Curr Pain Headache Rep (2013) 17:313
DOI 10.1007/s11916-012-0313-8

The Psychiatric Comorbidities of Cluster Headache

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Published online: 8 January 2013

Abstract Although the comorbidity of migraine has been extensively studied, the relationships between cluster headache and psychiatric disease have not been well-addressed. In this review the available literature concerning cluster headache and depression, anxiety, bipolar disorder, aggression, suicide, and their implications are discussed. Potential mechanisms, confounding variables, and unanswered questions are also addressed.

Keywords Cluster headache · Episodic · Chronic · Psychiatric · Comorbidity · Depression · Anxiety · Bipolar · Aggression · Suicide

Introduction

Primary headache disorders are increasingly conceptualized as chronic disorders with episodic manifestations [1]. This paradigm supports the growing notion that headache disorders are not just recurrent episodes of acute head pain with associated features, but are chronic, dynamic conditions that may progress, remit, and have structural and neuroradiographic markers of such change [2]. In line with the approach of headache disorders as chronic neurobiologic disease states, associated neuropsychiatric conditions are not unexpected.

Comorbidity is defined as the presence of separate illnesses in the same patient, greater than their co-occurrence by chance alone [3]. Comorbidity may occur because of different mechanisms: (1) one disorder unidirectionally incites the second disorder; (2) shared genetic risk factors lead to the development of both disorders; and (3) shared environmental risk factors lead to the development of both disorders [1].

Identifying psychiatric comorbidity in headache disorders is important to help identify neurobiologic similarities to gain greater insights into the genetics and pathophysiology of the index disorder. Clinically, comorbid psychiatric conditions often confer both difficulties and opportunities in the treatment of headache disorders. Treating psychiatric comorbidity in headache disorders may be important as the comorbid conditions may have bidirectional relationships that significantly contribute to the cumulative disease burden [4]. In addition, psychiatric comorbidity in some primary headache disorders, particularly migraine, may be risk factors for its transformation from its episodic to its chronic subform [5].

Unlike migraine, where psychiatric comorbidity has been extensively studied, the psychiatric comorbidity of cluster headache (CH), the most common of the trigeminal autonomic cephalalgias (TACs) has not been well-addressed, and its impact on CH course and chronicity is unclear. In this review I address the available evidence which centers on comorbid depression and anxiety, and contrast these rates to other primary headache disorders. I also review other psychiatric aspects including aggression and suicidality. Personality characteristics in CH have been extensively reviewed separately in this journal [6, 7]. Finally, I discuss potential pathogenetic mechanisms of comorbidity and discuss unanswered questions that remain.

Depression and Anxiety

Most studies addressing psychiatric comorbidity in CH have focused on depression and anxiety, likely because of their commonality and presumed role in the chronification of

This article is part of the Topical Collection on *Trigeminal Autonomic Cephalalgias*

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migraine [8–10]. Table 1 summarizes the methodologies and rates of depression and anxiety from various CH studies, most of which derive from single tertiary centers. Rates of depression and anxiety in these CH samples vary widely, likely related to different screening tools and ascertainment methodologies that evaluate for cross-sectional, 1-year, or lifetime prevalence.

Review of the Evidence

Jorge et al. conducted one of the first studies to evaluate for psychiatric comorbidity in CH in a single center, case–control study [11]. A group of 21 CH patients undertook semi-structured interviews and using DSM-IV criteria, they were diagnosed with having depression or an anxiety disorder in the previous year. The severity of these disorders was quantified using the standardized Hamilton Depression Rating Scale (HDRS) and the Hamilton Anxiety Rating Scale (HARS), and 21 tension-type headache (TTH) patients were used as controls, matched for age, sex, and educational level. None of the CH patients were diagnosed with a mood disorder, but 23.8 % fulfilled DSM-IV criteria for an anxiety disorder (14.3 % generalized anxiety disorder, 9.5 % panic disorder), and those rates where significantly higher than the anxiety disorder rates of the TTH controls. HDRS scores were the same between CH and TTH patients, but CH patients had significantly higher HARS scores than the TTH controls.

