Neurology, Psychiatry and Brain Research 31 (2019) 20–26

Contents lists available at ScienceDirect

Neurology, Psychiatry and Brain Research

journal homepage: www.elsevier.com/locate/npbr

Rethinking of the concepts: Migraine is an autoimmune disease?

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ARTICLE INFO

Keywords:
Migraine pathophysiology
Migraine aetiology
Autoimmunity
Regulatory T cells
Migraine prevalence
Adaptive immunity

ABSTRACT

Background: For more than a century, scientists have investigated the pathophysiology of migraine and debated on various mechanisms of pathogenesis, ranging from the vascular theory to cortical spreading depression. For some time now, there has been a debate on the role of autoimmunity in migraine pathophysiology.

Objective: Our earlier clinical studies had revealed intriguingly but convincingly that migraine patients had reduced regulatory T cells in peripheral blood, which is a strong evidence for autoimmunity. Therefore we wished to look for further evidences available literature to probe deeper into this postulate.

Methods: We searched pubmed, Embase, Scopus and web of science for further support /refute this postulate. This is not a metaanalysis or systematic review but an exploration for evidence to substantiate a novel hypothesis.

Results: Very recently, Nurkhametova et al, have suggested that immunological dysfunction and/or autoimmunity could play a role in the pathophysiology of migraine. Migraine like headaches are also common in several dyscollagenoses. There is also a comorbid association of migraine with atopic disorders incriminating an exaggerated immune response in migraine pathophysiology. Martin and his co-workers have illustrated through elegant studies that immunotherapy would significantly decrease the headache frequency in migraine patients. Further, migraine has been reported to affect women more commonly than men, especially in the young, which is consistent with its association with oestrogens, a hormone which enhances the humoral immunity in the body.

Conclusion: From these compelling evidences, authors further advocate that immunological dysfunction and/or autoimmunity is a plausible pathophysiology in migraine.

1. Introduction

Migraine is a chronic neurological disorder characterized by unilateral throbbing headache associated with premonitory symptoms such as tiredness, listlessness, yawning, craving for sweet, nausea, vomiting, photophobia and phonophobia and neurological dysfunction or aura such as visual, sensory and speech disturbances and loss of attention and mood changes, (Silberstein et al., 2005). Migraine usually begins at childhood or youth and may remain throughout one's life. From literature it is understood that 11% of general population i.e. around 303 million people experienced frequent migraine attacks (Matilde & Mathers, 2018) and it has been shown to be a leading source of absenteeism from work (Baigi & Stewart, 2015). In western countries, around 6–8 % of men and 15–25 % of women have been diagnosed with migraine (Matilde & Mathers, 2018). It is important to note that migraine is also a major health problem associated with paediatric population, affecting 1 to 3% of 7 years old and 4 to 11% of age group between 7 to 15 years (Lipton et al., 2001) which speaks for its telling negative impact on schooling and education. The World Health Organization placed migraine as one of the twenty most disabling medical illnesses on the planet (Stovner et al., 2007). In the Global burden of disease study 2010 (GBD2010), it was ranked as the third most prevalent disorder in the world and in GBD2015, it was ranked third–highest cause of disability worldwide in both males and females under the age of 50 years (Steiner et al., 2016). The estimated cost of migraine management in Europe is €27,000 million per year (Andlin-Sobocki et al., 2005) and migraine is ranked amongst the more expensive neurological disorders in Europe. Therefore the negative impact of migraine on the quality of a patient's life and on socioeconomic front cannot be overemphasized.

Migraine is accurately diagnosed based on the history of recurrent headache and associated symptoms (Evans, 2009) and is phenotypically identified and characterised by specific diagnostic criteria (International Classification of Headache Disorders 3rd version (ICHD-3)). Based on the symptoms and duration of attack, migraine could be classified into three types: Migraine without aura (MWOA), Migraine with aura (MWA) and chronic migraine (ICHD-3). Treatment of migraine is challenging and often involves specific abortive drugs,

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https://doi.org/10.1016/j.npbr.2018.11.003
Received 5 August 2018; Received in revised form 12 November 2018; Accepted 13 November 2018
Available online 27 November 2018
0941-9500/

avoidance of precipitants, long term prophylactic medications, behavioural and life style changes and modification of environmental factors such as temperature, allergens.

