

An Integrative Model of Migraine Based on Intestinal Etiology

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Abstract

Current perspectives of migraine emphasize a multifactorial approach which include neurological, vascular and gastrointestinal factors. In this context, a systemic model based on intestinal etiology is proposed to integrate the varied research and clinical findings in the migraine literature.

INTRODUCTION

Migraine is a complex, systemic disorder of unknown causation. Typically, migraine presents with various neurologic, vascular, and gastrointestinal symptoms. One of the major problems in understanding the etiology and pathophysiology of migraine is how to conceptualize both the nervous and vascular aspects of the syndrome. Traditionally, migraine has been regarded as a “vascular” headache due the obvious abnormalities in circulation to the head (Thomsen and Olesen, 1995; Agnoli and Marinis, 1985). More recently, nervous system involvement has been emphasized, with particular emphasis on the trigeminal or fifth cranial nerve (Buzzi et al., 1995) An integration of these two models has culminated in a trigemino-vascular theory which integrates nerve and circulatory processes (Buzzi and Moskowitz, 1992).

Although the neurovascular components are a primary focus in medical diagnosis and treatment, historical and contemporary viewpoints also attribute great significance to gastrointestinal features. “Gastrointestinal disturbances including nausea, vomiting, abdominal cramps, or diarrhea are almost universal.” (Silberstein, 1995, p. 387)

This article explores the concept of intestinal pathology as a significant etiological factor in migraine. The conceptual basis of the integrative approach advocated in this article is derived from the systems approach of Edgar Cayce as described by Mein et al. (1998). In essence, the model emphasizes that migraine is often a consequence of problems

in the intestinal system and enteric nervous system, rather than the brain or central nervous system. According to this theory, dietary or other irritations to the bowel are common causes of migraine. Therapeutically, a variety of natural remedies are utilized to reduce intestinal irritation, heal the gut, and improve neurovascular functioning. These treatments are a complement to standard medical treatments which are directed toward symptomatic relief.

Migraine is a general classification which probably encompasses various etiological subgroups. Designations such as abdominal migraine, dietary migraine, cervical migraine, menstrual migraine, etc. suggest that a multifactorial approach is needed to understand migraine.

This article considers the role of intestinal pathology as one subgroup, perhaps a major subgroup. Or alternatively, intestinal pathology may represent a common pattern which ties together various other subgroups into a more integrated model of migraine etiology.

INTESTINAL PATHOLOGY IN MIGRAINE

Historical perspectives on syndromes such as migraine tend to take all of the symptoms into consideration in a more systemic interpretation of the illness. Thus, the significant gastrointestinal aspects of migraine received much greater attention, both with regard to causation and treatment. The medical treatments prescribed for migraine in previous eras addressed the gastrointestinal features of the illness directly with a spectrum of relatively natural therapies intended to improve digestion, assimilation and elimination through the bowel (Musser and Kelly, 1912; Hare, 1912; Spear, 1916).

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Modern medical science has acknowledged the rediscovery of the abdominal connection in migraine in various ways. The most obvious is the recognition of a diagnostic entity called "abdominal migraine" (Bentley et al. 1984; Symon and Russell, 1986; Mortimer and Good, 1990; Santoro et al., 1990). Abdominal migraine is diagnosed most often in children. For example Mavromichalis et al. studied a consecutive series of 31 children (median age 12 years) suffering from migraine. Endoscopic oesophageal, gastric and duodenal biopsy were used to determine whether the complaints were of gastrointestinal origin. Of these 31 children, 13 (41.9%) showed esophagitis, 16 (51.6%) gastritis of corpus, 12 (38.7%) antral gastritis and 27 (87.1%) duodenitis. Thus, 29 of the 31 children studied had an underlying inflammatory lesion explaining their complaints. The researchers concluded, "Our findings provide further evidence that recurrent abdominal pain is an early expression of migraine and strongly support a causal link between recurrent abdominal pain and migraine." (Mavromichalis et al., p. 406)

The pathogenesis of abdominal migraine is unclear. One obvious factor in causation of this form of migraine is diet. In fact, diet (and associated allergic and inflammatory processes) have been implicated as primary causal factors in the full spectrum of migraine manifestations. This aspect of intestinal etiology in migraine will be discussed in the next section.