In the same year, Mitsikostas and Thomas published data from their center in Greece on a variety of primary headache disorder patients including 14 who had CH, and also applied the HDRS and HARS [12]. Overall 7 % of CH patients were depressed. On average, CH patients had lower HDRS and HARS scores than all other headache disorders, but higher scores than headache-free controls.

Robbins has presented data regarding the lifetime psychiatric comorbidity of 275 CH patients evaluated in his clinical practice, gleaned from direct patient interviews and

Table 1 Summary of studies evaluating depression and anxiety in cluster headache samples

Reference	Year	Population	Sample type	Sample size	Instrument	Results	
						depression rate	Anxiety rate
Cross-sectional prevalence studies							
Ertsey et al. [16]	2004	Hungary	Single tertiary center	ECH=35	Medical record review	8.6 % (“mild”)	NS
Gesztelyi G et al. [14]	2005	Hungary	Single tertiary center	CH=11	BDI	Only median BDI score reported	NS
Donnet A et al. [17]	2007	France	8 tertiary centers	CCH=107	HAD	43.0 %	75.7 %
Jelinski SE et al. [20•]	2007	Canada	5 tertiary centers	CH=19	BDI-II	21.1 %	NS
Robbins MS et al. [26•]	2012	United States	Single tertiary center	ECH=32	PHQ-9	6.3 % ECH	15.6 % ECH
				CCH=17	GAD-7	11.8.% CCH	11.8 % CCH
1-year prevalence studies							
Jorge R et al. [11]	1999	Argentina	Single tertiary center	ECH=21	HDRS HARS	0.0 %	23.8 %
Mitsikostas DD et al. [12]	1999	Greece	Single tertiary center	ECH=10 CCH=4	HDRS HARS	0.0 % ECH 25.0 % CCH	NS
Lifetime prevalence studies							
Robbins L [13][a]	2004	United States	Single tertiary center	CH=275	“Guidelines of DSM-IV” (combination of chart review and interviews)	29 %	24 %
Jürgens TP et al. [22•]	2010	Germany	3 tertiary centers	ECH=48	Mini-DIPS	31 % ECH	19 % ECH
				CCH=27		56 % CCH	22 % CCH
Zidverc-Trajkovic JJ et al. [25]	2011	Serbia	Single tertiary center	CH=130	Medical record review	4.6 % depression and anxiety	
Rozen TD et al. [30•]	2012	United States	Internet survey	CH=1134	Self-report	24 %	NS

Table adapted and expanded from Robbins MS et al., 2012 [26•]

[a] Preliminary report only

BDI Beck Depression Inventory; *CCH* chronic cluster headache; *CES-D* Center for Epidemiological Studies Depression Scale; *CH* cluster headache; *ECH* episodic cluster headache; *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders; *GAD-7* Generalized Anxiety Disorder 7-item scale; *HAD* Hospital Anxiety and Depression Scale; *HARS* Hamilton Anxiety Rating Scale; *HDRS* Hamilton Depression Rating Scale; *Mini-DIPS* Diagnostisches Kurz-Interview bei Psychischen Störungen; *NS* not studied; *PHQ-9* Patient Health Questionnaire

chart reviews, with diagnoses made using DSM-IV guidelines [13]. Although this data has only been presented in preliminary form, strengths include its large sample size as well as a relatively high representation of women (38.2 %) compared with other CH samples. The lifetime depression rate (unipolar or bipolar) was 24 % and the anxiety rate was 29 %. Compared with men, women had higher rates of depression (32 % vs 18 %) and anxiety (34 % vs 25 %).

A pair of smaller studies examined rates of depression in different tertiary care centers in Hungary. In a study examining disability and depression in low back pain and primary headache disorders, 11 CH patients were included [14]. The Beck Depression Inventory (BDI) scale was used [15], and CH patients had overall low scores (median=5, 25 %–75 % range: 4–8). Overall rates of depression based on a standard BDI cut score were not reported. In another study examining quality of life in a sample of 35 ECH patients, 8.6 % self-reported a history of mild depression [16].

