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Review

Irritable Bowel Syndrome and Migraine: Bystanders or Partners?

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Irritable bowel syndrome (IBS) and migraine are distinct clinical disorders. Apart from the characteristics of chronic and recurrent pain in nature, these pain-related disorders apparently share many similarities. For example, IBS is female predominant with community prevalence about 5-10%, whereas that of migraine is 1-3% also showing female predominance. They are often associated with many somatic and psychiatric comorbidities in terms of fibromyaglia, chronic fatigue syndrome, interstitial cystitis, insomnia and depression etc., even the IBS subjects may have coexisted migraine with an estimated odds ratio of 2.66. They similarly reduce the quality of life of victims leading to the social, medical and economic burdens. Their pathogeneses have been somewhat addressed in relation to biopsychosocial dysfunction, heredity, genetic polymorphism, central/visceral hypersensitivity, somatic/cutaneous allodynia, neurolimbic pain network, gonadal hormones and abuses etc. Both disorders are diagnosed according to the symptomatically based criteria. Multidisciplinary managements such as receptor target new drugs, melantonin, antispasmodics, and psychological drugs and measures, complementary and alternatives etc. are recommended to treat them although the used agents may not be necessarily the same. Finally, the prognosis of IBS is pretty good, whereas that of migraine is less fair since suicide attempt and stroke are at risk. In conclusion, both distinct chronic pain disorders to share many similarities among various aspects probably suggest that they may locate within the same spectrum of a pain-centered disorder such as central sensitization syndromes. The true pathogenesis to involve these disorders remains to be clarified in the future.

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Key Words
Biopsychosocial model; Comorbidity; Irritable bowel syndrome; Migraine; Quality of life

Introduction

Chronic pain in the body is obviously to interfere human daily activity leading to a poor quality of life (QoL). Therefore the American Society of Interventional Pain Physicians defined it as "pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal, that is associated with chronic pathologic processes that cause continuous or intermittent pain for months or years, that may continue in the presence or absence of demonstrable pathologies; may not be amenable to routine pain control meth-

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ods; and healing may never occur."[1] Actually, chronic pain is very common in the society with a prevalence involving almost one thirds of population. It is characterized by continuous or recurrent attacking, female gender predominance, moderate to severe intensity, multiple somatic complaints, related to family responsibility, burden to work and job, associated with depression and insomnia, high personal, social and economic costs, and multidisciplinary managements etc.[1,2] On the gastrointestinal (GI) tract, irritable bowel syndrome (IBS) is mainly defined according to the presenting chronic abdominal pain or discomfort plus changed bowel movement.[3] It is also common in the society with reported prevalence ranging 5-20%.[4] The general IBS characteristics are compatible well with those of chronic pain subjects. Accordingly, IBS individuals are also frequently associated with multiple comorbidities, e.g., genitourinary disturbances including interstitial cystitis, fibromyalgia, chronic fatigue, sleep disturbance, anxiety and even headache.[5-7] On the other hand, migraine, one of intractable headaches, as IBS, is associated with these comorbidities consisting of IBS, chronic fatigue syndrome and fibromyalgia etc.[8,9] For example, Tietjen et al[10] indicted that 24% of 1,413 migraineurs had IBS, and even 17% of these migraineurs were diagnosed with IBS according to the Rome II criteria. Apart from those pain disorders located at GI tract and central nervous system (CNS), painful bladder syndrome or interstitial cystitis subjects are also at high risk to have multiple comorbidities including IBS, migraine, depression, fibromyalgia and chronic fatigue etc.[11,12]

Because of these similarly overlapped comorbidites and the high prevalences in the population, an individual simultaneously to exhibit both migraine and IBS is not rare.[13] It is of interest whether the relationship between two extremely distinct pain disorders such as IBS and migraine is just coincidentally observed without any intimate significance each other or they may coexist within the spectrum of a specific pain centralized disease/disorder. Present review is to cite the limited publications and to address what are the probable similarities between migraine and IBS in terms of prevalence, gender characters, social and economic costs, pathogeneses, diagnostic criteria, treatments and prognosis. However, the detailed review of migraine knowledge may be beyond the interest and scope of this journal. Hence we just briefly introduce the interested parts of migraine related to IBS. The final answer to the addressed question remains waiting future elegant definition and incorporation to integrate these chronic pain-related disorders.