Irritable bowel syndrome (IBS) is a common disorder of the intestines characterized by abdominal pain, bloating, constipation and/or diarrhea. An association between migraine and IBS has been noted. Watson et al. (1978) observed that persons with the irritable bowel syndrome (IBS) have a significantly higher prevalence of migraine-like headache than age-matched control subjects. The researchers believed that the dispersed pattern of symptoms in IBS suggests that some agent, such as a hormone, may be acting systemically. In a postal questionnaire study involving 1620 participants, Jones and Lydeard (1992) found that migraine and related systemic symptoms were significantly more common in individuals with irritable bowel (IBS) than in persons without IBS. An earlier epidemiological study by Bommelaer et al. (1990) also indicated a strong association between migraine and IBS.

Using the ¹³C-urea breath test, Gasbarrini et al. (1998) found that in 225 consecutive migraine patients, helicobacter pylori was detected in 40% of the patients. In 83% of the patients who underwent therapy for eradication of the H. pylori there was a significant reduction in the intensity, duration and frequency of migraine attacks. The researchers concluded that H. pylori is common in patients

with migraine; bacterium eradication decreases migraine; and the reduction of vasoactive substances produced during infection may be an important pathogenetic mechanism in migraine.

Rousset et al. (1985) studied two hundred hospital patients with gallstones who had been cholecystectomized on account of typical biliary colics. The patients were shown to have a high rate of migraine and other systemic symptoms which are characteristic of migraine and intestinal illness including malaise, vertigo, flatulence, diarrhoea and/or constipation. The researchers concluded that the symptoms were indicative of real functional disorder.

DIET AND MIGRAINE

"An observed association between food consumption and migraine is of respectable antiquity" (Glover et al., 1983, p. 53). Fothergill observed that migraine-type headache is usually caused by inattention to diet, with specific foods (such as milk, butter, fat meats, spices, rich puddings) being especially potent in provoking the condition (Hanington, 1974). In 1885, Brunton linked the consumption of eggs and milk to migraine (Mansfield, 1987). Early in this century, Brown reported that migraine can be caused by foods. Accordingly, Brown claimed therapeutic efficacy in the use of diet in the prevention and treatment of migraine (Brown, 1921).

The conceptualization of migraine as a gastrointestinal allergic response also has historical precedent:

"The allergists have much to say which warrants careful evaluation as to the nature of the migraine episode as well as its etiology. They believe that fatigue, nervous and emotional factors produce changes in the motor activities of the gastrointestinal system which result in duodenal stasis. This promotes the absorption of the allergens to which the patient reacts in his inherent pattern of migraine. They report that accurate allergy diets result in complete relief in 30 per cent of migraine patients and partial relief in 45 per cent." (Gordon, 1942, p. 556).

More recently, Unger and Unger (1952) advocated a multifactorial etiology of migraine in which food and stress combined to cause the syndrome. In a study by Grant (1979), 60 migraine patients used an elimination diet to determine food intolerances. The commonest foods causing reactions were wheat (78%), orange (65%), eggs (45%), tea and coffee (40% each), chocolate and milk (37% each), beef (35%), and corn, cane sugar, and yeast (33% each). When an average of ten common foods were avoided there was a dramatic fall in the number of headaches per month, 85% of patients becoming headache-free. Grant concluded

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that both immunological and non-immunological mechanisms may play a part in the pathogenesis of migraine caused by food intolerance.

In 1980, Monro et al. reported that 75% of severe migraine patients have raised levels of food-specific IgE antibodies. Wilson et al. (1980) reported that migraine patients challenged with food antigens by skin-prick test showed a significant correlation between specific food allergens, the development of migraine headaches, and the appearance of abdominal symptoms. They concluded that the clinical features of migraine can be explained as a result of chemical mediators following antigen-antibody reactions in the brain and other tissues where specific antibodies are localized. However, a study by Merrett et al. (1983) failed to find a conventional allergic mechanism associated with food intolerance in migraine patients.

In a double-blind controlled trial of oligoantigenic (limited food) diet, Egger et al. (1983) reported the recovery of 93% of 88 children with severe frequent migraine. The oligoantigenic diet consisted of one meat (lamb or chicken), one carbohydrate (rice or potato), one fruit (banana or apple), one vegetable (brassica), water and vitamin supplements. An optional diet consisting of none of the foods in the first diet was offered to patients who did not respond to the first diet. After 3 or 4 weeks, patients who had no headaches or only one during the last 2 weeks of the diet were reintroduced to excluded foods one at a time in a double-blind format to verify that the foods were causing the migraine. 26 (70%) of 40 patients experienced migraine challenges to the reintroduction of provocative foods. Interestingly, in most of the patients in whom migraine was provoked by non-specific triggers (such as flashing lights), the provocation no longer occurred while they were on the diet. Also, associated symptoms (such as abdominal pain, behavior disorder, asthma, eczema) improved in most patients.