Donnet and colleagues addressed some aspects of psychiatric comorbidity in the context of a large, descriptive study of 113 chronic CH (CCH) patients across 8 tertiary care centers in France [17]. Of the cohort, 107 CCH patients completed the Hospital Anxiety and Depression scale (HAD) which ascertains for active depression and anxiety using a 14 item questionnaire [18]. Using validated cut scores of ≥8 [19] for both depression (HAD-Dep) and anxiety (HAD-Anx), 43.0 % of CCH patients had depression and 75.7 % had anxiety.

Another study addressed the lifetime depression rate among 19 CH patients across 5 headache centers in Canada [20•] using the updated version of the BDI (BDI-II) [21] after the publication of the DSM-IV. Using standardized cut scores, CH patients either had none/minimal (57.9 %), mild (21.1 %), moderate (5.3 %), or severe (15.8 %) depression. Using the BDI-II cut score of ≥20, 21.1 % of this small CH sample had active depression. If a more generous BDI-II cut score of ≥14 was used as a screen, 42.1 % would be considered to have at least mild depression.

In a large, well-designed, prospective study of 75 CH patients evaluated at 3 tertiary centers in Germany, Jürgens et al. screened for the lifetime presence of depression and anxiety disorders [22•]. Major strengths of this study included the first comparison of episodic CH (ECH) and CCH patients and CH patients both within (ECHa) and without (ECHi) active cluster attack periods. The screening tool applied derived from elements of the German version of the mini-DIPS, which is a validated clinical interview technique with structured questions. CCH patients had higher rates of most depressive and anxiety disorders than ECHa and ECHi, particularly for depression (56 % vs 27 % vs 36 %) and agoraphobia (33 % vs 15 % vs 5 %), although only descriptive statistics without comparisons for significance were reported. Rates of generalized anxiety disorder were 19 % for CCH, 8 % for ECHa, and 18 % for ECHi.

As a part of an advanced neuroimaging study of a cohort of 13 ECH patients at a German tertiary center, Seifert et al. used the German version of the Center for Epidemiological Studies Depression Scale (CES-D) to screen for active depression [23•]. Using the standardized CES-D cut score of ≥16 [24], 76.9 % had clinically meaningful depressive symptoms. In a larger study from a single headache center in Serbia published in the same year, Zidverc-Trajkovic and colleagues evaluated headache comorbidity in over 1000 primary headache disorder patients, including 130 patients with CH over a 7 year period [25]. Using medical record review, 4.6 % of CH patients had depression and anxiety disorders taken together.

Our center has recently undertaken a small study that has examined more closely depression and anxiety in 32 ECH and 17 CCH patients [26•]. We assessed for the presence of active depression using the Patient Health Questionnaire (PHQ-9) [27] and active depression using the Generalized Anxiety Disorder 7-item scale (GAD-7) [28]. Depression rates were fairly low in both ECH (6.3 %) and CCH (11.8 %), and the groups had similar mean PHQ-9 scores (3.1 vs 3.7, P=0.69). Anxiety rates in ECH were 15.6 % and in CCH were 11.8 %, with similar mean GAD-7 scores (3.8 vs 3.4, P=0.76). ECHa and ECHi patients had similar rates of depression and anxiety. Depression and anxiety commonly coexisted in both ECH (P=0.67) and CCH (P=0.97).

Also in this study, depressed and non-depressed, and anxious and non-anxious CH patients were directly compared. Depressed or anxious CH patients were more likely to present to care at a younger age and have attack-related nausea and prodromal symptoms [29]. Depressed CH patients were more likely to have a coexisting pain disorder and had undertaken twice as many prophylactic medication trials. However, depressed or anxious CH patients were similar to CH patients free of depression or anxiety in their proportions of CCH, substance abuse, and sociodemographic variables, including gender ratios, onset age, race, marital status, and education level.

