Undiagnosed mania in migraineurs and the phenomenon of migrainous joie de vivre

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Abstract

Background: Migraine and mood disorders are common clinical problems with significant disability. The aim of this study was to identify the prevalence of undiagnosed mania in migraneurs and to characterize their clinical features.

Materials and Methods: Patients attending the neurology outpatient department of a tertiary level teaching hospital during a period 01-01-2017 to 31-07-2017 were enrolled in this observational study.

Patients were diagnosed to have migraine as per International Classification of Headache Disorder 3 beta criteria. The Young's Scale was applied to subjects identified as having mania. The clinico-epidemiological features and the correlation between the occurrence and severity of manic symptoms and migraine were assessed.

Results: Majority were females, 162(76.8%) whereas males constituted only 49(23.2%). The mean age was 33.89($\pm$8).Only 34(16.1%) patients-29 females and 5 male patients had mood changes (p = 0.14).24 patients with nausea and vomiting had associated mood changes with no statistically significant difference among the groups (p=0.08).Only 12 subjects (5.7%) had aura during headache.5.2% of patients had mania with mean Youngs Mania Rating Scale(YMRS) of 32.36 ($\pm$8.3) in the sample. Five patients(45.45%) out of the 11 subjects who had mania in our study exhibited manic symptoms also during headache episodes.

Conclusions: Undiagnosed mania occurred at a rate of 5% in migraine patients in our study population. No definite clinical features like age or migraine features like aura were found to significantly correlate with the presence /severity of mania.45.45% patients had simultaneous mania symptoms and migraine, a phenomenon we term as" migrainous joie de vivre".

Keywords: Migraine, Mania, Migrainous joie de vivre.

Introduction

Migraine is the most common primary headache and is associated with significant disability. Mood disorders are similarly common and affect up to 15% of the world population. They can be classified into unipolar depression and bipolar disorders. Bipolar I disorder is defined when there has been at least one episode of mania, either currently or in the past while Bipolar II disorder is diagnosed if there have been one or more major depressive episodes plus at least one hypomanic episode and there never has been a manic episode. Various studies have shown a significant comorbidity of migraine with bipolar disorders. One study revealed a lifetime occurrence rate of bipolar disorder in migraine of 8.6%[1] while several studies have suggested that migraine is significantly associated with depression with a variability ranging from 8.6-47.9%.[2] A bidirectional relationship between migraine as well as bipolar disease has been proposed.[3] On the other hand, studies assessing the correlation between migraine and mania as such are scarce and data is not readily available. Hence the present study was designed to determine the comorbidity of migraine with hitherto undiagnosed mania and to determine the clinical features correlating the two disorders.

Materials and Methods

The study population was recruited from patients attending the neurology outpatient department of a tertiary level teaching hospital during a period from 01-01-2017 till 31-07-2017.Case ascertainment as migraine was done as per ICHD 3 beta criteria. A detailed history and clinical neurological examination was done. Neuroimaging studies (Computerised Tomography or Magnetic Resonance Imaging of brain) were done to rule out secondary causes. DSM 5 criteria was applied to identify cases of mania. The Young's Scale was applied to subjects identified as having mania. Exclusion criteria were as follows

1. Those below 18 years and above 60 years.
2. Those, already diagnosed/on treatment for psychiatric disorders.
3. Those with alcohol or substance abuse disorders
4. Those having other types of concurrent headache disorders-primary (including tension type and cluster headaches) or secondary.

Statistical analysis used: Descriptive statistical methods were used to assess the clinico-epidemiological features and Pearsons correlation test was used to assess the correlation between the occurrence and severity of maniac symptoms and migraine.

Results
Socio Demographic details
The sample was female predominant. Female were 162 in number (76.8%) whereas males constituted only 49

(23.2%). The mean age was 33.89 while SD was 8.465. Duration of disease was not normally distributed. The median (SD) was 6 years (6.58). Female subjects had significantly higher correlation with duration of illness than males (Female 110 mean rank; male 90.79 mean rank with p value of 0.0). The mean, median and SD of frequency (per month) were 5,3 and 5.5 respectively. The frequency distribution was as follows- 1(21.8%), 2(20.4%), 3(12.8%), 4(7.6%), 5(9%), 6(3.8%), 7(6.6%), 8(5.7%), 9(1.4%), 10(2.4%), 11(.5%), 12(.9%), 13(.5%), 13(.9%), 14(.5%), 16(.5%), 20(.9%), 21(.5%), 23(.9%), 25(.5%), 30(1.9%). Maximum subjects had 1 or 2 per month frequency.

