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Blood pressure changes in patients with migraine: Evidences, controversial views and potential mechanisms of comorbidity

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Running title:
Blood pressure changes with migraine

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Abstract:

Migraine and hypertension are common complaints and both have high prevalence worldwide. The comorbidity of migraine with hypertension is a common issue since 1913. Recent epidemiologic and population-based studies put some doubt regarding the association between migraine and hypertension, no association or even negative association was found by some authors. Authors who supported the positive association suggested that rennin-angiotensin system as a biological link between hypertension and CNS activities that are relevant for migraine pathogenesis. Authors who denied the association suggested a coincidental existence since any association between two prevalent health conditions is likely to be detected in large series. Authors who supported the negative association suggested a central regulatory and homeostatic process resulting in reduction of sensitivity to pain (a phenomenon called hypertension-associated hypalgesia). Baroreflex stimulation, endogenous opioids, catecholamines and calcitonin peptide may influence blood pressure and pain sensitivity in patients with migraine and lowers the number of migraine attacks in hypertensives. Despite the uncertainty still present in this field, a unifying view among most recent studies suggests that migraine is positively correlated with diastolic blood pressure but negatively correlated with systolic blood pressure and pulse pressure. Similar vascular risk profile and the abnormal properties of systemic as well as cranial arterial vessels exist in subjects with migraine and hypertension. On the other hand poor control of blood pressure may exacerbate the frequency and severity of migraine and other headaches. These evidences may suggest that both conditions may coexist as part of a systemic disease. Thus establishing the blood pressure should be a routine task in the assessment of all headache patients and the control of hypertension in migraine patients is an important factor for the success of migraine treatment and to lower cardio- and cerebro-vascular risks.

Introduction:

Migraine is a common chronic presenting complaint encountered in Neurology and Internal Medicine clinics. A series of population-based studies based on the new operational International Headache Society (IHS) criteria, has found that migraine, although common, has a variable prevalence worldwide. In European and American studies the one-year period prevalence of migraine in adults is estimated at 10-15%, significantly more women are affected than men, in a ratio of 2-3:l (1); In Japan the reported prevalence is 8.4% (2). In Africa, crude prevalence rate is estimated at 19 %, and specific rates of 26.8 % for women versus 9.4 % for men (3). In Arab countries, the migraine prevalence was 2.6–5% in Saudi Arabia and 7.9% in Qatar, while the 1-year migraine prevalence was 10.1% in Oman (4). In a study of Egyptian school children in Assiut, the prevalence of migraine is 16.6% (female to male ratio: 1.33) (5). Overall, migraine prevalence varies by age, gender, race, and income. Before puberty, migraine prevalence is approximately 4%. As adolescence approaches, prevalence increases more rapidly in girls than in boys. Migraine is most common in the third decade of life and in lower socioeconomic groups. It increases until approximately age 40, and then declines. Migraine is more frequent in women than men (1,6). Few studies of migraine incidence have been performed. A population-based study conducted by Rasmussen (6) showed that the annual incidence of migraine is 3.7 per 1,000 person years (women 5.8; men 1.6).

Hypertension and migraine are very prevalent disorders in general population and many old and recent studies suggested a relevant comorbidity between headache, migraine and arterial hypertension (7-11). However, in some recent studies and text-

2010
Vol.1
No. 2:2
doi: 10:3823/306

books, the relationship between migraine and hypertension is poorly characterized. Epidemiologic and population-based studies found no (12,13) or even negative (14) correlation between the two diseases.

In general, the relation between two disease states may be due to (15) **1)** an artifact of diagnostic uncertainty when symptom profiles overlap or when diagnosis is not based on objective markers, **2)** chance association or coincidental, **3)** unidirectional causality, such as migraine resulting in blood pressure changes due to headache-specific treatment, **4)** bidirectional causal association i.e. one disorder causes the other, **5)** a shared environmental or genetic risk for the two disease states that increase the risk of both conditions, In such cases, understanding these shared risk factors may lead to greater understanding of the fundamental mechanisms of migraine, or **6)** both conditions are manifestations of one systemic disease. However, the term comorbidity is used to refer to the greater than coincidental association of two conditions in the same individual (16).

