ipsilateral ear fullness and facial flushing between patients who received a diagnosis of cluster headache and patients who did not. None of the patients who did not fulfill all ICHD-II criteria could be categorized as cluster headache according to the ICHD-III beta criteria.

Conclusion

The results of this study do not support the addition of ear fullness and facial flushing to the new ICHD-III beta criteria.

Introduction

As there is no definitive biological marker, a diagnosis of cluster headache is based on patient's history, applying diagnostic criteria as offered by the International Classification of Headache Disorders (ICHD) since 1988 (ICHD-I).[1] In the revision of 2004 (ICHD-II), an adjustment was made to these criteria: a sense of restlessness or agitation as possible accompanying symptom during a cluster headache attack was added. Furthermore, the duration of remission periods in chronic cluster headache was changed from maximum a fortnight to one month.[2] Recently, the new ICHD-III criteria beta version was published.[3] The following possible accompanying symptoms have been added for the diagnosis of cluster headache in this version: i) the presence of ipsilateral sensation of ear fullness, and ii) ipsilateral forehead and facial flushing. The validity of these new diagnostic criteria remains to be established. The aim of this study was to investigate the presence of these additional symptoms in our Leiden University Cluster headache neuro-Analysis program (LUCA) population which encompasses self-reported cluster headache patients: patients fulfilling the ICHD-II criteria for cluster headache and patients who fail one or more of the cluster headache criteria. We aimed to assess how many patients who did not fulfil the previous ICHD-II criteria would be diagnosed as cluster headache according to the new ICHD-III beta version.

Material and methods

Study setting and patient selection

This cross-sectional cohort study was conducted as part of the LUCA program. The LUCA population is a nation-wide cohort of self-reported cluster headache patients of 18 years and older. Patients can enroll into the LUCA program through a web-based database which was promoted though different kinds of media. In addition, patients attending our outpatient headache clinic were also invited to participate in this program.

First, if patients fulfilled a set of screening criteria, they were sent a web-based extended cluster headache questionnaire, based on the ICHD-II criteria.[2]

This questionnaire was proven valid and accurate by performing a semi-structured telephone interview in 291 patients who had filled out the extended cluster headache questionnaire.[4] Using the interview as the gold standard, the algorithm of the extended cluster headache questionnaire has a specificity of 0.89. We consider the cohort a well-defined web-based cohort. Secondary, all patients were asked to fill out an additional questionnaire about ear fullness and facial flushing.

We used web-based questionnaires, except for patients without the ability to use the internet, who were allowed to fill out the questionnaires on paper. Only patients who filled out all the necessary items were included in this study.

Approval for the study was obtained by the local medical ethical committee of the Leiden University Medical Centre. All participants provided written informed consent.

Classification

Previously, the ICHD-II criteria were used to diagnose cluster headache in the LUCA program. We compared cluster headache patients diagnosed according to the ICHD-II criteria with those diagnosed according to ICHD-III criteria beta version thus adding ipsilateral sensation of ear fullness and ipsilateral forehead and facial flushing as criteria. For a compact overview of the criteria for cluster headache according to the ICHD-II and ICHD-III- beta version we refer to Supplementary Table 1. Patients who did not receive the diagnosis of cluster headache based on ICHD-II but fulfilled a cluster headache diagnosis based on the newly added criteria in the ICHD-III beta version (ear fullness and facial flushing) were directly interviewed (by IFC) for validation.

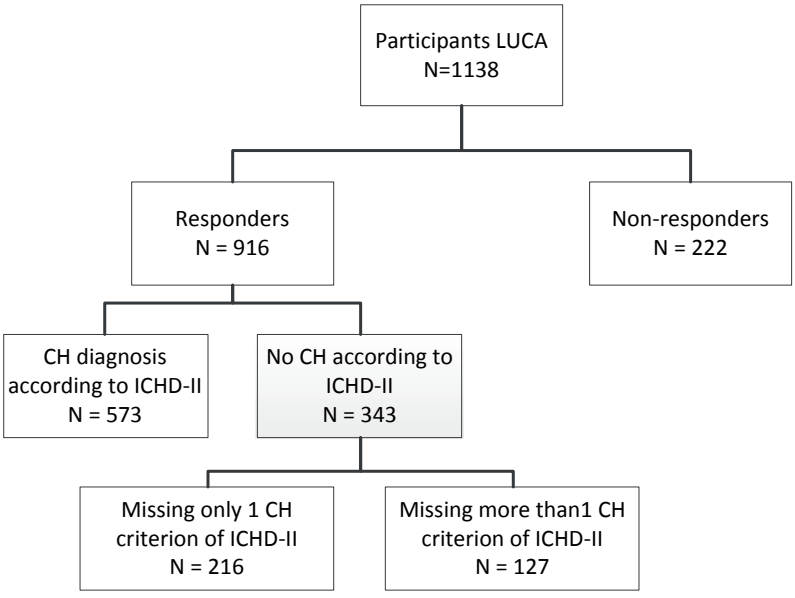
Statistics

Comparisons between responders and non-responders and subgroups of our LUCA population was performed by using a Mann-Whitney test or Kruskal Wallis test for ordinal data and χ^2-test for nominal data. Data analyses were performed using SPSS 20.0 (SPSS inc., IBM, USA). The statistical threshold was set to $p<0.05$.

Results

Of the 1138 LUCA patients who entered our web-based recruitment system, 916 patients (80.5%) returned our questionnaires on ear fullness and facial flushing (Figure 1). Non responder analyses showed that non-responders were younger, more often females and were more often diagnosed as "no cluster headache according to the ICHD-II criteria". The clinical characteristics of the responders and non-responders are summarized in Supplementary Table 2.

Figure 1. Flowchart study flow



LUCA: Leiden University Cluster headache Analysis program; CH: cluster headache; ICHD-II: International Classification of Headache Disorders version II.

According to the ICHD-II criteria 573/916 (62.6%) patients were diagnosed as cluster headache. The remaining 343/916 (37.4%) patients did not fulfil the ICHD-II criteria and therefore were not classified as cluster headache: 216/343 patients were missing one ICHD-II criterion and 127/343 patients were missing more than one ICHD-II criterion (Figure 1). Table 1 shows the demographic characteristics of the patients and reported autonomic symptoms. Patients fulfilling the ICHD-II criteria were significantly more often men (p<0.001), and a higher proportion reported a diagnosis of cluster headache by a physician (p<0.001). The number of autonomic symptoms was significantly higher (p<0.001) among patients with a cluster headache diagnosis.

Table 1. Demographic characteristics of the participants, and the number of autonomic symptoms

	All patients	**Cluster headache**	**No cluster headache**		
	(N = 916)	**(N = 573)**	**Missing 1 criterion (N = 216)**	**Missing > 1 criterion (N = 127)**	**P-value**
Demographics					
Male, n (%)	612 (66.8)	423 (73.8)	133 (61.6)	56 (44.1)	<0.001*
Age, mean ± SD, year	50.7 ± 11.9	50.7 ± 11.8	51.0 ± 11.5	50.1 ± 13.2	NS
Diagnosis CH by physician, n (%)		564(98.4)	198 (91.7)	96 (75.6)	<0.001*
Autonomic symptoms					<0.001*
No autonomic symptoms	14 (1.5)	2 (0.3)	3 (1.4)	9 (7.1)	
1 autonomic symptoms	49 (5.3)	13 (2.3)	7 (3.2)	9 (7.1)	
2 autonomic symptoms	63 (6.9)	32 (5.6)	18 (8.3)	13 (10.2)	
≥ 3 autonomic symptoms	784 (85.6)	524 (91.4)	188 (87.0)	92 (72.4)	
Missing data	6 (0.7)	2 (0.3)	-	4 (3.1)	

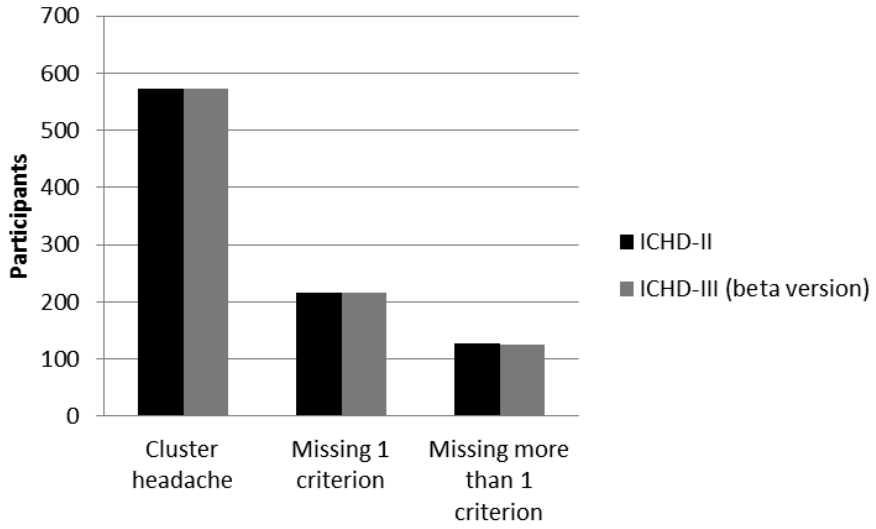
LUCA: Leiden University Cluster headache Analysis program; CH: cluster headache diagnosis according to the International Classification of Headache Disorders, second edition; CH minus 1: cluster headache minus one criterion according to the International Classification of Headache Disorders, second edition; CH minus > 1: Missing more than one criterion for the diagnosis cluster headache according to the International Classification of Headache Disorders, second edition.

* Significance level of P <0.05 (Kruskal Wallis test for ordinal data and χ^2-test for nominal data).

In 215 out of 216 patients, missing one ICHD-II criterion, autonomic symptoms or restlessness was not the missing criterion. Most often duration or frequency of attacks deviated from the criteria. In 1 out of 216 patients (0.5%) accompanying autonomic symptoms or restlessness was

the missing criterion. This participant reported ear fullness during cluster headache attacks in the additional questionnaire, but failed to recall this in the direct telephone interview. The new version of ICHD criteria did not lead to a diagnosis of cluster headache in this participant (Figure 2).

Figure 2. Diagnosis according to ICHD-II and ICHD-III criteria for cluster headache



ICHD-II: International Classification of Headache Disorders version II; ICHD-III (beta version): International Classification of Headache Disorders version III (beta version).

Of all patients classified with cluster headache, according to the ICHD-II criteria, 192/573 (33.5%) reported ipsilateral ear fullness and 113/573 (19.7%) ipsilateral facial flushing as shown in Table 2. Ipsilateral ear fullness was reported in 87/216 (40.3%) of patients classified as missing one ICHD-II criterion and ipsilateral facial flushing in 41/216 (19.0%). In patients classified as missing two or more ICHD-II criteria for cluster headache ipsilateral ear fullness was reported in 37/127 (29.1%) patients and ipsilateral facial flushing during their headache attacks in 22/127 (17.3%) patients. There was no significant difference in the newly added autonomic symptoms between patients diagnosed according to the ICHD-II criteria as having cluster headache and those missing one or more criteria for cluster headache.

Table 2. Ipsilateral feeling of ear fullness and facial flushing reported in the responders of the LUCA population according to the ICHD-II

	All patients	Cluster headache	No cluster headache		
	(N = 916)	(N = 573)	Missing 1 criterion (N = 216)	Missing > 1 criterion (N = 127)	P-value [e]
Ear fullness[a], n (%)	316 (34.5)	192 (33.5)	87 (40.3)	37 (29.1)	0.080
Facial flushing[a], n (%)	176 (19.2)	113 (19.7)	41 (19.0)	22 (17.3)	0.970

LUCA: Leiden University Cluster headache Analysis program; ICHD-II: the International Classification of Headache Disorders, second edition.

[a.] During a cluster headache attack.

Discussion

This is the first study that investigated the value of the newly added autonomic accompanying symptoms for diagnosing cluster headache. One third of cluster headache patients reported ipsilateral ear fullness and 20% ipsilateral facial flushing during attacks. However, there was no significant difference of these reported symptoms compared with patients that did not fulfil cluster headache criteria. Most importantly, none of the patients who previously did not fulfil all criteria for cluster headache could now be categorized as cluster headache according to the new ICHD-III criteria.

There is no consensus in the literature about the value of facial flushing in cluster headache. Facial flushing has often been reported during cluster headache attacks.[5,6] It was even used for the diagnosis in one of the pre-ICHD criteria.[7] After applying these previous criteria, others however, have suggested that facial flushing is not a symptom of cluster headache, because it was not observed at all in their cluster headache population.[8]

Ipsilateral ear fullness has been reported only once before as accompanying symptom in a case of cluster headache. However in this report, the limited description of the symptoms did not allow to apply the ICHD criteria for cluster headache, so a diagnosis remains doubtful.[9]

Facial flushing and ear fullness were often reported in our cluster headache population. However, there was no difference in the presence of these autonomic symptoms between the patients diagnosed as cluster headache and patients missing one or more criteria for the diagnosis of cluster headache according to the ICHD-II criteria in this study. Therefore, the additional diagnostic value for using these newly added symptoms seems low. Comparable, there has been a proposal for alternative diagnostic criteria for migraine without aura in the ICHD-II criteria using at least two of five associated symptoms (nausea, vomiting, phonophobia, photophobia and osmophobia) during the acute migraine attack. Although osmophobia was often reported in these migraine patients, it had a low sensitivity for diagnosing migraine and was therefore not added to the ICHD-III beta version criteria for migraine without aura.[10]

None of our patients who missed one ICHD-II criterion to be diagnosed as cluster headache could be diagnosed as having cluster headache according to the new criteria. Showing thereby the diagnostic gain of adding the new autonomic features is limited.

The strength of this study is the large sample size , well defined cohort and high response rate of more than 80%. A possible limitation is that not for all patients a golden standard verification of diagnosis was made by a physician. However, validation of our questionnaire showed high specificity in a previous study.[4]

In summary, the results of this study do not support the addition of ear fullness and facial flushing to the new ICHD-III beta criteria.

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Supplementary Table 1. Comparison ICHD-II and ICHD-III beta version criteria for cluster headache

ICHD-II	ICHD-III beta
A. At least 5 attacks fulfilling criteria B-D	A. At least 5 attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated	B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)
C. Headache is accompanied by at least one of the following: 1.ipsilateral conjunctival injection and/or lacrimation 2.ipsilateral nasal congestion and/or rhinorrhoea 3.ipsilateral eyelid oedema 4.ipsilateral forehead and facial sweating 5.ipsilateral miosis and/or ptosis 6.a sense of restlessness or agitation	C. Either or both of the following: 1. at least one of the following symptoms or signs, ipsilateral to the headache: a) conjunctival injection and/or lacrimation b) nasal congestion and/or rhinorrhoea c) eyelid oedema d) forehead and facial sweating e) ipsilateral forehead/ facial flushing f) ipsilateral sense of aural (ear) fullness g) ipsilateral miosis and/or ptosis 2. a sense of restlessness or agitation
D. Attacks have a frequency from one every other day to 8 per day	D. Attacks have a frequency from one every other day to 8 per day for more than half of the time when the disorder is active
E. Not attributed to another disorder	E. Not better accounted for by another ICHD-3 diagnosis

ICHD-II: International Classification of Headache Disorders, second Edition[2]; ICHD-III beta: International Classification of Headache Disorders, third edition beta version[3].

Supplementary Table 2. Clinical characteristics responders and non-responders

	Responders (N = 916)	Non-responders (N=222)	P value
Age (years), mean ± SD	50.3 ± 11.9	44.8± 11.7	<0.001*
Education (years), mean ± SD	12.8 ± 3.2	12.5 ± 3.5	NS
Male, n (%)	612 (66.8)	124 (55.9)	0.002*
Diagnosis ICHD-II[1], n (%)			0.002*
Episodic cluster headache	449 (49.0)	87 (39.2)	
Chronic cluster headache	124 (13.5)	29 (13.1)	
No cluster headache	343 (37.4)	106 (47.7)	

ICHD-II: International Classification of Headache Disorders, second edition.
* $P < 0.05$ (Mann-Whitney test for ordinal data and χ^2-test for nominal data).

CHAPTER 5

Aura in cluster headache: a cross-sectional study

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Abstract

Introduction

Aura symptoms have been reported in up to 23% of cluster headache patients, but it is not known whether clinical characteristics are different in participants with and without aura.

Methods

Using validated web-based questionnaires we assessed the presence and characteristics of attack-related aura and other clinical features in 629 subjects available for analysis from an initial cohort of 756 cluster headache subjects. Participants who screened positive for aura were contacted by telephone for confirmation of the ICHD-III criteria for aura.

Results

Typical aura symptoms before or during cluster headache attacks were found in 44/629 participants (7.0%) mainly involving visual symptoms (61.4%). Except for lower alcohol consumption and higher prevalence of frontal pain in participants with aura no differences in clinical characteristics were found compared to participants without aura.

Conclusion

At least 7.0% of the participants with cluster headache in our large cohort reported typical aura symptoms, which most often involved visual symptoms. No major clinical differences were found between participants with and without aura.

Introduction

Cluster headache is a rare headache disorder typically characterized by attacks of excruciating, unilateral temporal or (peri-)orbital pain lasting 15-180 minutes and associated with facial autonomic symptoms and/or restlessness.[1] Migraine-like aura symptoms have been reported in up to 23% of cluster headache patients.[2-5] For many clinicians, this seems much higher than to their clinical impression. The auras reported are most often visual and sometimes very short-lasting. Diagnostic criteria differ between migraine and cluster headache in the International Classification of Headache Disorders-III (ICHD-III beta).[1] In migraine with and without aura are the major subtypes.[1] Aura is not mentioned in the cluster headache criteria. Therefore, for a patient with cluster headache and typical aura, the criteria formulated for "typical aura with headache" seem closest.[1]

In migraine, attacks with aura are in general associated with a shorter and less severe headache phase.[6] This has led to the hypothesis that different mechanisms are involved in migraine with and without aura.[6-9] Here we set out to investigate whether attacks of cluster headache with and without aura differ with respect to the other clinical characteristics.

Material and methods

Study setting and participants selection

This explorative cross-sectional study was conducted as part of the ongoing, nation-wide, Leiden University Cluster Headache neuro-analysis programme (LUCA).[10] There have been earlier reports based on the LUCA programme including the results of studies on allodynia.[11-14] In one smaller study the results of an interview by phone regarding aura symptoms were reported (in Dutch).[13] Although the results did not differ substantially with the present study, the two studies cannot be compared completely as the previous study was smaller and did not use this aura questionnaire.

The LUCA website is heavily promoted throughout The Netherlands through professional contacts and various local lay and medical media to attract as many potential participants as possible. In addition, participants attending the LUMC and other headache clinics are invited as well to participate in the LUCA study.
For the LUCA study, persons of 18 years or older who are living in the Netherlands and who believe they have cluster headache, either confirmed or not by a physician, were invited to fill in a validated, web-based, screening questionnaire for cluster headache. The questionnaire is based on the ICHD-II criteria [15] and has a diagnostic specificity of 0.89 for cluster headache.[10] More details about the validation of this screening methods can be found in the report of Wilbrink et al.[10] In the Netherlands, the Dutch General Practitioners Guidelines recommend referral to a neurologist when one is suspecting cluster headache, for diagnosis and start of cluster headache treatment.[16] Therefore virtually all participants received a diagnosis by a neurologist. All people who screened positive received a second, more extensive web-based questionnaire which is based on the ICHD-II. As known, all participants fulfilling the ICHD-II criteria fulfill also to the ICHD-III beta version for cluster headache.[1,11]

For the present aura study, subjects diagnosed with cluster headache as described above received an email asking them to fill in an additional validated questionnaire about aura symptoms, which was previously found to have a positive predictive value of 88% and a negative predictive value of 70%.[17] The questionnaire contains questions regarding the presence, duration and clinical characteristics of visual, sensory, aphasic and dysarthric aura symptoms preceding or during cluster headache attacks. Also it contains questions about (comorbid) migraine. Those who did not respond to the initial email were reminded twice per email and when still not responding, they were contacted two times more (once by regular mail and finally once by telephone). All participants who screened positive for aura like symptoms were contacted by telephone for confirmation of the ICHD-III criteria for typical aura with headache for their cluster headache attacks, which took about 30 minutes per participant. Also they were asked about having migraine (with or without aura) according to the ICHD-III criteria. Only participants who had filled

in all items and were available for a telephone interview (when screened positive for aura like symptom) were included.

The study was approved by the local medical ethical committee of Leiden University Medical Centre and all participants provided written informed consent.

Statistics

No power analysis was performed for this cross-sectional study. Comparisons between attack characteristics was made using a Mann Whitney test for ordinal data, a $\chi 2$-test for nominal data, and an independent T test for interval data (two-tailed). No adjustments were made for multiple comparisons. Analyses were performed using SPSS 20.0 (SPSS Inc., IBM, USA). Statistical significance was set at $p<0.05$.

