Chapter 1
Introduction

1. Introduction

1.1 Definition

Migraine is a common disabling primary headache disorder as described by International headache society. Primary headaches are disorders which exist without an apparent cause with recurrent and persistent head pain in comparison to secondary headaches which coexist with specific inciting factors (Mier & Dhadwal, 2018).

Classification

International Classification of Headache disorders (ICHD-3), Beta version, classifies migraine headache into two major subtypes (i) *Migraine without aura* characterized by headache with specific features and associated symptoms and (ii) *Migraine with aura* characterized by transient focal neurological symptoms preceding or associated with headache.

The diagnostic criteria for migraine without aura are:

- At least five attacks fulfilling the following criteria
- Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- Headache should have at least two of the following four characteristics:
  - unilateral location
  - pulsating quality
  - moderate or severe pain intensity
  - aggravation by or causing avoidance of routine physical activity
- During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia. (International Headache Society [ICHD-3], 2013).

1.2 Disease prevalence

In the Global Burden of Disease studies initiated by the World Health Organization, migraine first featured in the year 2000 as one of the contributing disease. It ascended up the ladder from 19th in ranking in 2000 to 7th in 2010 (Steiner et al., 2013), to 6th in 2013 (Vos T et al., 2013) and 7th in 2015 (GBD, 2015). It is one among the 8 chronic diseases affecting more than 10% of the population (GBD, 2015). Migraine affects one in ten people worldwide and is more prevalent in females, students and urban residents. A study published in Journal of neurological sciences in 2017 showed the global prevalence of migraine as 11.6%. The prevalence across the continents showed 10.4% in Africa, 10.1% in Asia, 11.4% in Europe, 9.7% in North America, 16.4% in Central and South America (Woldeamanuel et al., 2016). The age adjusted 3month prevalence study among US adults above 18 years of age shows 19.1% females and 9% male suffer from migraine (Burch et al., 2015). Migraine affects 10-28% of children and adolescents, making it one of the most chronic conditions in pediatric populations (Verotti et al., 2012). The prevalence of migraine headaches among both adults and adolescent populations reflects a burdensome and debilitating condition that affects productivity and wellbeing (D'Amico et al., 2011). A population based study in Karnataka, Southern India showed that the age matched 1year prevalence of migraine was 25.2%, greater in females and peaked between 35-45 years of age in both genders (Kulkarni, 2015).

1.3 Triggers of migraine

(i) Dietary factors - Food items such as dairy, processed food, fermented, pickled and marinated food, and those which contain nitrates (hot dogs, salami, bacon), tyramine (aged cheese, beans, citrus fruits, avocado, banana, onion, red wine), caffeine and histamine (seafood) are found to be the triggers of migraine (Slavin &Ailani, 2017).

The onset of headache due to the above can be understood by theories of brain-gut axis where a sensitive nervous system develops hyper excitability as a response to multiple environmental and immunological factors (Cady et al., 2012)

Diet and nutrition can also bring about neurogenic and vascular inflammatory changes. Following ingestion of certain food, studies show that the rate in which neurons synthesize neurotransmitters is influenced (Wurtman, 1987). This can be supported by studies where decreased serotonin levels have shown to trigger migraine and diet has contributed to increase in serotonin levels (Young, 2007).

(ii) Environmental factors - Extreme weather conditions, travel strain, barometric pressure change, bright sunlight, flickering lights, air quality and odors, exposure to chemicals can be possible triggers for migraine (Friedman & De Ver Dye, 2009).

(iii) Life style factors - Factors such as stress, disturbed sleep pattern, excessive exercise, physical mental fatigue, irregular eating habits, smoking are possible triggers of migraine (Kelman, 2007).