The present article serves as an overview of the blood pressure changes encountered in patients with migraine. Studies in migraine literatures present in pubmed which highlighted migraine and blood pressure, migraine and hypertension, headache and blood pressure (publications till 2010) were checked. The reference lists of retrieved studies for additional reports of relevant studies were also checked. In this review, the evidences of comorbidity between migraine and high, low or normal blood pressure and the potential mechanisms of controversial views were discussed. It will be clear that despite the uncertainties regarding the presence of interictal blood pressure changes in patients with migraine, whether one condition leads to the other or both conditions are expression of similar systemic illness, both hypertension and migraine have to be carefully treated to avoid the development of cardio- and cerebrovascular complications.

Evidences of blood pressure changes in migraine:

A) Evidences that hypertension is positively associated with migraine:

Since several decades, the comorbidity of migraine with hypertension is a widely accepted issue despite the absence of confirmation by well-designed studies. In general, headache, particularly early-morning pulsating headache, is usually considered a symptom of hypertension and poor control of blood pressure may exacerbate the frequency and severity of migraine (17).

In 1913, Janeway (18) noted that migraine was common in subjects with arterial hypertension and since then the relation between blood pressure and headache has been examined in many studies (8-11,19-26). A higher prevalence of headache (27-30) and migraine (31,32) has been reported in hypertensive patients than among normo-tensive controls. On the other hand, a higher prevalence of hypertension has been reported in patients with headache (24,33-35); or migraine (36-38); than among headache free people.

Grebe et al. (39) retrospectively analyzed 64 files of headache outpatient clinic (Coimbra, Portugal), chosen randomly among patients suffering from migraine or tension headache. The authors found that the prevalence of hypertension was 35,9% among all patients (migrainous and non-migrainous headache), 28,5% among migraine patients and 44,8% among patients with tension headache. The prevalence of resistance to treatment was 39,8%, 34,3% and 41,3%, respectively. Of the patients resistant to treatment 60% were hypertensive and 62,5% of the hypertensive patients showed resistance to therapy. In the study of Prudenzano et al. (40), the authors found higher prevalence of hypertension in patients with tension headache. In 2005, Pietrini et al. (17) examined a total of 1486 consecutive outpatients with headache recruited from the department of Internal Medicine, Italy. In all headache groups, the prevalence of hypertension was higher than in general population. Hypertension was present in 28% of the patients, and was particularly common in medication-overuse headache (60.6%), chronic tension headache (55.3%), cluster headache (35%), episodic tension headache (31.4%), but less common in migraine without aura (23%) and migraine with aura (16.9%). In the preliminary case control study done by Hamed et al. (11) on 63 adult patients with migraine (n = 44) and tension headache (n = 19), the authors found higher systolic blood pressure in migraine without aura, transformed migraine compared to control subjects ($p<0.045$, $p<0.002$), while diastolic blood pressure was higher in patients with migraine with aura, transformed headache and tension headache ($p<0.041$, $p<0.002$, $p<0.002$) and in patients with tension headache than migraine with aura ($p<0.024$).

Information about the comorbidity of migraine and hypertension or hypertension frequency in migraine patients was also shown in large population based studies. In 2005, Scher et al. (41) studied 5,755 subjects from the Genetic Epidemiology of Migraine Study in the Netherlands and found higher blood pressure (systolic BP >140 mm Hg or diastolic BP >90 mm Hg) in individuals with migraine compared to those without migraine. In the population based study done by Gudmundsson et al. (42) evaluated 10,366 men and 11,171 women with migraine in a population-based study, the authors found that patients with migraine had higher diastolic blood pressure and lower systolic blood pressure and pulse pressure compared to controls. They also found that one standard deviation (1-SD) increase in diastolic blood pressure significantly increased the probability of migraine by 30% of women compared to 14% of men, while one standard deviation (1-SD) increase in systolic blood pressure

2010
Vol.1
No. 2:2
doi: 10:3823/306

and pulse pressure significantly decreased the probability of migraine by 19% and 13% of men and 25% and 14% of women, respectively.

