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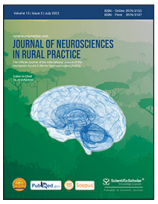

Original Article

Fatigue, chronic fatigue syndrome and migraine: Intersecting the lines through a cross-sectional study in patients with episodic and chronic migraine

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ABSTRACT

Objectives: Fatigue is a common symptom occurring in a variety of disorders. Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue as the core symptom. The risk of CFS is nearly 1.5 times higher in migraine while headaches have been reported in 59% of cases with CFS. However, details of its occurrence and severity remain largely unexplored. The primary objective of our study was to determine the occurrence and severity of fatigue and CFS in patients with episodic and chronic migraine. The secondary objectives were to define their relationship with other common comorbidities.

Materials and Methods: 60 migraine patients (30 each, episodic [EM] and chronic migraine [CM]) were recruited from Neurology Outpatient Department, GIPMER a tertiary referral center in New Delhi, India. Patients' headache severity was analyzed using the Headache impact test-6 (HIT-6) score while fatigue and other migraine accompaniments were assessed using Fatigue severity scale (FSS), Chalder fatigue scale, CDC diagnostic criteria for CFS, American College of Rheumatology Diagnostic Criteria for fibromyalgia, Hamilton Depression Scale, the Generalized Anxiety Disorder 7-Item Scale, and Epworth sleepiness Scale (ESS). Comparative analysis was further done among migraine patients with and without fatigue and CFS.

Results: The mean HIT-6 score was significantly higher in CM versus EM. The CM group had a higher mean FSS score (47.87 vs. 37.3 in EM; $P = 0.004$), a percentage of patients with severe fatigue (60% vs. 20% in EM; $P = 0.004$), and a higher percentage of patients with pathological fatigue (83.3% vs. 63.3% in EM; $P = 0.04$). Around 23.33% of CM patients fulfilled the criteria of CFS. Fatigue correlated positively with severity, frequency, attack duration and chronicity of the migraine episodes, along with depression, anxiety, and excessive daytime sleepiness.

Conclusion: Fatigue and related comorbid disorders are significantly more common in CM than in EM, expanding the morbidity of the condition and underscores the need to address these accompanying symptoms for devising a holistic treatment plan.

Keywords: Fatigue, Migraine, Anxiety, Depression, Chronic fatigue syndrome

INTRODUCTION

Migraine enthrals every clinician by the vastness of its manifestations, triggers, associated illnesses and the magnitude with which it impacts the human race. What initially begins as an episodic disorder, transforms into chronic at the rate of 3–14%/year.[1] Compared to episodic migraine (EM), chronic migraine (CM) is much more difficult to manage and is associated with a substantial disability and impairment in the quality of life (QOL). It affects around 1.4–2.2% of the general population[2] and accounts for around 40–65% of the headache cases seen in specialized clinics.[3]

Fatigue is a common accompaniment of migraine being encountered in around 70% of cases.[4] Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue and other physical symptoms not relieved by rest. The risk of CFS is 1.5 times higher in migraine, while headaches have been reported in up to 59% of cases with CFS.[5]

The current study aims to determine the occurrence and severity of fatigue and CFS in patients with EM and CM and to further define its relationship with other comorbidities such as fibromyalgia, depression, anxiety, and excessive daytime sleepiness (EDS) that accompany migraine.

MATERIALS AND METHODS

It was a cross-sectional observational study carried out in GIPMER, a tertiary referral center for neurology, Delhi, India, from February 2019 to July 2020. Patients, ≥18 years of age visiting the Neurology Outpatient Department or admitted to the ward fulfilling the International Classification of Headache

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Disorders-3 criteria of EM or CM were included in the study. We excluded patients with mental retardation, dementia, psychosis, traumatic brain injury, stroke or neurological deficit, history of alcohol and drug abuse, and uncontrolled medical disorders. Sixty patients of migraine (30 EM and CM each) were included in the study. All patients underwent detailed history and examination including headache, fatigue assessment, and evaluation of comorbidities. Details of the demographic profile, history, examination andinvestigations were recorded on a pre-designed pro forma.