Several external factors mentioned above might have an influence on the central nociceptive mechanisms. Studies demonstrate that peripheral and central sensitization of the trigeminovascular projection to the dural vasculature can exacerbate neuronal responses to innocuous mechanical and noxious intracranial dural inputs. This is considered a reason for trigger of migraine following physical activities such as exercise (Goadsby et al., 2017)

Sleep has been extensively studied as a cause of migraine. Lack of sleep, excess of sleep lead to migraine (Roth rock et al., 2010) and migraineurs report poor sleep quality and day time tiredness when compared to non-migraineurs (Zhu et al., 2013). Reduced serotonin (Panconesi, 2008), increased catecholamine's (Leiby et al., 1990) and hypothalamic orexinergic system (Holland, 2014) play a role in the onset of migraine. Orexin-containing neurons in the hypothalamus fire in wakeful states, and disruption of orexinergic signaling

results in excessive sleepiness. Orexinergic cells affect not only mono aminergic activity across the sleep cycle, but also pain modulation. The melatonin levels which get synthesized by the pineal gland during darkness may not trigger migraine but may predispose the onset of headache leading to awakening from sleep (Bruera, 2008). Since Hypothalamus is said to be involved in physiological functions as a regulator for homeostasis and therefore plays a key role in sleep cycle, thirst, feeding, arousal and urination. Hypothalamic activation has been demonstrated in migraine during and before an episode of migraine in imaging studies. We therefore understand how lifestyle plays a role as a trigger of migraine.

(iv) Other causes - Medications: Vasodilators, anti-hypertensives, diuretics, asthma medications, analgesic and ergotamine result in manifestation of Migraine.

Physical factors: Head trauma, adverse effect of invasive medical tests, exertion like sports and sexual orgasm also causes Migraine.

1.4 Pathophysiology

Migraine is a disturbance caused due to sensory processing with wide ramifications for the Central nervous system. It has a strong genetic predisposition and in clinical practice it is observed that most of the patients have first-degree relatives with migraine (Goadsby, 2012). The following are the theories which explain the pathophysiology behind the onset of migraine:

(i) Cortical spreading depression (CSD): It is a wave of cellular depolarization/excitation followed by hyperpolarization/inhibition in neuronal and glial cells that slowly spreads across the cerebral cortex (David & Dodick, 2018). This phenomenon initiates meningeal nociceptive receptors and trigeminal nociception triggering headache mechanisms (Pietrobon & Moskowitz 2018). Cortical spreading depression is said to activate neurons in the trigeminal

nucleus caudalis, leading to inflammatory changes in pain-sensitive meningeal vascular structures, which produces headache via central and peripheral reflex mechanisms

(ii) Vascular and Neurogenic theories: Vascular inflammation may contribute to migraine where dural vessels lead to neurogenic inflammation which activates sensory neurons, characterized by vasodilatation, plasma extravasation and release of pro inflammatory molecules from mast cells (Raddant and Russo, 2011). Studies have shown that migraine attacks are associated with release of vasoactive peptides such as calcitonin gene related petide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP-38) and the neurotransmitter nitric oxide (NO) (Kaiser &Russo, 2013)