The possible mechanisms of comorbidity of migraine with hypertension:

Shared biological mechanisms have been suggested as a link between migraine and hypertension. One such mechanism may be the rennin-angiotensin system, which is certainly involved in hypertension and has activities in the CNS that may be relevant for migraine pathogenesis (43-45). In support: **a)** attacks of migraine without aura and higher angiotensin converting enzyme activity are more frequent in subjects with angiotensin converting enzyme DD gene, and **b)** Clinical trials indicated that angiotensin-converting enzyme inhibitors as captobril and angiotensin II receptor blockers as Lisinopril are effective in the prophylactic treatment of migraine. In addition to their action on angiotensin-converting system, they alter sympathetic activity, inhibit free radical activity, increase prostacyclin synthesis and block the degradation of bradykinin, encephalin and substance P. All are implicated in the pathophysiology of migraine (44,45).

B) Evidences that hypertension is not associated with headache:

Most cross-sectional studies performed in unselected populations did not report significant association (negative or positive) between blood pressure and the prevalence of Headache. Chen et al. (46) found no association between migraine and hypertension in 508 young women with migraine and 3902 without migraine. In a cross sectional study of Wiehe et al. (12), the authors studied 1174 individuals older than 17 years, representative of inhabitants of Porto Alegre, RS, Brazil and complained of migraine or tension headache. The authors found that **i)** individuals with optimal or normal blood pressure complained of migraine more frequently than participants with high-normal blood pressure or hypertension, **ii)** episodic and chronic tension headache was not associated with hypertension in lifetime in the last year, and **iii)** individuals with migraine-like episodes of headache may have lower blood pressure than individuals without headache. In a cross-sectional study conducted in the hypertension clinic of a tertiary care University hospital in Brazil, Fuchs et al. (47), investigated 1763 subjects for the association between hypertension classified at moderate to severe stages and headache. The authors found that headache and hypertension was not associated. In addition, they found that pulse pressure and headache were inversely associated. In the large prospective study done by Hagen et al. (48), the authors estimated the relative risk of headache (migraine or non-migrainous headache) in relation to blood pressure at baseline in a total of 22 685 adults not likely to have headache, had their baseline blood pressure measured in 1984-6, and responded to a headache questionnaire at follow up 11 years later (1995-7). The authors found that subjects with a systolic blood pressure of 150 mm Hg or higher had 30% lower risk (risk ratio (RR) = 0.7, 95% CI 0.6-0.8) of having non-migrainous headache at follow up compared with those with systolic pressure lower than 140 mm Hg. For diastolic blood pressure, the risk of non-migrainous headache decreased with increasing values, and these findings were similar for both sexes, and were not influenced by use of antihypertensive medication. For migraine, there was no clear association with blood pressure. In the randomized sample of the Vobarno population done by Muiesan et al. (13) (Brescia, Italy), the authors evaluated the prevalence of headache in a general population sample (n = 301, 126 males, 175 females with age range 35-50 years) to determine its relationship to hypertension (diagnosed by office and/or 24 hours blood pressure). The authors found no differences in headache prevalence (58% vs 55%), migraine prevalence (32% vs 28%) and use of analgesic drugs in the presence of headache (82% vs 78%) between hypertensive (93.5% newly diagnosed, 6.5% treated) and normo-tensive subjects. The first population based study that uses International Headache Society (IHS) criteria for classification of headache found 11 % hypertension in 974 subjects (49). However, the study did not report any difference on incidence of headache between hypertensives and non-hypertensives.

In addition to the above, there is a consensus agreement within the International Headache Society that chronic arterial hypertension of mild to moderate degree does not cause headache but this may not be the case in patients with hypertension classified at more severe stages. Severe hypertension in the setting of new acute headache may indicate a serious underlying cause and requires urgent investigation (50).