Aetiopathology of migraine is not completely understood (Bussone, 2004; Tfelt-Hansen & Koehler, 2011; Burstein et al., 2015). For more than a century, scientists have investigated the pathophysiology of migraine and presented various reports ranging from the vascular theory to cortical spread depression theory. Unfortunately, none of the mechanisms have sufficiently explained the primary origin of migraine pain or migraine aura (Tfelt-Hansen & Koehler, 2011). Autoimmune mechanisms have been suggested in aetiology (Arumugam & Parthasarathy, 2016). Autoimmune diseases (AIDs) are conditions in which body immune cells mistakenly attack our own cells as an anamnestic reaction (Rose & Mackay, 2014). AIDs are one of the major healthcare crises facing the world today because of a multitude of triggering factors, their chronic nature, protean clinical manifestations and severity of the disease (Ramos-Casals et al., 2015). A high prevalence of AID of the order 10:1 has been observed in female compared to male, (Ramos-Casals et al., 2015). Natural history of these diseases are characterised by onset in young age, with worsening at reproductive stage (Bove, 2013). It is well documented that, over 80 diseases are due to the autoimmune mechanisms (Cho & Feldman, 2015). We believe there is a strong relationship between the pathogenesis of migraine and autoimmune mechanisms. In the current review, authors support and attempt to further conceptualize the involvement of immune dysfunction / autoimmunity in migraine.

2. Pathophysiology of migraine

Although, the exact aetiology of migraine is uncertain, following theories are widely accepted,

2.1. Cortical spreading depression (CSD) theory

One of the earliest and popular etiological theories of migraine was CSD. Cortical spreading depression (CSD) is a wave of electrophysiological hyperactivity in the cortex associated with long lasting blood flow enhancement, followed by a wave of inhibition (Hadjikhani et al., 2001) especially in the visual cortex area (Hadjikhani et al., 2001) during which many of the molecular species agents especially potassium ions, protons, nitric oxide, arachidonic acid and prostaglandins were found to be increased in rat cortex (Strassman et al., 1996). This was considered as a primary event in migraine headache (Pietrobon & Striessnig, 2003), and thought to be the reason for the activation of meningeal sensory neurons with resultant migraine pain initiation. Similar phenomena has been postulated in human migraine too by ictal studies although the occurrence of CSD in MWOA patients have not been established. Subsequently, it is being felt that CSD may be responsible for only aura and it may not be the exact trigger of migraine headache (Cui et al., 2014). In support of this, is a recent review of human studies refuting spreading depression demonstrating absence of functional equivalents in the ictal EEG records (Borgdorff, 2018). Therefore the robustness of CSD theory has become questionable and alternate triggering mechanisms need to be explored.

2.2. Vascular theory

In this theory, vasoconstriction and vasodilatation of meningeal or intracranial arteries have been attributed be the primary cause of headache (Wolff, 1948). However, a 3-Tesla magnetic resonance angiography (3 T-MRA) study in humans showed that there is no significant difference in diameter of the blood vessels or blood flow changes during migraine between baseline and ictal state and between homolateral and contralateral sides of the hemicrania (Schoonman et al., 2008). On the other hand, the selective 5HT1 F receptor agonist LY334370 (Ki for 5HT1 F receptor is 11.9 nM) has shown a significant anti migraines effect in clinical trials (Ramadan et al., 2003) but this effect again was unassociated with vasoconstriction and it was proven that LY334370 could be acting by blocking the transmission of nociceptive impulses within the trigeminal nucleus caudalis (Shepheard et al., 1999). A recent review had concluded that vasodilatation alone is not a trigger to cause migraine headache (Demarquay, 2014).