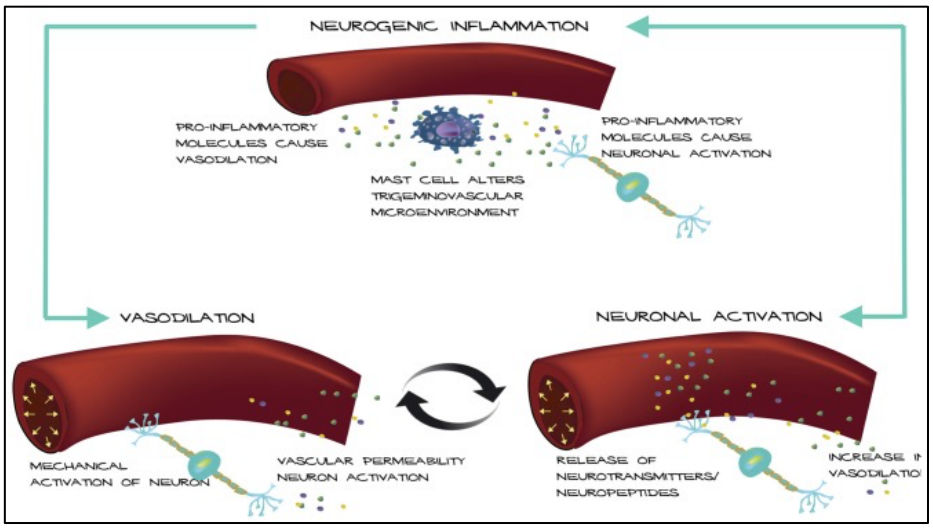

Fig 1: Model of vascular-neural coupling, Adapted from Mason & Russo, 2018

[The above diagram demonstrates Model of vascular-neural coupling. Mast cell activation and degranulation alter the trigeminovascular microenvironment via release of inflammatory molecules. Inflammatory molecules can mediate vasodilation of nearby vessels and cause nociceptor activation. Vessels can activate trigeminal neurons mechanically or by release of inflammatory mediators due to increased vascular permeability causing a positive feedback loop. (Mason & Russo, 2018)]

The characteristic throbbing pain in migraine is attributed to the activation of trigemino-vascular pathway. The pain begins when the nociceptive neurons which innervate the duramater, are activated and they release vasoactive neuropeptides such as calcitonin gene related peptide (CGRP).

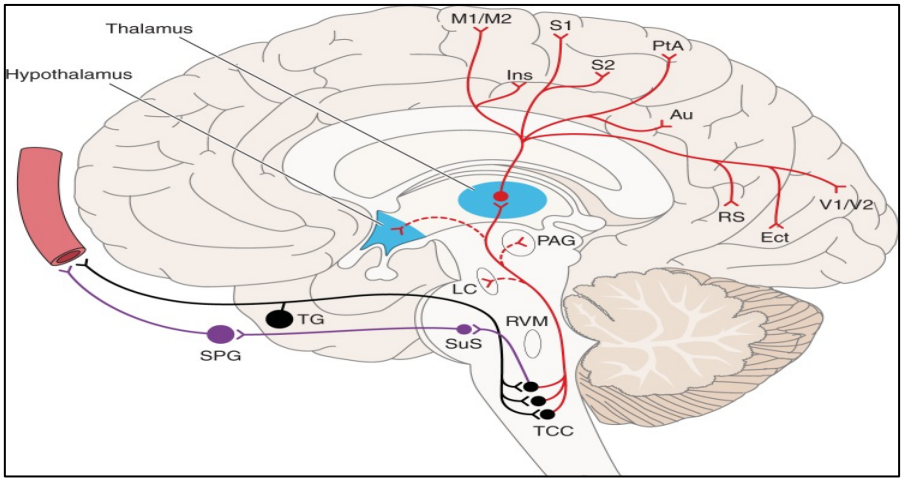

Fig 2: Anatomy of Trigemino-vascular system, Adapted from Goadsby et al., 2017

[The above diagram demonstrates the anatomy of trigeminovascular system–ascending projections. The trigeminal ganglion (TG) gives rise to pseudo-unipolar trigeminal primary afferents which synapse on intra- and extracranial structures (blood vessels) as well as the spinal cord trigeminocervical complex (TCC). Second-order neurons from the TCC ascend in the quintothalamic (trigeminothalamic) tract synapsing on third-order thalamocortical neurons. Direct and indirect ascending projections also exist to the locus coeruleus (LC), periaqueductal grey (PAG), and hypothalamus. The third-order thalamocortical neurons in turn synapse on a diffuse network of cortical regions including the primary and secondary motor (M1/M2), somatosensory (S1/S2), and visual (V1/V2) cortices. A reflex connection from the TCC to the superior salivatory nucleus (SuS) exists, which projects via the sphenopalantine ganglion (SPG) providing parasympathetic innervation to the extra- and intracranial structures. Ins, insula; PtA, parietal association; RS, retrosplenial; Au, auditory; Ect, ectorhinal; RVM, rostral ventromedial medulla]

(iii) Neuronal sensitization: The onset of migraine is attributed to the neurons becoming increasingly responsive to nociceptive stimulation. Sensitization results in decreased response thresholds, increased response magnitude, expansion of receptive fields, and development of spontaneous neuronal activity. The peripheral sensitization in afferent neurons and central sensitization in neurons of Brian and Spinal cord are said to play a role in somatic pain.