The possible factors or reasons for the denied association between migraine and hypertension:

The authors who found no association between migraine and arterial hypertension consider that the frequency rates of some common vascular risks (as hypertension) might be increased among patients with migraine which is also common (coincidental or chance association). Hypertension is also a common and consistent health problem in both developed and developing countries and its prevalence is currently rising steadily (51). In general population, the prevalence of hypertension is 28.7% (52). In economically developed countries, the prevalence of hypertension ranged between 20 and 50%. The prevalence of hypertension varies widely among different populations, with rates as low as 3.4% in rural Indian men and as high as 72.5% in Polish women (53). The estimated prevalence of hypertension in Egypt was 26.3%. Hypertension was slightly more common in women than in men (26.9% versus 25.7%, respectively) (54). Since both hypertension and migraine are frequent in popula-

2010
Vol.1
No. 2:2
doi: 10:3823/306

tion, any association between them is likely to be detected in large series. In fact individuals seeking medical care often show a high rate of association between two medical conditions which may be independent in the general population i.e., due to a Berkson's bias. In 10-20% of the population migraine and hypertension can be found together.

C) Evidences that hypertension is negatively associated with headache:

Recent large-sample prospective and population-based studies showed a negative correlation between migraine and hypertension (12,48,55) with lower systolic pressure levels in migraine patients than in controls. Another indirect indication of this paradoxical link is suggested by the positive results of ACE inhibitors and sartans for migraine prophylaxis (56,57).

Hegan et al. (48) and Wiehe et al. (12) showed that migraine patients had lower values of blood pressure. Tzourio's et al. (55) found lower blood pressure and reduced carotid-intima media thickness (evidence of hypertension) in migraine patients. Recently, Tronvik and his colleagues (14), looked at the association between migraine and non-migrainous headache and various measures of blood pressure: systolic, diastolic, mean arterial pressure (average of diastolic and systolic), and pulse pressure (systolic minus diastolic). The authors used both cross-sectional and prospective data from two large epidemiologic studies covering 51,353 men and women over the age of 20 living in Trondheim, Norway. The reason for the study was to explore the link between blood pressure and headache frequency, and how blood pressure medication affects that relationship. The two large studies were called HUNT1 (Nord-Trøndelag Health Survey 1984-1986) and HUNT2 (Nord-Trøndelag Health Survey 1995-1997). The main topics of HUNT-1 included blood pressure, diabetes mellitus, and health related quality of life (58,59). While HUNT-2 was more extensive than HUNT-1, and among several topics, HUNT-2 included 13 questions related to headache (58). In HUNT study, Tronvik and his colleagues observed that: **i)** increasing systolic pressure was linked with decreasing prevalence of migraine and non-migrainous headache (people with higher systolic blood pressure were up to 40 per cent less likely to have headaches), **ii)** The most robust and consistent association was the link between increasing pulse pressure and decreasing prevalence of both migraine and non-migrainous headache, **iii)** This link was present for both men and women, in both studies, and **iv)** The finding was less clear in cases where people were also taking blood pressure medication.

The possible mechanisms of the negative association between migraine and hypertension:

Researchers in Norway have shown that high blood pressure is linked to fewer headaches, possibly due to having stiffer artery walls which affects a homeostatic process that regulates blood pressure and decreases sensitivity to pain, i.e. a phenomenon called "hypertension-associated hypalgesia" (blood pressure linked reduction in pain sensitivity). In support: **a)** an inverse relationship between blood pressure levels and sensitivity to painful stimuli extends into the normo-tensive range (60), **b)** low pain sensitivity has been reported in hypertensive animals and humans and in groups deemed to be at an increased risk for the development of hypertension (61-63), and **c)** previous studies confirmed that increasing blood pressure was linked to decreasing amounts of chronic musculoskeletal pain in different parts of the body. In 2005, Hegan et al. (64) observed that individuals with a high blood pressure had a lower prevalence of chronic musculoskeletal complaints than individuals with a normal blood pressure. The authors also found that among 46 901 adults who participated in HUNT1 and HUNT 2 surveys, there was a strong linear trend of decreasing prevalence of chronic musculoskeletal complaints with increasing BP values (systolic and diastolic BP). The authors suggested that the phenomenon of hypertension-associated hypalgesia, may be one explanation for the negative association between migraine and musculoskeletal pains.

