

Systematic Review

Biomarkers in migraine: a sea of something

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ABSTRACT

Migraine is the most common headache disorder with high prevalence. Clinical features which forms basis for diagnosis are heterogenous, varying from person to person and in an individual patient from one headache to the next. In most of the migraineurs treatment is delayed, until the disease severity is high leading to significant disability and socioeconomic burden. Many patients receive various combination of prolonged therapy with no significant benefits. Identifying a biomarker might help in assessing the susceptibility, diagnosing the disease early, choosing appropriate therapeutic target and monitoring the disease course. Here in this review authors discuss most studied, promising biomarkers emerging in field of migraine. The keywords migraine, and biomarkers were used in the search engines of PubMed and Google scholar and articles identified were extensively reviewed. Genetic biomarkers ascertain susceptibility or predisposition to migraine and are valuable in diagnosis, developing novel therapeutic agents, assessing treatment response. This review briefs about most studied genetic and circulatory biomarkers of migraine. Further research into existing biomarkers with higher sample size, excluding confounding factors is necessary. Search for newer biomarkers which can be of great value in diagnosis and therapy is needed. Identifying a biomarker which is reliable, replicable, easily available and cost-effective is need of the hour in management of migraine.

Keywords: Biomarkers, Circulatory, Migraine, Neuropeptides

INTRODUCTION

Biomarker is need of the hour for many diseases and is considered as primary endpoint in clinical trials. World Health Organization (WHO) and in coordination with the other organizations, defines biomarker as “a substance, process or a structure, or its products that can be measured in the body and influence or predict the incidence of a disease outcome”.¹ A precise biomarker is one which reflects the pathophysiological process, of diagnostic and prognostic value and guides in therapeutic approach.

Migraine is a common disease with prevalence of 10-15% and a leading cause of disability. Despite being a common condition and known for several years, its pathophysiology has not been completely elucidated and

is diagnosed on clinical criteria. Identifying a biomarker for migraine would aid in the diagnosis, assist in day to day management and be of help in clinical research.

The word migraine is derived from Greek word ‘hemikrania’: hemi- half, krania-skull. Migraine is a recurrent, hemi cranial, pulsating, headache lasting for hours to days. Typical migraine consists of prodromal, aura, pain and postdrome phases. The pathophysiology of migraine involves a complex interplay between cortical spreading depression (CSD), trigemino-vascular system, neurotransmitters and migraine centre in the brainstem. The previous vascular theory of vasoconstriction causing aura and vasodilation leading to pain is incomplete and raises more questions than answers. The neurovascular theory gives broad insight into pathophysiology of migraine as on date. CSD caused by depolarisation

spreads from occipital lobe at rate of 3-4 mm/min, leading to activation of trigemino-vascular system. This in turn leads to secretion of neurotransmitters like substance P, CGRP, nitric oxide (NO) vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase activating peptide (PACAP). These substances cause vasodilation, extravasation of plasma, activation of trigemino-cervical system leading to pain. Further involvement of migraine generators in brainstem (periaqueductal gray matter, midbrain reticular formation, locus ceruleus), modulation of pain pathways to nociception, cutaneous allodynia and central sensitization causes augmentation of pain. It is believed that CSD leads to aura, involvement of trigeminal system, neurotransmitter and vasodilation causes initial pain and modulation of pain pathways causing augmentation. Understanding the pathophysiology will guide us in developing new therapeutic targets and biomarkers, which will benefit in approaching and treating migraine more effectively.

METHODS

This article reviewed potential biomarkers associated with chronic and episodic migraine. Literature searches of peer reviewed articles were conducted in PubMed database. Search words ‘biomarker’, ‘migraine’, ‘genetic’, ‘circulatory’, ‘Neuropeptides’ were used. Full text articles were analysed, and relevant references were taken.

DISCUSSION

Biomarkers of migraine can be divided into two categories: genetic and circulatory. Genetic biomarkers mainly include mutations/polymorphism of gene involved in predisposition and pathogenesis of migraine (Table 1).

Table 1: Genetic biomarkers.

Gene			
Ion channel	CACNA1A	P/Q type calcium channel	FHM 1
	ATP1A2	Na+/K- pump	FHM 2
	SCN1A	Voltage gated sodium channel	FHM 3
Enzyme	MTHFR	Methyl tetrahydrofolate reductase	Endothelial dysfunction, oxidative stress
	ACE	Angiotensin converting enzyme	
Neurotransmitter	HCRTR1	Hypocretin receptor	CSD, trigemino, vascular activation, pain modulation
	SLC6A4	Serotonin transporter	

Table 2: Circulating biomarkers.