Finally, Rozen and Fishman have provided the first large scale, internet survey-based study regarding CH across a national sample in the United States [30•]. The United States Cluster Headache Survey captured 1134 CH subjects from across the country, the largest sample size of any CH population presented in the literature. A history of self-reported depression was found in 24 % of the subjects. A subsequent analysis examined in detail gender differences in this CH sample, finding a higher rate of self-reported depression in female vs male CH subjects (31 % vs 21 %, P=0.0005) [31].

Overall, depression rates in CH patients range from 6.3 % to 43.0 % in cross-sectional studies and 4.6 % to 56.6 % in lifetime studies. Anxiety rates range from 11.8 % to 75.7 %

in cross-sectional studies and 4.6 % to 24 % in lifetime studies. The heterogeneity of the study samples and comorbidity screening techniques render drawing conclusions from these crude rates difficult.

Comparison to Other Primary Headache Disorders

Table 2 demonstrates rates of depression and anxiety of CH in comparison with other primary headache disorders from the various studies where they were directly contrasted. Migraine was the active headache disorder used most often as a comparator. Conflicting results were obtained, with rates of depression or anxiety in CH both higher and lower than migraine. In studies that stratified migraine to episodic migraine and chronic (or transformed) migraine [20•, 26•], depression and anxiety rates of CH were clearly lower than chronic migraine. In the studies where TTH was a comparator, CH had lower rates of depression [11, 12, 20•] but variable rates of anxiety [11, 12]. Drawing definitive conclusions from the available data is difficult because of the small studies and different methodologies, so there is no clear answer in terms of ranking these primary headache disorders in rates of psychiatric comorbidity.

Interestingly, Gestelgyi et al. [14] found that in primary headache disorders, compared with low back pain, the overall disability incurred by the pain disorder was the most important factor in the generation of depressive symptomatology. In low back pain, pain intensity followed by pain frequency was the most significant factors in driving depressive symptoms. In this prospective study where multivariate analysis was applied, only 11 CH patients were enrolled, so drawing definitive conclusions from this small subgroup of headache disorders is difficult. However, the study is insightful in that patients with CH, whose attacks are commonly accepted as more painful than migraine attacks, do not consistently feature higher rates of depression than migraine, which indirectly supports the observation that pain intensity may not be a major factor in driving depression in headache disorders. It is not clear if CH patients have more or less disability than migraine patients; studies also comparing their disability rates have yielded conflicting results [14, 16, 22•, 32–34].

Bipolar Disorder

The rate of bipolar disorder in CH patients is largely unknown, as most studies addressing psychiatric comorbidity have screened for unipolar depressive symptomatology rather than bipolar disorder. A link between the 2 disorders is plausible, as both have a periodiocity that may be generated by the hypothalamus, possess relationships with sleep, share

Table 2 Rates of depression and anxiety in cluster headache samples compared with other primary headache disorders

Reference	Disorder	Depression rate	Anxiety rate
Jorge RE et al. [11]	ECH	0.0 %	23.8 %
	ETTH	14.3 %	4.8 %
Mitsikostas DD et al. [12]	ECH	0 %	NS
	CCH	25 %	
	Migraine	5 %	
	TTH	2 %	
	"Mixed headache"	9 %	
Ertsey C et al. [16]	ECH	8.6 %	NS
	Migraine	26.4 %	
Jelinski SE et al. [20•]	CH	21.1 %	NS
	Migraine	17.1 %	
	Transformed migraine	36.1 %	
	TTH	28.3 %	
	NDPH	27.8 %	
Jürgens TP et al. [22•]	ECH	27 %–36 %	8 %–18 %
	CCH	56 %	19 %
	Migraine	29 %	17 %
Zidverc-Trajkovic JJ et al. [25]	CH	4.6 %	Depression and anxiety
	Migraine	5.1 %	
Robbins MS et al. [26•]	ECH	6.3 %	15.6 %
	CCH	11.8 %	11.8 %
	Episodic migraine	17.2%[a]	23.9%[b]
	Chronic migraine	30.2%[a]	NS

CCH chronic cluster headache; *CH* cluster headache; *ECH* episodic cluster headache; *ETTH* episodic tension-type headache; *NDPH* new daily-persistent headache; *NS* not studied

[a]Previously reported migraine controls in the population using the same methodology [56]

[b]Previously reported migraine controls from a single center setting using the same methodology [57]

neuroendocrine derangements, and even respond to effective specific therapies such as lithium [35].