2.3. Involvement of mast cell in migraine pathophysiology

Activation of pain fibre “meningeal nociceptors” is believed to play a key role in promoting the intracranial pain during migraine (Pietrobon & Striessnig, 2003; Strassman et al., 1996; Waeber & Moskowitz, 2005). The dura mater is heavily innervated with pain fibres along with neuro immunological cells like resident mast cells and granulated immune cells. These cells play a critical role in neural inflammation (Christy et al., 2013; Reuter et al., 2001). The activated meningeal nociceptors promote the release of neuropeptides such as “substance P” and “calcitonin-gene-related peptide (CGRP)”, which leads to the activation and degranulation of the resident dural mast cell (Ottosson & Edvinsson, 1997; Rozniecki et al., 1999). The c-fos immunohistochemistry expression has further demonstrated that the dural mast cell degranulation is also promoting downstream activation of nociceptive neurons in the spinal trigeminal nucleus (Levy et al., 2007). Another study reported that the mast cell activation during the migraine attack could be due to an elevated level of IgE in plasma (Gazerani et al., 2003). But this has not been reproduced by other investigators. That mast cell activation takes place both in MWA and MWOA, also supports our hypothesis of an alternate mechanism in migraine pathophysiology common for MWA and MWOA.

2.4. Genetic theory of migraine

Migraine is a common feature in autosomal dominant monogenic disorder CADASIL with Notch 3 mutation (Narayan et al., 2012). Mitochondrial disorders like MELAS is also associated with migraine. Mutation in four genes, namely, CACNA1A, ATP1A2, SCN1A and PRRT2 were predominantly identified in familial hemiplegic migraine previously (Jen, 2015) which has been further confirmed recently too (Carreño et al., 2013; Martínez et al., 2016). However, no specific common genetic mutation has been identified in primary migraine. Therefore the genetic influences in migraineurs could at best be conferring a susceptibility to internal and environmental triggers and current evidences suggest that the genetic mutation alone could not be the reason for migraine.

Currently a widely accepted theory is that the dysfunction of cortical activity results in cortical spreading depression (CSD) which is a primary mechanism for migraine (Bolay et al., 2002) and an important factor in the activation of the trigeminovascular system (TGVS) (Pietrobon & Striessnig, 2003). Activation of TGVS leading to the release of a neuro active peptide known as calcitonin gene-related peptide (CGRP) (Bolay et al., 2002) is now thought to be the key factor in the progression of migraine pain (Arulmani et al., 2004). Potent activation of TGVS also causes mast cell degradation followed by plasma protein extravasation in the dura mater (Bolay et al., 2002; Charles & Brennan, 2010; Markowitz et al., 1987) and secretion of other proinflammatory agents, leading to neuroinflammation and pain. However, none of these theories will sufficiently explain the initiating factors and triggering mechanisms of migraine (Robbins & Lipton, 2010).

3. Is migraine an autoimmune disease?

Recent experimental and supportive epidemiological evidences provide sufficient indications towards migraine being an autoimmune disorder and they are discussed in detail below.

3.1. Relationship of gender, hormones and gender-specific interventions to migraine and autoimmune disorders

Higher prevalence of migraine has been reported in women (Pietrobon & Striessnig, 2003). Estimated lifetime prevalence of migraine is 12% in male and 24% in female (Russell et al., 1995). The mechanism of sex differences in migraine prevalence has not yet been understood completely (Sacco et al., 2012). Hormonal imbalance is believed to be important factor with supportive evidence coming from the fact that, more than one out of every five females experienced migraine headache during menstrual cycle (Vetvik et al., 2014; Vetvik & MacGregor, 2017; Sacco et al., 2012), believed to be due to the hormonal influences of oestrogens. Though a clinical study has shown that there is no significant differences of plasma oestrogen levels during migraine attack compared to control group (Epstein et al., 1975) yet another showed the role of estradiol in autoimmune disease progression (Ghirardello et al., 2015). A systematic review of clinical studies discussed that a drop in oestrogens levels may prevent migraine attacks (Chai et al., 2014). It is widely accepted that oestrogens play a pivotal role in immune system (Kovats, 2015) and enhances the humoral immunity in the body (Cunningham & Gilkeson, 2011). Oestrogens receptors alpha (Eα) and beta (Eβ) are predominantly expressed in immune cells. Recent animal studies have shown that ERα in T cells is required for the development of T cell–dependent colitis (Mohammad et al., 2018). The higher prevalence of migraine in women could be due to the triggering effect of oestrogens on immune T cells rather than through any direct effect.