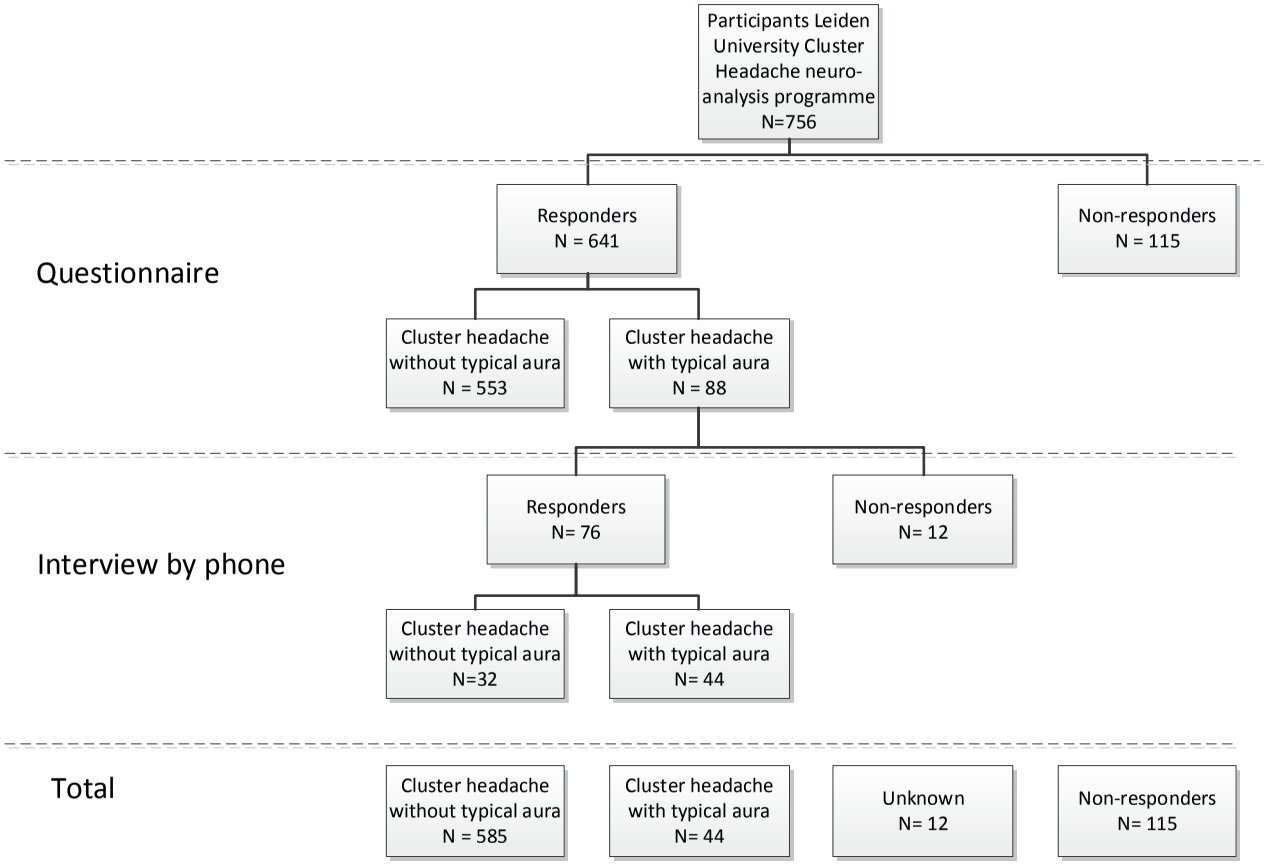
Results

By August 2014, there were 756 subjects with a questionnaire-based diagnosis of cluster headache in the LUCA database. In 720/756 (95.2 %) of these the diagnosis had been separately confirmed by a physician. 641/756 (84.8%) agreed to also fill in the aura questionnaire.

In the aura questionnaire 88/641 (13.7%) indicated to have aura like symptoms. To be accurate, we contacted these 88 participants by phone to assess the ICHD-III beta criteria for typical aura with headache. By means of the telephone interview, typical aura according the ICHD-III criteria beta was diagnosed in 44/88 participants and no aura in 32/88 (the remaining 12 did not participate in the telephone interview and were defined as unknown). Therefore, a total of 44 participants with cluster headache with aura and 585 participants with cluster headache without typical aura were available for further analysis (Figure 1).

Non-responder analysis revealed no significant differences in baseline characteristics between responders and non-responders of the questionnaire and if indicated telephone interview (Supplementary Table 1).

Figure 1. Flowchart study flow



Aura characteristics in cluster headache with typical aura

Visual symptoms were most frequently reported to be part of the aura (27/44; 61.4%), followed by sensory symptoms (17/44; 38.6%), dysarthria (12/44; 27.3%) and dysphasia (10/44; 22.7%) (Table 1). There was much overlap, but interestingly, isolated dysarthric, aphasic and sensory symptoms without visual symptoms were also reported.

Visual symptoms most often (70.4%) started before the cluster headache attack whereas sensory, dysarthric and aphasic aura symptoms started most often during the headache phase (Table 1).

Table 1. Typical aura symptoms according to ICHD-III beta version criteria

N =44	N (%)	Onset, N Before - During Attack
Isolated visual	14 (31.8)	10 – 4
Isolated sensory	5 (11.4)	1 – 4
Isolated dysphasia	4 (9.1)	1 – 3
Isolated dysarthria	6 (13.6)	2 – 4
Visual and sensory	4 (9.1)	4 – 1
Visual and dysphasia	1 (2.3)	1 – 0
Visual and dysarthria	2 (4.5)	1 – 1
Sensory and dysphasia	2 (4.5)	0 – 2
Visual, sensory and dysphasia	2 (4.5)	2 – 0
Visual, sensory and dysarthria	3 (6.8)	2 – 1
Visual, sensory, dysphasia and dysarthria	1 (2.3)	0 – 1

The median duration was 15 minutes for dysarthric symptoms, 20 minutes for visual symptoms and 25 minutes for both sensory and aphasic symptoms. Aura symptoms were not present during all cluster headache attacks. In participants with aura symptoms, roughly half of the attacks were accompanied or preceded by visual, sensory and dysarthric symptoms. Aphasic symptoms were reported in a smaller proportion of attacks (Table 2).

Table 2. Duration and frequency of aura symptoms during/before cluster headache attack*

	Visual aura N=27	Sensory aura N=17	Dysphasia aura N=10	Dysarthria N=12
Duration aura symptoms (minutes);median (min-max)	20 (5-60)	25 (5-60)	25 (3-120)	15 (7-75)
Cluster headache attacks with aura (%);median (min-max)	50 (5-100)	50 (1-100)	20 (1-100)	65 (15-100)

*Some participants reported more than one kind of aura as shown in Table 1.

Six out of these 44 participants reported also typical aura symptoms without headache, which occurred strictly with visual aura symptoms and fulfilled to the criteria of "typical aura without headache". None of these six participants reported to also have migraine.

Comparison between participants with typical aura and no aura

In each group 2/3 had episodic and 1/3 chronic cluster headache. The two groups did not differ in demographic and clinical characteristics except for lower alcohol consumption and higher prevalence of frontal pain in participants with cluster headache with typical aura (Table 3). Comorbid migraine was reported in 13.6% (N=6) of the participants with typical aura, of whom 2 females (33.3%) and 10.4% (N=61) of participants without typical aura of whom 34 females (55.7%). Those who experienced aura associated with cluster headache attacks experienced (mainly visual) aura associated with migraine in 4 participants and no aura associated with their migraine in 2 participants.

Three case-reports to illustrate the reported aura symptoms

- This man suffered from episodic cluster headache since he had become 30 years. He experienced a cluster headache bout every two years lasting 6 to 8 weeks. He had very severe pain right above the left eye together with ipsilateral conjunctival injection, lacrimation, ptosis and rhinorrhoea, with a sense of restlessness and agitation. An attack lasted about 3 hours without intervention and about 30 minutes with the use of oxygen only. About 30 minutes before the cluster headache attacks he experienced zig-zag figures in his left eye, which spreads gradually over 10 minutes and then stopped. Twenty minutes later the headache started. He reports these visual symptoms in 10% of his cluster headache attacks.
- A 57 years old woman had chronic cluster headache attacks, with about 3 attacks a week since the age of 51. The very severe left orbital attacks lasted about 60 minutes without intervention. They were accompanied with restlessness and agitation and ipsilateral conjunctival injection, lacrimation, ptosis, miosis and nasal congestion or rhinorrhoea. Before every attack she saw unilateral (left eye) blurry zig-zag figures and after several minutes she also developed a heavy and slurred speech. Both symptoms start 5 minutes before the headache and both disappear after about 20 minutes. We have classified this as both a visual and dysarthric aura.
- A 58 years old male was diagnosed with episodic cluster headache and he experienced twice a year a bout of 8-10 weeks. The very severe pain is located periorbitally and above the left eye and is accompanied by restlessness and ipsilateral conjunctival injection, lacrimation, ptosis, eyelid oedema, miosis and nasal congestion or rhinorrhoea. Without intervention the attacks last between 1,5 and 3 hours. Before about 80% of his attacks he experienced a slurred speech like being drunk for about 15-20 minutes. About 5 minutes after start of the slurred speech the headache starts. We classified this as dysarthria. His partner has noticed this difference in speech as well.

Table 3. Characteristics cluster headache participants: with versus without aura

	Cluster headache with aura (N= 44)	Cluster headache without aura (N= 585)	*p*-value
Demographic characteristics			
Age at onset (years) mean ± SD	30.2±11.9	30.3±12.8	0.954
Years of education mean ± SD	13.0±2.7	12.8±3.3	0.631
Male, *n* (%)	27 (61.8)	437 (74.7)	0.052
BMI mean ±SD	25.3±4.6	25.4±3.7	0.855
Migraine, *n* (%)	6 (13.6)	61 (10.4)	0.506
Drugs use, *n* (%)	1 (2.3)	63 (10.8)	0.074
Smoking (pack years) mean ± SD	15.9±15.1	17.9±16.0	0.429
Alcohol (glasses per week) mean ± SD	4.1±4.9	7.2±9.2	**0.030**
HADS[a] mean ± SD	11.7±9.2	10.9±7.6	0.551
Episodic cluster headache, *n* (%)	29 (65.9)	453 (77.4)	0.096
Cluster headache characteristics			
Severity of attack, *n* (%)			0.500
Severe	44 (100.0)	579 (99.0)	
Moderate	0 (0.0)	6 (1.0)	
Mild	0 (0.0)	0 (0.0)	
Location of the pain, *n* (%)[b]			
Periorbital	34 (77.3)	429 (73.3)	0.567
Retro-orbital	38 (86.4)	504 (86.2)	0.969
Frontal	34 (77.3)	337 (57.6)	**0.011**
Supraorbital	26 (59.1)	293 (50.1)	0.249
Jaw to temple	28 (63.6)	306 (52.3)	0.150
Temporal	34 (77.3)	476 (81.4)	0.504
Nature of headache, *n* (%)[b]			
Throbbing	21 (47.7)	295 (50.4)	0.730
Stabbing	43 (97.7)	524 (89.6)	0.088
Pressing	37 (84.1)	449 (76.8)	0.270
Autonomic symptoms			
Lacrimation	42 (95.5)	520 (88.9)	0.173
Conjunctival injection	32 (72.7)	406 (69.4)	0.667
Nasal congestion	35 (79.5)	411 (70.3)	0.191
Rhinorrhoea	30 (68.2)	425 (72.6)	0.523
Ptosis	32 (72.7)	361 (61.7)	0.149
Miosis	23 (52.3)	289 (49.4)	0.730
Forehead sweating	23 (52.3)	265 (45.3)	0.371
Eyelid oedema	20 (45.5)	213 (36.4)	0.231
Restlessness	35 (79.5)	483 (82.6)	0.595

$P < 0.05$ (Mann-Whitney test for ordinal data, independent T-test for interval data and $\chi 2$-test for nominal data). [a] HADS = Hospital Anxiety and Depression Scale. [b] More than one answer was possible.

Discussion

We assessed the presence of aura in 629 participants with cluster headache and compared the clinical attack characteristics of cluster headache participants with typical aura with those without aura. Typical aura was found in 7.0% of participants which lies within the range of other studies, in which aura prevalence varied from 0% to 23%.[2,13 18-22]

Consistent with the findings from previous studies[3,4,13], the most frequent aura symptoms were visual, which in our study started in most cases prior to the headache. Dysarthria and dysphasia, most often during the headache phase, was reported by 27.3% and 22.7% participants, respectively, which seems much higher than the 4.5% to 8% reported in previous studies.[2,4,5,13]

We and others[5] found no significant gender differences between participants with cluster headache with or those without aura. This is in contrast with migraine, as males proportionally have more often migraine with aura than females.[6,23] We found no difference in migraine comorbidity between cluster headache participants with and without typical aura.

In migraine with aura, the headache often lasts shorter and is less severe compared to those without aura.[6] We failed to find similar differences in attack characteristics between cluster headache with and without aura, except for more frontal pain and lower alcohol consumption in the former. The finding of a lower alcohol consumption in patients with aura is comparable with the situation in migraine, in which also a lower alcohol consumption was found in patients with aura.[24] Whether this implies that attacks with aura are more readily provoked by alcohol than attacks without aura remains a matter of speculation.

In participants with cluster headache with aura, we found a lower proportion of visual aura symptoms compared to aura studies in migraine. In migraine, visual symptom, sometimes combined with other aura symptoms, are reported in up to 99% of the migraine with aura patients.[25,26] A lower proportion of visual symptoms compared to migraine

was reported in cluster headache in earlier studies.[3,27] Moreover, those who experienced aura associated with their cluster headache attack, and were known with migraine as well, did not always experience an aura during their migraine attack. Bahra reported that as well: those with aura symptoms associated their cluster headache, did not have aura with their migraine headache in 60% of their cases.[3]

The strength of this study is the large sample size, a well-defined cohort, an overall high response rate of 83.2%, and detailed information on cluster headache characteristics. Limitations include the retrospectively collected aura data. The major limitation is that we expect that we have missed patients with aura symptoms by using this questionnaire[17] and are uncertain about the amount of missed patients. We may have missed differences in population characteristics. It is a challenge to attempt to answer questions regarding aura via a questionnaire. Our interviews by phone confirmed that diagnosing typical versus atypical aura by only using a questionnaire is insufficient and has a low predictive value. Therefore, we would strongly advise for future researchers to diagnose aura by face-to-face or telephone interview (our a sample).

Further research should focus on several questions (i) whether there are regional differences in aura prevalence related to cluster headache around the world, (ii) whether those with aura respond differently to standard treatment, (iii) if there are pathophysiological differences between those with and without aura and (iv) whether there is a cortical spreading depression in cluster headache as underlying mechanism of the aura symptoms.

Physicians should be aware that cluster headache seldomly can be preceded or accompanied by aura symptoms. In our opinion, there is no need to add a separate diagnosis of cluster headache with aura to the ICHD-III criteria or include aura in the list of cluster headache symptoms according to the ICHD-III criteria. When occurring, typical aura symptoms related to cluster headache can be classified as typical aura with headache as before.[1]

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Supplementary Table 1. Clinical characteristics of responders and non-responders

	Responders (N =629)	Non-responders (N=127)	P value
Age of onset, mean ± SD	30.3±12.7	29.7±12.6	0.759
Years of education, mean ± SD	12.8 ± 3.3	13.4±3.5	0.069
Male, n (%)	469(70.2)	80(69.6)	0.115
Episodic cluster headache[1], n (%)	482(76.6)	95(74.8)	0.659

[1]ICHD-III: International Classification of Headache Disorders, third edition beta version.
* $P < 0.05$ (Mann-Whitney test for ordinal data and χ^2-test for nominal data).

CHAPTER 6

Chronobiology and sleep in cluster headache

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Abstract

Introduction

Cluster headache attacks follow a striking circadian rhythm with an intriguing influence of sleep. We aim to investigate differences in sleep quality, chronotype, and the ability to alter individual sleep rhythms in episodic and chronic cluster headache patients versus controls.

Methods

Cluster headache patients and non-headache controls from the Dutch Leiden University Cluster headache neuro-Analysis program aged 18 and above completed web-based questionnaires in a cross-sectional study.

Results

A total of 478 episodic, 147 chronic cluster headache patients and 367 controls participated. Chronic cluster headache patients had more often early chronotypes than controls, as measured by mid-sleep phase (P=0.021 adjusted B -15.85 minutes CI -29.30;-2.40). Compared to controls, chronic cluster headache participants were less able to alter their sleep rhythms (P<0.001 adjusted B -1.65 CI -2.55;0.74), while episodic cluster headache participants reported more difficulty in coping with reduced sleep (P=0.025 adjusted B 0.75 CI 0.09;1.40). Sleep quality was reduced in both types of cluster headache compared to controls ("poor sleepers": 71.4% (105/147) in chronic and 48.3% (235/367) in episodic cluster headache versus 25.6% (94/367) in controls; both P<0.001; episodic adjusted B -1.71 CI 0.10;0.32; chronic adjusted B -0.93 CI 0.24;0.65).

Conclusion

Sleep quality is decreased in both episodic and chronic cluster headache, most likely caused by cluster headache attacks that strike during the night. Episodic cluster headache patients report more difficulty in coping with reduced sleep, while chronic patients are less able to alter their sleep rhythm. Although not directly proven, cluster headache patients will likely benefit from a structured, regular daily schedule.

Introduction

Cluster headache is a disabling primary headache disorder[1], associated with a lower quality of life[2] and considerable social impact.[3] One of the fascinating aspects of cluster headache is its episodic nature. Cluster headache attacks and attack periods often display an intriguing seasonal (autumn, spring) and/or circadian rhythmicity.[4-6] Up to 80% of patients report that attacks strike during (nocturnal) sleep.[4]

It has been hypothesized that the hypothalamus plays a pivotal role in the episodic nature and autonomic features of cluster headache.[7-9] A PET-study showed higher activation of the ipsilateral hypothalamus in episodic cluster headache patients during attacks.[10] Irregular sleep-wake patterns, decreased total amount and proportion of REM-sleep and longer REM-latencies were reported during, but not outside a cluster headache period.[11,12] These sleep abnormalities might be related to dysfunction of the biological clock, which resides in the suprachiasmatic nucleus of the anterior hypothalamus. Arkink et al. have reported an increase in the volume of the anterior hypothalamus in cluster headache patients versus controls, suggesting a structural change in the area of the suprachiasmatic nucleus.[13] Together, these findings may point at an association between sleep patterns and the biological clock in the pathophysiology of cluster headache.

Chronotype refers to interindividual differences in how the biological clock is entrained by light and darkness (going to sleep/waking up very early to going to sleep/waking up very late). The capability to cope with less sleep or cope with variation in sleep/wake pattern can also differ. These variations in circadian preference might explain differences in sleep quality in people with and without cluster headache.[14] Whether and how these differences influence cluster headache (or vice versa) is unknown. Insight into this matter may improve our understanding of the pathophysiology of this disorder.

In this study, we assessed (i) the distribution of chronotypes, (ii) the ability to alter sleep rhythms (i.e. the degree of difficulties adjusting sleep rhythm

when needed) by measuring amplitude and stability of circadian rhythms and (iii) sleep quality in a large well-characterized cohort of episodic and chronic cluster headache patients versus controls. Furthermore, we assessed (iv) an association between sleep patterns and the occurrence of individual cluster headache attacks.

Material and methods

Study design

This explorative cross-sectional study was conducted as part of the Leiden University Cluster headache neuro-Analysis program (LUCA).[15-21] The LUCA program was heavily promoted throughout The Netherlands to motivate as many potential cluster headache patients of 18 years and older to participate. In addition, patients attending the Leiden University Medical Center and other headache outpatient departments in the Netherlands were invited as well to participate. The LUCA program includes a validated, web-based, screening questionnaire for cluster headache based on the ICHD-II criteria [22] with a diagnostic specificity of 0.89.[15] All persons who fulfilled the ICHD-II criteria, also fulfilled to the ICHD-III Beta version for cluster headache.[16,22] All people who screened positive received a second, more extensive web-based questionnaire.

For this study, all available persons diagnosed with cluster headache were asked to fill out an additional questionnaire on sleep. This questionnaire included the Munich Chronotype Questionnaire, Circadian Type Inventory, the Pittsburgh Sleep Quality Index, and the Hospital Anxiety and Depression Scale.[23-27] For comparison, we included healthy controls who were screened for not having any primary headache like migraine, tension-type headache or cluster headache. The healthy controls were recruited as part of the LUCA and Leiden University Medical Center Migraine Neuro Analysis programmes (LUMINA).[28] They were recruited via public announcements, advertising in lay press and via the research website.

Persons who did not respond to the initial invitation to fill out the sleep questionnaire were reminded twice by email and once by phone. Only persons who completely filled out the sleep questionnaire were included in this study, because the questions were mandatory fields in our digital questionnaire (and therefore there was no missing data). There was thus no participants who did not fully complete the survey.