(iv) Serotonergic pathway: Serotonin (5-Hydroxytryptamine) vasoconstricts the nerve endings and blood vessels and therefore affects nociceptive pain. Low levels of Serotonin dilate the vessels leading to migraine. In the brain it is found that there are more number of neurons in dorsal raphe and trigeminal ganglia which are serotogenic. 5 out of the 7 receptor types are said to be responsible for migraine activity. 5-HT3, one of the receptors can control dopamine release, acetylcholine release and control GABAnergic system (Aggarwal et al., 2012)

1.5 Influence of migraine

There is huge personal, social and familial burden associated with migraine. Functional disability associated with migraine can lead to physical, psychological and social consequences (Dawn et al., 2009). Occupational, academic, social, leisure and family responsibilities are affected through migraine. Frequency of migraine has a positive correlation with disability.

An episode of migraine which is moderate in intensity can impair function and productivity. Quality of life is the way of perception of an individual in relation with his/her objectives, expectations, areas of interest and standards within his/her culture and fundamental values. Migraine predominantly affects females (3:1) affecting quality of life in peak years of productivity (Buse et al., 2010). It contributes extensively to the disease related burden reducing productivity and resulting in lowered Quality of life.

1.6 Treatment and management of migraine

The treatment of migraine is broadly classified into acute (abortive) and preventive (prophylactic) treatment. Acute treatment aims to stop and avoid progression of headache and preventive treatment given in the absence of headache aims at reducing the frequency and severity of migraine.

(i) Acute treatment*:* The initial option in the treatment of migraine was restricted to use of analgesics such as acetylsalicylic acid and acetaminophen. The combination of analgesics with caffeine, non-steroidal anti-inflammatory drugs such as ibuprofen etc. (Holland et al., 2012) were also the choice. Ergotamines, which act on serotonin receptors have been used with vasoconstriction being the mode of action. Triptans were the first class of drugs which were developed for acute migraine therapy acting on 5HT (serotonin) receptors with higher specificity, but have substantial limitations and contraindications (Thorlund et al., 2014).