The mechanism for hypertension-associated hypalgesia is not clear. but data from humans and rats suggest an interaction between the cardiovascular and pain regulatory systems.

A role for baroreceptors in mediating the blood pressure-pain sensitivity relationship has received some experimental and clinical support. Stimulation of the baroreflex arch (a homeostatic process that helps to maintain blood pressure) in response to increased blood pressure is assumed to inhibit pain transmission at both spinal and supraspinal levels, possibly because of an interaction of the centers modulating nociception and cardiovascular reflexes in the brainstem (65). The presence of the inverse association between blood pressure and pain sensitivity in the absence of clinical hypertension also support the view that some common central mechanism is underlying the antinociception and cardiovascular regulation rather than a specific effect of hypertension itself. Sanya et al. (66) assessed the baroreflex stimulations in 30 migraine patients in a headache-free phase. The authors applied oscillatory neck suction at 0.1 Hz (to assess the sympathetic modulation of the heart and blood vessels) and at 0.2 Hz (to assess the effect of parasympathetic stimulation on the heart) to assess the changes in power of the RR-interval and blood pressure fluctuations at the relevant stimulating frequency from the baseline values. The authors found that 0.1 Hz neck suction pressure were not significantly different between the patients and controls but the RR-interval oscillatory response to 0.2 Hz neck suction was significantly less in the migraine patients compared with the controls. This confirms that central autonomic changes are associated with the pathophysiology of migraine related blood pressure changes.

2010
Vol.1
No. 2:2
doi: 10:3823/306

Although endogenous opioids are necessary for full expression of the relationship between resting blood pressure and pain sensitivity (60,61), however, the absence of the effect of opioid blockade on the blood pressure pain sensitivity relationship, leaves a doubtful role of endogenous opioid as explanation to the relationship between resting blood pressure and pain sensitivity in migraine (60). Other neurotransmitters, like catecholamines, may also be involved (61). It has been found that a polymorphism of catechol-O-methyltransferase (COMT) gene, of which its protein product is an important enzyme for the metabolism of catecholamines, may influence the response to pain (67) and may also be important also for blood pressure regulation (68). In support, antihypertensive medications may have an influence on blood pressure-pain sensitivity relationship.

Hypotension and headache: is there a relationship?

No studies reported hypotension in the inter-ictal period. However, hypotension is not excluded as comorbid with migraine. In fact, with hypotension, a painful headache is commonly experienced when one bend over and suddenly move upright his/her head. This is also called orthostatic and occurs with dramatic changes in cranial blood pressure. Once triggered, hypotensive headache presents itself just like migraine and most other headaches.

Ictal hypotension has been reported by some authors. Recently, Seçil et al. (69), recorded blood pressure at 3 times in 62 normotensive patients with migraine: (1) just before or very early, (2) during (when headache peaks), and (3) 1 hour after the attack. The authors detected diastolic hypotension in a considerable number of patients before or very early, during, and after migraine attack (5.1%). The authors hypothesized that pathophysiological mechanisms (as autonomic dysfunction) are involved in migraine, which are still largely unknown, could lead to a decrease in blood pressure. Autonomic dysfunction is also reported in many functional neuroimaging studies (fMRI and PET) with migraine (49). It has been found that during migraine attacks, some substances are released especially calcitonin gene-related peptide (CGRP) (which is the main vasodilator) due to activation of contralateral locus ceruleus, dorsal pontine area and dorsal raphe nucleus. This peptide could be the reason of diastolic and systolic hypotension during the entire attack (70).