The study was approved by the local medical ethical committee of the Leiden University Medical Centre and all participants gave written informed consent.

Chronotype, sleep time and sleep duration

A Dutch version of the Munich Chronotype Questionnaire was used to assess the chronotype of participants.[28] Chronotype is the individual difference in diurnal preference for waking up and falling asleep. The original Munich Chronotype Questionnaire was developed to assign each individual to one of seven defined chronotype groups (extreme early, moderate early, slightly early, normal, slightly late, moderate late, extreme late), calculated by using the mid-sleep phase on free days.[24,25] Chronotype was corrected for individual sleep debt accumulated during the workweek according to Roenneberg et al.[29] Chronotype is also dependent on age and sex.[29]

Circadian rhythm amplitude and stability

A Dutch version of the Circadian Type Inventory was used to assess the ability to alter sleep rhythm (i.e. the degree of difficulties adjusting sleep rhythm when needed) by measuring the circadian rhythm amplitude and stability in headache participants and controls.[28,30] Rhythm amplitude was assessed via the factor "languid/vigorous". Languid types find it difficult to overcome drowsiness and feel lethargic following reduced sleep. Rhythm stability was assessed via the factor "flexibility/rigidity of sleeping habits". Rigid types have a preference to eat and sleep at regular times. A lower "languid/vigorous" score indicated greater ability to manage on less sleep, while a higher "flexibility/rigidity" score indicated greater flexibility in circadian rhythm. Vigorous and flexible types show better circadian adjustment both physiologically and psychologically.[30] The revised

Circadian Type Inventory questionnaire consisted of 11 items, with 5 answer options.[23,31] In this 11-item version, 50% of the sample variance was explained by the two factors languid/vigorous and flexibility/rigidity with an internal consistency of 0.72 for languid/vigorous and 0.79 for flexibility/rigidity.[23]

Sleep quality

A Dutch version of the Pittsburgh Sleep Quality Index was used to assess sleep quality.[28,32] The Pittsburgh Sleep Quality Index consists of 19 items grouped into 7 subscores. A person with a total Pittsburgh Sleep Quality Index score of ≥ 5 was defined as a poor sleeper with a sensitivity of 89.6% and a specificity of 86.5%.[26]

Circadian timing of attack onset

Cluster headache participants were asked to indicate during which part of the day the most and during which part the least attacks tended to appear. For this, 4-hour timeframes were chosen. Moreover, they were asked to report the effect of sleep duration and sleep onset on the frequency of their cluster headache attacks.

Statistics

No power analysis was performed for this explorative cross-sectional study. Baseline data were compared using Mann Whitney test for ordinal data, and Fisher's Exact test for categorical data.

Separate linear regressions were performed for each of the following six outcomes:1. sleep duration, 2. sleep onset, 3. midsleep phase, 4. chronotype distribution, 5. Languid Circadian Type Inventory score and 6. Flexibility Circadian Type Inventory score. All outcomes were checked for normality. In each model, the predictor of interest was headache diagnosis (episodic cluster headache, chronic cluster headache, and controls). The following possible confounders were added (entered) to each of the models : age (years), sex (male/female), years of education, BMI, recreational drug use (yes/no), alcohol use (glasses per week), smoking (packyears) and Hospital Anxiety and Depression Scale (HADS) total score.

A logistic regression model was used for the outcome of the Pittsburgh Sleep Quality Index scores (good versus bad sleeper) again with headache diagnosis as the predictor of interest. The same variables/confounders were added as in the linear regression models above.

The analyses were revised during the peer review process. Besides adjusting our for age (years) and sex (male/female), we also adjusted all regression models for years of education, BMI, recreational drug use (yes/no), alcohol use (glasses per week), smoking (packyears) and Hospital Anxiety and Depression Scale (HADS) total score (as described above). There were no post hoc analyses except for these revised analyses.

For all statistical hypotheses two-tailed testing was used. Due to the explorative nature of this study, no corrections for multiple comparisons were done. All data analyses were performed using SPSS 23.0 (SPSS Inc., IBM, USA), with the statistical threshold at $P<0.05$.

Results

A total of 804 cluster headache participants and 408 non-headache controls were eligible in the LUCA program in April 2015 and were invited. The response rate was 78.9% (634/804) in the cluster headache group and 90.0% (367/408) in the control group. Cluster headache had been diagnosed by a physician in 95.6% (606/634) according to the participants. Non-responder analysis among cluster headache patients revealed that they had a lower age of onset compared to responders (Supplementary Table 1).

Clinical characteristics

Compared to controls, episodic and chronic cluster headache participants more often were male, older, lower educated, shift-working, smoking, users of recreational drugs with a higher BMI and more often had higher scores on the Hospital Anxiety and Depression Scale. Chronic cluster headache participants more often were without work (Table 1).

Table 1. Characteristics of study population

	Chronic cluster headache[a] (N=147)	Chronic vs controls *p*-value	Episodic cluster headache[a] (N=487)	Episodic vs controls *p*-value	Controls (N=367)
Age (years), mean ±SD	48.5±11.3	0.001	50.4±12.1	<0.001*	43.9±15.5
Male, *N* (%)	109(74.1)	<0.001*	364 (74.7)	<0.001*	161 (43.9)
Years of education, mean ±SD	12.3±3.0	<0.001*	13.1±3.3	<0.001*	14.1±3.6
BMI[b], mean ±SD	25.6±4.3	<0.001*	25.3±3.6	<0.001*	24.0±4.0
Recreational drugs use, *N* (%)	20(13.6)	<0.001*	42(8.6)	0.005*	14(3.8)
Smoking (pack years), mean±SD	17.9±14.9	<0.001*	18.0±16.6	<0.001*	5.6±10.3
Alcohol (glasses per week), mean±SD	4.9±8.0	<0.001*	7.4±8.6	0.547	6.5±6.6
HADS[b] total score, mean±SD	14.4±9.1	<0.001*	10.0±7.1	<0.001*	6.4±5.5
Shiftwork ever, *N* (%)	52(35.4)	0.053	165(33.9)	0.020*	97 (26.4)
Shiftwork last week, N (%)	7(4.8)	0.814	35(7.2)	0.756	21 (5.7)
Not working, N (%) Retired, N (%) Inside a cluster headache period, N (%)	62(42.2) 10 (6.8) N/A	<0.001* 0.188	51(10.5) 74 (15.2) 45 (9.2%)	0.489 0.084	33 (9.0) 40 (10.9) N/A

*P < 0.05 (Mann Whitney test for ordinal data, and Fisher's Exact-test for nominal data), no correction for multiple testing

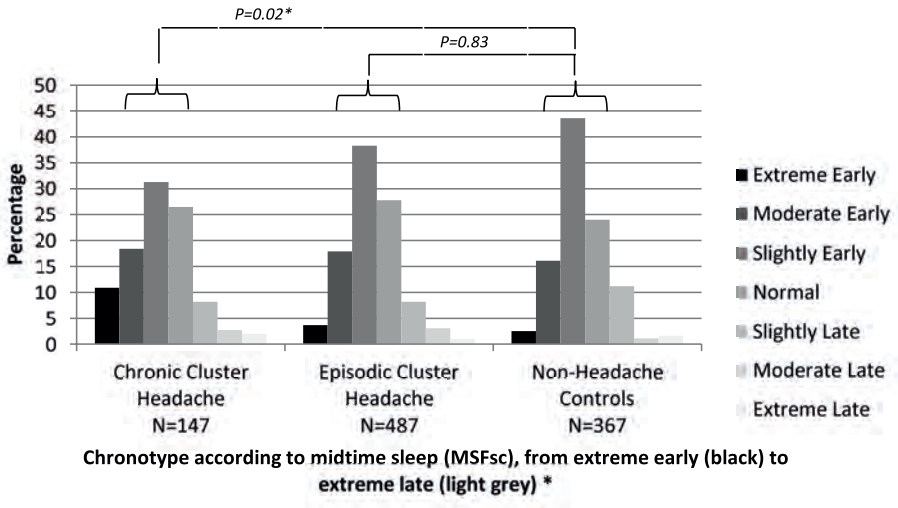
[a] according to ICHD-III beta version criteria.[1]

[b] BMI: Body Mass Index; HADS: Hospital Anxiety and Depression Scale; N/A: not applicable.

Chronotype

Participants with episodic cluster headache more often classified themselves as late chronotypes compared to both participants with chronic cluster headache and controls (proportion classified as: episodic 40%; *P*=0.041 adjusted B 0.13; CI 0.01;0.25,chronic 29.9%; *P*=0.503 adjusted B -0.06 CI -0.23;0.11, controls 28.9%). Chronotype distribution as measured by mid-sleep phase showed that chronic cluster headache participants more often had an earlier chronotype than controls (relatively *P*=0.834 adjusted B 1.03 minutes CI -8.58;10.65 minutes for episodic and P=0.021 adjusted B -15.85 minutes CI -29.30;-2.40 minutes for chronic; Figure 1).

Figure 1. The distribution of chronotypes by using mid-sleep phase



Notes: The objective distribution of chronotypes, calculated using mid-sleep phase, in episodic cluster headache, chronic cluster headache, and controls according to the Munich Chronotype Questionnaire. P values based upon a linear regression model corrected for age, sex, years of education, BMI, recreational drug use, alcohol use, smoking, and HADS total score. *P < 0.05.

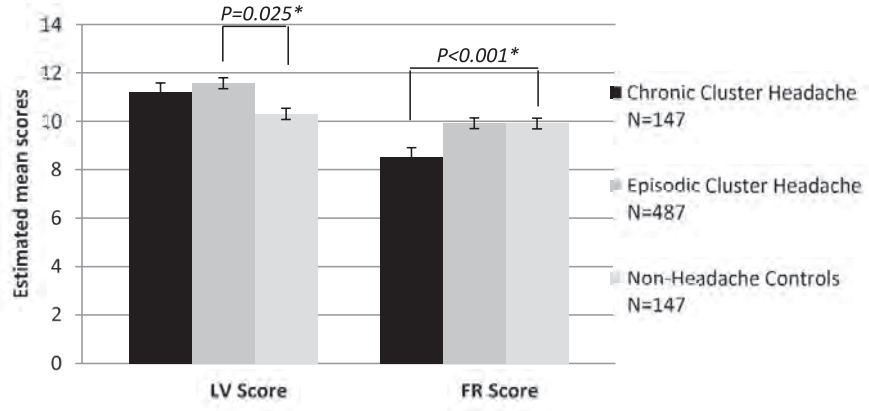
Sleep duration did not differ between both episodic and chronic cluster headache versus controls (relatively *P*=0.097 adjusted B -9.22 minutes CI -20.11;1.67 minutes for episodic and P=0.369 adjusted B -6.97 minutes CI -22.20;8.26 minutes for chronic). There was no difference in sleep onset between both episodic or chronic cluster headache patients and controls (relatively *P*=0.725 adjusted B -1.73 minutes CI -11.37;7.91 minutes for episodic and P=0.363 adjusted B -6.24 minutes CI -19.72;7.23 minutes for chronic). There were no differences between episodic cluster headache participants in versus outside a cluster headache period (mid-sleep phase: *P*=0.661 adjusted B 4.26 minutes CI -14.8;23.330; sleep duration: *P*=0.778 adjusted B -3.22 minutes CI -25.66;19.23 minutes; sleep onset: *P*=0.075 adjusted B 18.01 minutes CI -1.82;37.85 minutes).

Circadian rhythm amplitude and stability

Episodic cluster headache participants were more often languid types compared to controls, which was not the case in chronic cluster headache participants (episodic *P*=0.025 adjusted B 0.75 CI 0.09;1.40;

chronic *P*=0.632 adjusted B 0.22 CI -0.69;1.14). Chronic cluster headache participants more often were rigid types than controls (chronic *P*<0.001 adjusted B -1.65 CI -2.55;-0.74; episodic: *P*=0.515 adjusted B -0.22 CI -0.86;0.43) (Figure 2). Episodic cluster headache participants in a period did not differ from those outside a cluster headache period (languid *P*=0.379 adjusted B -0.58; CI -1.89;0.72; rigid *P*=0.873 adjusted B 0.11 CI -1.21;1.42).

Figure 2. Circadian Type Inventory scores episodic cluster headache, chronic cluster headache and controls, corrected for age and gender



Notes: Estimated Mean LV score (languid/vigorous score) and FR score (flexibility/rigidity score). Significant differences in languid/vigorous score are shown in the figure. P values based upon a linear regression model corrected for age, sex, years of education, BMI, recreational drug use, alcohol use, smoking, and HADS total score. *P < 0.05.

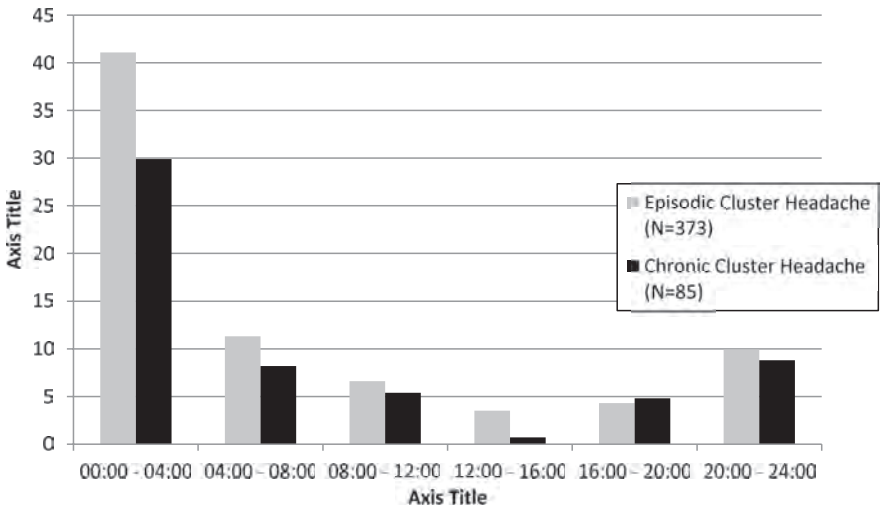
Sleep quality

Compared to controls, chronic and episodic cluster headache participants reported higher scores on all subgroups of the Pittsburgh Sleep Quality Index, which reflects lower sleep quality (Supplementary Table 2). Controls (25.6%; N=94/367) were less often "poor sleepers" compared to both episodic (48.3% poor sleepers; N=235/367 *P*<0.001 adjusted B -1.71 CI 0.10;0.32) and chronic cluster headache participants (71.4% poor sleepers; N=105/147 *P*<0.001 adjusted B -0.93 CI 0.24;0.65). Episodic cluster headache participants in a cluster headache period showed a lower sleep quality compared to those outside (inside a period: N=34/45 versus outside a cluster headache period: N=201/442; *P*=0.001 adjusted B 1.41 CI 1.80;9.25).

Circadian timing of attack onset

A predictable circadian pattern of attacks was reported in 76.6% (373/487) of episodic and 57.8% (85/147) of chronic cluster headache participants. Attacks occurred most often in episodic (53.6% 200/373) and in chronic cluster headache(51.8% 44/85) between 00:00 and 04:00 AM and least often (4.6% N=17/373 in episodic and 1.2% N=1/85 in chronic cluster headache) between 12:00 and 16:00 PM (Figure 3).

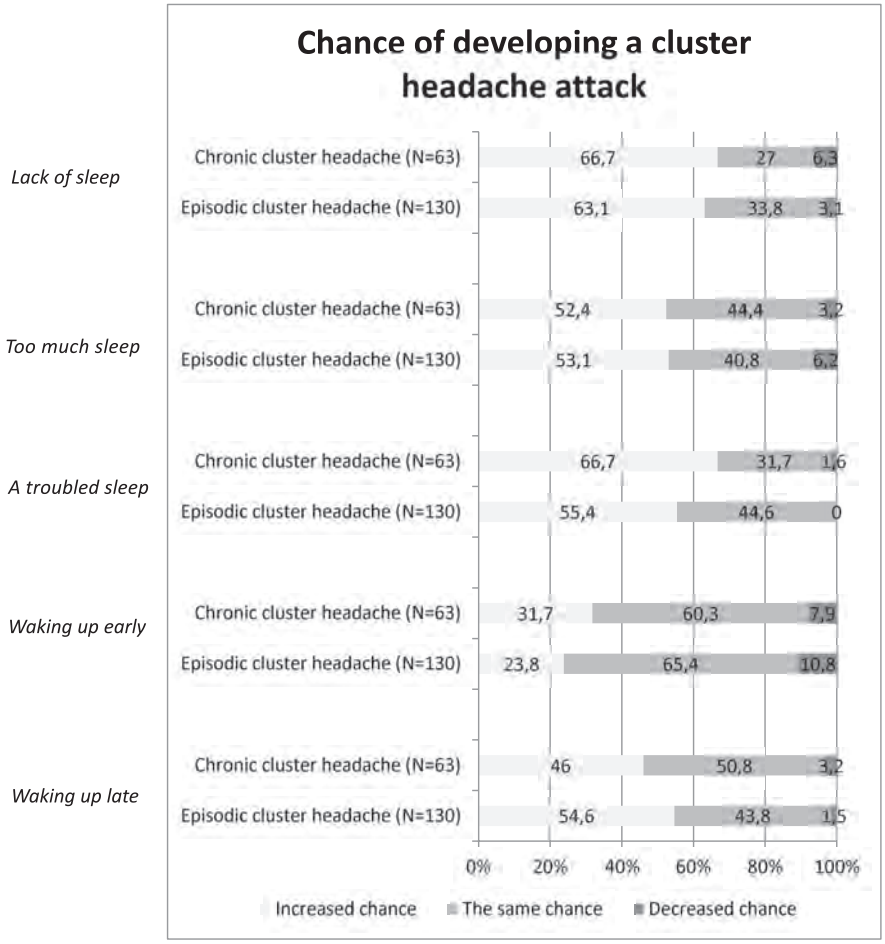
Figure 3. 4-hourtimeframes of cluster headache attack occurence



Sleep pattern

In 26.7% (130/486) episodic and 42.9% (63/147) chronic cluster headache participants an association between the sleep pattern and the probability of developing a cluster headache attack was reported. Lack of sleep (63.1% 82/130 in episodic and 66.7% 42/63 in chronic cluster headache) and troubled sleep (55.4% 72/130 in episodic and 66.7% 42/63 in chronic cluster headache) were most commonly reported. Too much sleep or waking up late increased the chance of developing an attack the next day according to about 50% of the participants (too much sleep: in episodic cluster headache 53.1% 69/130; in chronic cluster headache 52.4% 33/63; waking up late: in episodic cluster headache 54.6% 71/130; in chronic cluster headache 46.0% 29/63). Waking up early was generally reported to have no influence on the development of attacks (Figure 4).

Figure 4. Reported influence of sleep on developing a cluster headache attack



Discussion

In this large, well-characterized cluster headache and control population with a high response rate, we assessed the distribution of chronotypes, the ability to alter sleep rhythms and sleep quality. Furthermore, we assessed if there was a subjective association between sleep patterns and the occurrence of individual cluster headache attacks. Episodic cluster headache patients described themselves more often as having a late chronotype. However, this was not confirmed when assessing their chronotype by their mid-sleep phase. In contrast, chronic cluster

headache patients more often had an early chronotype compared to non-headache controls. Furthermore, chronic cluster headache patients were less able to alter their sleep rhythm; while on the other hand episodic cluster headache patients experience more difficulty in coping with reduced sleep. To our knowledge, these aspects of sleep rhythmicity were not assessed before in cluster headache. Sleep quality was decreased in both episodic and chronic cluster headache, probably in association with their predictable nocturnal headache attacks. Changes in sleep patterns were associated with headache attacks in nearly one third of the population studied.

Although episodic cluster headache patients more often classified themselves as "late" chronotypes, no actual difference with controls was found in chronotype distribution as measured by mid-sleep time. In two smaller studies chronotype was measured before with similar findings in episodic cluster headache.[4, 33] In another cohort, chronic cluster headache patients classified themselves more often as morning persons compared to episodic cluster headache patients.[6] We here report similar findings in the mid-sleep phase: chronic cluster headache patients more often had an early chronotype, suggesting an association between chronotype and the more severe form of cluster headache.

In our study cluster headache patients who reported an association between the occurrence of headache attacks an sleep, most often reported that these attacks occurred within 1-2 hours after falling asleep. Unfortunately, we were not able to analyze whether this is related to chronotype, because of the 4-hour timeframes we used in our questionnaire. Barloese et al. reported indeed an association between the occurrence of the first nocturnal attack and chronotype in cluster headache patients (the "morning type" being earliest (00:50), the "neither type" later (01:02) and the "evening type" later still (02:11)).[34]

Sleep quality was affected in episodic and even more in chronic cluster headache patients. Since chronic cluster headache is the most severe of the phenotypes, the difference in sleep quality and rhythm between chronic and episodic cluster headache are most likely associated with the

number of nights with cluster headache attacks, but other contributing factors cannot be excluded. The first option would, however, suggest that the direction of the association is that cluster headache influence sleep quality, pattern and rhythm (and not vice versa). However, this causality cannot be directly proven by our data. Lund et al studied the association between cluster headache and sleep using polysomnography. They concluded that disturbed sleep is rather due to a continuing or slowly recovering disturbance of sleep outside the cluster headache episode than due to a transient process associated with the cluster headache attacks themselves.[35] Although the exact causality remains unclear, association between cluster headache and sleep seems robust and remains intriguing.