In attempting to identify biochemical markers which distinguish dietary migraine from other forms of the illness, Glover et al. (1983) noted a deficiency of the enzyme phenolsulphotransferase. Phenolsulphotransferase is particularly active in the intestine where it probably serves to detoxify phenols which may be present in migraine triggers such as chocolate, cheese and citrus fruits. Ratner et al. (1983; 1984) demonstrated that some migraine patients suffer from lactase deficiency and milk allergy.

Monro et al. (1984) identified foods which provoked migraine in 9 patients. The patients were then given either sodium cromoglycate or placebo orally in a double-blind format, with foods previously identified as provocants. Patients given sodium cromoglycate experienced significantly less migraine symptoms than the placebo group, supporting the hypothesis of food-allergic etiology in migraine.

Mansfield et al. (1985) studied food allergy as a cause of migraine. Skin testing, elimination diets, double-blind challenges, and measurement of plasma histamine were performed on 43 adults with recurrent migraine. Thirteen subjects experienced 66% or greater reduction in headache frequency while on a diet free of milk, egg, corn and wheat. Double-blind challenges in 5 of 7 patients provoked migraine whereas placebo challenges produced none. The authors concluded, "In patients with chronic recurrent migraine, evaluation of the role of foods in causing their disease appears a worthwhile undertaking." (p. 129)

Hughes et al. (1985) utilized a nutritionally supported fast (NSF) and nutritional supportive diet (NSD) in the assessment and treatment of migraine. All 19 patients in the study showed exacerbation of symptoms during the fast followed by nearly complete relief of symptoms which the researchers interpreted as indicative of addictive withdrawal associated with food sensitivities. Longitudinal results (3 to 18 months) continued to show improvement in all 19 patients.

In seeking to understand how dietary etiology is related to the obvious central nervous system manifestations of migraine, the immune system has been cited as a possible pathophysiological link. The work of Martelletti et al. (1993) supports the hypothesis of an altered immune status in migraine without aura. Migraine may be due to a dysregulation of the bidirectional homeostasis actively operating between the immune system and central nervous system.

As an overview, Mansfield's (1987) excellent review of food allergy in migraine is highly recommended for anyone seeking an historical and conceptual overview of diet and migraine. A more general overview which reviews the role of food allergies, chemical components of foods, hypoglycemia, and taste aversion in migraine pathophysiology is provided by Perkin and Hartje (1983).

NEUROVASCULAR ASPECTS OF MIGRAINE

As inviting as the dietary migraine hypothesis is, it still does not adequately explain the obvious neurovascular aspects of migraine. In other words, what is the connection between the gut and the head in migraine? Usually, gastrointestinal features of migraine are simply regarded as side-effects of a primary central nervous system pathology.

There are two basic approaches to making the connection between intestinal causes (such as food allergies) and neurovascular symptoms. The chemical theory postulates that circulating substances produced in the gut trigger neurological reactions. "In simplest terms, the

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interaction of an allergen with IgE-specific antibody on a MAST cell leads to a cascade of events directed by a series of released mediators. A possible role for some of these mediators in the pathogenesis of the vasoconstriction and vasodilation of migraine is likely" (Mansfield, 1987, p. 315).

Another theoretical option involves nerve reflex from the peripheral nervous system to the trigeminovascular complex. Autonomic abnormalities in migraine are well known (Rubin et al., 1985; Havanka-Kanniainen et al., 1986). The vascular abnormalities in migraine may result from excessive sympathetic drive. From this perspective, neurological symptoms of the prodromal phase of classic migraine result from vasoconstriction, which is followed by vasodilation in later stages (Johnson, 1978). In addition to the vascular disturbance, other autonomic aberrations including emotional upset, increased irritability, sleep disturbance, appetite change, thirst, nausea, and temperature dysregulation are associated with migraine (Appel et al, 1992). Given the intimate relations between the autonomic and cranial nerves, perhaps autonomic dysfunction is carried over into the trigeminal nerves.

Apart from the standard view of how the autonomic (sympathetic/parasympathetic) nervous system functions, a new model is developing which acknowledges the presence of a third division to the autonomic system. Labeled the enteric nervous system (ENS), this extensive network of neurons widely dispersed throughout the gut, regulates gastrointestinal events such as peristalsis, blood flow, secretion, and absorption (Costa and Brookes, 1994; Goyal and Hirano, 1996; Gershon et al., 1994). The ENS can influence the central nervous system (CNS) both through nerve reflexes and the production of neuropeptides. It is estimated that 80% of vagal fibers are visceral afferents (Davenport, 1978). Recent work has also shown a vast overlap of neuropeptide activity in the gut and the brain (Pert et al., 1985). The ENS is an active area in physiological research with over 600 articles on Medline since 1985.