These scales were used for assessment:

Headache impact test (HIT-6)[6] was used to assess the disability and QOL. It comprises six items to evaluate the frequency of severe headache, limitations of ADL, desire to lie down, fatigue, irritability, and difficulty concentrating. Each of the items is scored according to frequency and generates a score from 36 to 78. The impact scores are classified as no (36–49), moderate (50–55), substantial (56–59), and severe (60–78) impact, respectively.

Assessment of fatigue in migraine

a) Fatigue severity scale (FSS):[7] is a subjective scale including 9 variables, each scored from (1 to 7), higher scores indicating severity. Score ≥2; pathological fatigue, further graded as mild (28–39), moderate (40–51), and severe (52–63) fatigue
b) Chalder fatigue scale:[8] subjective scale having 10 variables, assess both physical and mental fatigue, each is scored from (0 to 3). The total score is (0 to 33) onthe Likert scale. Score ≥22; pathological fatigue
c) Visual analog scale to evaluate fatigue severity (VASF) scale:[9] Overall fatigue was rated on a scale of (0–10), where 0; no and 10; worst fatigue experienced.

Assessment of CFS in migraine

CDC diagnostic criteria for CFS or myalgic encephalomyelitis: [10] includes new-onset fatigue of at least 6 months duration, not relieved by rest, not due to organic causes, and associated with four out of seven symptoms (sore throat, tender axillary or cervical lymph nodes, impaired memory/concentration, muscle pain, pain in several joints, unrefreshing sleep, and new headache).

Assessment of comorbidities associated with migraine and fatigue

a) Fibromyalgia: ACR diagnostic criteria for fibromyalgia[11] was applied which includes history of widespread pain, present ≥3 months
b) Hamilton depression scale[12] was used to assess depression. Although it contains 21 areas, the first 17 answers only, were used to calculate the patient's score. Scoring was done as: 0–7 = Normal; 8–13 = mild; 14–18 = moderate; 19–22 = severe; and >23 = very severe depression, respectively
c) Generalized anxiety disorder 7-item scale (GAD-7)[13] was used to assess anxiety. Each item is graded from 0 to 3. Score ≥10; GAD-7 (5–9 = mild; 10–14 = moderate; and ≥15 = severe anxiety, respectively)
d) Daytime sleepiness: Epworth sleepiness scale (ESS)[14] was used to detect and rate the severity of daytime sleepiness. It has 8 items with a score of 0–3 for each item. Score ≥12; pathological daytime sleepiness (0–10 = normal range; 10–12 = borderline; and 12–24 = abnormal).

The scores of the above results were noted and analyzed for both EM and CM patients.

Statistical analysis

The Chi-square test or the Fischer exact test, student *t*-test and Pearson's correlation tests were used for statistical analysis. The level of significance was, $P < 0.05$.

RESULTS

Sixty migraine patients were included, 50% were EM. Both the groups were evaluated and compared for demographic factors, headache characteristics, treatment profile, fatigue, and associated comorbid disorders, namely, depression, anxiety, fibromyalgia, and EDS. Of the total 60 cases of migraine, patients with and without fatigue and CFS were compared.

Baseline characteristics of EM and CM patients

The demographic factors were largely comparable in the two groups [Supplementary Table 1]. We observed that, a much larger proportion of the EM (53.3%) had positive family history compared to CM (33.3%); however, it was statistically insignificant. As expected, the mean total duration of migraine disorder was higher in CM than in the EM group (10.1 ± 7.59 vs. 6.97 ± 4.74 years, respectively, $P = 0.06$). The mean headache frequency was significantly lesser in EM (7.76 days/month range: 2–15 days) versus CM group (23.02 days/month range 15–30 days) ($P < 0.001$). Furthermore, CM patients had a significantly higher average duration of headache hours (11.05 range: 2–24 h) versus EM (7.67 range: 1–15 h) ($P = 0.024$). A larger percentage of EM patients reported headache triggers (66.67 vs. 53.33% of CM cases [$P = 0.04$]). The mean HIT-6 score was expectedly higher in CM (59.43 ± 6.74) than EM group (53.2 ± 8.41) ($P = 0.002$). We did not find any significant difference with regards to the usage of either the acute abortive medications or the prophylactic therapy among groups.