Furthermore, our recent studies provided evidences for worsening of migraine among women who underwent procedures such as hysterectomy, dilatation and curettage (D&C) or caesarean section for delivery (Arumugam & Parthasarathy, 2015). Also, migraine prevalence was observed significantly higher among patients even after one or two years from the date of caesarean section (Arumugam & Parthasarathy, 2015). There have been studies showing a link between caesarean section and triggering of autoimmune diseases such as Type-1 diabetes, Crohn's disease, multiple sclerosis and allergic diseases such as asthma, allergic rhinitis and atopic dermatitis (Neu & Rushing, 2011; Bach, 2002). The increased incidence of post caesarean headache in women could be due to an autoimmune mechanism triggered by caesarean. These authors caution that surgeries such as cervical dilatation and curettage as well as hysterectomy and caesarean section, despite being helpful and sometimes mandatory surgical interventions for special indications in human kind, are to be carried out only prudently (Arumugam & Parthasarathy, 2015). Preclinical studies have revealed that intestinal inflammation due to the abdominal incision leads to an activation of Toll-like receptor 2 resulting in the formation of functional Foxp3 (+) Treg cells (Neu & Rushing, 2011), which is a well-known immune modulator.

3.2. Relationship of age to Migraine and autoimmune disorders

An observation is that onset of migraine is more common in adolescence especially in the age of 16–28 years, a period which is correlated with highest levels of IgE (Fig. 1a), the well-known antibodies that mediate allergic reactions in body (Amarasekera, 2011). In our clinical studies the highest risk of migraine prevalence was observed in the age group of 16–20 years (Fig. 1b) (Arumugam & Parthasarathy, 2015), a period where IgE levels peak. The fact that in adolescence, both IgG levels and migraine attacks peak may make one wonder whether there is some association between migraine and mast cell mediated atopy, especially among adolescents.

3.3. Role of cytokines in migraine pain progression

Mast cell activation is known to be a key factor in migraine pain progression (Levy et al., 2007, 2009; Theoharides et al., 2005) and it occurs in both MWA and MWOA. Activation of mast cells increases the release of cytokines. The levels of pro- and anti-inflammatory cytokines such as IL-10, TNFα, and IL-1β during attacks were significantly higher in comparison to their levels outside attacks. Whereas, no changes in the levels of IL-6, IL-4, and IL-2 were observed in the patients of both MWA and MWOA outside and during the attacks (Perini et al., 2005). In addition to this, a recent animal study has also shown that CSD induced increased release of pro-inflammatory cytokines such as IFNγ and TNFα can lead to transient disruption of myelin sheaths of CNS axons (Pusic et al., 2015). The changes in IL-10 level may indicate the allergic response of CD4 + CD25 + Treg cells (Hawrylowicz & O'Garra, 2005) and it is relevant to the proposed immune theory of migraine pathophysiology. The fluctuations in the IL-10 level are indicative of allergic response of CD4 + CD25 + Treg cells (Hawrylowicz & O'Garra, 2005). This indicates that the pathophysiology of migraine may be associated with the levels of CD4 + CD25 + immuno regulator.

3.4. CD4 + CD25 + T regulator and other T cell levels in migraine patients

The link between immunological dysfunction and migraine can be explored by assessing the number and role of immune cells such as T lymphocytes, and their cytokine release pattern in patient of migraine and healthy volunteers. Since the regulatory T cells known as CD4 + CD25 + are the primary cells playing a pivotal role in human immunological homeostasis, its imbalance leads to autoimmunity (Dejaco et al., 2006; Mellanby et al., 2009; Olive, 2007; Costantino et al., 2008). Further assessment of the ratio between the CD4 + T helper cell (promoter cell) and CD8 + cytotoxic T cells (suppressor cell) may be relevant to functional status of immune system.

