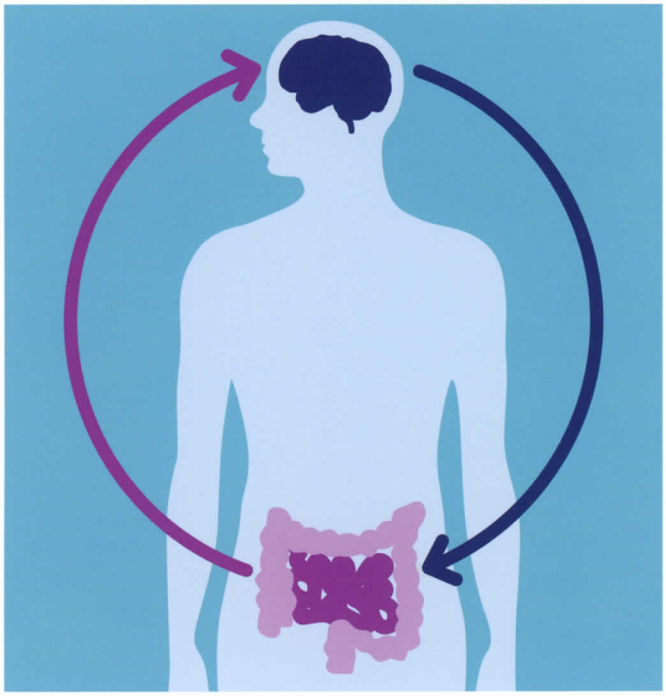
FACTSHEET

THE USE OF PROBIOTICS IN MIGRAINE: THE GUT-BRAIN CONNECTION

Migraine is a common, disabling, recurrent, neurovascular headache disorder. There is some evidence of a genetic predisposition to migraines but it is clear that other factors, such as environmental influences, also play an important role.[1]



MIGRAINE TYPES

Migraines come in various forms: common migraine (without aura), classic migraine (with aura or additional neurological symptoms), chronic (occurring more than 15 days a month), episodic (less than 15 days a month), menstrual, hemiplegic (involving weakness in one side of the body), abdominal and vomiting migraines. There are also a number of other associated headache disorders.

MIGRAINE PATHOPHYSIOLOGY

Migraines are complex and multi-factorial in nature and despite extensive research, their pathophysiology is yet to be fully understood. Bidirectional interactions between the peripheral and central nervous systems (CNS) are implicated,[2] with the primary dysfunction being in parts of the brainstem important for regulating vascular tone and pain sensation.[3] Vasodilation of cranial blood vessels in response to triggers is thought to stimulate the trigeminal nerve (a major pain pathway).[3] This induces the release of various neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P.[3] These peptides exacerbate vasodilation and cause neurogenic inflammation.[4] Imbalances in brain chemicals that help regulate pain in the nervous system also appear to play a role,[5] with low serotonin levels thought to sensitise trigeminal neuron nociceptors.[6] Interestingly, it has been observed that varying levels of ovarian hormones, especially oestrogen, influence serotonin neurotransmission and CGRP levels, making women more predisposed to attacks,[5] especially in the pre-menstrual and menstrual parts of their cycle.[7]

MIGRAINE AND THE GUT

Evidence has demonstrated that gut microbiota play a key role in the gut-brain axis and disturbances of intestinal flora may be associated with neurological disorders, including migraine.[8] Dysbiosis (a qualitative and/or quantitative change to the bacteria living in the gut) impedes mucosal immune function, motility, epithelial barrier integrity, and absorption of nutrients, all of which have possible implications for both Gastrointestinal (GI) and CNS disease.[9] Migraine is often accompanied by GI symptoms including diarrhoea, constipation and dyspepsia[9] and recent findings show a clear association between the prevalence of migraines and GI disorders such as IBS, IBD, coeliac disease, gastroparesis, gastroesophageal reflux and non-alcoholic fatty liver disease.[9-11] Children with migraine are also more likely to have experienced infantile colic (associated with dysbiosis in the gut),[12] leading some to suggest that colic may be an early life expression of migraine.[13]