Only 1 study has evaluated systematically for the presence of the bipolar spectrum of disorders in CH, a single center study undertaken by Robbins where the lifetime prevalence was assessed by chart review, a mood disorder questionnaire, the PHQ-9, and direct patient interviews [36]. In 287 total CH patients, the rates of bipolar disorder were 6.6 % overall, 6.4 % in ECH, and 6.8 % in CCH. Lifetime bipolar disorder rates in migraine were 8.6 % and CTTH were 4.5 %. Clearly, rates of bipolar disorder in CH and other headache disorders have been underestimated. The importance of making the diagnosis may impact headache care significantly, as mood stabilizers may be underutilized, which is unfortunate considering that many agents may improve both headache and bipolar disorder concurrently.

Aggression

Aggression is commonly seen in CH patients ictally; in fact, a sense of restlessness or agitation is one of the cardinal features of the CH attack, as defined by the second edition of the International Classification of Headache Disorders (ICHD-2) [37]. Upwards of 90 % of patients develop such behavior during attacks, which may include not just restlessness but a variety of complex, even violent, self-injurious behaviors [38]. Such restlessness may even be a sensitive and specific element to predict CH as the headache disorder diagnosis. Functional imaging has pinpointed the importance of the posterior hypothalamus in CH attacks, and it has also become a therapeutic target of deep brain stimulation [39]. As Luerding et al. reviewed, posterior hypothalamic involvement has been implicated in the formation of aggressive behavior outside of CH patients, and neurostimulation of this region anecdotally has ameliorated this behavior [40].

Luerding et al. formally evaluated aggression prospectively in a cohort of 27 CCH, 26 ECHa, 22 ECHi, and 24 migraine patients, as well as 31 headache-free volunteers, using a validated questionnaire [40]. CCH and ECHa patients largely had higher self-aggression/depression scores than other groups, but this difference did not reach significance when corrected for the use of multiple variables. In these patients, self-aggression/depression scores correlated strongly with depression symptoms and impairment overall. A strong positive correlation between aggression and CH was not observed, although like all CH studies, ictal derangements were not assessed with the inherent difficulty of CH patients completing questionnaires in an extreme state of pain. In addition, the questionnaire did not ascertain for outward manifestations of physical aggression, so unanswered questions remain.

Suicidality

Although CH often carries the nickname of "suicide headache," actual reports of suicide in CH patients are rare and have not been well-evaluated until recently [6]. In Rozen's large survey, 55 % of CH respondents admitted to suicidal thoughts over their lifetime, and 2 % of respondents admitted to actual suicide attempts [30•]. There were no significant differences between male and female subjects [31].

In the study regarding impairment in CH by Jürgens et al., thoughts about death and suicidal tendencies were observed in 22 % of CCH patients, followed by 15 % of ECHa patients, 14 % of ECHi patients, 4 % of migraine patients, and 3 % of non-headache controls [22•]. Robbins et al. found low rates of active suicidal ideation in their small sample: 6.3 % in ECH and 5.9 % in CCH patients.

Mechanisms

The underlying mechanisms and pathophysiology underlying the psychiatric comorbidity of CH are unknown. It is clear that CH is not just a trigeminal or neurovascular disorder in isolation but a CNS disorder that involves structures in the brainstem and the hypothalamus, which are also implicated in depression and anxiety. Seifert and colleagues studied 13 ECH patients who underwent FDG-PET scanning [23•]. Depression scores correlated with changes in glucose metabolism in the insular cortex, and pain disability scores correlated with metabolic changes in the amygdala, both of which are implicated in the pathogenesis of depressive and anxiety disorders. Interestingly, there was no covariation of depression scores with metabolic changes in the prefrontal cortex, a structure thought to be pivotal in major depression.

