Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 3 Issue 2 February 2019

Review Article

A Review on Pathophysiology, Diagnosis and Pharmacological Management of Spastic Colon

Amrish Kumar[1]*, Vrish Dhwaj Ashwlayan[2], Mansi Verma[2], Vipin Kumar Garg[3], Avnesh Kumar[2], Satish Kumar Gupta[4], Sameksha Koul[2], Anjana Sharma[2], Anurag Chaudhary[2], Anoop Kumar[2], Lubhan Singh[5], Abhinav Agrawal[6], Firoz Khan[7], Sandeep Soni[8], Harshit Sharma[9] and Hement Tyagi[10]

[1]Research Scholar, Pharmacology, Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Meerut, Uttar Pradesh, India

[2]Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Meerut, Uttar Pradesh, India

[3]Head of Department (Department of Pharmaceutical Technology) Meerut Institute of Engineering and Technology, Meerut, Uttar Pradesh, India

[4]Director (Department of Pharmacy), Meerut Institute of Technology, Uttar Pradesh, India

[5]Kharvel Subharti College of Pharmacy, Subhartipuram, Meerut, Uttar Pradesh, India

[6]Raj Kumar Goel Institute of Technology (Pharmacy), Ghaziabad, Uttar Pradesh, India

[7]Clinical Research Coordinator, Jubilant Generics, India

[8]KIET School of Pharmacy, Muradnagar, Gaziabad, Uttar Pradesh, India

[9]Scientific Analyst, Serdia Paharmaceuticals, Mumbai, India

[10]Department of Biotechnology, Meerut Institute of Engineering and Technology, Meerut, Uttar Pradesh, India

***Corresponding Author:** Amrish Kumar, Research Scholar, Pharmacology, Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Meerut, Uttar Pradesh, India. **E-mail:** amrish.kumar.miet@gmail.com.

Received: December 12, 2018; **Published:** January 21, 2019

Abstract

The Spastic colon is a disturbance in bowel movement. Patients who are suffering from Spastic colon have changes in bowel function like as constipation or diarrhea, and abdominal ache. Those patients have Spastic colon suffer from many difficulties, such as sexual activities, muscle aches and pains, fatigue, fibromyalgia syndrome, headaches, back pain, and sometimes those patients suffer from urinary symptoms like urinary urgency, urinary hesitation. Although Spastic colon is not a serious fatal medical problem. Patients who are suffering from Spastic colon tend to live longer, then those patients who do not have Spastic colon. Those patients have Spastic colon, like symptoms that those patients do not put other extra stress on the other vital organs in the body. Those people have Spastic colon should not be worried about it, that Spastic colon does not causes to other serious diseases. The major problem in those patients have Spastic colon, is changes in the quality of life of living beings. In this review article, the aim of authors to be review the epidemiology and pathophysiology of Spastic colon, which summarize diagnostic and treatment strategies.

Keywords: Spastic Colon; Crohn's Disease or Ulcerative Colitis; Urinary Urgency; Urinary Hesitation; Colon Cancer; Fibromyalgia Syndrome; Rectal Urgency

Abbreviations

IBS: Irritable Bowel Syndrome (Spastic Colon); IBS-D: Irritable Bowel Syndrome with Diarrhea; IBS-C: Irritable Bowel Syndrome with Constipation; IBS-M: Irritable Bowel Syndrome with Mixed Bowel; GI: Gastrointestinal Tract; F-GID: Functional Gastrointestinal Disorder; HAPC: High Amplitude Propagated Contractions; PI-IBS: Post infectious Spastic Colon (Irritable Bowel Syndrome).

Introduction

Spastic colon (IBS) is a functional bowel disorder which is characterized by chronic or re-institution of abdominal pain, which is

associated with either relief or exacerbation by defecation, or a change in bowel movements [1]. Collection of functional symptoms that are not attributable to structural, mucosal or biochemical disease of gastrointestinal tract is called Functional gastrointestinal disorder. Spastic colon is the most commonly diagnosed functional bowel disorder, in those people who are under age 50 [2]. IBS is related with psychological problems such as depression or anxiety [3], and patients living with IBS have been found to have a maximum risk of somatic symptoms than patients who have gastrointestinal tract symptoms in the absence of IBS [4]. Most studies revealed that Spastic colon is more common in women than men. Why are the mostly women more affected by Spastic colon it is not known. It is not possible that is due to hormonal differences between male and female. Rather it to be due to the process of sensations of men and women from the intestines, in this process central nervous system play a important role. Over the last 20 years, recent studies revealed that those patients who are with IBS tend to have higher levels of sensitivity in the intestines compared to patients who do not have IBS. The neuro-transmitters are available in the intestines, which provide signals, which initiate from the intestines to the brain, and also from the brain to the intestines. These "neuro transmitters" transmit message between nerve endings to carry signals between the brain and gut. Another large number of neurotransmitters which is present in the gut is serotonin. Some important factors must be considered which are responsible for the development of IBS, it is clear that after diagnosis. IBS with diarrhea, IBS with constipation, or mixed IBS play an important role in selection of diagnostic criteria and it's management. Variation in diet, variation in lifestyle, variation in medical setting, and variation in behavioral status have proven effective in randomized clinical trials for examination of IBS. Management of those patients having IBS is investigated by an individualized, holistic approach that embraces dietary, lifestyle, medical, and behavioral changes [5]. In North America, the population affected from IBS is approximately 12%. South America is more prevalent region than Southeast Asia. Abdominal pain and constipation are commonly reported in those women having IBS, whereas men are more commonly reported with diarrhea. Patients in America are equally disturbed among (IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and IBS with a mixed bowel pattern (IBS-M), while in Europe, IBS-C or IBS-M are more prevalent than IBS-D [6].