In our recent clinical studies Arumugam & Parthasarathy, 2016 revealed that a significant increase in CD4 + and decrease in CD8 + population were observed in both MWOA and MWA patients compared to healthy volunteers. Interestingly, no significant difference observed among the CD4 + and CD8 + populations between the MWOA and MWA patients, hence the aura symptoms may not be related to the levels of CD4 + and CD8 + population. Further, an increased CD4 + and decreased CD8 + to leads to the increased CD4:CD8 ratio in all migraine patients (Arumugam & Parthasarathy, 2016). Increased level of CD4 + counts in patients with migraine is in agreement with the sterile neurogenic inflammation hypothesis of migraine pathophysiology (Fusco et al., 2003; Levy, 2009; Turan et al., 2011; Tfelt-Hansen & Koehler, 2011). Another clinical study revealed that an increased CD4:CD8 ratio causes the production of cytokines and excessive immunological response (Emad & Emad, 2007). Hence, the increased CD4:CD8 ratio in the patients with migraine could be responsible for the production of cytokines and initiation of migraine pain. This observation is correlated with the current proposed hypothesis of migraine pathophysiology.

The above clinical study had also revealed that the level of CD4 + CD25 + Treg cell in peripheral blood of patients with migraine is low when compared to the healthy volunteers. However, no significant difference observed between the MWOA and MWA patients. Since the CD4 + CD25 + Treg cell populations are key players in immuno regulation and autoimmune disease progression (Dejaco et al., 2006; DiPaolo et al., 2005; Laurie et al., 2002; Mariño et al., 2009), the decreased levels of CD4 + CD25 + Treg cells in migraine patients support the proposed autoimmune hypothesis of migraine pathophysiology.

Recent clinical studies have also confirmed the changes in the levels of T regulatory cells in migraineurs compared to the healthy volunteers (Nurkhametova et al., 2018). These authors had also observed reduced level CD39 and CD73 expression in the peripheral blood of migraine patients (Nurkhametova et al., 2018). Fascinatingly, CD39/CD73 pathway plays a major role in adenosine mediated purinergic signals to the immune cells and alteration in this catabolic episode leads to the immunological dysfunction (Antonioli et al., 2013). Therefore, reduction in the level of CD39 and CD73 expression is further supporting our