The Risk of Irritable Bowel Syndrome Subjects Developing Migraine/Headache

As early as 1978, Watson et al[13] pointed out that half of IBS subjects simultaneously had migraine like headache, whereas only 18% of controls showed migraine. This coexistence was particularly observed among the females and young adults. Figure summarizes 6 studies which estimated the risk of IBS subjects to have coexisting migraine/headache. Apart from a very large-scale study,[17] all reports indicated that 25-50% of IBS subjects had either migraine or headache, whereas those of controls were only 4-19%. Even the Cole's study based on the US heath plan from 1996 through 2002 still confirmed the migraine risk with a crude odds ratio (OR) of 2.8, meanwhile the enrolled IBS subjects were also at high risk to experience fibromyalgia and depression. Overall, IBS subjects are at risk to have coexisting migraine/headache with an estimated OR of 2.66.

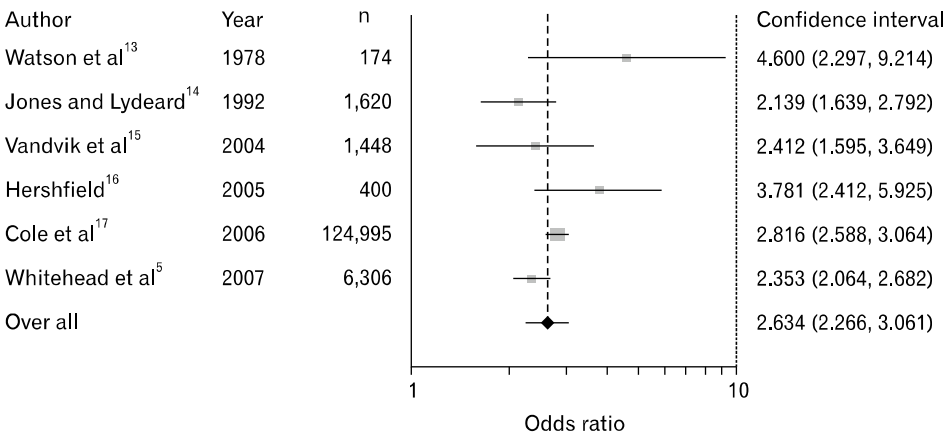

Figure. Meta-analysis of 6 studies to estimate the odds ratio of irritable bowel syndrome individuals to have coexisting migraine/headache.

Table. Comparison of the Characteristics Between Irritable Bowel Syndrome Subjects and Migraineurs

	IBS	Migraine
Community prevalence	5-10%	1-3%
Gender predominance	Female	Female
Associated comobidities		
Multiple somatic complaints	Yes	Yes
Psychiatric disturbances	Yes	Yes
Insomnia	Yes	Yes
Quality of life	Reduced	Reduced
Social, medical and economic costs	Yes	Yes
Symptoms		
Prodromal symptoms	No	Yes
Recurrence	Yes	Yes
Menstrual cycle impact	Yes	Yes
Pathogenesis		
Biopsychosocial model	Yes	Yes
Heredity, twin studies	Yes	Yes
Genetic polymorphism	Probable	Probable
Mitochondrial dysfunction, matrilineal	Probable	Probable
Hypersensitivity	Visceral, central	Trigeminal
Gonadal hormones modulated	Yes	Yes
Cutaneous/somatic allodynia	Yes	Yes
Neurolimbic pain network	Yes	Yes
5-HT related	Yes	Yes
Endocannabinoid deficiency	Probable	Probable
Abuses	Yes	Yes
Diagnosis		
Defined by symptom based criteria	Yes	Yes
Image findings	No	Yes
Characteristic pathology	No	Controversial
Treatment		
Multidisciplinary managements	Yes	Yes
Placebo effect	High	Moderate
5-HT agents	Yes	Yes
NK1 antagonists	Yes	Yes
Gabapentin	Probable	Yes
Melatonin	Yes	Yes
Psychological drugs	Yes	Yes
Behavioral therapy	Yes	Yes
Biofeedback	Yes	Yes
Botulinum toxin A injection	No	Yes
Surgery	No	Yes
IgG based elimination diet	Probable	Probable
CAM	Controversial	Controversial
Prognosis	Fair	Less fair
Cancer risk	No	No

IBS, irritable bowel syndrome; 5-HT, 5-hydroxytryptamine; NK, neurokinin; CAM, complementary and alternative medicine.