The current opinion of the comorbidity between blood pressure changes and migraine:

Recent evidences suggest that during attacks of migraine and in the interictal period, migraine patients have changes in the properties of the systemic as well as cranial vasculature, including: generalized peripheral vasoconstriction (71), increased diameter and/or decreased distensibility of peripheral blood vessels (72), decreased brachial artery flow-mediated dilatation and increased nitrate-mediated response (73), increased brachial artery intima-media thickness (72), presence of microvascular retinal abnormalities (74) and reduced number and function of circulating endothelial progenitor cells (EPC) which are surrogate biologic markers of impaired vascular function and higher cardiovascular risk (75). Nagai et al. (76) reported significant association between enhanced radial augmentation index and migraine. Augmentation index (AI) is a parameter of arterial stiffness that can be obtained from the central arterial waveform as the ratio of augmentation pressure by the reflection pressure wave to the pulse pressure. It has been reported that central AI is closely related to several risk factors for atherosclerosis and future cardiovascular events. AI can also be obtained from the radial arterial waveform. Since radial AI is closely associated with aortic AI, radial AI itself could provide information on vascular properties (77). In the study of Hamed et al. (11), the authors found that brachial artery flow mediated dilatation was lower in patients with transformed headache and is inversely correlated with systolic and diastolic blood pressure and carotid artery intima-media thickness of all groups of headache patients (migrainous and non-migrainous).

Previous studies confirmed that hypertension is associated with modification of the physical properties of large arteries which are concerned the geometry, wall elasticity, and wall viscosity of cranial and peripheral vessels vessel (78). These properties are shared in patients with migraine and hypertension. Together with the evidences for the presence of vascular risk profile in some patients with migraine which include: high blood pressure (35), disturbed lipid profile (79), elevated body mass index (BMI) (80), insulin resistance (81), metabolic syndrome (82), hyperhomocysteinemia (83), ischemic cerebrovascular stroke (84) and coronary heart disease (85), all indicate the possibility of migraine being a local manifestation of a systemic vascular abnormality rather than a primary cerebral phenomenon.

Clinical implications:

1) Based on the above information and despite the fact that there is still uncertainity regarding the comorbidity of blood pressure changes with migraine, establishing the blood pressure should be a routine task in the assessment of all headache patients and the control of hypertension in migraine patients is an important factor for the success of migraine treatment and to lower cerebrovascular risk (86,87). A unifying view among most recent studies suggests that migraine is positively correlated with diastolic blood pressure but negatively correlated with systolic blood pressure and pulse pressure (42,87,88). Some evidence suggests that poor control of blood pressure may exacerbate the frequency and severity of migraine and other headaches (17).

2010
Vol.1
No. 2:2
doi: 10:3823/306

2) Careful consideration of the therapeutic options is important for both migraine and hypertension. At present, acute treatment of migraine includes the use of non-steroidal anti-inflammatory drugs (NSAIDS) and triptans (5-HT agonists). However, some agents used to treat migraine can exacerbate hypertension and many of the drugs used to treat hypertension may cause headache. Triptans are vasoconstrictive and cannot be used in patients with cardiovascular diseases. A promising option is the use of antihypertensive drugs in migraine prophylactics. Recently, angiotensin converting enzyme inhibitors and blockers of angiotensin II provide beneficial results in migraine prophylaxis (44). A very recent progress for migraine therapy includes the introduction of CGRP antagonist (MK-0974 or telcagepant) which shows high efficacy in treatment of migraine attacks with no adverse cardiovascular risk (89).

3) Addressing the vascular comorbidities with vascular risk profile with migraine in experimentally large sample sized studies could be a big step towards understanding vascular component of migraine attacks as well as systemic end points of attacks. It is important to point that the bidirectional association between migraine, hypertension and vascular risk factors may increase the risk of arterial endothelial damage resulting in cardio- and cerebrovascular complications (11).

2010
Vol.1
No. 2:2
doi: 10:3823/306

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2010
Vol.1
No. 2:2
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2010
Vol.1
No. 2:2
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