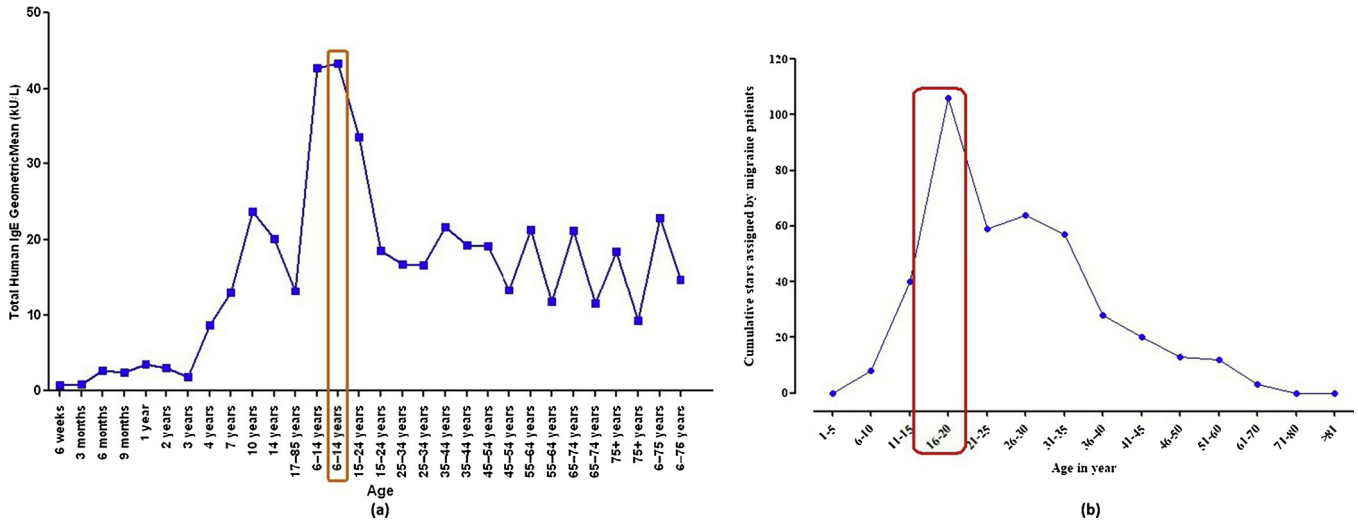

Fig. 1. a. IgE levels in plasma of various age groups of human subjects (Image adapted from Maurice et al., 2008. Handbook of Human Immunology, 2nd Edition, CRC Press). b. Image shows the association of age on migraine incidence (Image adapted from Arumugam & Parthasarathy, 2015).