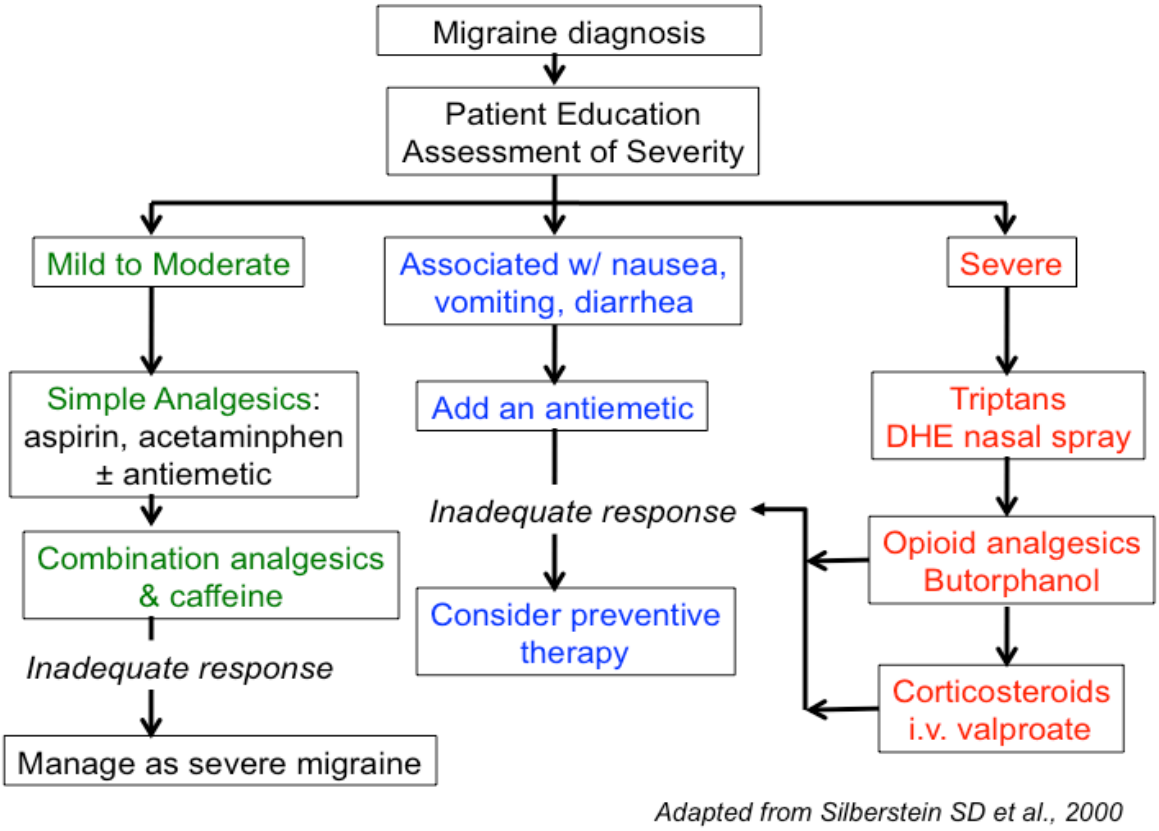

Fig 3: Details of Conventional Pharmacological treatment

(ii) Preventive treatment*:* It includes the class of drugs such as β-blockers, anti-epilectics (topimarate, valproic acid), Calcium channel blockers (flunarizine), angiotensin II receptor antagonist inhibitors (candesartan), and antidepressants (amitriptyline and venlafaxine) (Silberstein et al., 2012).

Newer pharmacological treatments for acute migraine attacks (Diener et al., 2015)

- Calcitonin gene related peptide receptor antagonist
- Serotonin 5HT receptor agonist
- Neuronal nitric oxide synthase (nNOS) inhibitors
- Transient receptor potential vanilloid (TRPV1) receptor modulators
- Propofol
- Benzopyran derivative.

Though there are interesting large range of therapeutics, many have not been able to achieve the expected efficacy. Studies therefore say that it is important to pursue definitive treatments for millions of individuals disabled though migraine.

1.7 Ayurveda and Yoga therapy

Ayurveda and Yoga are the traditional holistic systems of medicine which revolve around the two basic principles of treating a disease as well as preventing them.

Ayurveda considers health as a state of wellbeing resulting from a synergistic balance in *Doṣā* (Principal systems functions - *Vāta, Pitta* and *Kapha*), *Agni* (Digestive fire), *Dhatu* (Body tissues) and *Mala* (Excretory products). It also emphasizes on a blissful state of *Atma* (spirit), *Indriya* (sense organs) and *Manas* (mind) (Shastry, 1995). The *doṣā-Vāta, Pitta and Kapha* are the three principles which govern the physiology of the body. Each individual at birth has a different ratio of *Vāta, Pitta* and *Kapha* and this forms the psycho physiological constitution

