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The Relation between Episodic Headache and Chronic Daily Headache (CDH)

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Abstract

Chronic daily headache (CDH) involves the daily or almost daily occurrence of headache, which affects 3% to 6% of the general adult population, with about half accounted for by chronic tension(-type) headache and the other half by chronic migraine. Two thirds of CDH develops gradually out of episodic headaches, which in approximately one third is tension (-type) headache and in approximately two thirds is migraine. The transition from episodic headache to CDH can be abrupt or gradual and in case of the latter, risk factors have been identified. If these risk factors are more than associations, they may forewarn the clinician of an impending transition, although the transition takes a decade on average.

Insight into what drives the transition from episodic headache to CDH could be derived from the medical and psychiatric comorbidities of CDH versus episodic headache. These comorbidities are reviewed and discussed and proposed to be a manifestation of a systemic endocrine-metabolic disorder. The musculoskeletal component of this disorder, in particular its effect on the craniocervical muscles, is suggested to drive the high frequency of the headaches in CDH and constitutes the target of onabotulinumtoxinA's effectiveness in chronic migraine.

Keywords: Anxiety; Central sensitization; Chronic daily headache; Chronic migraine; Chronic tension-type headache; Comorbidities; Depression; Dysmenorrhea; Endocrine-metabolic disorder; Endometriosis; Headache amplifier; Headache chronification; Headache development; Headache presentation; Hypertension; Hypothyroidism; Insomnia; Menstrual-cycle disorders; Nausea; Neck pain; Neurogenic inflammation; Obesity; OnabotulinumtoxinA; Somatization disorder

Introduction

Chronic daily headache (CDH) involves the daily or almost daily occurrence of headache, which affects 3% to 6% of the general adult population [1], with about half accounted for by chronic tension(-type) headache and the other half by chronic migraine [2]. The difference between the two CDH conditions is the occurrence of migraine headaches in addition to the daily headaches in the latter and the absence of migraine headaches in the former. CDH can begin with daily or almost daily headaches, which could be referred to as *primary CDH*, but can also be preceded by headaches occurring on and off, that is, by episodic headache, which could be referred to as *secondary CDH*. In case of secondary CDH with episodic headaches preceding the occurrence of CDH, the transition can be abrupt or gradual. In case of gradual-onset secondary CDH, risk factors have been identified and if they are more than associations, may forewarn the clinician of an impending transition, although the transition takes a decade on average (*vide infra*).

Although the feature *par excellence* of CDH is the daily or almost daily occurrence of headache, not all headaches that occur with that frequency resort under the CDH umbrella. The daily or almost daily headaches that are not CDH can be captured under two denominators, that is, paroxysmal on the one hand and non-paroxysmal on the other. The paroxysmal daily or almost daily headaches that are not included in CDH are nocturnal migraine, cluster headache, paroxysmal hemicrania, and stabbing headache. These are episodic headache conditions with paroxysms of well-defined duration, namely several hours to a good part of the day in nocturnal migraine, 1-2 hours in cluster headache, 10-30 minutes in paroxysmal hemicrania, and seconds to 1-2 minutes in stabbing headache. The non-paroxysmal daily or almost daily headache that is not included in CDH either is hemicrania continua, an indomethacin-responsive headache syndrome described in 1984 by Sjaastad & Spierings [3]. Paroxysmal hemicrania and stabbing headache are treated preventively with indomethacin [4,5], while nocturnal migraine and cluster headache are treated basically

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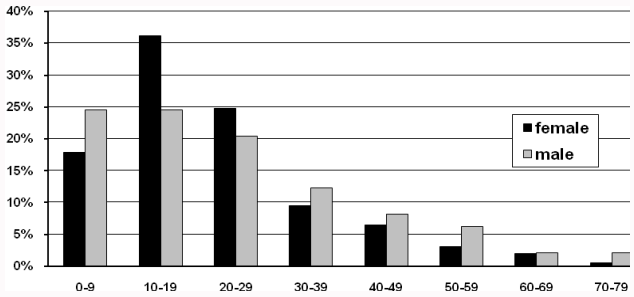

Figure 1: Distribution of the age of headache onset per gender (n = 251) [9].

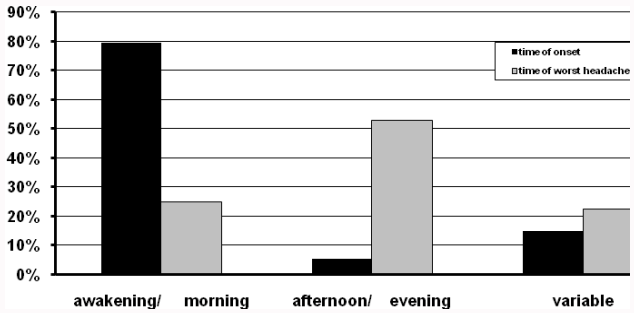

Figure 2: Diurnal pattern of the daily headaches (n = 214) [9].

abortively with the sumatriptan injection[6] and preventively with relatively high doses of verapamil [7].