Similarities and Distinctions Between Irritable Bowel Syndrome and Migraine

Briefly, Table compares the main clinical characteristics between IBS subjects and migraineurs. In fact, some statements were only cited from a single publication. It remains unknown whether these statements are really true based on their unique observations. Accordingly, their impacts are temporarily labeled as probable, while these declarations need more studies to elucidate or decline.

General Statements

Although IBS is common in the society, the reported prevalences may be quite different among the enrolled populations. For example, the IBS prevalences among community studies are usually about 5-10%, whereas those of selected population studies may be higher of up to 20%.[4,8,18,19] Besides, the majority of studies have confirmed female predominance in the society.[14,18,20-22] With regard to migraine, the reported prevalences range 1-20%.[5,8,13-16] Likewise, two large-scale national studies from US and Taiwan controls were 2.2% and 2.5%, respectively.[12,17] Of the Asian countries, the prevalence of migraine based on population studies ranges 0.6-1.7%.[23] Now the worldwide prevalence is believed to be around 1-3%.[24,25] Migraine also exhibits a female predominance.[8,9,22,26] Interestingly, the female predominance is particularly obvious among the victims associated with comorbidities in terms of depression, fibromyalgia, chronic fatigue syndrome, insomnia and temporomandibular joint disorder etc.[7,10,22,27] Sexual steroids may contribute to these pain disorders leading to involve all aspects of biological, sociocultural and psychological activities. As previously mentioned, IBS subjects often have many somatic comorbidities to consist of migraine, fibromyalgia, chronic fatigue syndrome, panic disorder, temporomandibular joint disorder, urological disorders, interstitial cystitis, sexual dysfunction, chronic pelvic pain and dysmenorrheal etc.[5,6,8,15-17,28-30] Furthermore, IBS subjects usually receive additional abdominal surgeries. It is likely due to their coexisting multiple somatic and psychiatric comorbidities leading to the unexpected surgeries.[31,32] Very similarly, migraineurs also manifest these overlapped comorbidities including IBS.[8,9,10,33,34]

Psychological Impacts, Qaulity of Life and Social Costs

Psychological issue has been an important and undivided part of IBS. It is why a biopsychosocial model is addressed as the updated pathogenesis of IBS.[35] For example, anxiety, emotional upset, insomnia, depression, hysteria, negative copying style, poor psychological scores, sick leave, agoraphobia, panic disorder, paranoia, neuroticism and somatization have been observed among the IBS subjects.[5,6,16,17,30,36-40] Similarly, migraineurs also have these psychiatric comorbidities.[9,10,25,41,42] Since the coexisting somatic comorbidities and psychiatric disturbances, IBS individuals are often to live with a poor QoL.[36,43,44] Accordingly, absenteeism to work or school and excessive visit to physicians are common among those individuals.[45-47] The motivation driving IBS individuals to visit physicians is complex. It is believed that the disease severity, distinct personality/emotional state, concern, cancer fear, misunderstanding, easiness of medical care access and socio-cultural background have been the driving factors.[18,48-50] Migraine itself also usually leads to the reduced QoL, poor work productivity and absenteeism.[51,52] Based on an SF-36 evaluation, IBS subjects did live in a lower level of QoL compared to controls, while several SF-36 scales were particularly lower among them compared to patients with migraine, asthma and reflux disease.[53] Another study indicated that the frequency of physician visit among IBS subjects was 2.6 times more than that of migrainerus, while the number to receive diagnostic or screening tests was also higher among the IBS subjects but the specialist consultation frequencies were similar between both disorders.[54] With regard to the financial burden including direct healthcare resources, indirect costs of absenteeism and loss of work productivity, the total cost of IBS subjects is similar to that of migraineurs.[55]

Symptoms and Diagnoses

Migraine is famous for its prodromal symptoms in terms of tiredness, difficulty in concentrating, stiff neck, mood changes and GI symptoms preceding the typical headache occurrence. It was estimated that at least one thirds of them had these warning symptoms with an average duration of 9.4 hours.[56,57] Unfortunately, the authors did not address what was the definition of GI symptoms in the study. It remains controversial whether these subjects' GI symptoms as the prodrome do have concomitant IBS. Apart from these prodromal symptoms, many migraineurs may have aura e.g., nausea, osmophobia, phonophobia and photophobia before the headache occurrence.[52,58] In contrast, no prodromal symptoms have been globally accepted before the occurrence of IBS.