Fatigue assessment

On comparing the groups for fatigue, we observed that the mean FSS was significantly higher in CM (47.87 ± 13.76) than in < EM (37.3 ± 13.38) (P = 0.004). Moreover, 60% of the CM had FSS (score>52; severe) versus 20% in EM (P = 0.004). On VASF scale, we observed that VASF (6–9): (76.7% in CM vs. 57.7% in EM [P = 0.024]). On the Chalder fatigue scale assessment, pathological levels of fatigue were observed in 83.3% CM versus 63.3% EM patients (P = 0.04). In addition, a significantly higher number of CM patients fulfilled the definition of CFS (23.3% CM vs. 13.33% EM [P = 0.038]). Thus, for all the fatigue parameters, the CM had significantly poorer scores. We observed a positive correlation between fatigue and severity, frequency as well as chronicity ofmigraine episodes [Supplementary Table 2]. The HIT-6 score also showed a statistically significant positive correlation with the FSS, thereby highlighting the impact of headache on QOL and subsequent disability.

Comparison among migraine patients with and without fatigue and CFS

Of 60 patients, 45 cases (75%) had fatigue. The comparative summary of migraine patients with and without fatigue is depicted in [Supplementary Table 3]. The age and sex distribution among the two groups were comparable. Among the headache parameters, we did not find any significant difference with respect to the age at headache onset, the headache frequency and the duration of headache episodes. However, the total mean duration of headache disorder was significantly higher in patients with fatigue (9.62 ± 6.52 years) versus without fatigue (5.25 ± 5.24 years) (P = 0.022). Furthermore, the mean VAS score for headache severity was more in the fatigue group versus without fatigue (P = 0.008). Similarly, the mean HIT-6 score was significantly higher in migraine cases with fatigue (59.36 ± 6.11) versus without (47.20 ± 6.81) (P = 0.028). No significant difference was observed with respect to the presence of fibromyalgia, depression and anxiety among the patients with and without fatigue. However, the ESS, was significantly higher in fatigue group (P = 0.048).

Only 11 cases (18.33%) had CFS in our study. For migraine patients with and without CFS, the demographic parameters were comparable. The headache characteristics among the two groups were comparable except for severity assessed on the VAS score which was significantly more in CFS group (P < 0.001) [Supplementary Table 3]. The mean HIT-6 score was also significantly more in CFS group (58.09 ± 2.55) than those without (39.1 ± 13.73) (P = 0.028). In addition, we observed that fibromyalgia, depression, anxiety, and ESS scores were significantly higher in CFS group.

DISCUSSION

Fatigue is a common symptom associated with many neurological disorders. It is often underdiagnosed because of its subjective nature. Fatigue and CFS, despite being the common companion of migraine, have not been researched extensively. A few studies have been done so far to understand fatigue in migraine.

In this study, we have analyzed, graded, and quantified fatigue. Mental and physical fatigue was both explored along with the comorbidities (depression, anxiety, EDS, and fibromyalgia). These comorbidities were further correlated with fatigue and CFS.

Concerning EM and CM, observations regarding age[15-17] and female preponderance were similar to the studies in past.[18] We found no comparable difference in the socioeconomic status in the two groups, however, contrary results have been observed in the literature. Patients suffering from CM were found to have lower household income and less likely to be employed full time and more likely occupationally disabled.[19-21] Ours is a government sector referral health center, hence selection bias may be a relevant confounder for this discrepant finding in our study.[15] Interestingly, family history of migraine was higher in EM compared to CM, reported variably in literature.[17,20,22,23] Headache characteristics were largely similar to that reported in the literature, except for the photophobia, phonophobia, and cranial autonomic symptoms (CAS). We reported higher incidences of photophobia and phonophobia in our study.[20] However, CAS was reported by a lesser number of our patients compared to other studies.[23] Surprisingly, we found the average headache duration in our CM group to be around 11.05 h only, which contrasts sharply from other reported studies in literature, as that by Kim and Park (32.7 h).[20] We also found, those with fatigue (9.62 ± 6.52 years) had a longer total duration of migraine disorder versusthe non-fatigue group (5.25 ± 5.24 years). Similarly, those with CFS had still a longer duration of migraine disorder (10.18 ± 6.52 years).