The association between migraines and GI disorders may be explained by increased intestinal permeability, which allows leakage of undigested food particles and endotoxins such as lipopolysaccharides (LPS) into the bloodstream, triggering inflammation.[6] Elevated pro-inflammatory cytokines are reported in both intestinal disorders characterised by increased intestinal permeability[14,15] and migraines during attacks.[16] It is hypothesised that inflammation and immune modulation originating in the GI tract could therefore act on the nociceptors of the trigeminal nerve, triggering migraines.[17] Food allergies and intolerances are also often associated with increased gut permeability,[18] which could provide one potential explanation for the high incidence of food triggers reported by migraine sufferers. Nitrate containing compounds (found in food additives and cardiac drugs) and tyramine containing foods are commonly implicated, with some research indicating that imbalances in bacteria within the oral cavity and gut involved in the processing of these compounds could be a contributing factor.[19,20]

USE OF PROBIOTICS IN MIGRAINE

Gut dysbiosis affects the normal assimilation of nutrients (eg. tryptophan metabolism), barrier permeability and mucosal immune cells, affecting in turn communication pathways. This is thought to result in an increase of gut peptides (↑ CGPR) and abnormal release of cytokines (↑ IL-10) and hormones (↓ serotonin).[21] On the other hand

probiotics act to help restore gut microbiota balance and improve digestion, nutrient absorption and detoxification.[22] They have also been shown to improve gut epithelial barrier function via modulation of the expression of tight junction proteins,[23] thereby modulating mucosal immune responses and reducing inflammation.[22]

CONCLUSION

It therefore appears that probiotic supplementation may be of benefit in migraine patients suffering with dysbiosis and increased intestinal permeability. A 2017 literature review assessing the relationship between gut microbiota and brain function with regard to migraines concluded *"an improvement in gut microbiota and reduction of inflammation can have positive effects on strengthening gut and brain function. Moreover, it can be inferred that probiotics may have a beneficial effect on the frequency and severity of migraine headache attacks."*[24] A number of studies are showing promising results in this regard and indicate that probiotics may offer a safe, well tolerated and effective alternative to conventional migraine therapy.

Study	Intervention	Outcome
A randomised double blind placebo-controlled trial[25,26]	100 patients suffering from chronic migraine (n=50) or episodic migraine (n=50), were recruited to receive either placebo or a 14 strain probiotic (*Bacillus subtilis* PXN 21, *Bifidobacterium bifidum* PXN 23, *Bifidobacterium breve* PXN 25, *Bifidobacterium infantis* PXN 27, *Bifidobacterium longum* PXN 30, *Lactobacillus acidophilus* PXN 35, *Lactobacillus delbrueckii* ssp. *bulgaricus* PXN 39, *Lactobacillus casei* PXN 37, *Lactobacillus plantarum* PXN 47, *Lactobacillus rhamnosus* PXN 54, *Lactobacillus helveticus* PXN 45, *Lactobacillus salivarius* PXN 57, *Lactococcus lactis* ssp. *lactis* PXN 63, *Streptococcus thermophilus* PXN 66) at a dose of $4x10^9$ (4bn) CFU/day for 8 weeks.	By the end of the 8 week trial, mean frequency of migraine attacks had significantly decreased in the probiotic groups compared to placebo (40% in the episodic group and 45% in the chronic group). Migraine intensity was also significantly improved in the probiotic groups compared to placebo (29% in episodic migraine and 31% in chronic migraine). In addition, the use of abortive medication, Migraine Disability Assessment Score (MIDAS) and attack duration were also significantly reduced.
An open label design[27]	40 patients with migraine headache received several nutrients including vitamins, minerals, micronutrients, herbs, and probiotics (*Lactobacillus acidophilus* DDS-1, *L. bulgaricus*, *Enterococcus faecium*, and *Bifidobacterium bifidum*) for 3 months (CFU count not reported).	80% of the migraine participants experienced almost total relief from migraine attacks, which also significantly improved quality of life during the 90 days of the study.
An open-label pilot study[28]	29 migraine patients took a multispecies probiotic (*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19 and *Lactococcus lactis* W58) at a dose of $5x10^9$ (5bn) CFU/day for 12 weeks.	Both the number of days and intensity of migraine decreased significantly compared to baseline data. Migraine associated disability also significantly improved through MIDAS score. Relevant adverse reactions did not occur and compliance was high.

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