The most common sleep-related triggers in our study were a lack of sleep and troubled sleep (i.e. moving and turning a lot). Nocturnal sleep per se and a lack of sleep have been reported as triggers before.[4, 36] It is telling that 42% of another cluster headache population even consciously changed their sleep habits in order to prevent headache attacks.[3]

In our population, shift work, which disturbs sleep rhythms, was associated with episodic cluster headache, which is in line with previous reports.[33, 36] As chronic cluster headache participants showed greater difficulty in adjusting their sleep rhythm and episodic cluster headache patients experience more difficulties in coping with less sleep, we wonder whether shift work might indeed trigger cluster headache in people that are already prone to develop this disorder.

The strength of this study are the large sample size, a well-defined cohort and, an overall highly motivated group as was reflected by the high response rate. Limitations include that we have no data regarding sleep patterns before the development of cluster headache. Also, participants of the LUCA program needed to have (at least once) online access to register for participation, which could have introduced a bias.

In this large study, we found differences in sleep patterns between cluster headache participants and controls. We would like to suggest that the

cluster headache attacks themselves are responsible for these sleep differences. However, the exact association between cluster headache and sleep remains unknown. Although not directly proven, it seems very likely that cluster headache patients will benefit from a structured, regular daily schedule.

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Supplementary Table 1. Clinical characteristics responders and non-responders

	Cluster headache			controls		
	Responders (N =634)	Non-responders (N=170)	*P* value	Responders (N =367)	Non-responders (N=41)	*P* value
Age of onset mean ± SD	30.7±12.6	26.7±12.6	0.004*	-	-	-
Years of education mean ± SD	12.9±3.2	13.0±3.6	0.453	14.1±3.6	14.8±3.6	0.094
Male n (%)	473 (74.6)	115 (67.5)	0.069	161 (43.9)	16 (39.0)	0.553
Diagnosis ICHD-III [1]:			0.946	-	-	-
Episodic cluster headache	487	131				
Chronic cluster headache	147	39				

* P < 0.05 (Mann-Whitney test for ordinal data, T-test for continues data and χ^2-test for nominal data), no correction for multiple testing.
[1]ICHD-III: International Classification of Headache Disorders, third edition beta version.[1]

Supplementary Table 2. Pittsburgh Sleep Quality Index per subscore

	Chronic cluster headache[a] (N=147)	Episodic cluster headache[a] (N=487)	Controls (N= 367)	*p*-value
Subjective sleep quality mean ± SD	1.57±1.45	1.14±1.06	0.71±0.064	P<0.001*
Sleep latency mean ± SD	1.49±0.083	1.08±0.050	0.75±0.051	P<0.001*
Sleep duration mean ± SD	0.96± 0.073	0.64±0.044	0.40±0.044	P<0.001*
Sleep efficiency mean ± SD	1.30±0.082	0.71±0.050	0.40±0.050	P<0.001*
Sleep disturbance mean ± SD	1.58±0.047	1.38±0.028	1.03±0.028	P<0.001*
Use of sleep medication mean ± SD	0.61±0.069	0.37±0.042	0.16±0.042	P<0.001*
Day dysfunction mean ± SD	1.39±0.063	1.04±0.038	0.61±0.038	P<0.001*
Total PSQI score mean ± SD	**8.91 ± 0.304**	**6.36 ± 0.184**	**4.07 ± 0.185**	**P<0.001***

* P < 0.05, GLM adjusted for age and sex, not corrected for multiple testing.
[a] according to the International Classification of Headache Disorders, third edition beta version.[1]

CHAPTER 7

Long lasting impairment of taste and smell as side effect of lithium carbonate in a cluster headache patient.

Case report and review of the literature.

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Abstract

Introduction

Preventive treatment with lithium carbonate is one of the therapeutic options in chronic cluster headache. Lithium can lead to a broad spectrum of severe side effects, many of which are generally unknown. We report on one of these side effects.

Case description

One week after starting treatment with lithium, a 55 year old man with chronic cluster headache noticed a strange and unpleasant taste of various foods and a diminished smell. After 4 weeks, he decided to stop the therapy because of these complaints, but 9 months later taste and smell had still not returned to normal.

Discussion

This is the first description of long-lasting dysgeusia and hyposmia as side effect of lithium therapy in cluster headache. Dysgeusia has only rarely been reported as side effect of lithium in other conditions and hyposmia has not previously been reported. Physicians should be aware of this rare, but severe, side effect when prescribing lithium.

Introduction

Cluster headache is a rare primary headache disorder characterized by attacks of excruciating, intermitting short-lasting unilateral temporal or orbital pain and ipsilateral autonomic symptoms.[1] Next to acute treatment, mostly also prophylactic treatment is prescribed to reduce the number of attacks. First-choice prophylactic treatment is verapamil, but when this is not effective or tolerated another option is lithium carbonate, which was shown to be effective in chronic cluster headache.[2,3] It is known that lithium has a broad spectrum of side effects, especially at high blood levels.[4,5] However, it is not generally known that lithium can lead to a long-lasting loss or change of taste and smell. Here, we report on a cluster headache patient with chronic cluster headache, who developed dysgeusia and hyposmia during lithium therapy.

Case report

A 55 year old man suffered from chronic cluster headache for more than four years. He had right-sided periorbital attacks with autonomic symptoms and an average duration of 30 minutes. As acute treatment he used sumatriptan subcutaneously with excellent effect. Because of the high frequency of the attacks (and very frequent sumatriptan use), he was tried on different prophylactic regiments. The effects of verapamil, methysergide, topiramate, indomethacin, valproate and greater occipital nerve blocks was insufficient. In 2015, he was on verapamil 480mg/day (higher doses had led to ankle oedema) and sodium valproate 2000mg/day and still had a high attack frequency. Therefore, lithium 800mg/day was added (he refused to first lower the other medication). When at the out-patient clinic four weeks later, he reported as side-effect a strange and unpleasant taste after eating various foods, a metallic taste and the loss of smell. These complaints had started after one week and had led him to stop lithium shortly before the appointment at the out-patient clinic. Impairment of smell and taste had started simultaneously and increased over time. He described a complete loss of smell of odours like gas or perfume and a chemical smell perception for fried meat and onions. He

also described an altered taste of various substances including coffee and chocolate. He reported to taste sweet, salty and sour food only minimally. The taste of creamy food like whipped cream, ice cream and mayonnaise and spiced food was diminished, but not completely lost. There were no disorders of smell or taste in his family. Serum level of lithium was 0.35 mmol/L (normal range 0.80-1.20 mmol/L) 13 days after starting treatment. A cerebral MRI did not show any abnormalities. According to the patient, the metallic taste quickly disappeared after stopping lithium intake, but the impairment of smell and taste at first even increased for several weeks, before reaching a stable level. Nine months later he was still using verapamil and sodium valproate, had no loss of appetite and reported a gain of weight. Taste and smell still had not improved.

Discussion

Our case is the first description of long-lasting hyposmia as side effect of lithium therapy. Moreover, it is the first report of long-lasting dysgeusia as side effect of lithium therapy in a cluster headache patient. Dysgeusia due to lithium treatment has been rarely reported before in patients with psychiatric illnesses.

A metallic taste is a well-known side effect of lithium therapy in up to 20% of the patients[6-8], but a non-metallic alteration in taste is rarely described. The first description of dysgeusia as side effect of lithium therapy was published in 1973. The patient described started on a low dose of lithium (750mg/day) and after several days reported a strange and unpleasant taste of various foods, which increased in time. He also reported an altered appetite. Taste and appetite returned to normal within 2 days after discontinuation of lithium.[9] A similar alteration of taste and appetite was found by Himmelhoch and Hanin in about 5% of 450 psychiatric patients on lithium therapy.[10] Three other cases were described with alteration in taste during lithium therapy[11-13], increasing over time in two of them.[11,13] The outcome was different in each case: in the first case taste returned to normal within a month after discontinuation of lithium therapy, the

second case reported moderately improvement over a longer period of time and in the last case the outcome was not reported.

The frequency of this complication of lithium is unknown. For example, in three large studies the side effects of lithium were investigated prospectively and no alteration in smell or taste was reported.[6-8] This could, however, be due to the fact that two of the studies used a questionnaire in which an alteration of taste or smell was not included.[6,7] Anyhow, it seems likely that this complaint is rarely mentioned spontaneously by the patient when not specifically asked for.

It is unknown if these symptoms are olfactory effects, taste effects, central effects or a combination of both. Himmelhoch and Hanin[10] found a high lithium concentration in the olfactory bulb, caudate and pituitary in rats when on lithium.[10] Our patient described an alteration of taste of various substances including coffee and chocolate and a reduction of smell, which both could reflect a reduced stimulation of the olfactory receptors via the retronasal route.[14] However, he also reported to taste sweet, salty and sour food only minimally, which could reflect taste-bud-mediated effects. In this particular case we would thus suggest a combination of several mechanisms.

Strictly spoken, the side effects in our patient could also be caused by the combined use of lithium and verapamil. Indeed, an earlier report described such combined neurotoxicity, but not including changes in smell or taste. Furthermore, in the patient described the side effects disappeared within 48 hour after discontinuing the therapy.[15]

Anyhow, physicians should be aware of this rare, but profound, side effect when prescribing lithium, especially so because this side effect can be long lasting even after lithium is discontinued, and because recovery is not always complete.

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CHAPTER 8

Increased use of illicit drugs in a Dutch cluster headache population

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Abstract

Introduction

Many patients with cluster headache report use of illicit drugs. We systematically assessed the use of illicit drugs and their effects in a well-defined Dutch cluster headache population.

Methods

In this cross-sectional explorative study, 756 persons with cluster headache received a questionnaire on lifetime use and perceived effects of illicit drugs. Results were compared with age and sex-matched official data from the Dutch general population.

Results

Compared to the data from the general population, there were more illicit drug users in the cluster headache group (31.7% vs. 23.8%; $P<0.01$). Reduction in attack frequency was reported by 56% (N=22) of psilocybin mushroom, 60% (N=3) of lysergic acid diethylamide and 50% (N=2) of heroin users, and a decreased attack duration was reported by 46% (N=18) of PSI, 50% (N=2) of heroin and 36% (N=8) of amphetamine users.

Conclusion

In the Netherlands, people with cluster headache more often use illicit drugs than the general population. The question remains whether this is due to an actual alleviatory effect, placebo response, conviction, or common pathophysiological background between cluster headache and addictive behaviours such as drug use.

Introduction

Cluster headache is a rare primary headache disorder characterized by severe unilateral headache attacks lasting 15 to 180 minutes accompanied by cranial ipsilateral autonomic symptoms.[1] Most persons suffer from the episodic form, in which attacks occur in clusters of weeks to months alternating with remissions of several months to years.[1] About 14% of people with cluster headache suffer from the chronic form and do not have attack-free episodes longer than a month.[1,2] Although most people with cluster headache can be successfully treated with regular medication, in 10-20% this is not effective.[3] These persons are more likely to experiment with alternative treatments[4], including illicit drugs.

Few epidemiologic studies have investigated the use of illicit drugs in cluster headache.[4-7] In two French studies, 26-32% of cluster headache patients used cannabis regularly, which is higher than in the general French population (7%).[6,7] The prevalence of cannabis use was considerably lower (10%) in an American cluster headache cohort.[7,8] Illicit drug use in cluster headache has been associated with younger age, male gender, and smoking. Use of alternative treatments in cluster headache has also been associated with lower income and higher annual attack frequency.[5,9]

Some patients report an acute effect of cannabis, cocaine, psilocybin mushrooms (PSI) and heroin.[4,10,11] In a small open study, 22 of 26 patients reported an acute effect on their cluster headache attacks after psilocybin mushrooms use.[11] In Italy, 7-19% of persons with cluster headache reported having tried cannabis as an acute treatment, but self-reported effects were inconclusive.[4,7] In 25% it even seemed to trigger attacks.[7]

Illicit drugs are not only described as acute treatment, but in several small studies also as alternative prophylactic treatment. Remission-extending qualities have been attributed to PSI, gamma-hydroxybutyrate (GHB) and lysergic acid diethylamide (LSD).[4, 11-13] GHB's sodium salt form (sodium oxybate) reduced attack frequency in five patients with cluster headache.[12,13] In a small study, patients report a perceived prophylactic effect of both LSD and PSI.[11]

While these possible alleviatory effects of illicit drugs in cluster headache are intriguing, the studies that have been conducted were all small and uncontrolled. Although restricted use of cannabis is legal in the Netherlands, the use of drugs in cluster headache has not been investigated. Here we systematically assessed (i) the use of illicit drugs in general and (ii) the use of several illicit drugs in a representative Dutch cluster headache population and compared this to the Dutch general population. Additionally, we determined whether illicit drugs influenced cluster headache attack duration and attack frequency in the Dutch cluster headache population.

Material and methods

Study design

This explorative cross-sectional study was conducted as part of the ongoing, nation-wide, Leiden University Cluster Headache neuro-analysis programme (LUCA) and compared to official data of the Dutch general population.

Cluster headache population

The LUCA program is heavily promoted throughout The Netherlands to attract as many potential cluster headache participants of 18 years and older as possible. In addition, participants attending the Leiden University Medical Center and other headache outpatient departments were invited as well to participate in the LUCA program. All possible participants were invited to fill out a validated, web-based, screening questionnaire about cluster headache based on the ICHD-II criteria for cluster headache.[14] The screener has been validated and has a diagnostic specificity of 0.89 for cluster headache.[15] All persons who fulfilled the ICHD-II criteria also fulfilled to the latest ICHD-III beta version for cluster headache.[16] All people who screened positive received a second, more extensive web-based questionnaire.

For the present study, persons who had been screened positive for cluster headache received an email asking to fill out a questionnaire

concerning illicit drug use. This questionnaire was designed by the authors (IFC and LAW) and included questions about lifetime use of illicit drugs and more specific the use of cannabis, cocaine, heroin, PSI, 3,4-methylenedioxymethamphetamine (MDMA), LSD, amphetamine and GHB. Also, the questionnaire included two questions about the effect on attack duration and attack frequency of these illicit drugs (three answer options: increased, no effect, decreased). Web-based questionnaires were used, except for persons not capable of using internet, who were allowed to fill out the questionnaires on paper. Those who did not respond to the initial email were reminded twice per email and when still not responding, they were contacted two more times (once by phone and once by email again). Only persons who filled out all items regarding drug use were included.

All LUCA data was securely stored in a web based database management system of ProMISe (Project Manager Internet Server), which meets ISO 27001 and the requirements for data-safety and privacy set by international law.

Dutch general population

Statistics Netherlands (Centraal Bureau voor Statistiek) provided data about the Dutch general population from their annual health survey, which monitors various health and life-style aspects including illicit drug use in the Dutch population. Each year, 15.000 randomly selected Dutch citizens of all ages are approached by mail to fill out their online survey. For our study, we only included data from persons 18 years and older. Statistics Netherlands supplies this data as anonymous categorical variables. The information is therefore not traceable to an individual.

For our study, we divided the data in three categories: all, persons classified as having headache (migraine or regular severe headache in the previous 12 months) and persons classified as having chronic pain (in the previous 12 months).

Ethical Approval

The LUCA study was approved by the local medical ethics committee of the Leiden University Medical Center. All participants of the LUCA study provided written informed consent. The survey in the Dutch general population by Statistics Netherlands was exempt from ethical approval according to Dutch laws, therefore no informed consent was needed.

Statistics

We have performed Chi-square test for categorical variables and independent t-test for continuous variables to describe the population characteristics as shown in Table 1. Chi-square test with Yates' correction and Fisher's Exact test (N<5 per group) were used to determine categorical differences in drug use between the cluster headache population and the general population, the headache subgroup and the chronic subgroup of the general population. All data analyses were performed using SPSS 23.0 (SPSS Incorporate IBM USA) with statistical significance set at $P<0.05$. No power analysis has been performed.

Results

Study population

By August 2014, there were 756 persons with self-reported cluster headache invited for this study of whom 85.1% (643 /756) filled out all necessary questionnaires. 613/643 (95.3%) had received a diagnosis of cluster headache by a physician. A total of 14.542/24.396 (59.6%) of the controls from the general population from the cohort 2014 and 2015 of the Statistics Netherlands responded to the questionnaire and were included in this study. In the Dutch general population cohort, 3457 (23.8%) persons reported having "chronic pain" and 2269 (15.6%) persons reported having "headaches".

Persons with cluster headache more often were male, higher educated, smokers, and drank less often alcohol compared to the Dutch general population (Table 1).

Table 1. Demographics of cluster headache population and the general population

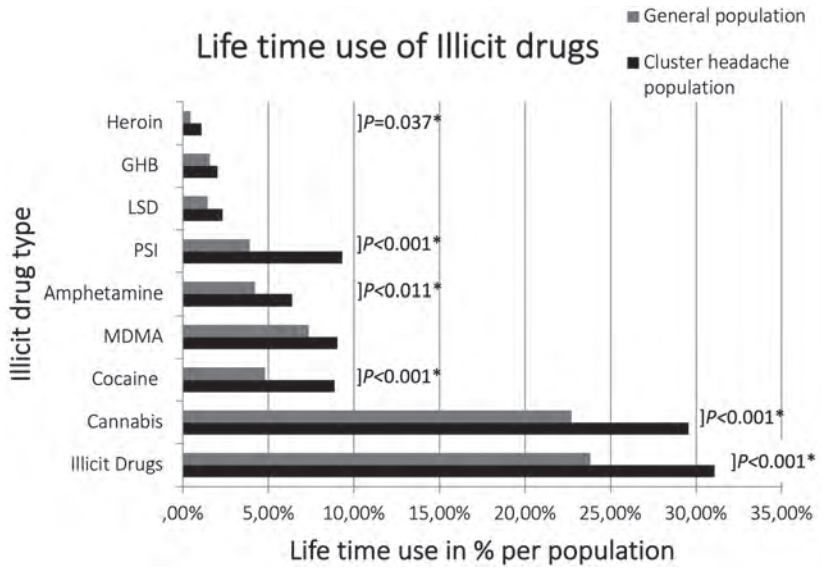
	Cluster Headache (n=643)	General population (n=14542)	*p*-value
Demographic characteristics			
Male, N (%)	470(73.1)	7072 (48.6)	<0.001*
Age (years), median ±SD	49.9 ±12.1	48.5 ±18.0	0.0048*
Education, N (%):			<0.001*
- Primary education	10(1.4)	1299(8.9)	
- Pre-vocational secondary education	151(23.5)	3001(20.6)	
- Secondary vocational education	236(36.7)	6151(44.2)	
- Higher professional education	157(24.4)	2682(18.4)	
- University education	80(24.4)	1411(9.7)	
Smoking, N (%)	342 (53.8)	3778(26.0)	<0.001*
Alcohol use, N (%)	481 (75.6)	11792 (81.1)	<0.001*
Body Mass Index, median ±SD	25.4±3.8	25.5±4.3	0.655
Episodic cluster headache, N (%)	492(76.50)	N/A	

* $P<0.05$ (χ^2-test with Yates' correction for categorical data, which were male, education, smoking and alcohol use. Single sample-test for interval data, which were Body Mass Index and Age).

Cluster headache compared to the general population

Participants with cluster headache more often used illicit drugs (31.7% vs. 23.8%; *P*<0.001; Figure 1), cannabis (29.5% vs. 22.7%; *P*<0.001), cocaine (8.9% vs. 4.8%; *P*<0.001), amphetamine (6.4% vs. 4.2%; *P*=0.011), PSI (9.3% vs. 3.9%; *P*=0.00) and heroin (1.1% vs. 0.5%; *P*=0.037).

Figure 1. Lifetime use of different types of illicit drugs in cluster headache and general population



Illicit drugs: all drugs; MDMA: 3,4-methylenedioxymethamphetamine; PSI: Psilocybin Mushroom; LSD: Lysergic acid diethylamide; GHB: Gamma-hydroxybutyrate.
* P<0.05 (χ^2-test with Yates' correction for categorical data).

Cluster headache compared to people with headache and the chronic pain in the general population

Persons with cluster headache more often used illicit drugs than persons from the general population classified as having headache (31.7% vs. 25.2; *P*=0.001) or chronic pain in the general population (31.7% vs. 20.3%;*P*<0.001). Compared to the headache subgroup of the general population all drugs except for GHB were used more frequently by cluster headache patients (Table 2) and compared to the chronic pain subgroup cannabis, cocaine, MDMA, amphetamine and PSI were used more often.