In the following, first the presentation of CDH will be described, followed by information regarding its development. As it is shown, two thirds of CDH develops gradually out of episodic headaches, which in approximately one third is tension(-type) headache and in approximately two thirds is migraine. The transition is truly very gradual and takes 11 years on average. Through association studies, risk factors have been identified but it is not known what exactly drives the transition from episodic headache, whether tension(-type) headache or migraine, to CDH. A theory will be developed that the transition from either type of headache to CDH occurs in a subgroup of patients who develop a systemic endocrine-metabolic disorder that is associated with frequent headache [8]. In the presence of a genetically determined headache amplifier, which, in the author's opinion, is the essence of migraine, chronic migraine will ensue; otherwise, chronic tension(-type) headache is the consequence. The basis of the theory lies in the constellation of co-morbidities seen with chronic migraine in comparison to episodic migraine.

Presentation of CDH

In a study of 258 CDH patients from a private headache practice, 19% were men and 81% women; their average age at consultation was 42 years [9]. The distribution of the age of (any) headache onset for the men and women separately is shown in Figure 1. Seventy seven percent of the patients, 69% of the men and 79% of the women, experienced the onset of headache before the age of 30 years. In 36% of the women and 24% of the men, the onset of headache occurred in the second decade of life The peak of headache onset in the second decade in women is consistent with the importance of the menstrual cycle in headache occurrence. It is probably driven to a great extent by the onset of menstruation (menarche) in the early teens and, to a lesser extent, by the initiation of estrogen-containing contraceptives in the late teens.

Table 1: Aggravating factors of the daily headaches (n = 258) [9].

Light	40%
Physical activity	33%
Bending over	33%
Noise	30%
Stress/tension	29%
Menstruation[1]	28%
Alcohol	20%
Coughing/sneezing	15%
Foods/drinks	13%
Lack of sleep	12%
Not eating on time	11%
Straining	10%
Weather changes	10%
Exhaustion	10%
[1]women only; n = 208	

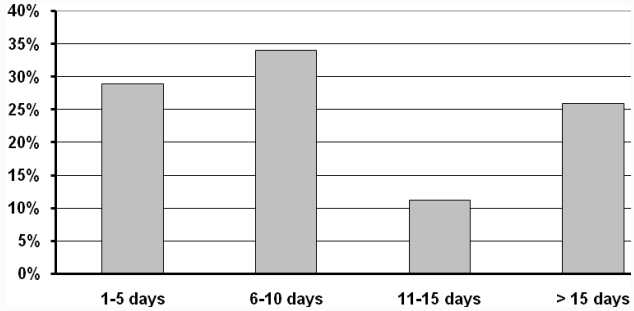

Figure 3: Frequency of the severe headaches in days per month (n = 197) [9].

With regard to diurnal pattern, the daily or almost daily headaches were present on awakening or came about in the course of the morning in 79% of the patients, came about in the afternoon or evening in 6%, and had a variable time of onset in 15% (Figure 2). In 25%, the headaches were worst on awakening or in the course of the morning; in 53% they were worst in the afternoon or evening and in 22% they were worst at a variable time of the day. CDH apparently comes in two distinct diurnal patterns, with the most common pattern being that of headaches gradually increasing in intensity as the day progresses, to become worst in the afternoon or evening. According to the results of the study, this was the pattern in more than half of the patients with CDH. The less common pattern, which could be referred to as "reversed diurnal pattern", is that in which the headaches are worst on awakening in the morning and gradually improve as the day progresses. This was the case in a quarter of the patients while in the remaining quarter the diurnal course of the headaches was variable.

The reversed diurnal pattern is associated with the most frequent nighttime awakenings with headache. In the study, nocturnal awakening by headache occurred at least once per week in 36% of the patients. Of those patients who were woken up by headache at least once per week, 48% experienced the worst headache on awakening or in the course of the morning, as opposed to 22% of the patients who were woken up by headache less than once per week.

With regard to associated symptoms, the daily or almost daily

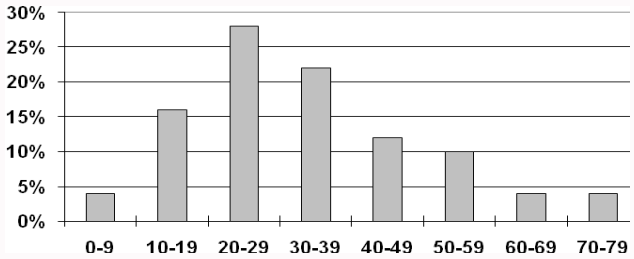

Figure 4: Distribution of the age of (daily) headache onset in the patients with primary CDH (n = 50) [10].