Female subjects had significantly higher frequency than males (Female Mean (SD): 5.38(5.9%), Male Mean (SD): 3.6(3.7%) p value 0.05%). 123 subjects (58.3%) suffered from nausea or vomiting during their headache episodes. No significant differences (p= 0.43) were noted in respect to gender regarding the occurrence of nausea or vomiting. Among female subjects 97 patients had nausea/vomiting whereas only 26% of male patients had nausea / vomiting. 161(76.3%) of patients had photophobia and photophobia while 50(23.7%) did not have it. 127 female subjects (78.4%) had photophobia and phonophobia as compared to 34 male subjects (69.4%) albeit not in a significant level (p=0.2). Only 34 (16.1%) patients-29 females and 5 male patients had mood changes(p = 0.14). 24 patients (11.4%) with nausea and vomiting had associated mood changes with no statistically significant difference among the groups (p=0.08). 26 patients(12.32%) who had photo/phonophobia had mood changes but there was no significant difference between the groups (p= 0.58). Among female patients, 42 (25.92%) had perimenstrual headache while only 15 (9.2%) had mood changes during perimenstrual period. Only 12 subjects (5.7%) had aura during headache. Among them 3 subjects had mood changes which is statistically insignificant. Mean(SD) of attack duration was 10.24 hours (9.02) with no significant difference between male(10.09) and female patients(10.06). There was no significant correlation between age and attack duration (Pearson's test). There is negative correlation between duration of disease and attack duration but not significant tested by Spearman correlation coefficient.

5.2% (11) of patients had mania with mean (SD) Youngs Mania Rating Scale(YMRS) of 32.36 (8.3)in the sample. There was negative correlation (via Pearson's correlation test) which was not significant between attack duration and YMRS score. Likewise, there is negative correlation between age, disease duration with YMRS score which are not statistically significant. None of the subjects who had aura during migraine headache attacks had mania. 1 patient who headache attacks with aura also suffered concomitant depression. Five patients(45.45%) {28 year male,39 year male,33 year male,44 year female and 18 year female} out of the 11 subjects who had mania in our study exhibited maniac symptoms (elated mood, a feeling of happiness, grandiosity, irritability) also during headache episodes. In the first patient these symptoms would develop just before the headache and would become full blown by the course of less than 30 minutes by which time a throbbing headache would develop with nausea, vomiting culminating in a full blown migraine headache attack which would be relieved in a period of 5-6 hours by rest in a quiet dark room or by analgesics. In the four other subjects, these symptoms would develop after the migraine headache had resolved. In all these subjects the magnitude of associated headaches during these manic symptoms was severe. The history given by these different subjects was remarkable for its consistency and similarity. All the subjects described that after several hours of severe headache with retching and vomiting, at a time concurrent with the reduction in intensity of headache, they started to develop an inexplicable feeling of warmth and happiness starting deep in the pit of the stomach and spreading upward over the course of a few minutes followed soon after by an elevation of mood. Associated symptoms included a euphoric feeling, a feeling that 'all was right with the world', a feeling that there would be a sudden dramatic improvement in his/her quality of life somehow, a tendency to talk/joke more, grandiosity, impetuosity (manifested by rash decisions at the workplace or by borrowing money from relatives and neighbors) and irritability.

Discussion

Many studies have been conducted to study the relationship between migraine and anxiety and depression.[4-6] Contrasted with this, the exact prevalence of bipolar disease spectrum or mania in chronic headache including migraine is controversial and largely underrated[7]

The term comorbidity is defined as the coexistence of any additional ailment in a person with an index disease.[8] Many studies have showed that there is an increased comorbidity with a 2 to 4 times probability of psychiatric disorders in migraineurs.[9-12]

In our study 5.2% migraineurs had associated mania. A cursory review of literature reveals variable results. For e.g. a study conducted by Fasmer et al[13] revealed a frequency of 11% of bipolar I disorder in their cohort of migraineurs as in our study.In that study 102 patients with an index episode of either mania or depression were compared with respect to the presence or absence of comorbid migraine. Compared to the patients without migraine, the patients with comorbid migraine had a higher frequency of bipolar II disorder (43% versus 10%), a lower frequency of bipolar I disorder (11% versus 33%) and an approximately equal frequency of unipolar depression. The study also revealed that the migraine patients had a higher frequency of affective temperaments and anxiety disorders as compared to non migraineurs. Thus the frequency of bipolar I disease was the lowest among affective disorders in migraineurs. Another important aspect regards the proposition that migraine may be associated with a more severe form of bipolar disease as manifested by a longer duration of bipolar disease and associated with greater social impairment[14] while the study by Fasmer et al did not support this contention in that they could not find significant correlation between the age of onset of major affective disorders and number of previous

episodes. Our study is also in concordance with this finding in that we could not find any correlation between age of onset, disease duration or severity of Youngs Mania score. Some studies have reported that the frequency of bipolar disease is higher in migraine patients with aura.[15-17] However in our study, none of the subjects with aura during migraine headaches had concomitant mania.