Gender differences

Males more often used illicit drugs compared to females as shown in Table 3 (cluster headache: 34.7% vs. 23.7%; *P*=0.008; general population: 29.2% vs. 18.5; *P*<0.001;). When specified for drug kind, only cannabis (33.0 vs. 20.2%; *P*=0.028) and LSD (3.25 vs. 0.0%; *P*=0.044) were more often used in males vs. females with cluster headache.

Table 2. Lifetime use of different types of illicit drugs in the cluster headache, headache and chronic pain subgroup

	Cluster headache (N=643)	General population: headache subgroup (N=2269)	*p*-value[a]	General population: chronic pain subgroup (N=3457)	*p*-value[b]
Illicit Drugs[1] N(%)	204(31.7)	571(25.2)	0.001*	701(20.3)	<0.001*
Cannabis N(%)	190(29.5)	549(24.2)	0.007*	670(19.4)	<0.001*
Cocaine N(%)	57(8.9)	101(4.5)	<0.001*	159(4.6)	<0.001*
MDMA[2] N(%)	58(9.0)	137(6.0)	0.010*	191(5.5)	0.001*
Amphetamine N(%)	41(6.4)	76(3.3)	0.001*	138(4.0)	0.009*
PSI[3] N(%)	60(9.3)	75(3.3)	<0.001*	121(3.5)	<0.001*
LSD[4] N(%)	15(2.3)	25(1.1)	0.030*	54(1.6)	0.219
GHB[5] N(%)	13(2.0)	27(1.2)	0.159	54(1.6)	0.500
Heroin N(%)	7(1.1)	9(0.4)	0.062	22(0.6)	0.202

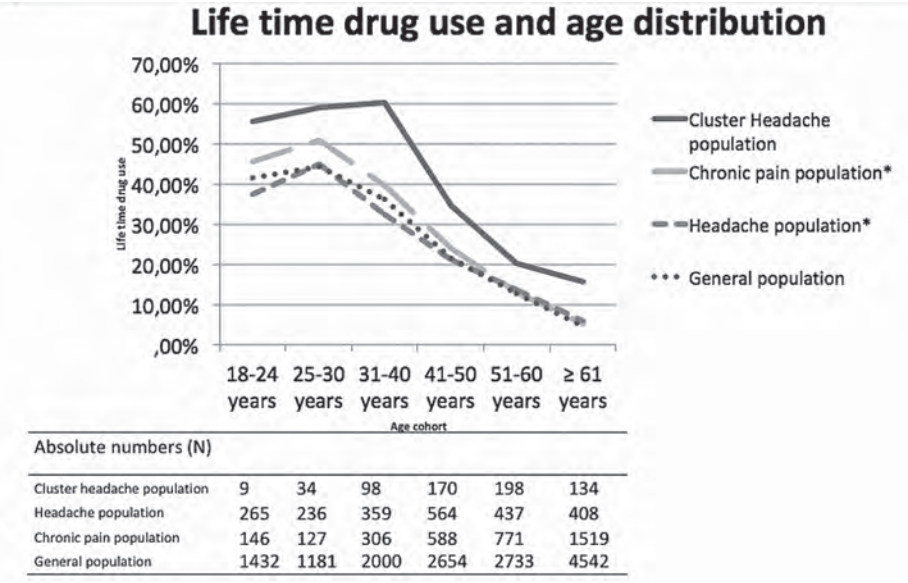
[1] Illicit drugs: all drugs; [2]MDMA: 3,4-methylenedioxymethamphetamine; [3]PSI: Psilocybin Mushroom; [4]LSD: Lysergic acid diethylamide; [5]GHB: Gamma-hydroxybutyrate; [a]*p*-value: *p*-value of comparison cluster headache population to the headache subgroup ; [b]*p*-value: *p*-value of comparison cluster headache population to the chronic pain subgroup.
* $P<0.05$ (χ^2-test with Yates' correction for categorical data).

Males with cluster headache more often used illicit drugs than males from the general population (34.7% vs. 29.2%; *P*=0.013), mainly cannabis (33.0% vs. 27.9%; *P*=0.019), cocaine (10.4% vs. 6.9%; *P*=0.006) and PSI (10.6% vs. 5.5%; *P*<0.001;Table 3). There was no difference in illicit drug use between females with and without cluster headache, except for PSI (5.8% vs. 2.3%; *P*=0.008).

Age differences

Age distribution of lifetime prevalence of illicit drug use followed the same pattern in persons with cluster headache as in the general population and its subgroups (Figure 2). Persons with cluster headache of all age cohorts, except between 18-24 (55.6% vs. 41.4% *P*= 0.502) and 25-30 (58.8 vs. 44.1% *P*= 0.127), used more illicit drugs than the general population.

Figure 2. Prevalence of lifetime use of illicit drug stratified to age cohorts



Absolute numbers (N)						
Cluster headache population	9	34	98	170	198	134
Headache population	265	236	359	564	437	408
Chronic pain population	146	127	306	588	771	1519
General population	1432	1181	2000	2654	2733	4542

*The headache and chronic pain population are subgroups of the general population.

Episodic versus chronic cluster headache

There were no differences between episodic and chronic cluster headache general illicit drug use (34.4% vs. 30.9%; *P*= 0.413) or for specific illicit drug use, except for a higher use of MDMA (13.9% vs. 7.5%; *P*= 0.027) and GHB (4.6% vs. 1.2%; *P*= 0.015) in chronic cluster headache.

Perceived effects of illicit drug use

Those who used illicit drugs during a cluster headache episode were asked about perceived effect on attack frequency and duration of an individual cluster headache attack. A decrease in attack frequency was reported for LSD (60.0%; N=3), followed by PSI (56.4%; N=22; Table 4). An increased attack frequency was reported for GHB (18.2%; N=2). PSI (46.2%; N=18) and heroin (50.0%; N=2) were most often reported to decrease the duration of individual cluster headache attacks. In contrast, cocaine (10.3%, N=3), GHB (9.1%; N=1), cannabis (5.8%; N=5) and MDMA (3.3%; N=1) were reported to extend the duration of individual cluster headache attacks.

Table 3. Lifetime use of different types of illicit drugs in the cluster headache and general population stratified to gender

	Females			Males			Cluster Headache		
	Cluster headache (N=173)	General population (N=7470)	*p*-value	Cluster headache (N=470)	General population (N=7072)	*p*-value	Female (N=173)	Male (N=470)	*p*-value
Illicit drugs[1] N(%)	41(23.7)	1385(18.5)	0.105	163(34.7)	2064(29.2)	0.013*	41(23.7)	163(34.7)	0.008*
Cannabis N(%)	35(20.2)	1319(17.7)	0.438	155(33.0)	1970(27.9)	0.019*	35(20.2)	155(33.0)	0.028*
Cocaine N(%)	8(4.6)	201(2.7)	0.192	49(10.4)	489(6.9)	0.006*	8(4.6)	49(10.4)	0.178
MDMA[2] N(%)	11(6.4)	380(5.1)	0.565	47(10.0)	681(9.6)	0.855	11(6.4)	47(10.0)	0.799
Amphetamine N(%)	6(3.5)	187(2.5)	0.588	35(7.4)	421(6.0)	0.224	6(3.5)	35(7.4)	0.329
PSI[3] N(%)	10(5.8)	171(2.3)	0.008*	50(10.6)	391(5.5)	<0.001*	10(5.8)	50(10.6)	0.43
LSD[4] N(%)	-	56(0.7)	0.639	15(3.2)	154(2.2)	0.202	-	15(3.2)	0.044*
GHB[5] N(%)	2(1.2)	64(0.9)	0.662	11(2.3)	165(2.3)	1.000	2(1.2)	11(2.3)	0.661
Heroin N(%)	1(0.6)	19(0.3)	0.368	6(1.3)	47(0.7)	0.143	1(0.6)	6(1.3)	0.696

[1] Illicit drugs: all drugs; [2]MDMA: 3,4-methylenedioxymethamphetamine; [3]PSI: Psilocybin Mushroom; [4]LSD: Lysergic acid diethylamide; [5]GHB: Gamma-hydroxybutyrate.

* $P<0.05$ (χ^2-test with Yates' correction for categorical data and Fisher's Exact Test for N<5).

Table 4. Perceived effects of different illicit drug use on duration of individual attacks and attack frequency for those who used illicit drugs during an cluster headache episode

	Cannabis N=86 (%)	Cocaine N=29 (%)	MDMA[1] N=30 (%)	Amphetamine N=22 (%)	PSI[2] N=39 (%)	LSD[3] N=5 (%)	GHB[4] N=11 (%)	Heroin N=4 (%)
Frequency, N (%)								
Decrease	15(17.4)	8(27.6)	11(36.7)	8(36.4)	22(56.4)	3 (60.0)	2 (18.2)	2 (50.0)
No effect	58(67.4)	18(62.1)	15(50.0)	12(54.6)	17(43.6)	2 (40.0)	7 (63.6)	2 (50.0)
Increase	13(15.1)	3(10.3)	4(13.3)	2(9.1)	0(0.0)	0 (0.0)	2 (18.2)	0 (0.0)
Unknown	-	-	-	-	-	-	-	-
Duration, N (%)								
Decrease	13(15.1)	7(24.1)	7(23.3)	8(36.4)	18(46.2)	1 (20.0)	1 (9.1)	2 (50.0)
No effect	57(66.3)	17(58.6)	20(66.7)	11(50.0)	18(46.2)	2 (40.0)	7 (63.6)	2 (50.0)
Increase	5(5.8)	3(10.3)	1(3.3)	-	-	-	1 (9.1)	-
Unknown*	11(12.8)	2(6.9)	2(6.7)	3(13.6)	3(7.7)	2(40.0)	2(18.2)	-

[1] Illicit drugs: all drugs; [2]MDMA: 3,4-methylenedioxymethamphetamine; [3]PSI: Psilocybin Mushroom; [4]LSD: Lysergic acid diethylamide; [5]GHB: Gamma-hydroxybutyrate.

* Not all patients used the drugs during an attack.

Discussion

In this study, Dutch persons with cluster headache more often used illicit drugs during their lifetime than persons from the general Dutch population. Especially cannabis, amphetamine, heroin and cocaine were more used by cluster headache patients. Although one would think this is due to alleviatory effects, most users with cluster headache reported no effect of these illicit drugs on their cluster headache attack frequency or duration when used during a cluster headache episode only. A very limited number report a positive effect of PSI and heroin on the duration of their individual cluster headache attacks and a positive influence of PSI and LSD on attack frequency. These possible influences of PSI and LSD should be interpreted with caution as these drugs were used in only a small fraction of the cluster headache population.

Both in our cluster headache population and in the general Dutch population a higher prevalence of illicit drug use was seen in males, which is in line with earlier studies.[5] Males more often exhibit risk taking behaviour.[17] Being a female cluster headache patient has been associated with a decreased response to acute treatment and with more painful nocturnal headache attacks.[18] In contrast, it has been suggested that bout frequency and duration are lower in females compared to males.[5] These gender differences might influence the use of illicit drugs in women. However, we did not observe an increased prevalence of illicit drug use in female patients.

An increased prevalence of PSI use was found in both females and males with cluster headache. This might be due to the fact that PSI has received Dutch media attention as an alternative cluster headache treatment.[19] Its efficacy, however, is limited as in a small retrospective study where an acute effect of PSI and even a termination of a cluster headache period was only found in half of the few patients studied.[11] Further research is therefore needed to shed more light on the acute and prophylactic effects of PSI in cluster headache.

Each cluster headache age cohort in our study used more illicit drugs than their age matched cohort in the Dutch general population, except for the 18-24 and 25-30 age cohorts which were however too small to reach significance. Overall lifetime use of illicit drugs was increased in the younger age groups independent of having cluster headache. This increased prevalence of illicit drug use in younger Dutch generations has been described before and has not been seen in other European countries except for Switzerland.[20,21] This seems to confirm the role of cultural differences between countries in drug use.

The increased prevalence of illicit drug use in persons with cluster headache compared to persons with chronic pain or further unspecified headache, suggests that increased use is specific for cluster headache and not linked to headache or chronic pain per se. There are several possible explanations for this finding.
First, the question remains whether some illicit drugs actually have alleviatory effects on cluster headache. Possibly, certain illicit drugs may interact with the unknown process that causes cluster headache. Cannabis acts on cannabinoid receptors that are widespread throughout the brain.[22] The hypothalamus has cannabinoid receptors and has been implied in the pathophysiology of cluster headache.[23,24] In contrast to the sedative qualities of cannabis, cocaine is a strong stimulant, also known for its capacity as a local anaesthetic and vasoconstrictor.[25,26] Intranasal cocaine administration is reported to block pain caused by a nitroglycerin-induced cluster headache attack in about 30 minutes.[27] However, since the majority of respondents described illicit drugs to have no effect on their cluster headache attacks, it remains questionable whether the possible alleviatory effect of illicit drugs on cluster headache is the actual reason for the increased prevalence of use.
Second, there could be an association between cluster headache and a tendency for addictive behaviour as suggested before.[28,29] This would also be in line with our finding that persons with cluster headache are more inclined to smoke.
Third, the reputation of illicit drugs among persons with cluster headache combined with the attention that these substances receive on cluster headache blogs, social media and in some recent publications, may

stimulate more patients to try these illicit drugs to treat their cluster headache.[30] Last, the placebo effect could have overestimated the effects attributed to the various illicit drugs.

Limitations of this study include the fact that the data analysis needed to be stratified for age groups and gender, because the population data received from the Statistics Netherlands consisted of categorical age data. Age and gender were thus not full co-variates in the analysis and it was not possible to correct for other variables. We therefore tried to give the reader insight into age (Figure 2) and gender distribution (Table 3). Because of the small number of cluster headache patients who used certain drugs, we expect that for those drugs the comparison between females and males could have been underpowered. Possibly, differences were larger than we could demonstrate. The higher education level of cluster headache patients is possibly a bias of the internet-based recruitment. As higher education is protective towards drug use this might have negatively influenced the results. This could mean that the difference between drug use in the cluster headache versus the general population would be even larger than the difference we found.

The headache subgroup of the general population could have included cluster headache patients. We included data from a representative sample of the Dutch general population (N=14542) and cluster headache has a known prevalence of 1 in 1000 patients.[31] As such, the sample could include 14-15 cluster headache patients. We expect that all these possible cluster headache patients are listed in the headache subgroup, which would amount to 14-15 out of 2268 persons. Even if so, we expect that this small number of potential cluster headache patients did not influence the outcome of the headache subgroup.

Our questionnaire did not ask about motives for drug use and the time between filling out the questionnaire and drug use itself. Furthermore, it should be noted that our findings on effects of illicit drugs on cluster headache were all self-reported and should thus be met with caution, since placebo effect could have overestimated the effects.

In conclusion, in the Dutch cluster headache population there is a higher prevalence of illicit drug use compared to the general Dutch population. This might be due to an actual acute or prophylactic effect, but also to a common pathophysiology between cluster headache and sensitivity for drug use. Another explanation could be a false conviction in people desperately seeking relief of their cluster headache and/or to the almost mythological reputation of illicit drugs in the cluster headache community.

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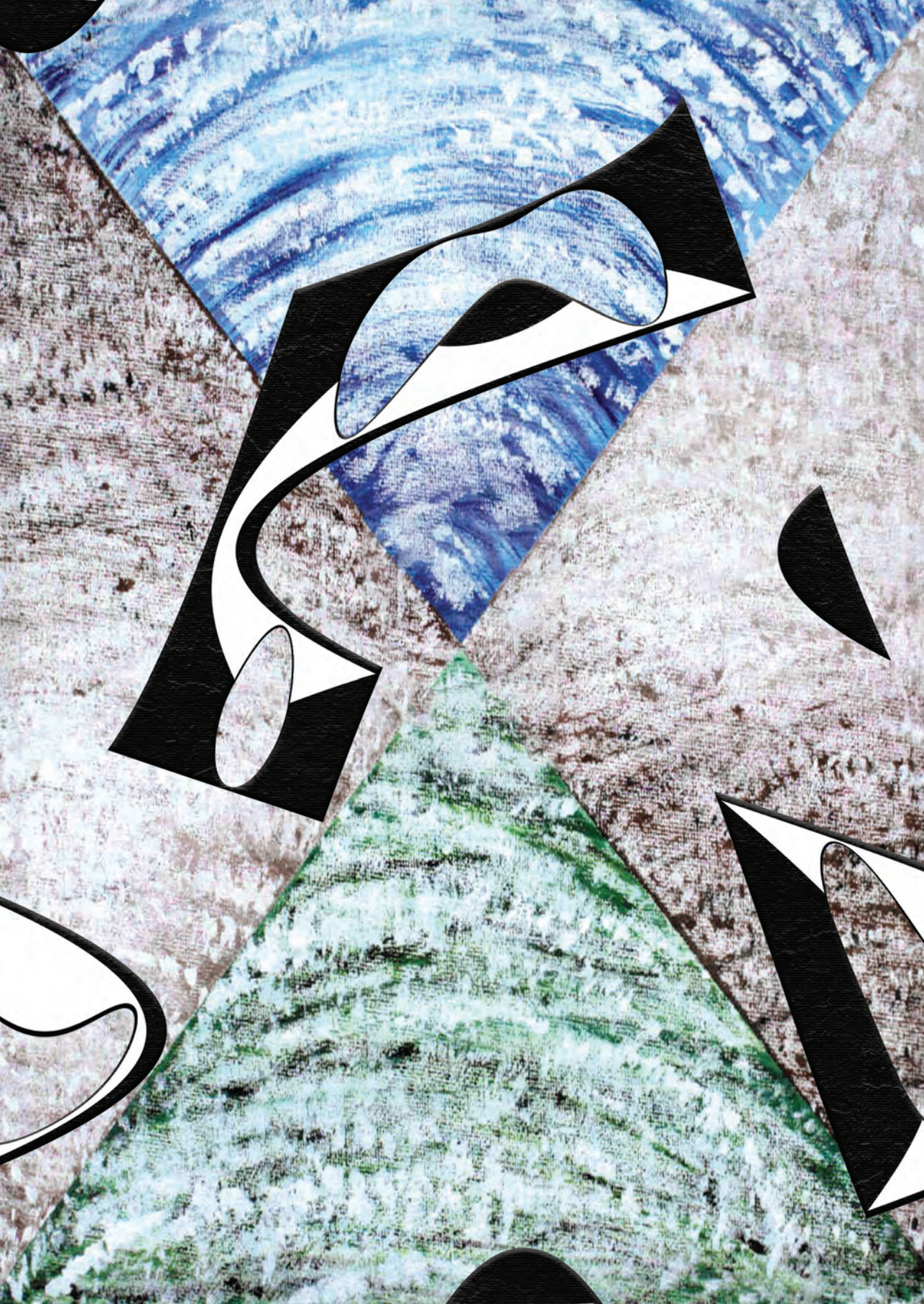

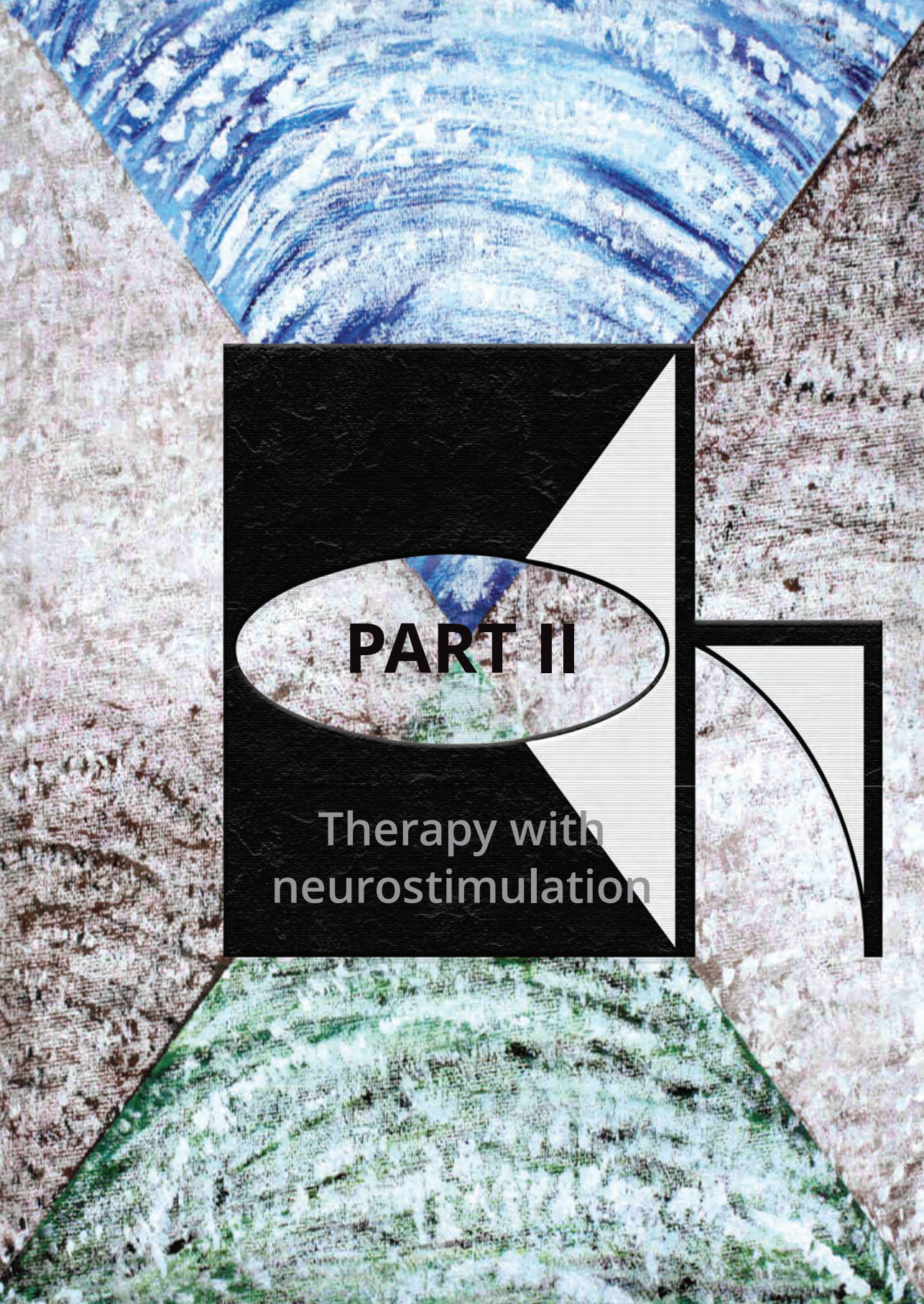
PART II
Therapy with neurostimulation

CHAPTER 9

Effective occipital nerve stimulation during pregnancy in a cluster headache patient

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Letter to the Editor

Dear Editor,

Cluster headache is a rare primary headache disorder characterized by attacks of excruciating, intermitting short-lasting unilateral temporal or orbital pain.[1] Cluster headache in pregnancy can be difficult to treat because of a limitation in treatment options. The only acute treatment that is not harmful during pregnancy is oxygen inhalation. However, this is effective in about 60% of patients.[2,3] Sumatriptan can be considered, but is not recommended during pregnancy due to a lack of controlled prospective studies about prenatal toxicity. However, a retrospective study of over 600 women reported a lower rate of congenital malformations in children of women who had been using sumatriptan during their pregnancy than in the average population and another observational study reported no signal of teratogenicity associated with major birth defects for sumatriptan.[4,5] The available prophylactic drug treatments are not recommended during the pregnancy because of a lack of controlled prospective studies about their prenatal toxicity.[6] Here, we report a possible alternative prophylactic cluster headache treatment during pregnancy.