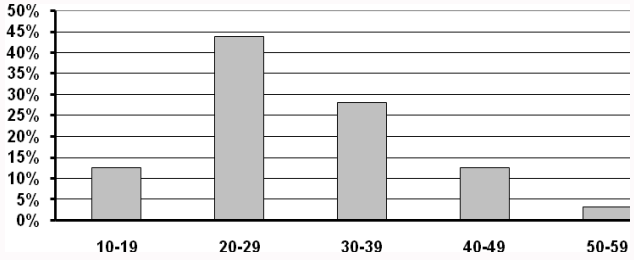

Figure 5: Distribution of the age of (daily) headache onset in the patients with abrupt-onset secondary CDH (n = 32) [12].

headaches were at least twice per week associated with nausea in 35% and with vomiting in 9%. With regard to the laterality of the headaches, 36% were unilateral, 50% bilateral and 14% either unilateral or bilateral. The unilateral headaches had a fixed lateralization to the right or left side in 83% and alternated between the two sides of the head in 17%. The aggravating factors of the daily headaches are shown in Table 1. Apart from light and noise, most common were physical activity, bending over, stress or tension, and menstruation.

Ninety four percent (94%) of the CDH patients experienced severe headaches in addition to the daily headaches. The distribution of the frequency of the severe headaches in days per month is shown in Figure 3. Twenty six percent of the patients experienced severe headaches more than 15 days per month; otherwise they experienced severe headaches mostly 10 days per month or less (63%). The results suggest that the vast majority of CDH patients who seek specialty care for their headaches, have chronic migraine as opposed to chronic tension(-type) headache. With regard to laterality, the severe headaches were unilateral in 43%, bilateral in 42%, and either unilateral or bilateral in 15%. The unilateral headaches had a fixed lateralization in 79% and alternated between the left and right side of the head in 21%. One would expect the severe headaches to be lateralized more often than the daily headaches but this was not the case. With regard to associated symptoms, the severe headaches were at least twice per month associated with nausea in 76% and with vomiting in 38%.

In the development of CDH, medication intake is considered to play an important role, in particular the intake of analgesic and vasoconstrictor medications (*vide infra*). A widely used vasoconstrictor for the abortive treatment of headache is caffeine in beverages, especially coffee, but also in prescription and non-prescription medications. Adding up the caffeine use from all these sources, 43% of the CDH patients used less than 100 mg of caffeine per day, 35% between 100 and 300 mg, and 22% more than 300 mg. The average caffeine intake was 170 mg per day, which is approximately the equivalent of two cups of coffee. With regard to analgesic use and excluding opioid- and barbiturate-containing medications, 26% of the CDH patients used less than 500 mg of aspirin-equivalents per day and 48% less than 1,500 mg. The average analgesic intake was 1,860 mg of aspirin-equivalents per day, which is roughly the same as that found by Mathew et al. [10] in their CDH patients. However, it is about half of that reported by Kudrow in his landmark paper on the paradoxical effect of frequent analgesic use on headache [11].

Development of CDH

Of the 230 CDH patients with known onset of the daily headaches, 22% experienced daily headaches from the onset [12]. This could be called primary CDH, in the same way as we speak of primary and secondary chronic cluster headache. The remaining 78% initially experienced intermittent or episodic headaches, that is, had secondary CDH. The distribution of the age of onset of the (daily) headaches in the patients with daily or almost daily headaches from the onset, or primary CDH, is shown in Figure 4. Sixty six percent (66%) of the patients experienced the onset of the daily headaches between the ages of 10 and 39. Of the patients with daily headaches but who initially had episodic headaches, that is, of those with secondary CDH, 19% experienced an *abrupt* onset of the daily headaches and 81% a *gradual* one. The distribution of the age of onset of the daily headaches in the patients with abrupt-onset secondary CDH is shown in Figure 5. This age distribution does not differ from that of the patients with primary CDH as shown in Figure 4. The circumstances related to the onset of the daily or almost daily headaches in the patients with primary CDH and in those with abrupt-onset secondary CDH are shown in Table 2. The table also shows the circumstances of daily-headache onset for the two groups combined, as there was no difference in distribution of the circumstances between the two groups. The most common circumstance of daily headache onset in the two groups combined was head, neck, or back injury, caused by a motor vehicle accident in 61%. It is followed by flu-like illness or sinusitis and medical illness or surgical procedure as causes of daily-headache onset. Examples of medical illness associated with the (abrupt) onset of CDH are colitis, fibromyalgia, vertigo, encephalitis, and meningitis. There were also no differences between the patients with primary CDH and those with abrupt-onset secondary CDH with regard to the following features: gender distribution, time of daily headache occurrence, worst headache time daily, nocturnal awakening, laterality of the daily headaches, occurrence and frequency of severe headaches, laterality of the severe headaches, and parental occurrence of headache. The

Table 2: Circumstances of (abrupt) onset of daily or almost daily headaches [12].