The ENS received its name from British physiologist Johannes Langley who recognized the relative independence of the abdominal nervous system. Focusing on the ganglia of the gut, he believed that they do more than simply relay and distribute information from the cerebral brain. He was unable to reconcile conceptually the great disparity between the enormous numbers of neurons [2×10^8] in the gut and the few hundred vagus fibers from the cerebral brain, other than to suggest that the nervous system of the gut was capable of integrative functions independent of the central nervous system (Wood, 1994). Langley labeled the brain in the gut the enteric nervous system (ENS).

Although for several decades Langley's work was

ignored, modern medical research has finally rediscovered the enteric nervous system. In fact, research on the nerve connections in the abdomen represents one of the exciting areas of physiological research:

"To a considerable extent, the new interest in exploring the ENS has come from the realization that both the ENS and the remainder of the autonomic nervous system are richly endowed with neurotransmitters and neuromodulators. Many substances are found in both the bowel and the brain, a coincidence that strikes most observers as intrinsically interesting, if not immediately explicable." (Gershon et al., 1994, p. 386)

"The similarity between the structure of the ENS and that of the brain, combined with the ability of the ENS to mediate relatively simple behaviors, suggests that general principles can be derived from studies of the ENS that will eventually be applicable to the CNS. Given the unique position of the ENS as the only peripheral system capable of autonomous function, it seems more likely that such principles will emerge from investigations of the ENS than from studies of other aggregates of peripheral ganglia. The parallel between the bowel and the brain also suggests that newly discovered principles of central neural function may find applicability in studies of the ENS, in a sort of reverse form of reductionism whereby the brain serves as a model for the gut." (Gershon et al., 1994, p. 414)

In addition to the biochemical and structural similarities between the cerebral brain and the gut brain, contemporary researchers are drawing computer analogies and using information processing models to describe the relationship between the brains of the body.

"The cephalic brain communicates with the smaller brain in the gut in a manner analogous to that of interactive communication between networked computers. Primary sensory afferents and extensions of intramural neurons in the gut carry information to the central nervous system. Information is transmitted from the brain to the enteric nervous system over sympathetic and parasympathetic pathways.... The current concept of the enteric nervous system is that of a minibrain placed in close proximity to the effector systems it controls. Rather than crowding the hundred million neurons required for control of the gut into the cranial cavity as part of the cephalic brain, and transmitting signals over long-unreliable pathways, natural selection placed the integrative microcircuits at the site of the effectors." (Wood, 1994, p. 424)

In summary, there are a variety of possible pathways by which intestinal irritation can be transmitted to the CNS. In particular, the enteric nervous system is a plausible link

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between intestinal and cerebral pathology.

SOMATIC DYSFUNCTION AND MIGRAINE

According to the Glossary of Osteopathic Terminology, somatic dysfunction refers to “impaired or altered function of related components of the somatic (body framework) system” (Kirksville College of Osteopathic Medicine, 1990). Somatic dysfunction covers a wide variety of musculoskeletal pathologies commonly referred to as subluxations, osteopathic lesions, etc.

In reviewing the historical and modern perspective on the causes and treatment of migraine, it must be noted that considerable attention has been given to the role of somatic dysfunction. Somewhat like the diet/migraine connection, there are numerous historical and modern adherents of somatic dysfunction as a significant factor in migraine. The point of this section is not to attribute migraine to “pinched nerves” or imply that spinal manipulation is necessarily a primary treatment of migraine. Rather it is to briefly review the literature and note its relevance to an intestinal etiology of migraine.

Historically, numerous sources in the manual therapy literature (primarily osteopathic and chiropractic) state that structure does affect function and that physical manipulation is efficacious in the treatment of migraine (Barber, 1898; Hazzard, 1905; American College of Mechano-Therapy, 1910). More recent examples of this sort of thinking are also in the literature (Parker et al., 1978; Vernon, 1995; Nelson et al., 1998).

The obvious explanations of somatic dysfunction as an etiological factor focuses on nerves which either directly affect the trigeminal (fifth cranial nerve) or disturb the vasomotor regulation of circulation. Presumably, relieving pressures on the relevant nerve centers addresses the causes of migraine in some cases. In particular, temporomandibular joint dysfunction (Clifford et al., 1996; Knutson, 1999) and cervical spine dysfunction (Vernon et al., 1992; Blau and MacGregor, 1994) have been shown to contribute to migraine.