A 32-year-old woman, suffering from cluster headache since the age of 25 years, was diagnosed with medically intractable chronic cluster headache with an average of nine attacks per week. She participated in our ongoing study on occipital nerve stimulation (ONS) in chronic cluster headache as prophylactic treatment.[7] After the ONS implantation, her attack frequency dropped to once per week and the pain intensity of the remaining attacks diminished as well. Having at first decided to refrain from pregnancy due to the lack of possible attack treatment, she brought up her wish to become pregnant 18 months after ONS implantation. At that time, she used sumatriptan SC and oxygen as acute treatment and ONS as prophylactic treatment. Shortly thereafter, she indeed became pregnant. During the first 3 months of her pregnancy she refrained from sumatriptan SC and treated the remaining cluster headache attacks successfully with oxygen (9 L/min). An ultrasound after 10 weeks pregnancy did not show any foetal abnormalities. During the second trimester she only needed

sumatriptan SC once, the attack frequency had dropped to one attack per 2 weeks. Another ultrasound after 20 weeks of pregnancy also showed no abnormalities. During the last trimester, attack frequency further dropped to one attack per 6 weeks, for which oxygen remained effective. At 35 weeks of pregnancy she did not recharge her ONS battery correctly and noticed an increase of cluster headache attacks to one attack per day 10 days later. At that time, she recharged the ONS correctly. She did not notice a decrease in attacks after turning the ONS on again. Parturition was induced at 38 weeks pregnancy because of these frequent cluster headache attacks. At that time, the ONS was turned off and switched on directly after she gave birth. The parturition was uncomplicated except for a surgical removal of the placenta. The baby made a good start and did not have any birth defects. The day after giving birth, high frequent severe cluster headache attacks occurred, which did not respond to oxygen. After consultation with the gynaecologist, breastfeeding was stopped and the patient received sumatriptan SC as acute treatment. The attack frequency and intensity diminished slowly. She became attack-free with ONS treatment after 4 weeks.

This is a unique case of an uncomplicated pregnancy in a patient having effective ONS treatment for chronic cluster headache. We therefore suggest that ONS can be an alternative preventive treatment for women of reproductive age with medically intractable cluster headache and a (future) wish to become pregnant, as it seems not to have any pharmacological influences during pregnancy and lactation. The frequency of attacks dropped during pregnancy until the last week before delivery, when the ONS was accidently off, due to inaccurate battery reloading. As no rechallenge took place, we do not know if the increase in attacks was caused by the withholding of continuous ONS, a possible hormonal influence or a fluctuation in the cluster headache pattern itself. From our own experience, we know that withholding ONS can result in an increase of cluster headache attacks after initial effective treatment. We suggest that a hormonal influence probably was unlikely, as earlier retrospective reports reported no relation between hormonal changes and cluster headache attacks.[8,9] However, prospective studies on cluster headache during pregnancy are lacking. Only in a few cases

was an increase or decrease in frequency or severity of cluster headache seen during pregnancy, but probably must be explained by the natural, fluctuating course of cluster headache.[9]

In conclusion, this case suggests that ONS is a safe and effective prophylactic treatment for cluster headache during pregnancy.

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CHAPTER 10

Differential efficacy of non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: a meta-analysis

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Abstract

Introduction

Two randomized, double-blind, sham-controlled trials (ACT1, ACT2) evaluated non-invasive vagus nerve stimulation (nVNS) as acute treatment for cluster headache. We analyzed pooled ACT1/ACT2 data to increase statistical power and gain insight into the differential efficacy of nVNS in episodic and chronic cluster headache.

Methods

Data extracted from ACT1 and ACT2 were pooled using a fixed-effects model. Main outcome measures were the primary endpoints of each study. This was the proportion of participants whose first treated attack improved from moderate (2), severe (3), or very severe (4) pain intensity to mild (1) or nil (0) for ACT1 and the proportion of treated attacks whose pain intensity improved from 2–4 to 0 for ACT2.

Results

The pooled population included 225 participants (episodic: $n = 112$; chronic: $n = 113$) from ACT1 ($n = 133$) and ACT2 ($n = 92$) in the nVNS ($n = 108$) and sham ($n = 117$) groups. Interaction was shown between treatment group and cluster headache subtype ($p < 0.05$). nVNS was superior to sham in episodic but not chronic cluster headache (both endpoints $p < 0.01$). Only four patients discontinued the studies due to adverse events.

Conclusion

nVNS is a well-tolerated and effective acute treatment for episodic cluster headache.

Introduction

Cluster headache is a highly disabling brain disorder typically characterized by attacks of excruciating unilateral headache associated with ipsilateral cranial autonomic features and often an urge to move.[1] Attacks last from 15 minutes to 3 hours and may occur up to eight times a day, frequently at night.[2] About 80% of patients have episodic cluster headache, in which attacks come in periods lasting from 1 week to several months and are separated by attack-free periods of more than 1 month. The remaining 20% experience chronic cluster headache, in which attacks continue to recur for more than 1 year without attack-free periods longer than a month.[3]

Research into differential treatment effects among episodic and chronic cluster headache subtypes warrants further attention in clinical trials. Cluster headache therapy for the acute treatment of both subtypes should preferably have a low adverse event profile and be easy to use and must be fast acting because the pain builds up quickly and is extremely severe. Current acute treatments for cluster headache, although limited, have shown efficacy, but clinical disadvantages include daily dosing limitations[1], cardiovascular contraindications[4], inconvenience, and/or unavailability. Pain-free rates of up to 49% (subcutaneous sumatriptan) at 15 minutes have been reported in clinical studies of triptans for the acute treatment of cluster headache[5], and inhalation of 100% oxygen was shown to relieve attacks at 15 minutes in 78% of patients.[6] Results for episodic and chronic cluster headache subtypes are not commonly evaluated separately, likely because of the much smaller chronic cluster headache subgroups typically enrolled.[7-9] Studies that separately evaluated both subtypes demonstrated higher treatment effects in episodic cluster headache than in chronic cluster headache but were not powered to dissect any differential effects.[7,10,11] Consistent with these findings, recent data suggested that a monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) ligand was ineffective for the preventive treatment of chronic cluster headache but effective for preventing attacks in episodic cluster headache.[12]

Non-invasive vagus nerve stimulation (nVNS; gammaCore; electroCore, Inc., Basking Ridge, NJ, USA) is a novel, easy-to-use, non-invasive neuromodulation treatment option for cluster headache.[13] In ACT1, acute nVNS treatment showed efficacy in participants with episodic cluster headache but not in the chronic cluster headache subgroup or in the total population that included all participants of both subtypes.[11] The ACT1 trial was underpowered for analysis of the differential effect size in episodic and chronic cluster headache separately. A further study using the same nVNS and sham devices (ACT2) had similar results.[10] The study designs and populations of ACT1 and ACT2 were similar, particularly in terms of sham and active stimulation and data collection. This allowed for pooled data analysis and, because of greater statistical power, formal verification of possible differential effects of nVNS in episodic and chronic cluster headache. Given the rarity of the disorders, combined analysis of both studies may also provide a more complete depiction of the efficacy, tolerability, and application options of nVNS in the two different cluster headache subtypes. We present here a pooled data analysis of both studies, focusing on the possibility of differential effects in episodic and chronic cluster headache.

Material and methods

Study design and participants

We pooled and analyzed the data of all 225 participants (age 18 years or older) with episodic (*n* = 112) or chronic (*n* = 113) cluster headache[2] from two prospective, randomized (ratio 1:1), double-blind, sham-controlled, multicenter clinical trials. Demographic data for both trials were self-reported by participants and were validated by the investigator. The trials had similar designs with a few exceptions. The main difference was the primary endpoint. For ACT1, this was "the proportion of participants whose first treated attack had improved (on a 5-point pain intensity scale) from pain intensity of moderate (2), severe (3), or very severe (4) to mild (1) or nil (0) at 15 minutes after treatment initiation". For ACT2, the primary outcome was "the proportion of all treated attacks that had improved from pain intensity 2-4 to 0 at 15 minutes after treatment initiation for that

attack." ACT1 had a 1-month double-blind period followed by a 3-month open-label phase, whereas ACT2 had a 1-week run-in period followed by a 2-week double-blind period and then a 2-week open-label phase. In both studies, participants had to treat attacks as soon as possible after onset with three consecutive 120-second applications of nVNS. In ACT2, however, participants could apply up to three additional stimulations if not pain-free at 9 minutes after initiation of the first treatment. Finally, although in ACT1 all treatments were applied to the right cervical vagus nerve, in ACT2 the participants were encouraged to treat ipsilateral to the pain.

Both studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and local laws. The protocols were reviewed by the appropriate national regulatory agency for each site, and additional reviews were completed by regional or local independent ethics committees as required. The studies were registered at ClinicalTrials.gov (ACT1[11]: NCT01792817 and ACT2[10]: NCT01958125), and all participants had signed informed consent forms prior to study inclusion.

Data sources

We pooled the final data sets from ACT1 and ACT2 and used the full analysis set to analyze all efficacy endpoints and adverse events in the total population and separately in the episodic and chronic cluster headache subgroups.

Statistical analyses

We used logistic regression models to estimate odds ratios and associated 95% confidence intervals (95% CIs) for (i) the proportion of participants whose first treated attack had improved from pain intensity 2-4 to 0-1 at 15 minutes after treatment initiation (the ACT1 primary endpoint) and (ii) the proportion of participants in whom ≥ 50% of all treated attacks had improved from pain intensity 2-4 to 0-1 at 15 minutes after treatment initiation. Analyses resulting in pooled estimates included site as a covariate in the logistic regression models.

Generalized linear mixed-effects regression models (with logit link and binomial response distribution) were used to estimate the proportion of all treated attacks that had improved from pain intensity 2–4 to 0 at 15 minutes after treatment initiation for that attack (the ACT2 primary endpoint). Population averaged/marginal models (to account for repeated headache attacks within patient) were utilized, and the structure of the covariance matrix was specified as compound symmetry. P values for comparisons between the nVNS and sham groups were determined from resulting F tests.

Individual participant data were used in the meta-analysis. Fixed effects meta-analysis models were used to estimate the pooled effects of nVNS treatment, given the small number of studies being pooled and because the ACT1 and ACT2 studies were homogeneous for participant populations and results. In addition, there was no evidence of treatment by study interactions for any of the outcomes examined.
In the meta-analysis models, interactions between treatment group and cluster headache subgroup were examined to determine whether the magnitude of treatment effect varied significantly by cluster headache subtype.

First-order interactions between treatment group and cluster headache subgroup were examined to determine whether the magnitude of treatment effect varied significantly by cluster headache subtype.

Two-sided p values < 0.05 were considered statistically significant. p values are provided for all efficacy analyses without adjustment for multiple comparisons. Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

In total, we included 225 participants in the pooled efficacy analysis, 133 from ACT1 and 92 from ACT2, who comprised the intent-to-treat populations and were randomly assigned to nVNS (n = 108) or sham (n

= 117). Demographic and baseline characteristics were reported for the pooled safety population and did not differ between the nVNS and sham treatment groups (Table 1). Participants with chronic cluster headache were about 3 years older at disease onset than participants with episodic cluster headache ($P < 0.05$).

Table 1. Demographic and Baseline Characteristics (Pooled Analysis)

Characteristic	By Treatment Group		By Cluster Headache Subgroup	
	nVNS (*n* = 124)	Sham (*n* = 129)	Episodic (*n* = 131)	Chronic (*n* = 122)
Age, mean (SD), years	45.4 (12.4)[a]	47.8 (11.2)[b]	47.3 (12.4)[c]	45.9 (11.1)[d]
Male, No. (%)	94 (76)	105 (81)	106 (81)	93 (76)
Ethnic origin, No. (%)[e]				
Asian	5 (4)	1 (1)	4 (3)	2 (2)
Black	5 (4)	7 (5)	9 (7)	3 (3)
White	113 (91)	120 (93)	117 (89)	116 (95)
Missing	1 (1)	1 (1)	1 (1)	1 (1)
Cluster headache type, No. (%)				
Episodic cluster headache	65 (52)	66 (51)	131 (100)	0
Chronic cluster headache	59 (48)	63 (49)	0	122 (100)
Age at cluster headache onset, mean (SD), year	30.8 (13.8)[a]	33.5 (13.2)[b]	30.7 (13.9)[c]	33.9 (13.0)[d]
Treatments used to manage cluster headache, No. (%)				
Acute n/N (%)	114/123 (93)	121/125 (97)	121/130 (93)	114/118 (97)
Prophylactic n/N (%)	75/123 (61)	92/125 (74)	83/130 (64)	84/118 (71)
ACT1 population, No. (%)	73(59)	77 (60)	101 (77)	49 (40)
ACT2 population, No. (%)	51(41)	52(40)	30 (23)	73 (60)

Abbreviations: nVNS: non-invasive vagus nerve stimulation; SD: standard deviation.
[a] *n* = 108; [b] *n* = 115; [c] *n* = 120; [d] *n* = 103, [e] Percentages may not add up to 100% because of rounding.

Between–cluster headache type interactions

There was a first-order interaction between treatment group and cluster headache subtype ($P < 0.05$) in models estimating the ACT1 and ACT2 primary endpoints in the ACT1, ACT2, and pooled populations (Table 2). Thus, results are presented overall and by cluster headache subtype.

Table 2. Interaction model results

ACT1 Primary endpoint	Estimate	SE	Wald Chi-square	Pr>Chisq
ACT1	0.5290	0.2428	4.7468	0.0294
ACT2	0.4611	0.2683	2.9534	0.0857
Pooled	0.4588	0.1642	7.8111	0.0052
ACT2 Primary endpoint	**Estimate**	**SE**	**Wald Chi-square**	**Pr>Chisq**
ACT1	2.1267	0.9507	2.24	0.0270
ACT2	2.1778	1.0512	2.07	0.0412
Pooled	1.9577	0.6403	3.06	0.0025

SE: standard error.

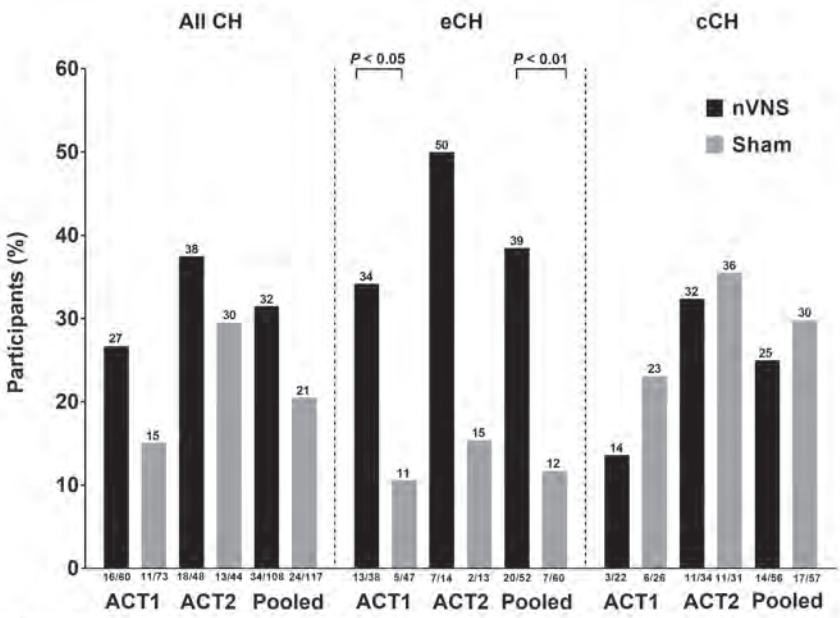
Treatment response at 15 minutes in first treated attack

Among participants with episodic cluster headache, more participants treated with nVNS than with sham achieved the ACT1 primary endpoint: improvement of the first treated attack at 15 minutes to pain intensity 0-1 in the ACT1 (absolute difference, 24%; $P = 0.01$) and pooled (absolute difference, 27%; $P < 0.01$) study populations, but not in the ACT2 study population (absolute difference, 35%; $P = 0.07$; Figure 1).

Proportion of all attacks pain-free at 15 minutes

Among participants with episodic cluster headache, the proportion of all treated attacks that had improved at 15 minutes to pain-free (the ACT2 primary endpoint) was higher in the nVNS-treated group than in the sham-treated group for ACT1 (absolute difference, 9%; $P < 0.05$), ACT2 (absolute difference, 41%; $P < 0.05$), and pooled (absolute difference, 22%; $P < 0.01$) study populations (Figure 2).

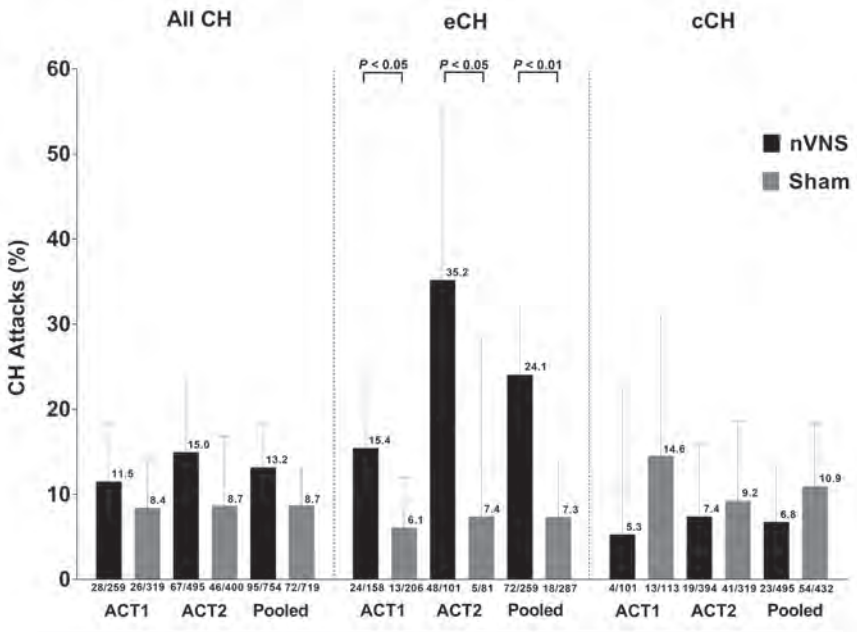
Figure 1. Proportion of participants who responded at 15 minutes for the first treated attack



	All CH			eCH			cCH		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
ACT1	2.05	0.87, 4.84	0.10	4.37	1.39, 13.71	0.01	0.53	0.12, 2.41	0.41
ACT2	1.43	0.60, 3.42	0.42	5.50	0.88, 34.46	0.07	0.87	0.31, 2.43	0.79
Pooled	1.72	0.93, 3.17	0.08	4.67	1.77, 12.32	<0.01	0.74	0.32, 1.72	0.48

Abbreviations: CH: cluster headache; cCH: chronic cluster headache; CI: confidence interval; eCH: episodic cluster headache; nVNS: non-invasive vagus nerve stimulation; OR: odds ratio.
Note: P values are from logistic regression; pooled analyses included study as a covariate.