	Primary CDH (n = 51)	Abrupt-onset secondary CDH (n = 34)	Combined group (n = 85)
Head/neck/back injury	25%	29%	27%
Flu-like illness/sinusitis	12%	18%	14%
Medical illness/surgical procedure	14%	15%	14%
Miscellaneous	18%	12%	15%
No apparent reason	31%	26%	30%

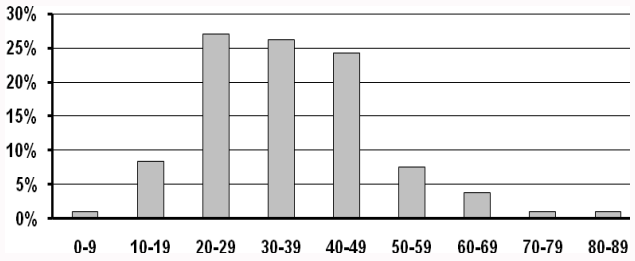

Figure 6: Distribution of the age of daily headache onset in the patients with gradual-onset secondary CDH (n = 106) [12].

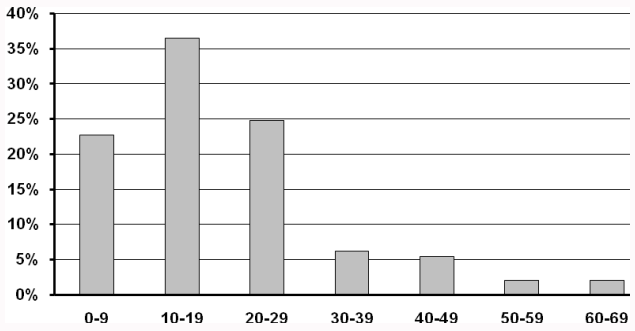

Figure 7: Distribution of the age of initial headache onset in the patients with gradual-onset secondary CDH (n = 145) [12].

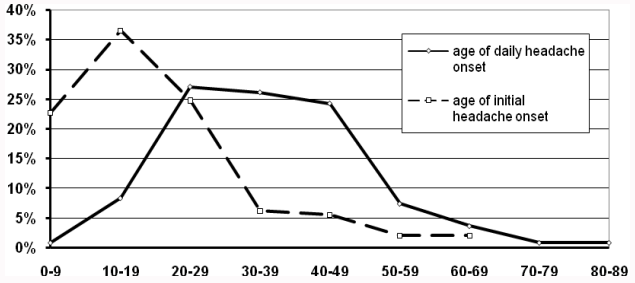

Figure 8: Distribution of the age of initial and daily headache onset in the patients with gradual-onset secondary CDH (n = 106 and 145, respectively) [12].

only difference between the two groups was the association of the daily and severe headaches with nausea. Nausea was more common in the patients with abrupt-onset secondary CDH than in those with primary CDH. The difference is probably due to the fact that 57% of the patients in the abrupt-onset group had a prior history of severe headaches, which tend to be associated with gastrointestinal symptoms.

The distribution of the age of onset of the daily or almost daily headaches in the patients with gradual-onset secondary CDH is shown in Figure 6. Seventy eight percent (78%) of the patients experienced the onset of daily headaches between the ages of 20 and 49. The distribution of the age of onset of the initial, episodic headaches in this group is shown in Figure 7. The two figures are combined in Figure 8, which shows the distribution of the age of initial and daily headache onset in the patients with gradual-onset secondary CDH. The average duration of the transition of the headaches from episodic to almost daily was 11 years, which is reflected in the figure by the separation of the two distributions by approximately a decade.

With regard to parental occurrence, headache in the father and/or mother was more common in the patients with gradual-onset

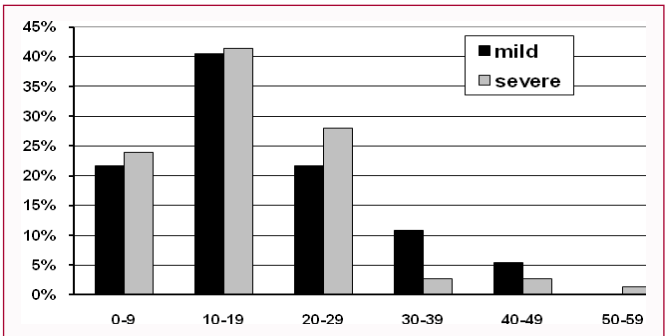

Figure 9: Distribution of the age of headache onset in the patients with gradual-onset secondary CDH, separately for those with initially mild headaches (n = 37) and those with initially severe headaches (n = 75) [13].

Table 3: Features of the initial episodic headaches in the patients with gradual-onset secondary CDH [13].

		Mild	Severe
Headache intensity (n = 112)		33%	67%
Associated symptoms		(n = 12)	(n = 61)
	Nausea	25%	84%
	Vomiting	0%	72%
Headache frequency		(n = 25)	(n = 60)
	≤4 per month	60%	73%
	5 – 9 per month	28%	18%
	10 – 19 per month	8%	7%
	≥ 20 per month	4%	2%

secondary CDH than in the combined group of those with primary CDH and abrupt-onset secondary CDH (69% *versus* 45%). This is interesting because conditions that develop abruptly generally have less of a genetic involvement than do those that develop gradually. On the basis of the information gathered on parenteral headache occurrence, this also seems to be the case in CDH.