Fatigue is a vague and definitely a multifactorial symptom, related to a multitude of factors, including but not limited to the state of general health, sleep, mood, effect of medications, apart from the very existence of underlying migraine disorder itself. The current study revealed fatigue in around 67% of EM and 83% of CM cases. Similar to our observation, Spierings and van Hoof found fatigue in 70% of headache sufferers which was significantly higher than the controls.[4] Likewise, fatigue was reported in more than 50% of the patients with headaches in several studies.[24-26] Moreover, Peres *et al.* found pathological fatigue in 84.1% in their study.[27] We also found statistically significant higher fatigue scores in patients with CM compared to EM. Our study also unveiled the positive correlation of fatigue with severity, frequency, and chronicity of the migraine episodes. In another study

comparing between EM and CM, the mean FSS score was found to be significantly higher in the CM, along with poor sleep quality worse depression and anxiety scores.[26] This asserting presence of fatigue in migraine speaks of the altered nociception in migraine and the widespread brain network dysfunction including the limbic system, hypothalamus, thalamus and the other pain areas such as periaqueductal gray, dorsolateral pons, rostroventral medulla, and amygdala.

In this cohort, 18.33% fulfilled the diagnosed criteria for CFS. A previous study from Taiwan found that the risk of CFS was 1.5 fold in the migraine cohort than the comparison cohort and the adjusted cumulated incidence increased in the follow-up years.[5] Peres *et al*. observed CFS in 66.7% of their CM cases.[27] Moreover, this observation has been largely bidirectional with studies reporting prevalence of migraine in the CFS cohort as well. CFS patients were reported to have a higher prevalence of migraine with and without aura compared to healthy controls, hypothesizing that central sensitization implicated in migraine pathophysiology may contribute to CFS mechanisms as well.[28] We had a peculiar observation that HIT-6 scores were significantly higher in migraineurs with CFS than those without. Does it mean that the severity of headaches more robustly alter the nociception as well as the central sensitization, altering the neurochemical milieu which underlies the mechanism of CFS also? This underpins the importance of timely, adequate, and robust treatment strategies for migraine which can potentially alter CFS mechanics as well. To the best of our knowledge, the relationship of HIT-6 score with CFS has not been elucidated so far in the literature.

Fibromyalgia commonly accompanies migraine, and we also observed higher incidences with CM as reported in the literature.[29] Exceptionally high female occurrence was reported by Ifergane *et al*.[30] Interestingly those having fibromyalgia were also found to have moderate to severe fatigue. The prevalence of fibromyalgia was 82% in those with migraine and CFS, the incidence of fibromyalgia and CFS in migraine patients is yet to be reported. Hudson in their study on 33 patients with fibromyalgia found that 55% of them suffered from migraine and 70% of them had CFS.[31] Fatigue, CFS and fibromyalgia are so closely interloped and probably share a common pathophysiology, and it is expected to find them clustered together in CM patient cohort.

Dissecting the presence of fatigue, independent of entities such as sleepiness and depression, is a challenging task in headache practice and there is clearly a woven interplay of these factors. More so in migraine, it gets difficult to clearly delineate these entities and translate into real time management strategy for patients. Nevertheless, the association of anxiety and depression with migraine is reported frequently in the literature. Our study also found comorbid depression and anxiety in one-third of the EM and half of CM patients. The difference in depression and anxiety in acute versus chronic migraine patients has been studied in past and reported in accordance with the present study.[26] In a study of 101 patients of transformed migraine, Peres *et al*. found depression in 88% of their cohort.[29] A large population-based survey from France reported 51% of the migraineurs had coexistent depression and anxiety.[32] This survey also highlighted the lack of influence of these comorbidities on the medical consultation rate in migraineurs, reflecting the poor accountability they receive despite causing significant morbidity. Similarly, these comorbidities do not have a place when selecting the acute abortive treatment for migraine hence forth undermining their important role.[33]

Sleep disturbance is a common substrate for fatigue, mood disturbance, and serves as a migraine trigger also. Interestingly, we observed significantly higher ESS scores in both groups. Borderline to EDS was found in 73%of the CM and 40% in EM. Moreover, ESS scores were significantly higher in migraine patients both with fatigue and CFS than those without. Whether sleep contributes to fatigue in migraine, or fatigue exists as a separate comorbidity, is difficult to define. However, since the pathomechanisms seem to be intertwined, it is hard to independently define their causative roles.