Figure 2. Proportion of All Treated Attacks That Achieved Pain-Free Status at 15 Minutes



	All CH					eCH					cCH				
	nVNS		Sham			nVNS		Sham			nVNS		Sham		
	GEE Model Adjusted %	95% CI	GEE Model Adjusted %	95% CI	*P*	GEE Model Adjusted %	95% CI	GEE Model Adjusted %	95% CI	*P*	GEE Model Adjusted %	95% CI	GEE Model Adjusted %	95% CI	*P*
ACT1	11.52	7.00, 18.38	8.40	4.92, 13.96	0.38	15.44	9.49, 24.12	6.09	3.00, 11.96	0.03	5.29	1.06, 22.49	14.56	6.07, 31.00	0.25
ACT2	14.96	9.01, 23.82	8.66	4.24, 16.86	0.20	35.18	19.12, 55.48	7.41	1.59, 28.44	0.04	7.41	3.28, 15.89	9.22	4.33, 18.57	0.69
Pooled	13.16	9.28, 18.35	8.68	5.66, 13.08	0.13	24.05	16.68, 33.38	7.34	3.75, 13.89	<0.01	6.75	3.28, 13.39	10.94	6.30, 18.33	0.28

Abbreviations: CH: cluster headache; cCH: chronic cluster headache; CI: confidence interval; eCH: episodic cluster headache; GEE: generalized estimating equation; nVNS: non-invasive vagus nerve stimulation.
Note: P values are from F tests; pooled analyses included study as a fixed effect. Graphed data are GEE model adjusted percentages with 95% CIs. Data for number of subjects using treatment/total number of subjects with data (n/N) attacks are unadjusted numbers.

Key secondary endpoints

The proportion of participants who were pain-free at 15 minutes in ≥ 50% of their treated attacks was higher for nVNS than for sham (absolute difference, 18%; *P* = 0.01) in participants with episodic cluster headache in the pooled study population (Figure 3A). The absolute difference for this endpoint in episodic cluster headache was 14% (*P* = 0.05) in the ACT1 study population and 28% (*P* = 0.11) in the ACT2 population. There were no other treatment differences for this endpoint in any of the other study populations. The proportion of participants who were pain-free or with mild pain at 15 minutes in ≥ 50% of their treated attacks was higher for

nVNS than for sham in participants with episodic cluster headache in the ACT1 (absolute difference, 19%; $P = 0.04$), ACT2 (absolute difference, 49%; $P = 0.02$), and pooled (absolute difference, 27%; $P < 0.01$) study populations. The ≥ 50% response rates for pain freedom or mild pain at 15 minutes also favored nVNS in the total population of the ACT2 (absolute difference, 26%; $P = 0.01$) and pooled (absolute difference, 14%; $P = 0.01$) study populations (Figure 3B).

Adverse events

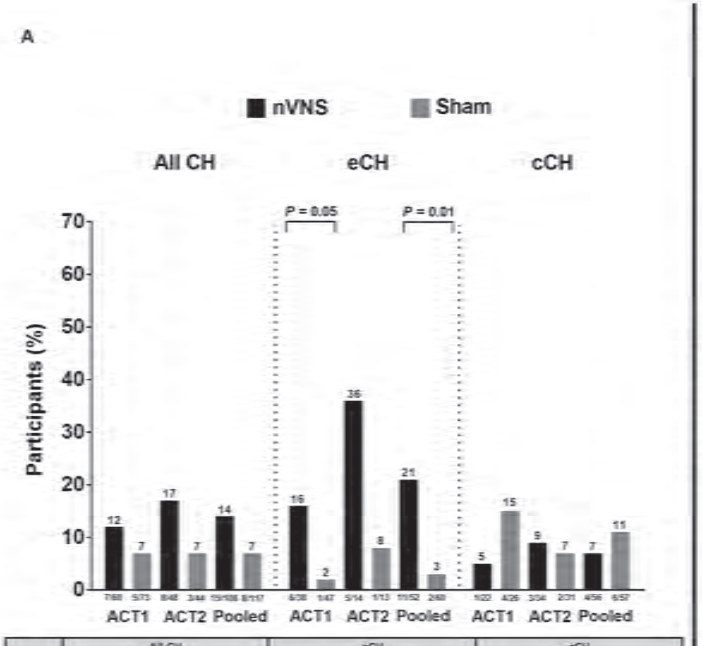
Thirty-eight participants in the nVNS group and 45 participants in the sham group experienced at least one adverse event (Table 3). Two participants in the nVNS group had at least one serious adverse event (SAE): one participant in ACT1 reported exacerbations of cluster headache and one in ACT2 reported lower abdominal and back pain. In the sham group of ACT2, one participant reported anxiety and depression as an SAE. Among the pooled adverse event data, the most common adverse device effect of nVNS was perioral muscle contraction during treatment, with all other adverse device effects that were reported by ≥ 5% of participants (i.e. most common) occurring in the sham group. In ACT1, the most common adverse device effects of nVNS were lip of facial drooping, pulling, twitching (i.e. occurring in ≥ 5% of participants). In ACT 2, application site irritation, application site paresthesia, and skin irritation were the most common adverse device effects of nVNS (i.e. occurring in > 1 participant). There were no serious adverse device effects.

Table 2. Incidence of Adverse Events, Serious Adverse Events, and Adverse Device Effects (Pooled Data)

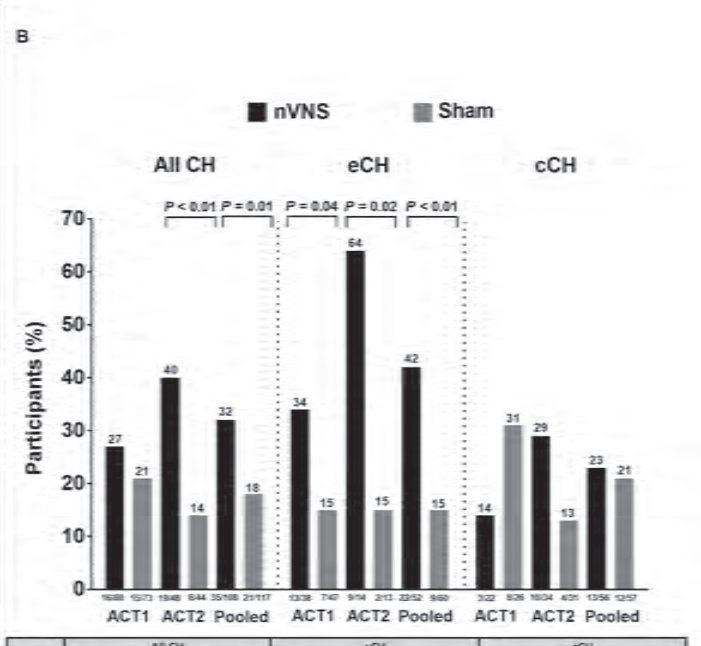
AEs and ADEs	nVNS (*n* = 123)[a]	Sham (*n* = 129)
Participants with ≥ 1 AE, No. (%)	38 (31)	45 (35)
Participants with ≥ 1 SAE, No. (%)	2 (2)[b,c]	1 (1)[c,d]
Participants with ≥ 1 ADE, No. (%)	20 (16)	34 (26)
ADEs occurring in ≥ 5% of participants in either treatment group, No. (%)		
Dysgeusia	0	8 (6)
Erythema at treatment site	0	9 (7)
Perioral myokymia during treatment	8 (7)	0

Abbreviations: ADE: adverse device effect; AE: adverse event; CH: cluster headache; nVNS: non-invasive vagus nerve stimulation; SAE: serious adverse event.
[a] One patient from the safety population assigned to the nVNS group (n=124) provided only baseline data and was therefore excluded from the safety analysis.
[b] Included 1 participant with an SAE of CH (2 occurrences) in ACT1 and 1 participant with SAEs of lower abdominal pain and back pain in ACT2.
[c] SAEs were not considered related to the study device.
[d] Included 1 participant with SAEs of anxiety and depression in ACT2.

Figure 3. Pain-free (A) or responder (B) status at 15 minutes for ≥50% of attacks



	All CH			eCH			cCH		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
ACT1	1.80	0.54, 5.98	0.34	8.63	0.99, 75.12	0.05	0.26	0.03, 2.54	0.25
ACT2	2.73	0.68, 11.05	0.16	6.67	0.66, 67.46	0.11	1.40	0.22, 9.01	0.72
Pooled	2.16	0.88, 5.33	0.09	7.68	1.59, 37.10	0.01	0.67	0.18, 2.51	0.55



	All CH			eCH			cCH		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
ACT1	1.41	0.63, 3.15	0.41	2.97	1.04, 8.46	0.04	0.36	0.08, 1.55	0.17
ACT2	4.15	1.47, 11.71	<0.01	9.90	1.54, 63.67	0.02	2.81	0.78, 10.15	0.11
Pooled	2.17	1.17, 4.04	0.01	4.12	1.66, 10.21	<0.01	1.14	0.47, 2.78	0.77

Discussion

We pooled the data of two large clinical trials, ACT1 and ACT2, to enable both a formal analysis of acute efficacy separately for episodic and chronic cluster headache and a larger pooled analysis of tolerability. Meta-analysis of the entire population of 225 participants demonstrated significant efficacy of nVNS as an acute treatment for episodic cluster headache but not for the acute treatment of chronic cluster headache. The data show that repeated use of nVNS was well tolerated and that there were no obvious short-term safety concerns.

A recent mechanistic model of autonomic function provides further insights into the possible differential efficacy of nVNS observed between the two cluster headache subtypes. Reductions in kinetic oscillation stimulation–induced lacrimation in healthy subjects suggested that the symptom relief seen with nVNS in ACT1 and ACT2 was likely attributable to a bilateral inhibitory effect on parasympathetic output of the trigeminal autonomic reflex.[14,15] The possibility of a differential parasympathetic response among patients with episodic and chronic cluster headache could play a role in the differential acute efficacy of nVNS between the episodic and chronic cluster headache subgroups in the ACT1 and ACT2 studies. Several other mechanistic studies were previously reported, suggesting that multiple distinct mechanisms may contribute to the efficacy of nVNS as an acute treatment. In animal models, two doses of vagus nerve stimulation (VNS) inhibited acute nociceptive activation of trigeminocervical neurons for up to 3 hours[16], and VNS attenuated pain responses and Fos protein expression.[17] In healthy volunteers, nVNS caused activation of the nucleus tractus solitarius as measured with functional magnetic resonance imaging.[18] Taken together, the beneficial acute effects of nVNS in episodic cluster headache seem biologically plausible.

There are a number of possible explanations for why patients with chronic cluster headache have a poorer response to acute treatment. Inter-paroxysmal pain is considerably more common in chronic than in episodic cluster headache[19], complicating achievement of pain-free

status in the chronic subgroup. The presence of inter-paroxysmal pain was not measured in ACT1 or ACT2, representing a limitation of this pooled analysis. This information may have provide further insight into the observed differences among the two cluster headache subtypes. Spontaneous transitions from episodic to chronic cluster headache, and *vice versa*, do occur and are unpredictable.[20,21] Given the cohort size, such transitions may have occurred in at least some participants, potentially influencing treatment response. A possible pathophysiological reason for a differential treatment response in episodic and chronic cluster headache involves differences in gray matter volume in pain processing areas.[22] Such differences likely reflect the brain's adaptive capacity to different stimuli.[23] There may also be differences in brain pharmacology between chronic and episodic cluster headache.[24] Although establishing causal links to chronicity is challenging, such differences may contribute to disparity in treatment response. Central sensitization is considered essential for the pathologic mechanisms underpinning the chronification of primary headache disorders.[25] The changes underlying treatment refractoriness in some patients with chronic cluster headache may involve consolidation of neuronal connections and networks in the disease mechanism.[25]

Several similarities of ACT1 and ACT2, including participant characteristics, overlapping outcome measures, and use of the same nVNS and sham devices, allowed for pooled data evaluation of differential effects in episodic and chronic subtypes, but the trials also have differences. The double-blind period in ACT1 was 4 weeks, whereas in ACT2 it was 2 weeks to minimize exposure to sham. Because both studies were acute attack treatment trials and cluster headache attacks are clinically stable, this should not have been a major issue. The allowance of extra pulses in ACT2 may have contributed to the greater efficacy seen in ACT2. Application of three consecutive stimulations takes 6-8 minutes; given the 15-minute endpoint, the paradigm may have biased against a response in the total population. We also do not know whether the move from right-sided stimulation to stimulation ipsilateral to the pain was important. The anatomy suggests that the vagal afferents are bilateral. This may have increased the placebo rate, which would have rendered a positive outcome more challenging. Taken together, the similarities seem

more relevant than the only minor dissimilarities, thus allowing for meta-analysis of both studies.

The results from this pooled analysis offer additional evidence for the clinical utility and advantages of nVNS in patients with cluster headache. Adverse events were mild, and there were no safety concerns during the trial. Long-term safety can be judged only after monitoring repeated use of nVNS over longer periods. The portability of nVNS and the fact that, in contrast to triptans, nVNS may be used more than three times per day and without major restrictions to co-medication highlight its practical utility. The ability to use the device in patients with cardiovascular contraindications to triptans is an important advantage of nVNS.[4] In previous trials, nVNS therapy was associated with adherence rates ≥ 90% and treatment satisfaction rates ≥ 50% and was generally regarded as easy to use.[13]

The apparent lack of acute nVNS efficacy in subjects with chronic cluster headache attacks is somewhat surprising, considering that clinical efficacy has been shown when nVNS was used preventively in patients with chronic cluster headache.[13] However, the combined ACT1 and ACT2 data, as well as recent data for a CGRP-targeted monoclonal antibody[12], reinforce previous data that suggest that acute[13,26] and preventive[27] treatments are more challenging in chronic than in episodic cluster headache. Consistent with this, a consensus statement from the European Headache Federation recommended amending the International Classification of Headache Disorders[2] to include a sub-classification for treatment of refractory chronic cluster headache.[28]

The differential results in chronic versus episodic cluster headache have important implications for participant selection and minimum size of future therapeutic studies in cluster headache. Clinical trial design requirements, the challenges encountered selecting eligible participants, and patient motivation to enroll have generally shifted the selection of study participants toward an episodic subtype dominance.[6] Attack numbers in patients with cluster headache often exceed limits for triptan therapy, making these patients more likely to overuse opioids and other

analgesic medications[29], generally precluding inclusion in controlled trials. Combining participants with episodic and chronic cluster headache into one analysis may distort outcomes and, driven by the dominance of participants with the episodic subtype, may result in a potentially false conclusion that both groups are responders. Our analysis represents the first adequately powered analysis to assess the differential effect of a specific treatment between the two forms of cluster headache. The results underline the importance of redoubling efforts at developing further suitable acute treatments for patients with chronic cluster headache.

Conclusion

nVNS is effective in aborting attacks in episodic cluster headache. It does not show the same acute efficacy in patients with chronic cluster headache. The clearance of nVNS for the acute treatment of episodic cluster headache by the US Food and Drug Administration was, in part, based on findings from this analysis of the ACT1 and ACT2 studies. In all patients, nVNS is well tolerated. nVNS offers several advantages over existing treatment options, including its ease and flexibility of use and its ability to be used for as many attacks as the patient experiences per day, without restrictions to daily number of treatments and co-medications. nVNS is also not contraindicated in cardiovascular disease. Additional studies are needed to further elucidate the mechanism of action and possibly related reasons for failure in the acute treatment of chronic cluster headache, including potential studies of the effects of nVNS on parasympathetic output from the trigeminal autonomic reflex for patients with episodic and chronic cluster headache. This could lead to better understanding of the pathogenesis of cluster headache.

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CHAPTER 11

Summary and general discussion

Nederlandse samenvatting
List of publications
Curriculum Vitae
Dankwoord

Summary and general discussion

Cluster headache is severe, very disabling and results in a diminished quality of life.[1] The aim of this thesis is to gain more understanding of clinical aspects of cluster headache and to evaluate various aspects of neurostimulation therapies in cluster headache. In this chapter, the results of this thesis are summarized followed by concluding remarks and thoughts about future perspectives.

Part I - Clinical aspects

Chapter 1 provides a general introduction about cluster headache, its clinical presentation, epidemiology, pathophysiology, and the challenges of current treatment options. It also describes the aims of the thesis.

Chapter 2 deals with secondary headaches mimicking cluster headache and other so-called trigeminal autonomic cephalalgias (TACs). The ICHD-III beta version criteria[2] state that "when a new headache with characteristics of a TAC occurs for the first time in close temporal relation to another disorder known to cause headache, the new headache is coded as a secondary headache attributed to the causative disorder". So, even when a patient has a typical phenotype of one of the TACs, the diagnosis must be that of the underlying lesion. In **chapter 2,** 53 recent cases are described with a typical TAC-phenotype due to an underlying structural lesion: 19 resembling cluster headache, 6 hemicrania continua and 28 SUNCT/ SUNA. The suggested causative disorders include prolactinomas, glioblastomas, arteriovenous malformations, arterial dissections and various inflammations. Remarkably, in more than 40% of the cases with a SUNCT/SUNA-phenotype, trigeminal nerve compression was thought to be the cause. The number of secondary headaches with a TAC-phenotype attributed to a causative disorder reported in the literature suggests that symptomatic TACs must be very rare. Nevertheless, it is of crucial importance to identify a structural lesion when a secondary headache mimicks a TACs, as that underlying cause will influence treatment and outcome.

Chapter 3 describes a patient with so-called Cluster-Tic syndrome, in which cluster headache and trigeminal neuralgia attacks co-occur. About 40 patients are described in the literature so far. Like in **chapter 2**, this case shows that it is important to search for underlying structural lesions by means of a cerebral MRI. Here, a possible causative compression of the trigeminal nerve by the petrosal vein was expected. After microvascular decompression of the trigeminal nerve, a positive effect on both the cluster headache and the trigeminal neuralgia attacks was seen. The response in this patient resembles the response after such decompression in SUNCT/SUNA patients.[3,4] It indicates that vascular (arterial or venous) decompression of the trigeminal nerve in Cluster-Tic syndrome can be considered when there are signs of compression of the trigeminal nerve on cerebral MRI.

Chapter 4 focuses on the consequences of recently proposed changes in the ICHD-III beta version of the International Classification of Headache Disorders for diagnosing cluster headache.[2] Compared to the ICHD-II criteria[5], ipsilateral sensation of fullness in the ear and ipsilateral forehead/ facial flushing were added to the diagnostic criteria. A well-defined Dutch cohort of self-reported cluster headache patients from the Leiden University Cluster Headache neuro-analysis (LUCA) programme was used in this study.[6] Both people fulfilling and almost fulfilling the ICHD-II cluster headache criteria were approached and specifically asked for an ipsilateral sensation of fullness in the ear and ipsilateral forehead/ facial flushing. No additional value of the proposed changes for diagnosing cluster headache was found. None of the patients who did not fulfil all ICHD-II criteria could be diagnosed with cluster headache according to the ICHD-III beta criteria.[5,7] Therefore, the addition of these two symptoms does not have additional value to the diagnostic cluster headache criteria.

Chapter 5 focusses on aura symptoms as a part of cluster headache attacks in the LUCA population. Seven per cent of the cluster headache patients reported typical aura symptoms according to the ICHD-III beta criteria. Other clinical characteristics were similar between those with and without aura, except for a lower alcohol consumption and higher prevalence of frontal pain during a cluster headache attack in the patients with aura.

Chapter 6 describes sleep quality, chronotype and the ability to alter individual sleep rhythms in episodic and chronic cluster headache patients compared with healthy controls. Chronic cluster headache patients had more often early chronotypes. The ability to alter sleep rhythms, however, was diminished in chronic cluster headache patients. A severely decreased sleep quality was two to three times more often reported in cluster headache patients than in healthy controls, suggesting a relation between cluster headache attacks and sleep quality.

Chapter 7 illustrates a cluster headache patient with long-lasting dysgeusia and hyposmia after lithium use. Lithium carbonate is the second choice as prophylactic cluster headache treatment, but has many possible severe side effects. Dysgeusia is a very rare side-effect of lithium, mainly described in patients who used it for a psychiatric indication.[8-12] Hyposmia has not previously been reported at all. The side effects led to a change in appetite and a resulting gain of weight in the patient described. We believe it of importance that headache specialists who prescribe lithium are aware of these very rare, but severe side effects.