With regard to the intensity of the initial episodic headaches, in the 145 patients with gradual-onset secondary CDH, the headaches were mild in 33% and severe in 67% (Table 3) [13]. The mild headaches were associated with nausea in 25% and with vomiting in 0% as opposed to the severe headaches, which were associated with nausea in 84% and with vomiting in 72%. With regard to the frequency of the initial episodic headaches, there was no difference between the mild and severe headaches. The mild headaches occurred less than twice per week in 88% and the severe headaches in 91%.

Table 4 shows the features of the daily headaches separately for those patients whose initial episodic headaches were mild and for those whose initial episodic headaches were severe. There were no differences between the two groups with regard to any of the features studied. The two groups also did not differ significantly from each other with regard to the age of onset of the initial episodic headaches, is shown in Figure 9. From a classification perspective, does it make sense to distinguish between primary and secondary CDH as was done, and within the latter group, between abrupt- and gradual-onset? Judging from the age of onset of the daily headaches, gender distribution, headache presentation, circumstances of headache onset, and parental headache occurrence, there does not seem to be a reason for the differentiation between primary CDH and secondary CDH with abrupt onset. The two groups should probably be considered as having one and the same CDH condition, which could be referred

Table 4: Features of the daily or almost daily headaches in the patients with gradual-onset secondary CDH of those with initially mild *versus* those with initially severe episodic headaches [13].

			Initial headaches mild	Initial headaches severe
Gender			(n = 37)	(n = 75)
	Female		84%	80%
	Male		16%	20%
Diurnal headache pattern				
	Time of headache onset		(n = 36)	(n = 75)
		Awakening/morning	83%	69%
		Afternoon/evening	3%	9%
		Variable	14%	22%
	Time of worst headache		(n = 33)	(n = 67)
		Awakening/morning	39%	18%
		Afternoon/evening	39%	55%
		Variable	22%	27%
Nocturnal headache awakening			(n = 34)	(n = 70)
	At least once/week		29%	39%
Associated symptoms			(n = 37)	(n = 70)
	Nausea		41%	43%
	Vomiting		8%	13%
			(n = 37)	(n = 75)
Laterality	Unilateral		32%	48%
	Bilateral		57%	39%
	Uni/bilateral		11%	13%
Occurrence of severe headaches			(n = 37)	(n = 74)
			97%	96%
Associated symptoms of severe headaches			(n = 36)	(n = 69)
	Nausea		75%	87%
	Vomiting		37%	48%
Frequency of the severe headaches			(n = 29)	(n = 62)
	1 – 5 days/month		35%	31%
	6 – 10 days/month		31%	31%
	11 – 15 days/month		14%	19%
	16 – 20 days/month		3%	8%
	≥ 20 days/month		17%	11%
			(n = 35)	(n = 70)
	Unilateral		43%	53%
	Bilateral		49%	33%
	Uni/bilateral		8%	14%

to as abrupt-onset *CDH*, representing 37% of CHD patients in the study. However, this group should probably be distinguished from the one with CDH with gradual onset because of the very different development of the headaches and the difference in parental headache occurrence. The latter group could be referred to as having *gradual-onset CDH* and constitutes the topic of the remainder of this chapter.

CDH comorbidities

Insight into what drives the transition from episodic headache to CDH, that is, the development of gradual-onset CDH, could be derived from the medical and psychiatric comorbidities of CDH *versus* episodic headache. The studies that have been conducted focus on migraine and relate to the differences in comorbidities between episodic and chronic migraine, the latter being a subcategory of CDH. Migraine is to a great extent a female condition with a male-to-female ratio in terms of population prevalence of 1 to 2-3 [14]. Estrogen hormones undoubtedly play an important role here as suggested 1) by the common onset of migraine in women at menarche, with the use of an estrogen-containing contraceptive, or during and particularly after pregnancy [15] and 2) by the occurrence or worsening of migraine in women particularly perimenstrually [16]. Determining menstrual-cycle and menstruation disorders in woman with episodic *versus* chronic migraine, Spierings and Padamsee [16] found a statistically significantly higher occurrence of menstrual-cycle disorders in

general, that is, oligomenorrhea, polymenorrhea, and irregular cycle, in women with chronic migraine (41.2% *versus* 22.2%; p = 0.05) as well as dysmenorrhea (51.0% *versus* 28.9%; p = 0.04). Particularly the menstrual-cycle-disorder finding suggests a higher prevalence of endocrinopathy in women with chronic migraine, in comparison to those with episodic migraine.