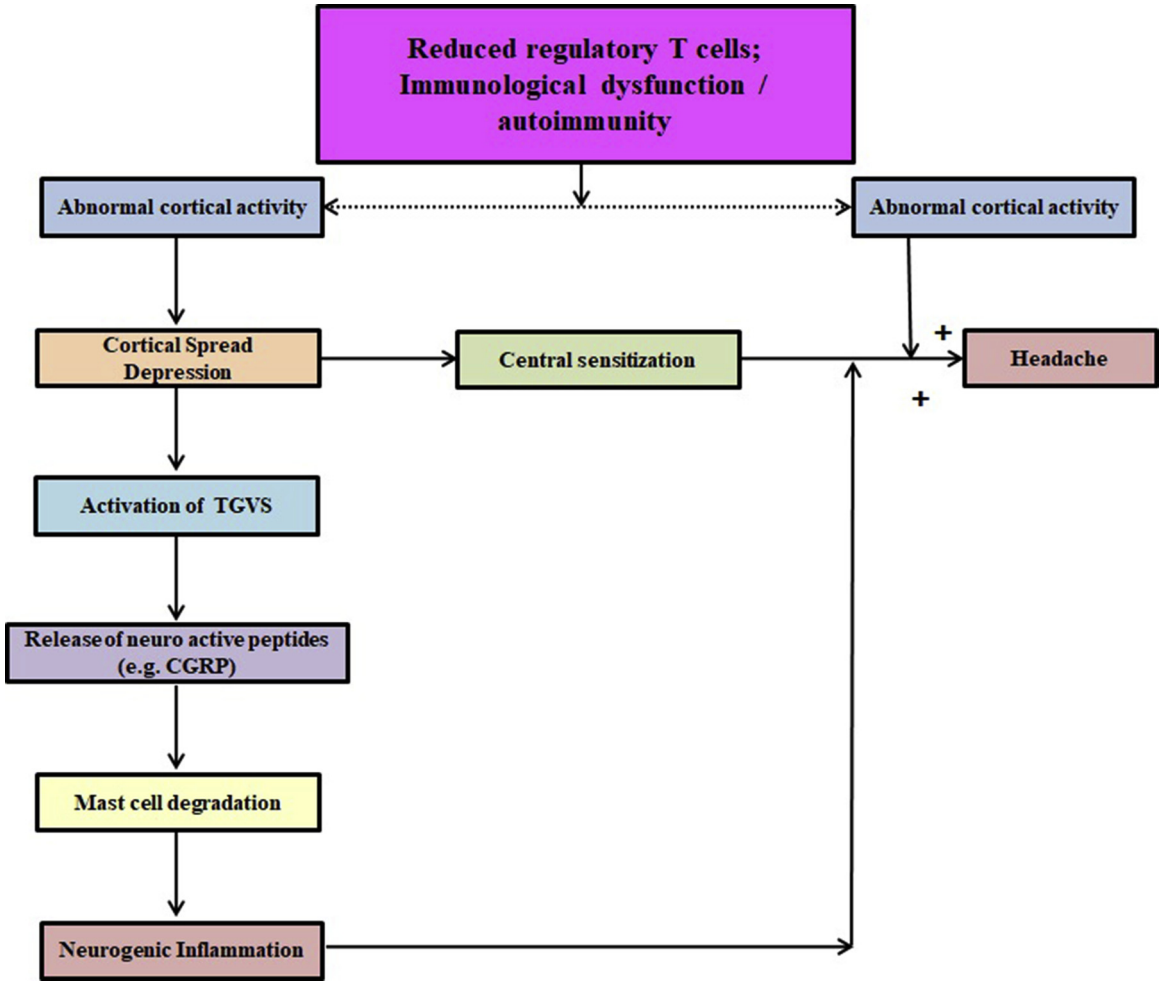

Fig. 2. Novel Auto-immune hypothesis of pathophysiology of Migraine. (Modified from flow chart adapted in Pietrobon & Striessnig, 2003).
The initial trigger/cause of abnormal brain stem activity was left as question in the original figure Pietrobon & Striessnig, 2003. With the accumulating evidence levels of immune cells in peripheral blood of migraine patients, we are proposing that the trigger/agent could be the immune dysfunction.

hypothesis of the involvement of immune cells in migraine pathophysiology.

In another clinical study, Islam and his co-workers revealed that significant levels of anticardiolipin (aCL) antibodies and anti-β2-glycoprotein I (β2GPI) auto antibodies in otherwise primary migraine patients compared to healthy volunteers, the association with presence of these antibodies suggesting migraine could be an autoimmune disorder (Islam et al., 2017).

Recent clinical studies have confirmed the changes in the levels of T regulatory cells in migrainous compared to the healthy volunteers (Nurkhametova et al., 2018). In addition to this, the author has also observed reduced level CD39 and CD73 expression in the peripheral blood of migraine patients (Nurkhametova et al., 2018). Fascinatingly, CD39/CD73 pathway plays a major role in adenosine mediated purinergic signals to the immune cells, alteration in this catabolic episode leading to the immunological disorder (Antonioli et al., 2013). Therefore, reduction in the level of CD39 and CD73 expression is further supporting our hypothesis of the involvement of immune cells in migraine pathophysiology.

3.5. Co-existence of migraine with atopic and autoimmune disorders

Clinical studies proved the comorbid association of migraine with atopic disorders (Ozge et al., 2006; Peng et al., 2018) and pointed towards the role of an exaggerated immune response in migraine pathophysiology. Changes in the level of Antiphospholipid antibodies (APLA) lead to the multi system complex autoimmune disorder namely Antiphospholipid syndrome (APS), which can involve body tissues including skin, reproductive, musculoskeletal and nervous system (Noureldine et al., 2017). A number of clinical studies had observed the association of migraine with APLA (Noureldine et al., 2017). In support of that, Systemic Lupus Erythematosus (SLE) an autoimmune disorder associated with APLA is also noted to be highly comorbid with migraine. (Glanz et al., 2001; Tjensvoll et al., 2011),

3.6. Association of migraine with psychiatric morbidity: the psychoimmunological trigger postulation

Recent clinical reviews concluded that up to 50% of patients with autoimmune disorder have associated psychiatric disorders such as depression and anxiety (Pryce & Fontana, 2017). Migraine can occur without triggers sometimes, and one school of thought is that prevalence of migraine without triggers could be the consequences of depression (Garvey et al., 1984). Psychiatric comorbidity of migraine is poorly understood. Some longitudinal clinical studies concluded that correlation of migraine and depression is bidirectional, which denote migraine increases the risk of depression and depression increases the risk of prevalence of migraine (Breslau et al., 2003; Modgill et al., 2012). One way of explaining the comorbid association of depression could be exaggerated response of immune dysfunction (Oliveira et al., 2017). However a Cochrane database review shows that selective serotonin reuptake inhibitors (SSRI) are no more efficacious than placebo in patients with migraine over 2 months continuous treatment (Moja et al., 2005). Further evidences also exist for the involvement of immunological dysfunction and / or autoimmunity in migraine headaches (Bruno et al., 2007; Heesen & Engler, 1993; Kemper et al., 2001; Tfelt-Hansen & Koehler, 2011; Islam et al., 2017).