Chapter 8 evaluates the use and effects of illicit drugs in the LUCA population as it was reported before in other cluster headache populations from different countries.[13-16] The background of our study, however, differ from previous studies as: (i) restricted cannabis use is legal in the Netherlands, and (ii) we were able to study a rather large cohort cluster headache patients, which gave the opportunity to stratify for age, gender and cluster headache form. The LUCA population was compared to the Dutch general population and two subpopulations with headache and chronic pain. There were relatively more illicit drug users in the cluster headache population than in the Dutch general population. Only a few cluster headache patients reported a reduction in attack frequency by illicit drug use: 56% of Psilocybin Mushroom users (N=22), 60% (N=3) of Lysergic acid diethylamide (i.e. LSD) (N=3) and 50% of heroin users (N=2). A decreased attack duration was reported by 46% (N=18) of PSI, 50% (N=2) of heroin and 36% (N=8) of amphetamine users. These figures should be interpreted with caution, because of the small number of subjects in each group who actually used these illicit drugs during a cluster headache episode.

Part II - Therapy with neurostimulation

Chapter 9 shows a patient with occipital nerve stimulation as prophylactic cluster headache treatment during pregnancy. It is known that women with cluster headache are afraid to become pregnant because during pregnancy there is no safe prophylactic or attack-treatment for them. As a result, females having their first cluster headache attacks before their first pregnancy were shown to have fewer children than those who already had children before the first cluster headache attack.[17,18] There were female patients who even intentionally had no children at all because of cluster headache.[18] During pregnancy, acute treatment is limited to oxygen which is not often very effective and prophylactic treatment is not recommended for possible prenatal toxicity.[19] In this chapter, a former ICON study participant[20] is described who became pregnant while on occipital nerve stimulation as prophylactic cluster headache treatment. It was an uncomplicated pregnancy and childbirth. A default in battery charging of the occipital nerve stimulator resulted in a temporary return of attacks. Occipital nerve stimulation could be a possible effective and safe prophylactic treatment option during pregnancy for those women suffering from chronic cluster headache.

Chapter 10 describes the pooled analysis of two randomized controlled trials of the acute effect of vagal nerve stimulation in episodic and chronic cluster headache. Unique about this analysis is the large number of both episodic and chronic cluster headache patients from different countries and continents (although most patients were Caucasian). This is the first meta-analysis of pooled randomized clinical trials of an acute cluster headache treatment in which it was possible to evaluate the differences in efficacy between chronic and episodic cluster headache. The comparison was possible as the studies in this pooled analysis were very similar in design. External vagal nerve stimulation seemed to be an effective acute treatment alternative for episodic, but not for chronic cluster headache patients.

Concluding remarks and future perspective

LUCA programme

This thesis is partly based on an analysis of data from the large cluster headache population of the Leiden University Cluster Headache neuro-analysis (LUCA) programme (**chapter 4, 5, 6 and 8**), a well-defined cohort of self-reported cluster headache patients, which were recruited through local and digital media and the outpatient department of the Leiden University Medical Center. It was shown that the screening questionnaire has a specificity of 0.89 for a diagnosis of cluster headache according to the ICHD-II criteria.[5,6] A possible limitation of this population is that only Dutch patients participated. Therefore, we cannot extrapolate the results to other populations. As most data were collected retrospectively a recall bias may have occurred.

From cluster headache diagnosis to personalised medicine

An important question is whether it is possible to formulate a personal treatment algorithm based on the characteristics of an individual cluster headache patient.

Of course, first it is of crucial importance to make a right diagnosis and differentiate patients with cluster headache from those with another headache-type. In the past, this differentiation proved to be very difficult.[21] After making a cluster headache diagnosis, if possible, within this group of patients a distinction must be made between the episodic and chronic form on the basis of the criteria. In chronic cluster headache remissions last much shorter than in episodic cluster headache.[2,22] Although this distinction is important, it seems that it is also of clinical importance to raise the question whether we should not focus in many patients on the personal consequences of the disease by measuring its burden on the individual patient and in this way try to develop a more personalized treatment plan, not only based on the rigid criteria. Recently, two new ways to measure cluster headache severity have been proposed: the Cluster Headache Index and the Cluster Headache Severity Scale.[23,24] The Cluster Headache Index consists of a calculation including attacks per day, hours per attack, days per cluster headache period and amount of

cluster headache periods per year.[23] The Cluster Headache Severity Scale is slightly different and takes into account the number of attacks per day, attack duration and period duration.[23] Both scales can be valuable clinical tools for measuring individual cluster headache burden, but also for intra-individual comparisons over time. Maybe they can result in the ultimate goal: a scale that predicts individual treatment outcome. Using "big data" various factors should be taken into account for such a predictable model. As examples, so far, it has been reported that gender[25,26] and the course of the disease[27] have significant influences on the response to treatment. It would be of great clinical importance if future scales could indeed indicate which acute or prophylactic treatment options should be initially used to come to the most likely successful outcome in an individual with cluster headache. We believe that such an approach can be a first step to personalised cluster headache clinical practice.

Aura and cluster headache

The occurrence of an aura is mainly known from migraine. Our study (**chapter 5**) and several other studies, however, showed that a considerable portion of cluster headache patients regularly experiences an aura as part of their attacks as well. There seem to be some differences between the reported aura characteristics in migraine and cluster headache. The aura duration we found in cluster headache was mostly shorter than in migraine, which is in accordance with a previous finding.[28] Also, dysarthria and dysphasia as aura symptoms were more often reported in cluster headache than in migraine. However, visual aura symptoms remained still the most frequently reported aura symptoms in both migraine and cluster headache.

Cortical spreading depression, which is a wave of cortical hyperexcitability, is shown to be the cause of aura symptoms in migraine. Increased cortical excitability has been found as well in the hemisphere ipsilateral to the side of the headache in episodic cluster headache.[29] Remarkably, inhibition of cortical excitability is thought to be the mechanism behind the acute effect of external vagal nerve stimulation[30], which indeed is effective in episodic cluster headache patients. This shows that cortical involvement could be of crucial importance for hypotheses about the (episodic)

cluster headache pathophysiology and thus also for its treatment. So, other novel treatment options influencing cortical excitability should also be explored in cluster headache.[31]

Neurostimulation in cluster headache

Several neurostimulation options have been explored in cluster headache such as stimulation of the sphenopalatine ganglion, the occipital nerve and the vagal nerve. Even deep-brain stimulation of the posterior hypothalamus was considered an option. Invasive neurostimulation can have severe side effects such as wound infection or migration of leads or devices. Deep brain stimulation has even led to a lethal intracerebral haemorrhage in one of the described study patients.[32]

Occipital nerve stimulation is a promising treatment for those patients not responding to regular prophylactic options, the so-called "medically intractable" chronic cluster headache patients.[33] ICON, our randomized controlled trial, was recently finished and results are expected soon.[20] Hopefully, this is a prophylactic option for these patients. Further research focused on the physiological responses after neurostimulation in healthy controls[34-36] and cluster headache patients might give further clues regarding the pathophysiology of cluster headache. fMRI studies on the effect of vagal nerve and occipital nerve stimulation such as carried out in healthy persons maybe can serve as example for cluster headache.[34,35]

New non-neurostimulation targets in cluster headache

Calcitonin gene-related peptide (CGRP) related treatment has been suggested as new target for prophylactic cluster headache treatment. CGRP is increased in both saliva and blood during cluster headache attack periods.[37] Also, CGRP provokes attacks in the active phase of episodic and chronic cluster headache, but not during the remission phase in episodic cluster headache.[38] Four phase III studies are currently underway evaluating the prophylactic effect and safety of these drugs in cluster headache.[37] These are the drugs fremanezumab and galcanezumab. Results of these promising drugs are expected in the near future.

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Nederlandse samenvatting

Clusterhoofdpijn is ernstige en beperkende ziekte wat zorgt voor een verminderde kwaliteit van leven. Het doel van dit proefschrift is om meer begrip van de klinische aspecten van clusterhoofdpijn te verkrijgen en om de diverse aspecten van neurostimulatie behandeling in clusterhoofdpijn te evalueren. In deze samenvatting worden de resultaten van het proefschrift weergegeven.

Deel I – Klinische aspecten

Hoofdstuk 1 is een algemene (Engelse) introductie over cluster hoofdpijn, de klinische presentatie, epidemiologie, pathofysiologie en de uitdagingen van huidige behandelmogelijkheden. Het beschrijft ook het doel van het proefschrift.

Hoofdstuk 2 beschrijft ziektebeelden die zich kunnen presenteren met symptomen lijkend op de groep hoofdpijnsoorten genaamd te samen 'trigeminale autonome cephalalgias' (TACs), waaronder clusterhoofdpijn ook valt. De ICHD-III beta versie criteria geven aan dat "wanneer een nieuwe hoofdpijn met karakteristieken van een TAC voor het eerst ontstaat in relatie met een andere aandoening, waarvan bekend dat dit hoofdpijn kan veroorzaken, we de nieuwe hoofdpijn bestempelen als secondaire hoofdpijn gerelateerd aan de andere aandoening. In **Hoofdstuk 2** worden 53 casussen beschreven met typische TAC-symptomen door onderliggende aandoeningen: 19 lijkend op clusterhoofdpijn, 6 op hemicrania continua en 28 op SUNCT/ SUNA. De gesuggereerde oorzakelijke aandoeningen bevatten onder andere prolactinomen, glioblastomen, arterioveneuze malformaties, arteriële dissecties en diverse ontstekingen. Opmerkelijk was dat trigeminale zenuwcompressie in meer dan 40% van de casussen met SUNCT/SUNA-symptomen werd aangewezen als oorzakelijke aandoening. Desalniettemin suggereert de literatuur dat het aantal keer dat een TAC een onderliggende aandoening heeft zeldzaam is. Ondanks deze zeldzaamheid, blijft het belangrijk om

onderliggende pathologie te herkennen, want dit heeft invloed op de benodigde behandeling en uitkomst.

Hoofdstuk 3 beschrijft een patiënt met het Cluster-Tic syndroom, waarbij zowel cluster hoofdpijn als trigeminusneuralgie aanvallen voorkomen. Ongeveer 40 patiënten zijn reeds eerder beschreven in de literatuur. Net als in **hoofdstuk 2**, laat deze casus zien dat het belangrijk is om onderliggende pathologie uit te sluiten middels een MRI scan van de hersenen.
In deze casus werd compressie van de trigeminus zenuw door de petrosale ader verdacht als oorzaak voor de hoofdpijn aanvallen. Na microvasculaire decompressie van de trigeminus zenuw, werd er een positief effect gezien zowel op de cluster hoofdpijn als trigeminusneuralgie aanvallen. Het effect in deze patiënt is vergelijkbaar met wat eerder werd geobserveerd in SUNCT/SUNA patiënten en geeft aan dat vasculaire decompressie van de trigeminus zenuw overwogen kan worden bij patiënten met het Cluster-Tic syndroom, wanneer er aanwijzingen zijn voor trigeminus compressie op de MRI scan van de hersenen.

Hoofdstuk 4 focust zich op de consequenties van de recent voorgestelde veranderingen voor de definitie clusterhoofdpijn in de 'ICHD-III beta versie - International Classification of Headache Disorders'. Vergeleken met de eerdere 'ICHD-II criteria', ipsilaterale gevoel van een vol oor en ipsilatere roodheid van gelaat/voorhoofd waren toegevoegd aan de diagnostische criteria. In deze studie werd gebruik gemaakt van een goed beschreven Nederlands cohort van zelf-gerapporteerde clusterhoofdpijn patiënten van de Leiden Universiteit Clusterhoofdpijn neuro-analyse (LUCA) programma.[6] Zowel mensen die aan de ICHD-II criteria van clusterhoofdpijn voldeden als mensen die er bijna aan voldeden warden benaderd met de vraag of zij ipsilaterale gevoel van een vol oor en/of ipsilatere roodheid van gelaat/voorhoofd ervaarden gedurende de hoofdpijnaanvallen. De voorgestelde veranderingen voor de diagnose clusterhoofdpijn liet geen toegevoegde diagnostische waarden zien. Van de mensen die niet voldeden aan de ICHD-II criteria kon niemand gediagnosticeerd worden met clusterhoofdpijn volgens de nieuwe ICHD-III beta criteria.[5,7]

Hoofdstuk 5 focust zich op aura symptomen als een onderdeel van clusterhoofdpijn aanvallen in de LUCA onderzoekspopulatie. Zeven procent van de clusterhoofdpijnpatiënten rapporteerden typische aurasymptomen (volgens de ICHD-III beta criteria). Andere klinische karakteristieken waren vergelijkbaar in degenen met en zonder auraverschijnselen, behalve een lager alcoholgebruik en een frequenter voorkomen van frontale pijn gedurende een clusterhoofdpijnaanval in patiënten met auraverschijnselen.

Hoofdstuk 6 beschrijft slaap kwaliteit, chronotype en de mogelijkheid om aan te passen aan een ander slaappatroon in episodische en chronische clusterhoofdpijn patiënten in vergelijking met gezonde controles. Chronische clusterhoofdpijnpatiënten hadden vaker een vroeg chronotype (vroeg wakker en vroeg slapen). De mogelijkheid om zich aan te passen aan een slaapritme was verminderd in chronische clusterhoofdpijnpatiënten. Een ernstig verminderde slaapkwaliteit was 3x zo vaak gerapporteerd in clusterhoofdpijn patiënten vergeleken met gezonde controles, wat suggereert dat er een associatie is tussen clusterhoofdpijn en slaap kwaliteit.

Hoofdstuk 7 illustreert een clusterhoofdpijn patiënt met langdurige dysgeusie (veranderde gewaarwording van smaak) en hyposmie (verlies van reukzin) na gebruik van lithium. Lithium carbonaat is de tweede keus als preventieve clusterhoofdpijn behandeling, maar kan vele ernstige bijwerkingen hebben. Dysgeusie is a erg zeldzame bijwerking van lithium en de bijwerking is voornamelijk beschreven in patiënten die lithium gebruikten voor een psychiatrische aandoening. Hyposmie is niet eerder beschreven in de literatuur. Deze bijwerkingen hadden invloed op de eetlust en resulteerden in een gewichtsverlies in onze casus. We zijn van mening dat het belangrijk is dat hoofdpijnspecialisten die lithium voorschrijven op de hoogte zijn van deze zeldzame, maar ernstige bijwerkingen.

Hoofdstuk 8 evalueert het gebruik en effect van drugs op clusterhoofdpijnaanvallen in de LUCA onderzoekspopulatie. Recreatief drugsgebruik is eerder beschreven in studies uit andere

landen[13-16]. Het verschil met dit onderzoek is dat we een grote groep clusterhoofdpijnpatiënten hebben onderzocht, waardoor er gestratificeerd kon worden voor leeftijd, geslacht en clusterhoofdpijn subform. Ook is beperkt gebruik van cannabis legaal in Nederland. De bevindingen van de LUCA populatie werd vergeleken met de algemene Nederlandse populatie en twee subpopulaties met hoofdpijn en chronische pijn. Er werd meer recreatieve drugs gebruikt in de clusterhoofdpijn populatie versus de algemene Nederlandse populatie. Een zeer beperkte groep clusterhoofdpijnpatiënten gaven aan dat de aanvalsfrequentie afnam bij drugsgebruik: 56% van de paddo gebruikers (psilocybine; N=22), 60% van de LSD gebruikers (N=3) en 50% van de heroïne gebruikers (N=2). Een vermindering van de aanvalsduur werd aangegeven door 46% van de paddo gebruikers (N=18), 50% van de heroïne (N=2) en 36% van de amfetamine gebruikers (N=8). De gevonden resultaten dienen voorzichtig geïnterpreteerd te worden, gezien de kleine aantallen die daadwerkelijk deze recreatieve drugs hebben gebruikt tijdens een clusterhoofdpijnperiode.

Deel II – Behandeling met neuromodulatie

Hoofdstuk 9 beschrijft een patiënt met occipitale zenuwstimulatie als preventieve cluster hoofdpijnaanval gedurende haar zwangerschap. Het is bekend dat vrouwen met clusterhoofdpijn terughoudend zijn om zwanger te worden, omdat er zeer beperkte behandelmogelijkheden zijn tijdens deze periode. Eerder onderzoek liet zien dat vrouwen die clusterhoofdpijn ontwikkelden voor hun eerste zwangerschap minder kinderen hadden dan degenen die al kinderen hadden voor hun eerste clusterhoofpijnepisode.[17,18] Er waren zelfs patiënten die bewust geen kinderen hadden vanwege de clusterhoofdpijn.[18] Zuurstof is als aanvalsbehandeling mogelijk, maar vaak niet erg effectief en profylactische behandeling is geheel niet aanbevolen vanwege de mogelijke prenatale toxiciteit.[19] In dit hoofdstuk wordt het effect van profylactische clusterhoofdpijn behandeling middels occipitale zenuwstimulatie beschreven bij een zwangere voormalig ICON onderzoek deelneemster[20]. Het was een ongecompliceerde zwangerschap en geboorte. Een fout in

het opladen van de batterij van de occipitale zenuwstimulator zorgde tijdelijk voor terugkeer van de aanvallen. Occipitale zenuwstimulatie zou een mogelijke effectieve en veilige preventieve behandeloptie kunnen zijn gedurende zwangerschap voor vrouwelijke clusterhoofdpijnpatiënten.

Hoofdstuk 10 beschrijft een meta-analyse van twee gerandomiseerde gecontroleerde onderzoeken naar het effect van nervus vagus stimulatie als aanvalsbehandeling in episodische en chronische clusterhoofdpijn. Het grote aantal episodische en chronische cluster hoofdpijn patiënten is uniek in deze analyse, waardoor dit de eerste meta-analyse is waarin onderscheid werd gemaakt in het effect in episodische en chronische clusterhoofdpijn patiënten. De vergelijking was mogelijk doordat beide onderzoeken die in de meta-analyse waren opgenomen erg op elkaar leken wat betreft de onderzoeksopzet. Deze meta-analyse liet zien dat externe nervus vagus stimulatie een effectieve aanvalsbehandeling is voor episodisch, maar niet voor chronische cluster hoofdpijn patiënten.

List of publications

Peer-reviewed scientific papers

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12. **I.F. de Coo**, J.C.A. Marin , S.D. Silberstein, D.I. Friedman, C. Gaul, C.K. McClure, A. Tyagi, E. Liebler, S.J. Tepper, M.D. Ferrari, P.J. Goadsby. Differential efficacy of non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A meta-analysis. Cephalalgia. 2019;39(8):967-977.
13. H.C. Diener, P.J. Goadsby, M. Ashina, M.A. Al-Karagholi, A. Sinclair, D. Mitsikostas, D. Magis, P. Pozo-Rosic, P. Irimia Sieira, M.J. Làinez, C. Gaul, N. Silver, J. Hoffmann, J. Marin, E. Liebler, M.D. Ferrari, for **the PREMIUM studygroup**. Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomised, sham-controlled PREMIUM trial. Cephalalgia. 2019;39(12):1475-1487.

Bookchapter

1. **I.F. de Coo**, L.A. Wilbrink, J. Haan. Cluster headache: clinical features and management. Oxford Textbook of Headache Syndromes: mastering headache diagnosis and treatment. Oxford University Press, *April 2020*

Curriculum Vitae

Ilse Frederieke de Coo was born on August 22, 1987 in Heerenveen, the Netherlands. She received her secondary school degree in 2005 at the Rijksscholengemeenschap in Steenwijk and started the same year with her study Medicine at the Rijksuniversiteit Groningen. During medical school she participated in the Public Health committee of the International Federation of Medical Students Association (IFMSA) and was committee member of the Fundraising Diner 2010 at the Medical Spectrum Twente in Enschede. She gained her first research experience during her work as Medical Research Assistant at Xendo, a pharmaceutical research company in Groningen. During her study she performed an internship in Krakow, Poland and one in Dar-el-Salaam, Tanzania. She performed her research internship at the Isala Klinieken in Zwolle on the treatment of migraine in children by general practitioners before referral to secondary care. In the spring of 2012 she obtained her Master's degree in Medicine.

Afterwards, she worked as a resident in Neurology (ANIOS) at the Isala Klinieken in Zwolle. In October 2012 she started as a PhD candidate at the Department of Neurology at Leiden University Medical Center. The results of this work are described in this thesis. In 2017, she received the award for the best poster at the 18th Congress of the International Headache Society in Vancouver, Canada. In January 2017 she started to work as a resident (ANIOS) in Neurology at the Reinier de Graaf Gasthuis in Delft. In September that same year she started her training to become a medical rehabilitation physician at Basalt Rehabilitation Center in The Hague, which is still ongoing.

Ilse lives in Leiden with her husband Jochem.

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