Comparing women with episodic migraine with those with chronic migraine, Tietjen et al. [17] found a statistically significantly higher prevalence of endometriosis in the latter (64% *versus* 36%; p = 0.002). Endometriosis is defined as the presence of endometrium in the pelvis and/or abdomen outside the uterus. It affects approximately 7% of women of childbearing age, mostly between the ages of 25 and 40 years. Expanding on the theme of comorbidities in episodic *versus* chronic migraine, Bigal et al. [18] found statistically significantly higher odd ratios for asthma (2.4), allergies (3.5), hypertension (6.9), and hypothyroidism (8.4) in chronic migraine. Allergies and hypothyroidism as increased comorbidities in chronic migraine were *not* confirmed by Ferrari et al. [19] and neither was hypothyroidism by Spierings and Padamsee [16]. Ferrari et al. [19] confirmed hypertension and added insomnia and constipation as well as psychiatric, gastrointestinal, musculoskeletal, ocular, genitourinary, hematologic, cerebrovascular, and cardiac disorders. They did not describe any of these disorders in detail but common conditions seen with chronic migraine, apart from insomnia, constipation, and dysmenorrhea are, in random order: anxiety, depression, Post-traumatic stress disorder (PTSD), fatigue, myalgias of various sorts, including myofascial Temporomandibular disorder (TMD), cervicalgia, and lumbago, fibromyalgia, gastritis, acid reflux (GERD), chronic nausea, Irritable bowel syndrome (IBS), and menstrual-cycle disorders.

Sancisi et al. [20] specifically looked at insomnia in 105 CDH patients of whom 54 had (probable) chronic migraine and 41 chronic tension-type headaches, with or without medication overuse. They compared them with 102 age- and gender-matched episodic headache patients, not further specified. Insomnia was statistically significantly more common in the CDH patients than in those with episodic headache: 67.6% *versus* 39.2% (p<0.0001). Along with insomnia, snoring/sleep apnea and daytime sleepiness were also statistically significantly more common: 48.6% *versus* 37.2% (p = 0.01) and 36.2% *versus* 23.5% (p = 0.04), respectively. Interestingly, they found a family history of episodic headache to be equally common in the two groups (approximately two thirds) but a family history of chronic headache was almost three times more common in the CDH patients (38.1% *versus* 13.7%; p = 0.001) [21].

Regarding the musculoskeletal disorders, neck pain was specifically studied by Florencio et al. [22], who compared 65 patients with chronic migraine with 104 patients with episodic migraine. They found 63% of the chronic migraine patients to have neck pain as opposed to 36% of those with episodic migraine, a statistically significant difference although the p-value was not mentioned. They also reported an increased prevalence of difficulty sleeping in the chronic migraine patients *versus* those with episodic migraine (69% *versus* 44%; p<0.001), confirming the above observations. In terms of pain in the neck and shoulder muscles Landgrafet al. [23] compared two groups of adolescents with episodic migraine, that is, with headaches less than once per week (n = 99) and headaches weekly (n = 195), with those with chronic migraine (n = 66). They also included a control group without headache in their study (n = 241) and found

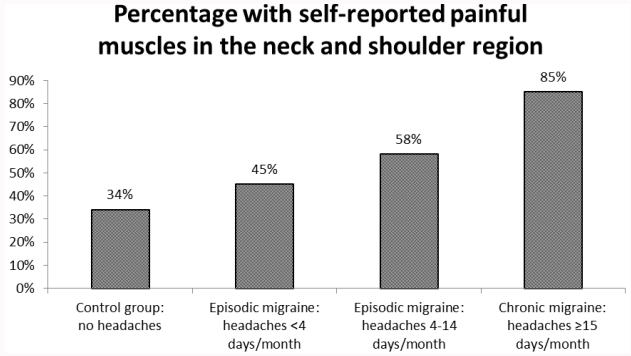

Figure 10: Percentage of adolescents with self-reported pain in the neck and shoulder muscles, comparing those with low- and high-frequency episodic migraine with those without headaches (control group) and those with chronic migraine (test for trends: p<0.0001) [23].

the prevalence of muscular pain to increase from 33.6% in the control group, 45.4% in the less-than-once-per-week group, to 58.5% in the weekly group, and to 84.5% in the adolescents with chronic migraine (test for trends: p<0.0001) (Figure 10). A comprehensive review of the psychiatric comorbidities of chronic *versus* episodic migraine was provided by Buse et al. [24]. They looked at depression, anxiety disorders, Post- traumatic stress disorder (PTSD), and substance abuse. They found moderate-to-severe depression and a medical diagnosis of depression almost twice as common in chronic than in episodic migraine. The same was true for moderate-to-severe anxiety and a medical diagnosis of anxiety was almost 1½ times as common in chronic migraine than in episodic migraine. The situation is less clear for PTSD and there is no evidence to suggest that substance abuse is more often associated with chronic migraine than it is with episodic migraine. In migraine in general, substance abuse may be twice as common as in the general population, an association that was lost, however, after adjusting for depression and PTSD.

The American Migraine Prevalence and Prevention (AMPP) study showed that episodic migraineurs in 43.7% have nausea with their headaches more than half of the time [25]. They found this to be statistically significantly more often in women than in men and correlated, among others, with greater headache-related disability. They also observed that these migraineurs were twice as likely to progress to chronic migraine, than those with headache-related nausea less than half of the time. The study also looked at abortive medication use, efficacy of abortive treatment, and the risk of progression to chronic migraine [26]. They found almost half of the migraineurs to rely on simple analgesics or NSAIDs for the abortive treatment of their headaches, approximately one-third on combination analgesics, a little over 20% on triptans, and a little less than 20% on opioids or barbiturate-containing analgesics. With regard to triptan use, this is an amazingly low penetration of this class of specific abortive migraine medications that has been on the market for more than 25 years. It is an effective class of medications that, also according to the study, makes its users more likely to be in the favorable treatment efficacy categories. Which treatment efficacy category one is in as a migraineurs also determines the likelihood of progression to chronic migraine, which is 1.9% for the maximum treatment efficacy category, 2.7% for the moderate efficacy category, 4.4% for the poor category, and 6.8% for the very poor category.