The IBS symptoms are characterized by recurrence as other functional GI disorders or alternatively to speak wax and wane expression.[3,35,59,60] Migraine similarly displays the recurrent character.[24,25,52,61,62] Interestingly, both extremely distinct disorders are exactly diagnosed according to the symptomatically based criteria, while these criteria are continuous in evolution whenever their understanding and knowledge are updated. For example, IBS is globally based on the famous Rome criteria.[3,59] On the other hand, diagnosis of migraine is mainly defined according to the criteria concluded from the second edition of the International Classification of Headache Disorders (ICHD-2) and its modification.[52,63,64] Since both disorders are female predominant, it is observed that menstrual cycle does enhance their pain severity.[22,65] Consequently, sex steroids likely play a role to modulate the nociception leading to an enhanced symptoms among the females particularly occurring in their cycles, while their psychosocial factors may additionally modify the finally perceived pain sensation.[22,66]

Pathogeneses

Biopsychosocial Model

The dysfunctional biopsychosocial model attempts to unify various aspects in terms of biology, psychiatry and society to address why IBS is widely to involve these independent aspects.[35,59] However, the biopsychosocial model is not only confined to the functional GI disorders but also adopted among many pain disorders including migraine, tension headache, temporomandibular joint disorder, chronic fatigue syndrome and fibromyalgia etc.[27,67,68] Accordingly, the concept of central sensitivity syndromes is tried to unite these comorbidities which apparently share the biopsychosocial dysfunction.[69]

Heredity Impact

Regarding the hereditary impact, it remains controversial whether IBS is an inheritable disorder. In contrast, migraine is somewhat related to the heredity.[70] For example, migraine is a remarkable phenotype of several genetically determined vasculopathies including cerebral autosomal dominant arteriopathy with

subcortical infarcts and leucoencephalopathy, retinal vasculopathy with cerebral leukodystrophy and hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopahty etc.[71] A meta-analysis collected from 52 twin studies indicated that heredity accounted for 50% migraine/tension headache, whereas those of back/neck pain and IBS were 35% and 25%, respectively.[72] It is considered that genetic factor may be partially responsible for these pain-related disorders.

Genetic Polymorphism

Genetic polymorphism has been extensively studied among the IBS subjects and several candidate genes are indicated to be significant among the small-scale studies. Unfortunately, recent reviews conclude that their suggested associations are very limited.[73,74] On the other hand, several genetic polymorphisms probably increase thrombotic disorders among the migraineurs; however, these putative genes are extremely different from those linked to IBS. For examples, migraine related candidate genes include *factor V Leiden*, factor V (*H1299R*), prothrombin (*G20210A*), factor XIII (*V34L*), *β-fibrinogen* and lipoprotein receptor (*LRP1*) etc, whereas IBS related candidate genes consist of serotonin transporter (*SLC6A4*), norepinephrine transporter (*NET*), alpha-2A-adrenergic receptors (*ADRA2A*), interleukin-10 (*IL-10*), G protein β3 subunit (*GNβ3*) and sodium channel (*SCN5A*) etc.[73,75,76] In fact, the potential functions of these genetic variants are controversial because they result in a small to moderate risk of developing migraine which means that migraine is a heterogeneous disorder. Until now, neither IBS gene nor migraine gene has been globally identified and accepted.

Mitochondrial Dysfunction

Among the possibility of maternal inheritance, mitochondrial dysfunction and mitochondrial DNA sequence variants were addressed closely to bowel dysfunction, migraine and depression with reported prevalences of 60%, 54% and 51%, respectively, whereas those of probable non-maternal inheritance were only 16%, 26% and 12%, respectively.[77] Unfortunately, the authors did not clearly illustrate whether the bowel dysfunction meant IBS. However, they subsequently concluded that the defective mitochondrial energy metabolism among the matrilineal relatives probably leads to these disorders including IBS.[78]