3.7. Other supportive evidence and limitations

Recently, the selective CGRP antagonists have been approved for the migraine prevention/treatment. CGRP, an endogenous vasodilator, is expressed in the trigeminal ganglion and it plays an integral role in migraine pathophysiology. It is acting through specific CGRP receptors (Hay & Walker, 2017), which appended throughout the body including immune cells, especially in inflammatory T helper cell (Th17). Activation of these receptors mediates IL-17 production through cAMP/PKA pathway (Mikami et al., 2012). There is a growing evidence of the involvement of CGRP and its receptors in the autoimmune encephalomyelitis via cAMP/PKA (Mikami et al., 2012; Sardi et al., 2014). Further, the dramatic effectiveness of immunotherapy of migraine with monoclonal antibodies to CGRP receptors raises questions whether this response is CGRP receptor specific or due to a more generalised immunosuppression.

Preclinical animal models show that CSD triggers transient increase in the extracellular concentration of potassium, glutamate, and ATP as well as an inflammatory cascade that results in COX-2 production and meningeal mast cell degranulation which leads to the potential activation of nociceptive receptors (Karatas et al., 2013; Molchanova et al., 2004; Schock et al., 2007; Vyskocil et al., 1972). The immediate onset of headache after aura could be due to the release of such chemicals into the cortical interstitial fluid during CSD. Glymphatic system is now thought to play a vital functional role in this chemical waste clearance from the brain. In support of this, recent animal studies have shown that in migraine, there is an abnormal closure of perivascular space during CSD. (Schain et al., 2017). Though any role of immune cells in glymphatic system pathways in CSD or migraine has not been established yet, this could be an area for fertile research in migraine.

To top up all these arguments, Martin and co-workers have shown that immunotherapy would significantly decrease the headache frequency in migraine patients (Martin et al., 2011). Steroids are also useful in status migrainosus, a condition characterised by persistent severe migraine.

4. Summary

Many theories have been proposed for the pathophysiology of migraine, but none sufficiently explains mechanisms of origin of migraine. Both migraine and autoimmune disorders have similar age of onset and remission. Both migraine and AID are more common in women and menstrual phases with hyperoestrogenism and obstetric interventions can trigger migraine, which could be immune mediated. The efficacy of migraine prevention by monoclonal antibodies against CGRP receptor is dramatic. Several studies have also illustrated response of status migrainosus and migraine to steroids. CSD induced toxic chemicals in cerebral glymphatic system and its impeded clearance may have a role in progression of migraine and the role of immune cells in this field could be an exciting area for future research. Our recent findings have shown that CD4 + CD25 + regulatory population were less – a strong indicator of autoimmunity- in migraine patients compared to the healthy volunteers. Recent works showing reduced level of CD39 and CD73 expression in the peripheral blood of migraine patients and its role in adenosine mediated purinergic signals to the immune cells played by CD39/CD73 pathway also point towards an immune hypothesis of migraine. Therefore we wish to propose that migraine could have an autoimmune mechanism of origin or it could even be an autoimmune disorder. Based on this a novel hypothesis link between autoimmunity and migraine pain pathophysiology is outlined below (Fig. 2). The proposed mechanism of origin of migraine may open new avenues for a better understanding of the pathophysiology of migraine and this could pave way to development of new treatment options.

Conflict of interest

The authors have no conflict of interest.

Ethical statement

No animal or human studies were performed

Financial disclosure

There is no financial provision for the review.

Acknowledgements

Author would like to thank JIPMER e-library facility and national knowledge network, India for providing access to scientific journals and other relevant e-data.

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