An interesting facet of affective symptoms in migraine which was revealed in the present study was the occurrence of manic/ hypomanic symptoms during the course of the migraine attack, either before or after. It is well known that migraine is not uncommonly accompanied by various psychiatric symptoms. Rare case reports are available in literature regarding the occurrence of hypomania as an aura in migraine. Datta SS et al reported the case of a 19 year old man who presented with prominent behavioral symptoms associated with migraine headaches suggestive of hypomania both preceding and concurrent with the headache.[18] The authors postulated that these symptoms could either be a prodrome or aura but concluded that the possibility of them being symptoms of aura were higher as all episodes were followed soon by development of headache. However the authors also cautioned that the association of migraine with hypomania could well be a coincidence and these finding needs to be corroborated with further case reports. In this regard, it is interesting that only one of our patients had similar symptomatology temporally related to headache (preceding headache) while the other four had predominantly post headache symptoms. We call this phenomenon" migrainous joie de vivre" and postulate that it is due to increased intracellular calcium signaling.

An interesting feature of mania as compared to other affective disorders is that of its complex clinical spectrum ranging from the very mild form of hyperthymia that does not impair social or occupational functioning, cyclothymia characterized by mild mood swings, subthreshold hypomania, hypomania and mania with psychosis and gross impairment of function.[19] It is also highly variably variable in various clinical features including age of onset and recurrence.[19] Numerous diseases have been found to be associated with secondary mania. One of the most important cause is stroke especially right sided frontotemporal infarcts.[20] Post stroke mania is associated with white matter changes, venticulomegaly, older age and adverse cardiovascular outcome.[21] Other causes of secondary mania include Cushings disease, certain dementias including neurosyphilis, HIV, vitamin B12 deficiency, right sided brain tumors, meningitis, thyrotoxicosis, hypo or hyperparathyroidism, multiple sclerosis, Huntington disease, traumatic brain injury, complex partial seizures, uraemia etc. The initial onset of mania usual occurs between late teens to early 30s.All these secondary causes are not only associated with a later onset but also associated with more cerebrovascular mortality and more neuroimaging findings like white matter hyper intensities.[22]

Elevated intracellular calcium signaling has been found in different types of cells including blood platelets, lymphocytes and olfactory neurons in manic patients.[23]

Dubovsky SL et al have suggested that this hyperactive intracellular calcium ion signaling is not the result of a circulating factor based on their study involving measurement of intracellular calcium levels in normal platelets after incubating them with plasma ultrafiltrate from patients with bipolar disorders.[24] Rather, it is proposed that hyperactivity of neuronal calcium sensor (NCS 1) may be responsible for the increased release of stored intracellular calcium. NCS 1 is activated by Inositol Triphosphate 3 or protein kinase C both derived from cell membrane phosphoinositide turnover or by mitochondrial dysfunction.[25] This is similar to the so called phenomenon called windup involved in the pathogenesis of migraine. Pain conducting C-fiber activation elicits slow synaptic potentials the summation of which at relatively low-afferent frequencies produces windup.[26,27] Windup results in increased synaptic efficiency (enhanced responses in the conditioning nociceptor pathway)[28] such that neurons that exhibit windup are less sensitive to opioids than those that do not exhibit windup.[29] Of particular interest is the fact that windup is accompanied by increased intracellular calcium due to increased calcium entry via N-methyl-D-aspartate (NMDA) channels, which in turn induces the translocation from cytosolic to membrane bound form and activation of protein kinase C.[30] Thus elevated intracellular calcium signaling and protein kinase C activation play similar roles in the pathogenesis of migraine as well as mania. We postulate that this could wholly or partly account for the coexistence and overlapping symptomatology of mania and migraine in the patients in our study.

Conclusion

Undiagnosed mania occurred at a rate of 5% in migraine patients in our study population.

No definite clinical features like age or migraine features like aura were found to significantly correlate with the presence /severity of mania. However a study with larger sample size could potentially develop stronger statistical power to elicit such associations.

45.45% patients with mania and migraine develop their symptoms during headache attacks, the so-called migrainous joie de vivre.

In view of the relatively low prevalence of mania in migraineurs, it is probably not time wise cost effective to routinely screen for mania in migraine patients. However, in migraineurs who develop hypomanic/manic symptoms during the headache attack, it is advisable to screen for mania. This has both diagnostic and therapeutic implications in that it would enable the clinician not to miss a diagnosis of concurrent mania which could have deleterious consequences. This could also help the physician to proactively prescribe mood stabilizing medicines like sodium valproate which would be beneficial in the management of migraine as well as mania and avoid those like serotonin reuptake inhibitors which would worsen the mania and the ultimate outcome.

Conflict of Interest: None.

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