Migraine Comorbidities - A Discussion

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Abstract
Comorbidity refers to the presence of an additional co-existing ailment in a patient with a particular index disease. Migraine co-morbidities have been reported in various clinical and case control studies. Comorbidities impose a high socio-economic burden on society and compromise the quality of life in migraineurs. There are several factors which can complicate the investigation of co-morbidity. They have to be differentiated from migraine equivalents. Abdominal pain, vertigo or visual hallucinations in migraineurs may suggest an alternative diagnosis or may be confused with co-morbidities. The goal of this review is to help identify comorbidities in diagnosed cases of migraine and to understand their overall impact on this complex headache disorder.

Introduction
The term ‘comorbidity’ was introduced by Feinstein. A coexisting disorder is likely to cause more distress, poor response to treatment and may also lead to unnecessary investigations and referral. Migraine is a common neurological disorder affecting 18% of females and 6% of males. Patients with migraine are more likely than non-migraineurs to have coexisting disorders. Merikangas and Fenton, after analyzing data from an epidemiological study in the U.S. population found migraine to be associated with disorders of cardiovascular, gastrointestinal, neurologic and psychiatric disorders. The following conditions may occur more frequently in persons with migraine.

1. Psychiatric disorders
   a. Depression
   b. Anxiety
   c. Panic disorder
   d. Bipolar disorders
2. Neurologic disorders
   a. Epilepsy
   b. Stroke
   c. Multiple Sclerosis
3. Cardiovascular disorders
   a. Hypertension
   b. Heart Disease
   c. Patent Foramen Ovale
4. Miscellaneous disorders
   a. Asthma/allergy
   b. Gastro-intestinal disorders
   c. Coeliac disease

Psychiatric Disorders
People with migraine are more likely to have psychiatric disorders and vice-versa. The co-morbidity of depression with migraine has received most attention for several reasons. The prevalence of migraine is relatively high in women, and women are also more prone to depression. Depression is four times more common in migraine than in the general population. Lipton et al. examined the effect on Health Related Quality of Life (HRQoL) in co-morbid migraine and depression and found that the quality of life was significantly reduced in subjects with co-morbid depression and migraine. Therefore the presence of migraine should be considered an important physical symptom in clinic-based major depressive disorder samples. Simultaneous management of depression and severe headaches, especially migraine, might improve the Health Related Quality of Life in these patients. A previous study conducted at the same setting found that more than 10% of study patients had depressive personality and this was highest of all the other personality types.

Cross-sectional associations and bidirectional associations between migraine and a variety of psychiatric and somatic conditions have been reported in literature. Patel and colleagues assessed the prevalence of major depression in individuals with migraine. The overall prevalence of major depression was 28.1% for migraine, 19.5% for probable migraine, 23.9% for migraine and probable migraine pooled together and 10.3% for the control group. A cross-sectional study of more than 50,000 adults by Zwart and colleagues measured the co-occurrence of headache and depression or anxiety disorders. Overall, individuals with migraine headache were more likely to have depression (odds ratio [OR] = 2.7 [2.3–3.2]) or anxiety disorders (OR = 3.2 [2.8–3.6]) than non-headache controls. Similar associations were seen for non-migraine headache and depression (OR = 2.2 [2.0–2.5]) or anxiety disorders (OR = 2.7 [2.4–3.0]). There was a linear trend associated with headache frequency. Thus, for migraine headache less than 7 days per month, 7–14 days per month, >15 days per month, respectively, the association with depression was OR = 2.0 (1.6–2.5), OR = 4.2 (3.2–5.6), and OR = 6.4 (4.4–9.3).

Neurologic Disorders
a. Epilepsy
   Epilepsy and migraine may share a similar pathophysiology. Antiepileptic drugs are used as effective prophylactic migraine treatment, suggesting common mechanisms in migraine and epilepsy. Genetic studies also have suggested a link between epilepsy and some types of migraine.
   The median prevalence of epilepsy in migraineurs is 6%, compared with 0.5% in the general population. Among people with epilepsy, 8%-23% have migraine headaches, compared with 12% in the general population. Patients with partial and generalised forms of epilepsy are likely to have migraines, with the maximum incidence in those with posttraumatic epilepsy.
b. Stroke
   Ischemic stroke
   The association between migraine and ischemic stroke is well proven. A meta-analysis of 11 case-control studies and three cohort studies showed that the risk of stroke was...
increased in migraineurs (pooled relative risk [RR] = 2.16, 95% confidence interval [CI] = 1.9–2.5) compared to non-migraineurs. This risk was nominally higher for migraine with aura (MA), (RR = 2.27; 95% CI, 1.61–3.19) but was also apparent in patients with migraine without aura, (RR = 1.83; 95% CI, 1.06–3.15).

Two large longitudinal studies added to the evidence linking migraine and ischemic stroke. The relationship between migraine and stroke was assessed, as a part of the Women’s Health Study, using a large cohort and data prospectively gathered over an average of more than 10 years. Compared with non-migraineurs, participants reporting history of migraine or migraine without aura had no increased risk of any stroke type. Participants who reported migraine with aura had increased adjusted hazards ratios (HRs) of 1.53 (95% CI, 1.02–2.31) for total stroke and 1.71 (95% CI, 1.11–2.66) for ischemic stroke but no increased risk for hemorrhagic stroke. The increased risk for ischemic stroke was further magnified (HR = 2.25; 95% CI, 1.30 to 3.91) for the youngest age group in this cohort (45–54 years). The associations remained significant after adjusting for cardiovascular risk factors and the same was not apparent with non-migraine headache.