Central and Visceral Hypersensitivity

Visceral hypersensitivity has long been known leading to IBS, while the hypersensitivity is not only confined to the bowel but also involves upward to CNS.[60,79,80] Besides, the visceral sensitivity is usually gender determined since sexual steroids may enhance its perception among the female IBS subjects.[65,66,81] On the other hand, migraine, a primary brain dysfunction, is an interictal hypersensitivity to some sensory stimuli leading to the episodic activation and sensitization of trigemino-vascular pain pathway and the following headache consequences.[61,62] Sexual steroid receptors are believed to exist in the trigeminal circuits to modulate the nociceptive signals from various origins. In addition, 5-hydroxytryptamine (5-HT) has been one of the important neurotransmitters connected to migraine and its synthesis is enhanced in brain by estrogen.[22] It is likely why the females are common to have migraine and shown more severe symptomatic response. Accordingly, both IBS and migraine do exhibit a hypervigilance phenomenon responding to exogenous and endogenous stimuli although the triggers and routes of their afferent pathways may be different.[82]

Allodynia

Allodynia is a central hypersensitivity phenomenon with diminished threshold to triggers. Overall, 60% migraineurs have cutaneous allodynia which means the central sensitization at the trigeminal neurons. The allodynic migraineurs have more triggers compared to non-allodynic counterparts.[61,83] Besides, coexisting IBS and other factors such as female, comorbitidies of chronic fatigue syndrome, fibromyalgia, current depression and anxiety have been the risk factors developing cutaneous allodynia among the migraineurs.[10] Apart from visceral hypersensitivity, IBS subjects had increased cutaneous hypersensitivity following a series of repetitive nociceptive stimuli, while this increased pain sensitivity was blocked via administered dextromethorphan. This study suggests that N-methyl-D-aspartate receptor is likely the mechanism responsible for the somatic allodynia among the IBS subjects.[84] Likewise the migraine, the central, visceral and cutaneous thermal hypersensitivities are already confirmed among the IBS subjects.[85]

Neurolimbic Pain Network Dysfunction

Abnormal pain modulating circuits in the brainstem are believed as the mechanisms leading to migraine; particularly the periaqueductal gray has been labeled as migraine generator. Image study already confirmed the abnormal functional connectivity between brainstem and cortical (limbic) centers. Accordingly, a model of dysfunctional neurolimbic pain network is recently proposed to illustrate the bidirectional interaction of pain

and mood.[86] Regarding IBS, the cortical projection and modulation of received peripheral sensory stimuli are complex. Briefly, prefrontal lobe may modulate the neural activities coming from limbic and paralimbic regions, anterior cingulate cortex and hypothalamus, which in turn down modifies the activities of descending inhibitory and facilitatory pathways through the periaqueductal gray and pontomedullary nuclei. The neuronal activities among these corticolimbic pontine networks can coordinate the final perception of cognitional and emotional impacts on the visceral pain and discomfort.[87] The putative neurolimbic pain network of migraine maybe adoptable to the IBS although the neuro-pathways or networks of both disorders may not be exactly the same.

Neuropeptides

Basically, 5-HT exists abundantly in the gut with the roles to modulate gut movement, sensation, secretion and blood circulation, and this substance is still an essential CNS neurotransmitter to activate many neuronal functions particularly the mood.[87,88] The defective 5-HT activity either in gut or CNS has been shown to contribute to the pathogenesis of IBS. It is why its agonists and antagonists are employed to treat IBS.[87,89,90] Similarly, 5-HT related agents e.g., sumatriptane ($5\text{-HT}_{1B/1D}$ agonist) have been long used to treat migraine.[89] It means that defective 5-HT in CNS is also one of the mechanisms leading to migraine.[91] Usually, the 5-HT receptors related to treat migraine and anxiety mainly involve 5-HT_1 and 5-HT_2 including their subtypes, whereas those regarding IBS management are chiefly 5-HT_3 and 5-HT_4.[89] However, 5-HT_3 receptor mediates the releasing of various neurotransmitters in terms of dopamine, cholecystokinin, acetylcholine, glutamine, substance P, even itself etc. Its agonists have been effective in treating some chronic hyperalgesic disorders including IBS, migraine and fibromyalgia.[90] As 5-HT, cannabinoids (CB) own the ability to govern GI functions such as movement, sensation and secretion, the activation of CB1 and CB2 receptors appears ideal to treat IBS since this disorder is closely related to dysfunctional gut movement, sensation and secretion.[92] Regarding migraine, cannabinoids have shown dopamine blocking and anti-inflammatory abilities in alleviating trigeminovascular activation through the CB1 receptor which are also ideal in treating chronic headache as well as fibromyalgia. Besides, genetic study did confirm the impact of CB1 gene variant on the altered trigeminovascular function among a subset of migraineurs.[93,94] The endocannabinoid deficiency may be another candidate inducing these pain-related disorders.