A less conspicuous pathophysiological pattern associated with somatic dysfunction is the effects of disturbed nerve reflexes on the vegetative functions of the digestive system and intestinal tract. The vagal parasympathetic nerves which innervate the abdominal viscera parallel the spine along the cervical vertebrae. Disruption of vagal impulses can adversely affect intestinal functioning. Notably, the splanchnic sympathetics along the thoracic vertebrae also contribute to intestinal functioning. Both aspects (sympathetic and parasympathetic) of autonomic functioning coordinate closely with the ENS as described above.

Charles Hazzard, a well known and respected early osteopathic physician, recognized the various possibilities of somatic dysfunction in the etiology of migraine:

“Lesions act by disturbing sympathetic relations, reflexly causing the headaches, just as may be the case in reflex headache from uterine prolapsus. They all act by stoppage of blood flow. This may occur in several ways. The vertebral arteries may be occluded by pressure from the displaced cervical vertebra; the clavicle may hinder venous flow in the external and internal jugulars, the sympathetic irritation may set up vaso-motor reflexes and prevent proper circulation. A lesion may cause headache by direct pressure of the luxated vertebra upon a nerve fiber. A very common place for this to occur is at the atlas which impinges branches of the suboccipital nerve sent to supply the occipito-atlantal articulation. The same thing is apt to occur at any of the upper three cervical vertebra, the corresponding nerves sending branches to supply sensation to the scalp. Contraction of tissues over branches of the fifth nerve, or at their foramina of exit may cause headache. Reflexes or direct irritation of the fifth nerve may cause it. Lesion in the splanchnic area is often responsible for migraine.” (Hazzard, 1905, p. 278-279)

The premise that somatic dysfunction is a cause of migraine and that manual therapy is a suitable treatment is certainly controversial. To be sure, more research is needed in this area. With regard to the systemic model presented in this article, somatic dysfunction and its treatment should be considered as a possible factor in migraine, either directly with regard to effects via the trigemino-vascular system, or indirectly via abdominal visceral etiology. Assessment for somatic dysfunction and appropriate spinal manipulation with special attention to the cervical vertebrae and thoracic splanchnics are recommended as reasonable adjuncts to the explicitly intestinal therapies described elsewhere in this article.

CLINICAL IMPLICATIONS

Given the significant literature linking migraine to intestinal pathology and diet, it is reasonable to provide an initial assessment to determine whether the migraine patient fits the profile for intestinal etiology. A food/symptom diary is a simple tool for evaluating the role of diet in migraine. The patient is instructed to record food and beverage consumption which is compared to migraine episodes. The patient may already be aware of food triggers which can be easily documented in a clinical interview.

An elimination diet is another valuable assessment tool.

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Raskin and Appenzeller recommend that a strict diet be adhered to for two weeks. The diet consists solely of distilled water, lettuce, cauliflower, carrots, boiled or baked potatoes, cottage cheese, chicken, olive oil, and distilled white vinegar. Similar elimination diets have been advocated by many of the authors cited in the earlier diet section. Most have in common the elimination of highly suspect foods such as milk, wheat, corn, soybean, peanut, chocolate, alcoholic beverages. Carter (1985), Diamond et al. (1986), and Mansfield (1988) provide clear and practical guidelines for assessment and application of dietary principles for migraine in a clinical setting.

Manual therapy to address somatic dysfunction is also recommended. In addition to standard evaluation for cervical and temporomandibular joint dysfunction, assessment should focus on the autonomic centers in the cervical and thoracic splanchnic. Standard osteopathic or chiropractic treatment is provided depending upon assessment of these areas.

Other physiotherapies may also assist with improving intestinal and nervous system functioning. For example, Bjork (1983) recommended colonic irrigation to decrease irritation in the large bowel. This may be indicated in cases presenting with chronic constipation or an x-ray of the colon showing fecal cakes or intestinal blockage.

Thus, diet, manual therapy, and physiotherapy are complementary treatments. They are components of an integrative model in which relatively natural therapies address the underlying causes of the illness, in addition to standard medical treatment for symptomatic relief.

CONCLUSION

The etiology of migraine involves varied factors, both specific and nonspecific. Based on the literature, the intestinal etiology model described in this article provides a conceptual framework for understanding certain systemic features of migraine. Clearly, intestinal etiology in migraine does not account for all the varied manifestations of the illness. Yet it does provide a plausible approach for integration of some of the diverse research and clinical information in the literature. A complementary medicine model, in which standard medical treatments (which can often provide temporary symptomatic relief) are integrated with natural therapeutics (intended to address more fundamental causes), is proposed as a plausible next step in the treatment of migraine. Additional research is needed to further document the clinical effectiveness of this model, to evaluate the role of intestinal pathology in migraine, and to determine which elements of the treatment protocol contribute to positive outcomes.

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