Of the comorbidities mentioned above, hypertension was looked at from a mechanistic perspective [27] and also a factor not

mentioned yet, that is, obesity [28]. In general, hypertension *perse* is not a cause of headache but a relatively sudden increase in arterial blood pressure, a so-called hypertensive crisis, certainly is [29]. There is little doubt, however, that hypertension in the presence of a headache condition, be it episodic or chronic, tends to make the headache condition worse and should be addressed in its overall management. The mechanistic view expressed assumes that repeated migraine attacks result in inflammatory arteriopathy of the cranial blood vessels, which supposedly is aggravated by hypertension [27]. However, although migraine probably involves an inflammatory vascular component in the generation of the headache (*vide infra*), there is no evidence that this particular mechanism is aggravated by hypertension.

Regarding obesity, which in and by itself is not associated with headache either, including migraine, the proposed mechanistic relation, interestingly, focuses on obesity as a pro-inflammatory state [28]. Obesity is apparently associated with increased plasma levels of calcitonin gene-related peptide (CGRP) and decreased levels of orexin A [29]. Orexin A is a peptide involved in the modulation of appetite and energy homeostasis and in animal experiments has been shown to inhibit the mechanism of neurogenic inflammation, which has been implicated in migraine to cause perivascular inflammation [30]. Of the two epidemiological studies that looked at obesity and migraine, one showed a correlation between body mass index (BMI) and the proportion of subjects with *episodic* migraine with >10 headache days per month: BMI <25, 4.6%; BMI 25-30, 5.8%; BMI 30-35, 13.6%; and BMI ≥ 35, 20.7% [31]. The other study showed that among the migraineurs with daily headaches, that is, those with CDH, the ones with a BMI ≥ 35 were overrepresented in comparison to those with BMIs between 25 and 35 but not in comparison to those with BMIs <25 [32]. Presented differently, of the chronic migraine subjects in the study, 49% had a BMI <25, 22% between 25 and 30, and 29% ≥ 35; hence, no evidence that CDH is associated with obesity.

Regarding hypothyroidism, although not generally recognized, the condition can be associated with headache, which improves with levothyroxine treatment. In a prospective study of 102 patients with *de novo* hypothyroidism, 31 or 30.3% had a recent history of headache [33]. In comparison, cold intolerance, dry skin, and delayed ankle-reflex relaxation were present in 30.4% of the patients, bradycardia in 28.4%, brittle hair in 24.5%, and loss of eyebrow hair in 20.6%. The headache was bilateral in 80%, non-pulsatile in 90%, non-paroxysmal in 95%, and mild in 89%, suggesting the presentation to be mostly that of chronic tension-type headache, like chronic migraine a subcategory of CDH. The patients were treated with levothyroxine 100 mcg per day and the headaches improved around the 15th day of treatment in 18 of the 31 (58.1%) and had disappeared in 13 during a 12-month follow-up (41.9%).

Multisystem disorder

The patient with multisystem complaints, like the one with chronic migraine tends to be, is a medical enigma. In psychiatry, there is a nosological entity known as somatization disorder, which entered the Diagnostic and Statistical Manual of Mental Disorders in its 3rd edition in 1980 [34] and exited in its 5th edition in 2013 [35]. Briefly, it is defined as a polysymptomatic disorder that begins before the age of 30 years, extends over a period of years, and is characterized by a combination of pain, gastrointestinal, sexual, and pseudo-neurological symptoms. Under its diagnostic criteria, it is added that the numerous physical complaints result in treatment being sought or in significant impairment in social, occupational, or other important areas of functioning.

In the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders, a totally different approach is taken [35]. Now, more than 3 decades later, it is no longer considered appropriate to give an individual a diagnosis of a mental disorder, solely because he or she has complaints for which a medical cause cannot be established. It is stated that the previous criteria, those for somatization disorder, overemphasized the centrality of medically unexplained symptoms and that a diagnosis of somatic symptom disorder, the term that replaced somatization disorder, can also accompany diagnosed medical disorders. Hence, somatic symptom disorder is a secondary diagnosis that can be made, if there are:

1. One or more somatic symptoms that are distressing or result in significant disruption of daily life;

2. Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns; and

3. Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically more than 6 months).