Abuses

Childhood maltreatment or abuse is a major and global public health problem with severe impact to both physical and mental health even its influence extends into adulthood. For example, childhood sexual abuse has been one of important psychological factors connected to adult IBS, and especially these victims often display severe pain perception, psychological distress, and poorer health outcome. Their perceptive patterns can be centrally confirmed via neuro-image studies showing an enhanced nociception.[95,96] With regard to migraine, epidemiological studies already indicate the close association of childhood abuse and headache. It alternatively suggests that early life stress is one of the possible migraine pathogeneses, and a differential impact determined by sexual abuse.[97,98] Considered both disorders together, a New Zealand women study observed that migraine had a trend of childhood sexual abuse, whereas adult physical abuse was remarkably associated with it. In contrast, neither various childhood nor adult abuse was responsible in IBS.[99]

Image Studies and Pathology

Since IBS is believed to be a functional GI disorder, it means that neither structural nor biochemical abnormalities can be identified among these individuals. Based on the validated criteria, images are not essential to diagnose it.[3,35] In fact, a review confirmed that image study has no definite role to diagnose IBS, and its clinical employment is just to exclude any organic lesions which display mimic IBS symptoms such as diverticulosis, colon cancer, inflammatory bowel diseases and celiac disease even ovarian cancers etc.[100] Surprisingly, very few IBS patients were reported to have abnormal small intestinal pathology in terms of myenteric ganglionic degeneration, increased number of interstitial cells of Cajal, infiltration of CD3+ T lymphocytes, hypertrophy of longitudinal muscles, etc via full-thickness biopsy. Nevertheless, these preliminary observations were experimentally based only. Using this measure and yielding pathological observations clinically to diagnose IBS are absolutely unpractical.[101]

With regard to migraine which also behaves as a functional disorder, it does have a lot of structural abnormalities via modern neuro-images such as cerebral vascular events, white matter lesions, grey matter density alterations, iron deposition, and microstructural brain damage etc. especially among the women. However, these structural defects do not correlate well with the number or frequency of occurred migraine headache even with

progression of lesions.[102,103] It is of interest what these brain white matter lesions mean pathologically. Currently, these lesions have been suggested as infarct in origin resulted from hypoperfusion or embolism rather than arteriosclerosis or small vessel disorder, while its exact etiology is really unknown since postmortem report is still unavailable.[104] Migraine existed in some specific syndromes e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, hereditary endotheliopathy with retinopathy, nephropathy and stroke, stroke-like episodes and cerebroretinal vasculopathy etc, in which they may have obvious brain microangiopathy. In addition, patent foramen ovale is commonly observed among migraineurs than controls.[104] Overall, these structural changes are not the pathognomic characteristics of migraine since other diseases for example stroke may associate these signs. The brain characteristic pathological lesions among migraineurs remain debatable, whereas the existence of peripheral neural pathology is most unlikely.[105]

Treatments

Basically, an ideal medical treatment is best according by known pathogenesis of this disease/disorder. It is apparent that the clear or the unique the pathogenesis, the effective the treatment will be achieved. For example, *Helicobacter pylori* eradication has been a perfect measure to treat peptic ulcer diseases since the end of 20th century. If a disease or disorder can be recommended to treat via multidisciplinary managements, it means that its true pathogenesis remains too controversial or heterogeneous. For instance, there are a lot of extremely varied modalities consisting of receptor targeted new drugs, antispasmodics, antibiotics, probiotics, antidiarrheals, laxatives, bulking agents, psychological drugs and measures such as behavioral therapy, biofeedback, even complementary and alternative medicines (CAM) etc. recommended to treat IBS until now.[3,18,48,59] Very similarly, there are also multidisciplinary managements including receptor targeted new drugs, antiepileptic drugs, vasodilators, antispasmodics, steroids, non-steroidal anti-inflammatory drugs, psychological drugs and measures such as behavioral therapy, biofeedback, CAM and even considered surgeries recommended to treat migraine.[106,107] Interestingly, a subset of IBS subjects experience an unexpected good efficiency to placebo treatment up to 40-50%.[59,108] Because the placebo responded subjects manifest their expectancy, with repetition of administration named conditioning and a non-specific psychological effect supported from givers, this placebo effect can be well demonstrated in brain via functional neuro-image.[109] It is reasonable to expect that migraineurs may exhibit a substantial placebo effect. Actually, a meta-analysis pointed out that the efficacies of acute migraine treatment using placebo via oral or cutaneous routes were 25% and 32%, respectively, whereas those achieved at home and hospital were 27% and 32%, respectively.[110]

