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Metabolic Syndrome in Migraine Patients: Recent Findings and Treatment Approach

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Abstract

The neurovascular theory explains migraine to be a result of complex pathophysiological changes leading to activation of trigeminal nociceptors by several inflammatory mediators. Different classes of drugs have been used to control migraine where specific class of drugs inhibit only specific mediators while sparing others, resulting into suboptimal treatment response. Migraine is also reported by a significant proportion of patients suffering with various metabolic syndrome related conditions. The chronic inflammation caused by metabolic disruptions has been the leading cause that contributes in inducing and worsening migraine attacks. Treating these patients for conditions such as obesity and insulin resistance has resulted in significant improvement in alleviating migraine episodes. These findings provide opportunities to devise a comprehensive migraine treatment regimen that combines pharmacotherapy with metabolic corrections, lifestyle changes and diet therapy to achieve improved treatment outcome.

Keywords: Migraine; Metabolic syndrome; Chronic inflammation; Obesity; Insulin resistance

Migraine and Current Treatment Options

Migraine is the third most prevalent neurological disorder worldwide. As per the latest estimate, US have 38 million migraine patients, with women comprising 85% of them [1]. It is more debilitating than a simple headache due to associated 'aura' like conditions that includes nausea, photophobia or phonophobia. The pathophysiological basis of migraine has been explained in terms of neurological changes originating from hypothalamus and brainstem and spreading to central trigeminovascular neurons where consequent inflammatory pathways release various inflammatory mediators including histamine, prostaglandins, leukotrienes, cytokines and tryptase [2]. These mediators act on pain nociceptors of trigeminovascular system inducing headache. While neurological theory has gained more support recently, vascular theory was once considered as the root cause of the migraine. As per vascular theory, abnormal vasodilation of cranial blood vessels results into release of pain mediators which activate pain nociceptors located on trigeminal nerves that closely follow cranial blood vessels [3]. More recently, research is focused on CGRP as pain mediator. CGRP is a prominent neuropeptide expressed in 35-50% of neurons in the trigeminal ganglia and exert vasodilation effect [4].

Significant amount of research has been conducted to understand the root cause that triggers migraine, yet a significant proportion of migraine patients do not receive optimal treatment with currently approved medications. While various professional bodies (e.g. America Headache Society) recommend Triptans, ergotamine derivative, as well as NSAIDs as first line of treatment [5], patients often fails to get satisfactory pain relief leading to need of repeated use of triptans or NSAIDs or their combination for treating same episodes [6]. Medication overuse itself results into further headache episodes and is reported by as much as 50% of patients in headache centers [6].

While research to better understand pathogenesis of migraine and find better medication is attracting significant investment, there is also a need to look at the emerging knowledge about the interplay between metabolic complications and migraine. The understanding would enable devising an optimal strategy to treat acute migraine, a disease with devastating socioeconomic burden.

Migraine and Metabolic Syndrome

Irrespective of the source, neurogenic or vascular, that triggers inflammatory immune response, the involvement of inflammatory

mediators in activation of nociceptors is well established. Further, the fact that migraine patients respond to specific treatment such as triptans, as well as non-specific treatment such as NSAIDs, implies no specific mediator can be singled out, which is confirmed by various reports that ascribe the inflammation to several mediators as described above. What has not been explored much, however, is if the inflammatory mediators are specific to the triggers in migraine patients or they preexist in migraine patients making them more susceptible to the triggers. That brings us to the question if there is any link between metabolic syndrome and migraine.

Metabolic syndrome, as defined most recently by International Diabetes Foundation (IDF, 2005) [7], is present if two or more of following criteria are present along with obesity: hyperglycemia, high triglycerides level, low HDL cholesterol and hypertension. Each of these factors has been linked to a chronic inflammatory state which is similar to those observed in migraine patients. For example, higher level of insulin in subjects with hyperglycemia activates 'eNOS' leading to increased 'NO' production [8]. 'NO' is a key mediator in inducing vasodilation and consequent migraine. Recent reports of migraine patients citing fasting as one of the prominent onset trigger and prevalence of insulin resistance in migraine patients validate this correlation [9]. In migraine patients, the average yearly number of headache days significantly increased with onset of diabetes [10]. Similarly, in obese patients, expanded adipose tissues result in increased macrophage recruitment which leads to chronic inflammatory condition [11]. In several clinical studies, obesity has been linked to migraine, especially the pain severity.

Presence of inflammation as the common component in various 'metabolic syndrome' related conditions and migraine patients and reported higher prevalence or severity of migraine in such patients provides an opportunity to explore therapies that address the inherent chronic inflammatory conditions rather than the symptomatic manifestations. More specifically, metabolic correction accompanied

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with lifestyle changes would likely enable a significant proportion of migraineurs to achieve a long-lasting migraine relief without heavily seeking preventive therapies that provide temporary symptomatic relief [12] conducted a review of previous studies on childhood migraine and concluded that restoration of ideal body weight of obese children and adolescents would reduce migraine frequency, use of analgesic therapy and risk of progression to chronic migraine. In another study, [13] conducted bariatric surgery on 24 mostly female obese patients who had persistent severe headache as one of the symptom of their obesity related disease. Significant reduction in headache days as well as severity was reported. Greater weight loss increased the probability of >50% reduction in headache days. While there is significant volume of information on how metabolic disruptions induce migraine, more work needs to be done in forms of controlled studies to evaluate the long term benefits of metabolic correction on reducing migraine episodes, severity and progression to chronic migraine.

Role of Diet in Migraine Treatment

Diet is key component of 'metabolic syndrome' treatment regimen where optimizing intake of specific macro- and micronutrients have been demonstrated to result in controlling various conditions including obesity, insulin resistance, hypertension and dyslipidemia. It's no surprise; therefore, that diet has also been shown to play an important role in migraine therapy. Caffeine, alcohol as well as foods containing gluten and histamine are linked with migraine and elimination of these foods in susceptible patients result in prevention of migraine headache [14]. In a randomized, double blind, cross-over study on 35 patients diagnosed with migraine with aura demonstrated a significant correlation between diet restriction and frequency of migraine attacks [15]. In this study, diet's propensity to induce IgG antibodies was shown to be the key component in deciding the influence of diet migraine episodes. In another study [16] demonstrated that a low-fat, plant based diet can be an effective in controlling migraine frequency and severity. There are several similar studies that explain how migraine patients who are allergic to certain foods are able to control their migraine episodes as well as severity by being mindful of their diet. Again, immune response to these foods plays a significant role in these patients.

Conclusion

Migraine headache is a consequence of immune reaction that activates nociceptors through various inflammation mediators. In fact inflammation is the root cause of several diseases. With progress in understanding pathophysiology, we are gaining deeper insights into how certain diseases are interlinked due to similar pathogenesis.

Metabolic syndrome is being increasingly recognized as a condition with chronic inflammatory conditions. Migraine, a leading neurological disease, has multifactorial triggers with chronic inflammatory condition playing a key role. Further studies measuring the effect of metabolic corrections by weight reduction, diet correction, lifestyle changes, etc. on progression of migraine would enable patients and caregivers to treat migraine in a more effective way.

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