It seems clear from both laboratory studies and dramatic pharmacologic responsiveness that serotonergic dysfunction is important in the pathophysiology of CH [41]. Leone and colleagues administered the central serotonergic agonist m-chlorophenylpiperazine to a series of 23 ECH patients in an active attack period but not taking prophylaxis in comparison with matched controls [42]. The ECH patients had reduced serum cortisol and increased prolactin levels in comparison with controls, which suggests impaired CNS serotonergic functioning. Aggression and self-injurious behavior, as prominently featured during CH attacks, may be also associated with decreased serotonergic tone. In addition, 5-HT_7 receptors play an important role in the hypothalamus in the generation of circadian rhythms, and may be a plausible pharmacological target for CH treatment [41]. Interestingly, 5-HT_7 receptor antagonists may also become an emerging class of rapidly acting antidepressant medications [43].

The production of inflammatory cytokines may represent another mechanism underlying the association of headache disorders and psychiatric comorbidity, which includes bipolar disorder [44]. Studies have demonstrated both elevated IL-2 gene expression [45] and soluble receptor levels [46], and IL-1β serum levels [47] during active CH attack periods. Inflammatory cytokines have been implicated in the pathogenesis of depression [48] and bipolar disorder [44], although the association is less clear for anxiety disorders [49]. A sizeable minority of patients with major depression possesses elevated inflammatory markers including multiple cytokines, inflammatory disorders are associated with higher rates of major depression, and cytokine therapy is associated with a high risk of developing subsequent depression [48]. Supportive of the possible sequence of CH occurring prior to depression onset [50] inflammatory cytokine release during repetitive CH attacks may contribute to the genesis of depression.

Confounders and Unanswered Questions

The limited data available are also confounded by a number of variables that may play important roles in coexisting psychiatric disease in CH patients, which may include high rates of substance abuse, past head trauma [51], sleep disturbances [52], and even coexisting migraine [53]. Importantly, an emerging body of evidence suggests that a history of childhood abuse is a risk factor for the later development of migraine [54]. In CH this association remains entirely unexplored. The presence of prophylactic medications and frequent corticosteroid use in this population may also confound ascertainment of the pure association between CH and psychiatric disease.

Another aspect crucial to understanding these relationships is to fully elucidate whether or not the comorbidity is truly confined to CH attack periods. CH patients who have depression or anxiety may be more likely to have attack period related premonitory symptoms [26•, 29] which can have overlapping features with depression and anxiety disorders. Rates of comorbidity of ECH patients in and out of attack periods have only been studied cross-sectionally, with mixed results [22•, 26•]. Longitudinal, prospective studies of CH patients would be ideal to address this important question.

The temporal course of psychiatric comorbidity in CH also remains unclear from published studies, and it is uncertain if the relationship is unidirectional or bidirectional. In their well-executed population study, Breslau and colleagues have demonstrated that the relationship between major depression and migraine is bidirectional, where depression predicts new onset migraine and migraine predicts incident major depression [50]. However, for non-migraine severe headache disorders, only a unidirectional relationship was found, where non-migraine headache predicted new onset depression but depression did not predict incident non-migraine headache. This finding suggests that the mechanism of psychiatric comorbidity in non-migraine headache disorders such as CH may be different, and that CH may be causal in the generation of major depression.

Finally, an important methodological aspect relates to the best screening tool for depression and anxiety to use in CH patients and perhaps patients with headache in general. The PHQ-9 and GAD-7 scales have been suggested by expert opinion [55], and were used in 1 CH study [26•]. They have also been used in large headache epidemiology studies which provide a source for comparison with subjects in the general population who have both episodic and chronic migraine [56]. However, these scales have not been validated in headache populations.

Conclusion

Cluster headache comorbidity has not been well-studied until recently. Available data is mostly derived from single center studies addressing depression and anxiety using variable methodologies, producing a wide range of rates of coexisting psychiatric disease in both ECH in and out of attack periods and CCH. Prospective, longitudinal studies of patients both in and out of their attack periods would be very helpful in addressing unanswered questions that should lead to greater understanding of CH and may impact management of this debilitating disorder.

Disclosure No potential conflict of interest relevant to this article was reported.

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