called *Prakṛti*. The concept of *Prakṛti* is unique to Ayurveda and it determines physiological strengths and weakness, mental tendencies and susceptibility to illnesses of various types. The *dhatus* mentioned support the bodily tissues and the *mala*s are the excretory products. Ayurveda is effective in treating chronic non communicable diseases using *ahāra* (diet), *vihāra* (lifestyle) and *auṣadha* (medication). The three pillars of health are diet and digestion, elimination and sleep. Diet and lifestyle have been elaborated for each season, region and also in the management of a disease. Ayurveda recommends *pañcakarma* which is used to detoxify the body and is followed up with *rasayana* (rejuvenative medicine). *Vamana* expels mucous and toxins from stomach and respiratory system. *Virecana* expels excess bile and Pitta toxins from small intestine and liver while *Basti* cleanses and nourishes the large intestine. Nasya strengthens the supraclavicular region and raktamokṣaṇa cleanses the blood stream. This is followed up by herbal preparations and guidelines for daily regimen (Sharma et al., 2007). *Yoga* is an ancient system used to harmonize the body mind and soul. Yoga therapy is an intervention used in the management of health problems with various components of Yoga such as loosening practices (*śithilīkaraṇa vyayama*), postures (*āsana*), regulated breathing (*prāṇayama*), relaxation, meditation, diet, code of conduct and philosophy. It is based on the principles of *Panchakoṣa* (five sheaths of human existence) drawn from the *Taittiriya Upaniṣad* (Nikhilananda, 1994).

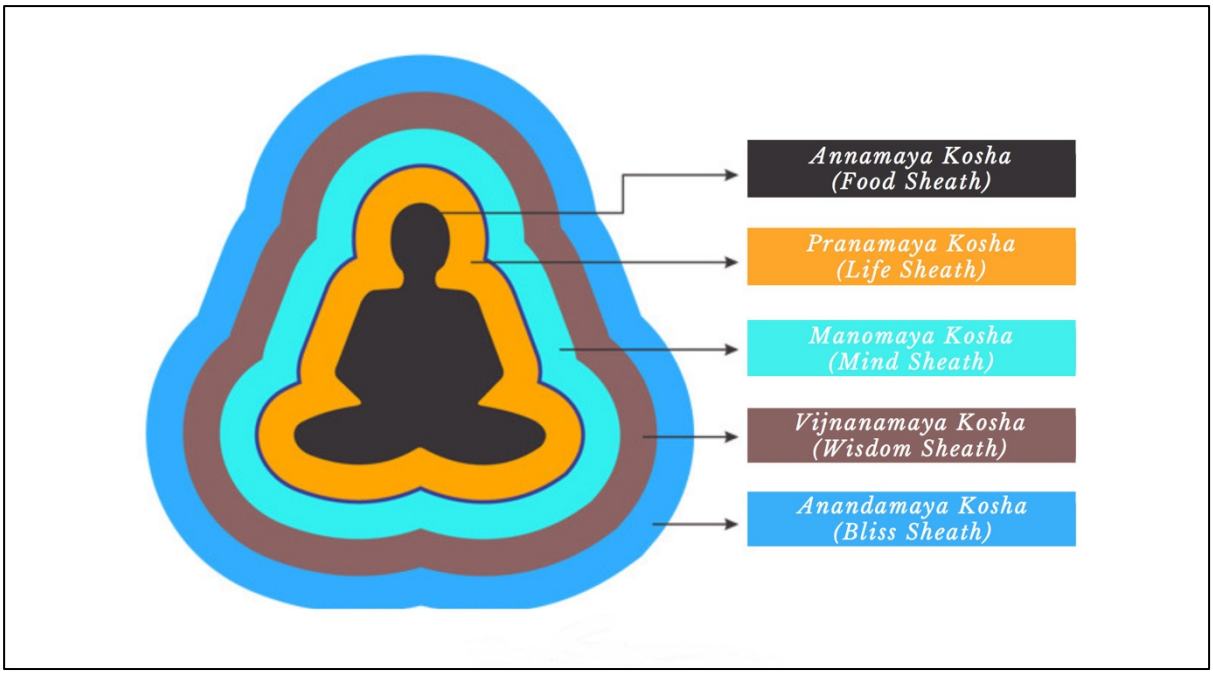

Fig 4: Concept of Panchakosha, concept adopted from Nagarathna & Nagendra, 2008.