Some therapeutic options are simultaneously and additionally recommended to manage both disorders. For example, neurokinin-1 (NK1) receptor antagonists are expected to treat IBS and migraine because NK1 receptors are observed in GI tract as well as in CNS.[111] Gabapentin, an antiepileptic, has been an alternative or combined agent to support the migraine treatment but with less level of evidence based.[112] Regarding IBS, this agent obviously reduced the sensory threshold of diarrhea-predominant subjects via rectal barostat study compared to placebo treatment. It remains unknown whether it can be safely employed to treat these IBS subjects.[113] Melatonin owns an antinociceptive effect on spinal cord and supra-spinal levels with a mechanism involving opioid, benzodiazepine, α1- and α2-adrenergic, serotonergic and cholinergic receptors. Exogenous melatonin replacement is somewhat effective to treat these pain disorders such as migraine, IBS and fibromyalgia.[114,115]

Diet therapy such as immunoglobulin G based elimination was claimed effective in reducing the scales of both IBS and migraine.[116]

Both acupuncture and CAM have long been used to treat IBS and migraine. According to the critical reviews, most studies were unfortunately not well randomized and placebo-controlled and only conducted on small and limited scales, therefore their final efficacies are still unresolved.[117-119] With regard to the surgery, the surgical deactivation of trigger sites of migraineurs is reported as a strong evidence for successful and persistent effect.[120] In addition, peripherally intramuscular injection of botulinum toxin A with repeated cycles is effective in treating and preventing migraine occurrence with reduced headache-related disability and improved functioning, vitality and psychological distress. The antinociceptive effect on migraine of this agent probably involves some inflammatory mediators such as calcitonin gene-related peptide, glutamate, and substance P from the peripheral termini of migraine related nociceptors.[121,122] Unlike the suggested applications on migraine, neither surgery nor botulinum toxin A injection has been recommended to treat IBS until now.

Prognoses

Apart from the severe pounding at the QoL of victims and no known cure measures, IBS itself is a pretty benign disorder. It means that IBS never increases the cancer risk on its main targeted organ.[123] Surprisingly, a Danish nationwide long-term follow-up IBS cohort study even indicated that these IBS subjects had a diminished colon cancer risk with OR of 0.67.[124] In contrast, migraine does not meet such favorable prognosis, and the victims may carry these risks in the future including suicide attempt, subclinical brain lesions such as iron deposition and stroke etc.[125-127] However, the migraineurs can be reassured first that there is no serious underlying nature when a correct diagnosis is established.[128] It probably means that the future brain tumor risk is not increased. With regard to the brain tumor itself, the only addressed risk is mutagen sensitivity while migraine looks not to be included.[129]

Conclusions

Both IBS and migraine, the famous and common pain-related disorders, are usually to have many overlapped somatic and psychiatric comorbidities. The IBS subjects may have the coexisting migraine with an OR of 2.66. Both disorders share many similar characteristics in terms of high prevalence, female predominance, reduced QoL, burden to social and economic costs, chronic and recurrent manifestations, pathogeneses, hereditary effects, criteria based diagnoses, multidisciplinary measures and options to treat, placebo effect and no cancer risk etc. However, these similarities do not mean the exact coincidence each other but distinct characteristics remain existed in their respective clinical manifestations. These more or less similarities are likely to suggest that both disorders may locate within the spectrum of a pain-centered disorder such as addressed central sensitization syndromes, while its true pathogenesis to involve these pain-related disorders remains to be elucidated in the future.

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