Pathophysiology

Psychosocial factors

In the last of the 19th century Sir Wiliam Osler wrote that patients with 'mucous colitis' have a normal colonic epithelium and suffered from colicky abdominal pains [7]. Substantial evidence supports that the psychological stress play a key role in the pathophysiology of gut motor dysfunction [8]. The psychological disturbance at the initiation during observational period represented a predictive factor for the development of IBS at the end of follow-up. However, FGID, diagnosed at baseline which was significantly associated with higher levels of anxiety and depression at follow-up [9].

Intestinal Motility

Manometry studies revealed alteration in colonic and small intestinal motor function pattern including a higher number of high amplitude contractions (HAPCs) [10], and enhanced responses to food ingestion [11], cholecystokinin [12], or the stress hormone corticotrophin releasing factor [13,14]. Compared with healthy volunteer, IBS-D patients revealed accelerated colonic transit [15].

Visceral Hypersensitivity

Visceral hypersensitivity is a general problem in functional gastrointestinal disorder, associated with non-cardiac chest pain, functional dyspepsia, and IBS [16]. Visceral hypersensitivity is considered as a key element in the pathogenesis of IBS [17]. 95% of IBS patients was initially detected with Hypersensitivity to balloon distension of the rectum [18], but subsequently shown to be present only in about half of patients, those who are living with IBS-D [19]. On performing a large sample studies then the study revealed that, and normosensitive IBS patients, compared with those IBS patients, who are with rectal hypersensitivity had more pain, bloating, and diarrhea [20,21]. Functional magnetic resonance imaging and positron emission tomography of brain revealed that, in response to experimental rectal distension, compared with healthy controls IBS patients, reveal enhanced activation of those areas which are involved in pain processing like thalamus, insula and anterior circulate cortex [22]. The results of the brain imaging studies revealed that, brain activation and reported pain to peripheral stimuli should be considered with caution as they are highly influenced by the patient's psychological status [23,24].

Intestinal Gas

Mostly patients with IBS consider that, bloating is extremely distressing and about two-thirds of them consider it the worst of their symptoms [25,26]. 75% bloating is more commonly occur in those patients who are living with IBS-C, 41% bloating is occur in those who are living with IBS-D (41%), and in IBS-C bloating is correlated with abdominal distension [27,28]. It is unclear till now that increased amount of gas in the intestine is responsible for bloating [29]. Another point of view according to Serra., *et al*. [30], revealed that that 18 out of 20 IBS patients, compared with only 4 of 20 healthy volunteer, developed gas retention, gastrointestinal symptoms or abdominal distension after an infusion of a gas mixture in the next to the duodenum part of small intestine.

Luminal factors and Microbiota

Food ingestion often aggravates symptoms in patients with IBS. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), these are those components which are poorly absorbed in the small intestine and reach in the colon, where they are fermented by bacteria and intestinal gas will be produced which stimulate the colonic motor activity. The diets which contain low-FODMAPs had present have been shown to be beneficial for IBS patients, although the exact role of these diets in IBS and their applicability in everyday practice remains unclear [31]. Non-coeliac gluten sensitivity is another interesting area of development of IBS. [32]. A randomised, controlled trial revealed that a gluten-containing diet versus a gluten-free diet in IBS-D, revealed that those group receiving gluten had increased chances of bowel movements, intestinal permeability, and peripheral blood immune responses [33]. The microbiota play a functional role in FGID including IBS has been the subject of an exhaustive recent trend [34]. These patients revealed alteration in bowel physiology including alteration in bowel transit times while those patients with normal microbiota had more psychological impairment [35]. Patients with IBS had increased faecal levels of acetic acid and propionic acids the two type of acids correlated with the severity of abdominal pain and bloating [36]. About 25% of patients who are living with IBS-D had greater levels of intra-colonic bile acids as the result of bile acid malabsoption or excessive bile acids biosynthesis in the liver [37,38]. The valuable mechanisms involved in this effect, is the mutation of bile acids transporter in ileum [39], and the decreased expression fibroblast growth factor 19 (FGF19), which is produced by ileal enterocytes and regulates bile acids synthesis in the hepatocyte through a negative feedback mechanism [40].