The pathophysiology of a disease in yogic approach is understood through the concept of '*Ādhi*' mentioned in *Yoga Vāsiṣṭa.* These concepts are helpful in understanding the modern day psychosomatic illnesses and disorders.

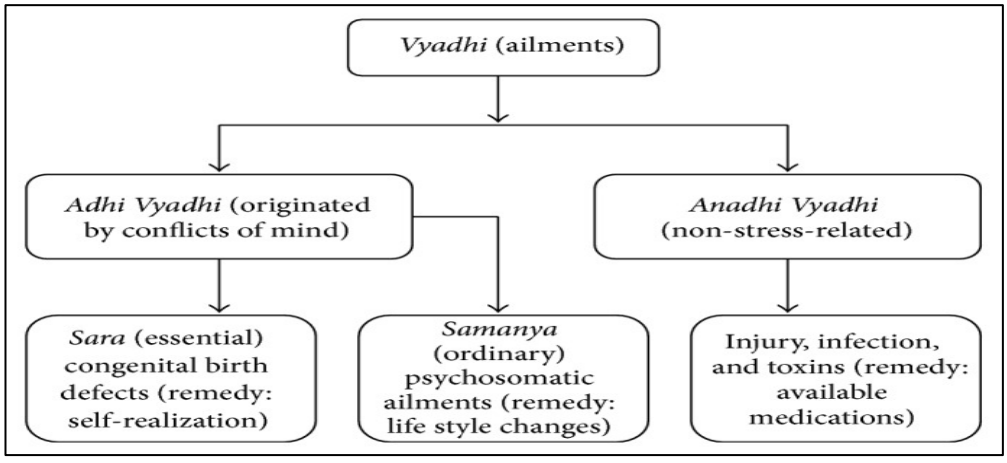

Fig 5: Concept of *Ādhija* and *Anādhija Vyadhi*, adapted from Nagarathna & Nagendra, 2008.

Practice of Yoga exhibits many benefits including improved flexibility, muscle strength, blood circulation and oxygen consumption. Yoga practices can reduce stress, improve physical, psychological and social domains for a better quality of life (Chung et al., 2012)

1.8 Need for the study

Migraine is associated with varied degree of disability and conventional medicine is unable to offer long term solutions without side effects. Studies have shown that the adherence to prophylactic treatment of conventional medicine is low and more than 50% of migraineurs discontinue such treatment, regardless to the class of medicine taken (Berger, 2012). Medication overuse is also an associated issue owing to use of Non-Steroidal Anti Inflammatory Drugs (NSAIDS) with or without doctor's prescription (Miller & Matharu, 2014). The use of Complementary and Alternative medicine is in rise and it has been noticed that CAM in migraine or in patients with severe headache is popular as they feel it is congruent to their beliefs in health and lifestyle and has lesser known side effects with less dependency on medication (Wells et al., 2011). The idea of Integrative medicine is gaining popularity and its use is increasing in the management of chronic conditions (Millstine, 2017). The pivotal medical science around which integrativeness and complementarity sought to be developed is bound to vary in different regions of the world. Such models of integrative medicine will be relevant in different social settings, will be influenced by cultural and intellectual roots along with the history of health care in that particular society (Shankar, 2010). In the Indian context, an unbroken evolution of Ayurveda therefore becomes the pivot to develop an integrative model along with yoga. Ayurveda and Yoga independently offer treatment for migraine as explained in traditional texts. But integrating the two traditional systems would enhance the benefits as they would focus on the physical and mental wellbeing for better recovery. The present study was therefore designed to understand influence of a combined

Ayurveda and Yoga therapy based intervention on migraine related disability, Quality of life, psychophysiological arousal and range of symptoms associated with migraine. This would also contribute to generation of more scientific evidence for integrative treatment protocols.