The second prospective study used data from the Atherosclerosis Risk in Communities Study and included more than 12,000 men and women aged 55 and older. Compared with participants without migraine or other headache, migraineurs had a 1.8-fold increased risk of ischemic stroke (RR = 1.84; 95% CI, 0.89–3.82). Similarly, in the Stroke Prevention in Young Women study, women with MA had 1.5 greater odds of ischemic stroke (95% CI, 1.1–2.0).

Subclinical Brain Lesions
Deep brain lesions, found incidentally on neuroimaging, have been reported more frequently in migraineurs. In a population-based study from the Netherlands, Kruit and colleagues14,15 randomly selected approximately 150 individuals from each of three groups for neuroimaging (MA, MO, and nonmigraine controls). Individuals with a history of stroke, transient ischemic attack (TIA) or abnormal neurologic examination were excluded. This study included evaluation of magnetic resonance imaging by a neuro-radiologist who was blinded and aura classification was performed under the supervision of expert headache diagnosticians without knowledge of the magnetic resonance imaging results. Overall, there were no differences between migraineurs and controls in the prevalence of clinically relevant infarcts. However, those with Migraine with aura (MA) had significant increase of subclinical infarcts in the cerebellar region of the posterior circulation. The highest risk for these lesions was seen in those with MA and with more than one headache attack per month (OR = 15.8; 95% CI, 1.8–140). In addition, women with migraine were about twice as likely to have deep white matter lesions as nonmigraineurs (OR = 2.1; 95% CI, 1.0–4.1). Consistent with earlier studies on clinical stroke and white matter abnormalities, these findings were independent of the presence of cardiovascular risk factors.

c. Multiple Sclerosis
Headache and migraine are common features of multiple sclerosis (MS) and can influence diagnosis and treatment. Likewise, MRI lesions found in migraine patients without other neurological deficits can cause diagnostic confusion. One case-control study has shown association of MS with migraine and they reported migraine as being the second highest associated risk factor for developing MS. These results support the hypothesis that the etiology of MS includes both genetic and environmental risk factors.

3. Cardiovascular Diseases
Cardiovascular conditions that can be comorbid with migraine include stroke, hypertension and these cardiac manifestations have been widely studied.

a. Hypertension
Though various large scale community surveys could not prove any correlation between hypertension and migraine, in a cross sectional survey of adults in general population Rasmussen and Olesen17 found that women with migraine had significantly higher diastolic blood pressure than those without migraine. In contrast to these epidemiological studies, nearly all case control studies have reported a positive association. Gardener et al18 found that mean systolic blood pressure was higher in migraineurs over age 40 than among age matched controls.

b. Heart Disease
Heart diseases including mitral valve prolapse, coronary artery disease, ischemic heart disease, angina, and arrhythmias have also been associated with migraine. There have been no large-scale, prospective epidemiologic studies specifically examining the association between migraine and these heart diseases. Results from case-control studies could not establish positive association between migraine and heart disease after control of well established risk factors.

c. Patent Foramen Ovale
Patent Foramen Ovale (PFO) is a small flap-like opening between the right atrium and the left atrium that persists after age 1 year. It is present in up to 25% of the population. PFO has been linked to stroke and previous studies indicated an increased prevalence of patent foramen ovale (PFO) in migraineurs with aura and an increased prevalence of migraine and migraine with aura in persons with PFO. In quantitative systematic review of articles on migraine and PFO, the estimated strength of association between PFO and migraine, the OR was 5.13 (95% CI, 4.67–5.59) and between PFO and migraine with aura the OR was 3.21 (95% CI, 2.38–4.17). The association between migraine and PFO was OR 2.54 (95% CI, 2.01–3.08). The grade of evidence was low to moderate. Research is currently on to establish whether or not the link exists and if it does to investigate whether or not closing the PFO leads to an improvement in migraine.

Miscellaneous Disorders

a. Asthma and Allergy
The association between migraine and allergic conditions including food allergies, asthma and bronchitis has also been well investigated. Von Behren et al.20 in a community-based survey of adults, reported that migraine was associated with asthma among women. Earlier studies have reported relative risks of 1.9 for asthma and 4.1 for allergies. Irrespective of the specific type of allergic condition assessed
in the studies, a strong and consistent association between allergic conditions and migraine has been found in clinical studies of both children and adults.

b. Gastrointestinal Disorders

The lack of a clear distinction between recurrent abdominal pain and undiagnosed abdominal migraine often presents problems when examining the relationship between migraine and abdominal pain.

The association with gastric ulcers was observed in case-control samples from clinical settings and yielded relative risks ranging from 1.9 to 2.5, whereas Chen et al. 21 reported that ulcers were only associated with migraine among smokers

c. Coeliac Disease

An Italian study found that about 4% of migraine sufferers may have coeliac disease compared to less than 0.4% of the general population.22

Conclusion

Migraine has been found to have a strong association with mood and anxiety disorders, stroke, epilepsy and allergies. As these associations can alter the clinical course by affecting the prognosis and therapeutic options, these can also lead to poor response to treatment, therefore co-morbidities associated with migraine need to be classified and analysed separately.

References