Calcitonin gene related peptide (CGRP)
Adipocytokines: adiponectin and leptin
Cytokines: IL-1, IL-6, TNF-α and IL-10
Serotonin
Melatonin
Prostaglandins
Apolipoprotein E

Genetic biomarkers

Various studies have been done in attempts to identify genetic mutations/ polymorphisms that may be associated with development of migraine. The genetic basis of familial hemiplegic migraine (FHM) a rare subtype of migraine with aura and transient hemiplegia is well understood. Mutations associated with FHM have been demonstrated in three genes - CACNA1A (FHM1), ATP1A2 (FHM2), and SCN1A (FHM3) - which have autosomal-dominant mode of inheritance.³ In a population-based genome-wide analysis that included 5122 patients with migraine and 18,108 controls, single-nucleotide polymorphisms significantly associated with migraine included rs2651899 (1p36.32, PRDM16),

rs10166942 (2q37.1, TRPM8), and rs11172113 (12q13.3, LRP1).⁴ An another genome-wide association study identified 2 susceptibility loci of migraine without aura: MEF2D and TGFBR2.⁵

Polymorphism in MTHFR gene (MTHFR 677C>T) causes hyper homocysteinaemia resulting in oxidative stress and endothelial dysfunction leading to increased migraine susceptibility. Studies in Angiotensin enzyme converting enzyme polymorphism (ACE D/I), implicated in oxidative stress have shown protective effects against migraine.⁶ Serotonin and hypocretin are involved in migraine by virtue of involvement in CSD, activation of trigeminovascular system and pain modulation. Drugs affecting serotonergic transmission are beneficial in migraine.

In a study by Kowalska et al hypocretin receptor gene (HCRTR1) polymorphism conferred an increased risk of migraine. However, no association was found between 5-HTTLPR polymorphism of serotonin transporter gene (SLC6A4).⁷

ApoE, CGRP, matrix metallo proteinase-3 (MMP-3), aromatase enzyme, AMPA receptor gene polymorphism has been implicated in causation of migraine.⁸⁻¹¹

Circulating biomarkers

Calcitonin gene related peptide (CGRP) is an extensively studied biomarker of migraine. Following triggers of migraine, it is released by the trigeminal nerve endings. It dilates the blood vessels, acts as a proinflammatory mediator and modulates the transmission of nociceptive impulses to brain. Studies have shown increased serum concentration of CGRP in migraineurs especially during the ictal phase with decrease in concentrations following the treatment and reduction of pain severity.¹²⁻¹⁵ Thus, by virtue of reflecting the pathophysiology and therapeutic response CGRP promises to be a novel biomarker. FDA has recently approved monoclonal antibodies against CGRP in treatment of migraine.

Adipocytokines like adiponectin and leptin secreted by adipose tissue can cause neuroinflammation. Receptors for adipokines are situated in brainstem, hypothalamus, sub-fornical organs. Acting through Nuclear factor κ B (NF κ B) they induce secretion of proinflammatory cytokines IL-6 and TNF- α , thus playing a role in migraine. In studies concerning adiponectin and migraine, Total adiponectin (T-ADP) levels in serum were elevated in migraineurs compared to controls.¹⁶ Additionally, levels of T-ADP and high molecular weight adiponectin (HMW-ADP) increased during ictal phase and showed decreasing trends in responders following treatment.¹⁷

Cytokines are involved in inflammation, endothelial dysfunction, pain modulation and sensitization and thus have a role in most aspects of migraine pathophysiology. Studies have shown that proinflammatory cytokines like IL-1, IL-6, TNF- α and anti-inflammatory cytokines like IL-10 were increased during the ictal phase in migraineurs.¹⁸⁻²⁰

Apolipoprotein E (ApoE) is involved in transport and metabolism of lipids and facilitates production of CGRP. It is proposed that CSD leads to increased expression of ApoE gene.²¹ This is substantiated by an increase in the serum levels of ApoE during the ictal phase among migraineurs. In addition, increased levels of ApoE were observed among patients with migraine in the interictal period when compared to controls.²²

A study by Ferrari et al has shown increased levels of serotonin during attacks of migraine as compared to the baseline or controls.²³

Melatonin is believed to be involved in circadian rhythms and headache disorders. Levels of its metabolite 6-sulphatoxymelatonin in urine is decreased during acute attacks and this is reversed in the pain free period.^{24,25}

Prostaglandins (PG) are involved in the pathology of menstrual migraine and their levels are increased in serum during attacks of menstrual migraine and in the menstrual fluid of women with dysmenorrhea. A study of

15 women with menstrual migraine associated with dysmenorrhea indicated that saliva levels of PGD₂, PGF₂, and thromboxane A₂ (TXA₂) were elevated at 2 and 4 hours after the onset of headache attacks, and PGE₂ was elevated at 4 hours, and that these changes correlated with headache pain.²⁶

Although genetic biomarkers ascertain susceptibility or predisposition to migraine and are valuable in diagnosis, developing novel therapeutic agents, assessing treatment response; availability, cost and ethical considerations may impede its use in routine management of migraine. However, they may be of considerable benefit in migraine research. A single or small combination of circulating biomarkers which can assimilate the above said benefits, which are readily available and cost effective will help us in approaching and treating migraine better.

CONCLUSION

This review briefs about most studied genetic and circulatory biomarkers of migraine. Further research into existing biomarkers with higher sample size, excluding confounding factors is necessary. Search for newer biomarkers which can be of great value in diagnosis and therapy is needed. Identifying a biomarker which is reliable, replicable, easily available and cost-effective is need of the hour in management of migraine.

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