We also observed that worse fatigue scores had a correlation with the presence of depression and anxiety, strengthening the fact that all these three comorbidities, anxiety, depression, and EDS parallel the fatigue in patients with migraine. The previous studies have highlighted that anxiety and depression are the most relevant comorbidities in patients with migraine and maybe the most relevant to co-address, significantly influencing the treatment outcomes.[34] Although our study utilizes a predesigned set of questionnaires for the syndromic diagnosis of these psychiatric conditions, we believe in the concept that in the context of pain disorders, these psychiatric symptoms should be viewed more as a continuum of symptoms and hence they add to a more wider concept of underlying disturbed neurochemical and pathobiological milieu and should preferably be viewed holistically. Disturbed sleep architecture, excessive fatigue, mood disturbances, and migraine all are so closely and pathomechanically linked that what patients reported subjectively, the observed scores and what translates into a discrete evidence on functional neuroimaging is fascinating to believe.

There are few limitations to our study. We used FSS for assessment of fatigue, which assesses fatigue within the last 1 week period. Ideally, assessment of fatigue should be done during different phases and in between the migraine attacks. In addition, a large number of patients had psychiatric comorbidities which inherently influence the fatigue assessment. Since our study is a clinic-based study

in a tertiary center where more severe or disabling patients are usually seen and treated, selection bias adds to the concern. We had designed this primarily for the assessment of migraine characteristics with and without fatigue as our primary objective. Hence, no control was included.

CONCLUSION

Overall, fatigue, CFS, and related co-morbid disorders are more common and severe in CM compared to EM. Comorbid disorders, namely, depression, anxiety, fibromyalgia, and daytime sleepiness are commoner among migraine with fatigue compared to those without.

Migraineurs need to be assessed and treated for their headache and associated co-morbid disorders which may account for the poor response to treatment. Behavioral therapy and patient awareness is crucial. Larger population-based studies are needed for future research. Awareness of migraine related fatigue will help formulate the optimal treatment strategy in an otherwise chronic disabling disorder that requires not only medical therapy for headache but also targeted management of fatigue and its related co-morbidities besides psychosocial intervention and support for best results.

Declaration of patient consent

The authors certify that they have obtained all appropriateconsent.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY

Table 1: Comparison of demographic variables, migraine characteristics, fatigue parameters and comorbidities among patients with EM and CM.

Characteristics	EM cases (*n*=30)	CM cases (*n*=30)	*P*-value
Age in years (mean±SD)	30±8.5	32.33±10.71	0.823
Gender, females (%)	23 (76.7%)	27 (90%)	0.166
Educational status- illiterate, *n* (%)	7 (23.3%)	7 (23.3%)	0.976
Family history of migraine, *n* (%)	16 (53.33%)	10 (33.3%)	0.118
Age of onset (before 18 years), *n* (%)	5 (16.7%)	9 (30%)	0.222
Duration migraine in years (mean±SD)	6.97±4.74	10.1±7.59	0.06
Severity of headache, moderate/severe, *n* (%)	17 (56.7%)/12 (40%)	19 (63.33%)/10 (33.33%)	0.864
HIT-6 score, (mean±SD)	53.2±8.41	59.43±6.74	0.002
FSS score, (mean±SD)	37.3±13.38	47.87±13.76	0.004
CFS, *n* (%)	4 (13.33%)	9 (23.33%)	0.038
Fibromyalgia, *n* (%)	6 (20%)	10 (33.3%)	0.243
HAM-D score, (mean±SD)	8.83±5.49	11.77±7.52	0.09
GAD-7 score, (mean±SD)	6.9±5.93	8.8±6.04	0.224
ESS score, (mean±SD)	10±4.92	11.93±4.82	0.130

EM: Episodic migraine, CM: Chronic migraine, HIT-6: Headache impact test-6, FSS: Fatigue severity scale, CFS: Chronic fatigue syndrome, HAM-D: Hamilton Depression Scale, GAD-7: Generalized anxiety disorder 7, ESS: Epworth sleepiness Scale, SD: Standard deviation

Table 2: Correlation of variables with the FSS score in patients with migraine (all EM and CM cases).