Apart from being ascribed to a somatization disorder, the comorbidities as seen, amongst others, with chronic migraine have also been described as central sensitization syndromes [36]. These syndromes have been attributed to "central sensitization" and, hence, in this context are given a neurological rather than psychiatric explanation. The idea behind central sensitization is that there is activation of nociceptive C- and Aδ-fibers in peripheral tissues, causing a barrage of impulses entering the central nervous system. In the central nervous system, they activate second-order neurons to the extent that hyperexcitability develops, involving nociceptive as well as non-nociceptive neurons. As second-order neurons are also subject to descending facilitatory and inhibitory influences, these modulatory systems may also partake in the pathogenesis of the syndromes. The theory mostly derives its support from Neuro-physiological studies of a sensory nature, suggesting hypersensitivity to electrical, thermal, or mechanical stimuli. With psychiatry having abandoned somatization disorder and medicine looking to explain the comorbidities neurologically, the author, a neurologist, would like to move the pendulum back to medicine and suggest a systemic endocrine-metabolic disorder. The metabolic aspect of this disorder centers around energy metabolism, accounting for the fatigue, that is, lack of metabolic energy, as an almost ubiquitously present symptom among the comorbidities. Metabolic energy is essential for the functioning of all organs in the body and a disturbance in this system could easily explain a multisystem disorder. However, the picture does not tend to be complete without implicating the endocrine system, particularly the female reproductive system. Of course, part of the endocrine system, the thyroid system, also plays an important role in energy metabolism and a two-way interaction may well exist.

Migraine is considered to belong to the central sensitivity syndromes [36] but it is the author's opinion that it is not and that, instead, it is more like a headache amplifier, genetically determined and familial in nature [8]. A patient affected by the multisystem comorbidity disorder becomes a chronic migraine sufferer if he or she also harbors the constellation of genes that transfers the vulnerability to migraine.

The above reasoning potentially takes us away from thinking of migraine as a disease, neurological or otherwise. Instead, it takes us in the direction of thinking of migraine as a headache amplifier, genetically determined and familiar in nature. To a great extent, migraineurs get headaches from the same triggers as non-migraineurs [37], the difference being the intensity and, consequently, the duration and associated symptoms of the headaches. In a minority, the brain gets involved as well, maybe in a parallel rather than sequential manner in relation to the headache [38,39], generating the transient focal neurological symptoms that we have come to know as migraine aura symptoms. It would also redirect our attention to the mechanisms involved in the migraine headache if we wish to understand its true origin. Neurogenic inflammation has been suggested as one of the mechanisms involved and may well harbor the secret of migraine [30]. It is postulated that the migraine headache amplifier as hypothesized lies in the threshold with which the mechanism of neurogenic inflammation is activated. There is room for this to be a dimmer switch rather than an on-off switch to account for the great variety in migraine expression or phenotype. The demonstrated benefit of the anti-CGRP(-receptor) antibodies is certainly in line with this thinking as 1) CGRP or calcitonin gene-related peptide plays a pivotal role in neurogenic inflammation [40] and 2) the antibodies have preliminary evidence of efficacy in episodic as well as chronic migraine [41-46].

Treatment responsiveness of episodic *versus* chronic migraine has not been studied well but there is evidence from clinical trials that topiramate is effective as preventive treatment in both [47-50], while botulinum toxin is only effective as preventive treatment in chronic migraine [51,52]. In regard to the latter, the FDA labeling for Botox® (Allergan, Parsippany, New Jersey), the best known and most widely used botulinum toxin formulation, states: "BOTOX® (onabotulinumtoxinA) is a prescription medicine that is injected to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day in people 18 years or older. It is not known whether BOTOX® is safe or effective to prevent headaches in patients with migraine who have 14 or fewer headache days each month (episodic migraine)".

Regarding the differential benefit of botulinum toxin in chronic *versus* episodic migraine, the lack of benefit in the latter suggests that the medication does not have its mode of action specifically related to the migraine headache mechanism. A long-acting muscle relaxant, it acts on the craniocervical hypertonia where the injections are placed. Along with the genetically determined and inherited headache amplifier, the craniocervical hypertonia causes persistent migraine headaches or, in other words, chronic migraine, a major subcategory of CDH.

Epilogue

The subcategory of CDH referred to as chronic migraine has been much more extensively studied than the one referred to as chronic tension(-type) headache. Hence, it is known for chronic migraine that the condition is much more likely to be associated with a variety of comorbidities than its episodic counterpart, episodic migraine. These comorbidities have been looked at from the perspective of migraine chronification, that is, the progression from episodic to chronic migraine. Associations with headache frequency have been established, particularly for pain in the neck and shoulder muscles [23] and headache-related nausea [26]. However, associations do not necessarily imply causation although in the author's opinion, the association with pain in the neck and shoulder muscles is causative. The pain relates to the craniocervical hypertonia mentioned above, the target of botulinum toxin's beneficial effect in chronic migraine. The author sees the medical and psychiatric comorbidities of chronic migraine, including the craniocervical hypertonia, as the consequences of a systemic endocrine-metabolic disorder. It is this disorder that accounts for the high frequency of the headaches in chronic migraine in which the intensity of the headaches is accounted for by a genetic and inherited headache amplifier.

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