Variables	*P*-value (r)
Age of headache onset	0.768 (−0.039)
Total duration of migraine disorder (years)	0.010 (0.329*)
Severity of headache	<0.001 (0.545**)
Frequency/month	0.006 (0.349**)
Duration of each episode in hour	0.091 (0.220)
ESS score	<0.001 (0.497**)
HIT-6 score	<0.001 (0.840**)
HAM-D score	0.0002 (0.453**)
GAD-7 score	0.0001 (0.471**)

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). EM: Episodic migraine, CM: Chronic migraine, HIT-6: Headache impact test-6, FSS: Fatigue severity scale, HAM-D: Hamilton Depression Scale, GAD-7: Generalized anxiety disorder 7, ESS: Epworth sleepiness Scale

Table 3: Comparison of demographic variables, migraine characteristics, fatigue parameters and comorbidities among migraine patients with and without fatigue.

Fatigue			
Characteristics	**Migraine patients with fatigue (*n*=45)**	**Migraine patients without fatigue (*n*=15)**	***P*-value**
Age in years (mean±SD)	32.67±10.31	28.00±6.30	0.105
Gender, females (%)	36 (80%)	14 (93.3%)	0.23
Age of onset (mean±SD)	22.44±7.5	22.60±5.38	0.941
Mean duration of migraine in years (±SD)	9.62±6.52	5.25±5.24	0.022
Average headache frequency, days/month	16.35±9.49	12.86±6.50	0.149
Duration of headache episodes in hours (mean±SD)	8.86±6.00	7.06±4.86	0.298
Severity of headache, moderate/severe *n* (%)	52 (55.6%)/20 (44.4%)	11 (73.3%)/2 (13.3%)	0.008
Patients on prophylactic therapy, *n* (%)	37 (82.2%)	9 (60%)	0.078
HIT-6 score, (mean±SD)	59.36±6.11	47.20±6.81	0.028
Fibromyalgia, *n* (%)	13 (28.9%)	3 (20%)	0.5
HAM-D score, (mean±SD)	11.27±6.86	7.40±5.38	0.05
GAD-7 score, (mean±SD)	8.58±6.24	5.67±4.82	0.10
ESS score, (mean±SD)	11.69±4.87	8.8±4.57	0.048
CFS			
Characteristics	**Migraine with CFS cases (*n*=11)**	**Migraine without CFS cases (*n*=49)**	***P*-value**
Age in years (mean±SD)	31.36±7.26	31.53±10.15	0.959
Gender, females (%)	10 (90.9%)	40 (81.6%)	0.456
Age of onset (mean±SD)	21.18±3.46	22.78±7.55	0.499
Mean duration of migraine in years (±SD)	10.18±6.52	8.16±6.47	0.355
Average headache frequency, days/month	19	14.69	0.15
Duration of headache episodes in hours (mean±SD)	10.45±6.08	7.95±5.60	0.196
Severity of headache, moderate/severe *n* (%)	0/11 (100%)	36 (3.5%)/11 (2.4%)	<0.001
Patients on prophylactic therapy, *n* (%)	11 (100%)	35 (71.4%)	0.043%
HIT-6 score, (mean±SD)	58.09±2.55	39.10±13.73	0.028
Fibromyalgia, *n* (%)	9 (81.8%)	7 (14.3%)	0.001
HAM-D score, (mean±SD)	17.27±6.74	8.73±5.66	0.001
GAD-7 score, (mean+SD)	13.27±6.53	6.63±5.23	0.001
ESS score, (mean+SD)	15.64±4.13	9.92±4.49	0.001

HIT-6: Headache impact test-6, FSS: Fatigue severity scale, CFS: Chronic fatigue syndrome, HAM-D: Hamilton Depression Scale, GAD-7: Generalized anxiety disorder 7, ESS: Epworth sleepiness Scale, SD: Standard deviation