Mucosal Permeability

Intestinal mucosal barrier play, a vital role in regulating intestinal permeability. In the making of intestinal mucosal barrier, the mucus layer, the enterocytes, and intercellular tight junctions (TJs) are necessary components which are stay between epithelial cells. Disruption of the mucosal barrier leads visceral hypersensitivity and pain perception. Greater mucosal permeability has been first shown in patients with post-infectious IBS (PI-IBS) by means of the lactulose/mannitol method [41], and subsequently confirmed in patients who developed IBS after a waterborne outbreak of gastroenteritis in Walkerton, Ontario [42]. Greater intestinal permeability has been shown also in patients with non-specific IBS [43]. Electron microscopy studies revealed that the enlarged paracellular spaces and cytoskeleton condensation are responsible for TJs dysfunction in second part of the small intestine of IBS-D patients [44]. Piche., *et al.* [45], demonstrated that colonic biopsies studied had significantly revealed greater permeability when compared to controls. Greater permeability was associated with significantly lower expression of tissue zonula occludens mRNA when compared to asymptomatic controls. The trigger mechanism which involved in the greater intestinal permeability of IBS remains elusive. Recent studies suggest the mechanism behind it's, participation of stress [46], food allergy [47], or gluten.

Gastrointestinal Infections

For the development of IBS, acute gastroenteritis is the strongest known risk factor [48]. After bacterial infection (e.g. Shigella, Salmonella, and Campylobacter) or viral gastroenteritis, PI-IBS may occurs [49]. Polymorphisms for genes is a genetic factor which is involved in the control of pro-inflammatory cytokine production (IL-6), host-bacteria interactions and epithelial paracellular permeability, have been reported in patients with PI-IBS [50].

Neuro-immune interactions

Gastroenteritis and the higher prevalence of IBS in patients associated with inflammatory bowel diseases in remission, microscopic colitis or coeliac disease on a gluten free diet, are responsible for the pathogenesis of IBS [51]. IBS supernatants, infused by a mesenteric artery of the isolated intestinal rat loop, elicited higher sensory fibre activation compared to control supernatants [52]. According to Cenac., *et al.* [53], showed intracolonic injection of IBS supernatants in mice evoked visceral hypersensitivity. Using sophisticated computerised optical techniques, according to Buhner., *et al*. [54], revealed a rapid histamine, serotonin, and protease-

dependent hyper-activation of human enteric nerves in response to IBS supernatants. Mostly these effects could be reduced by using inhibitors/antagonists of immune mediators or serotonin. [55]. The severity and frequency of perceived abdominal pain in IBS patients were directly proportional to the number of activated mast cells in proximity of nerve endings [56].

Serotonin

5-hydroxytryptamine, is secreted by enterochromaffin cells in response to mechanical and chemical stimuli. Serotonin regulates and stimulates the function like secretion, motor, and sensation of the gastrointestinal tract acting on receptors spread all over the gut. The biological activity of 5-HT is terminated by the serotonin reuptake transporter (SERT) which is located on enterocytes [57]. The most prominent role of serotonin in IBS is supported by the therapeutic efficacy of serotonin- 3 receptor antagonists and serotonin- 4 receptor agonists on IBS symptoms [58]. Patients with IBS-C were detected with decreased postprandial 5-HT platelet-depleted plasma levels [59]. Elevation in plasma levels of serotonin indicated under fasting and fed conditions in those patients who are with IBS-D or PI-IBS, suggesting a reduced 5-HT reuptake and/or metabolism [60]. Different-different studies demonstrated a reduced SERT expression in the colon of patients with IBS [61], have been reported. A study confirmed that the spontaneous release of 5-HT was significantly increased in patients with IBS irrespective of bowel habit and correlated with the abdominal pain [62].

Genetic Factors

Interactions between environmental and genetic factors exhibits as IBS. Studies based on epidemiological suggest a role of genetic predisposition in the formation of IBS [63]. Recent small studies revealed polymorphisms in serotonergic [64], and inflammatory genes as susceptibility SNPs for IBS [65]. Neuropeptide S receptor gene (NPSR1), a gene involved in inflammation, anxiety and nociception [66]. Hepatic bile acid synthesis regulated by a functional Klotho β gene variant was associated with colonic transit in IBS-D [67]. Zucchelli*., et al*. [68] demonstrated in two independent cohorts from Sweden and USA a strong association between rs4263839 in TNFSF15 and IBS, particularly IBS-C in the largest genetic factors. The gene which is involved in Th17 immune response and IBS (although in this case with a different subtype, i.e. IBS-D) was recently replicated in UK patients. TNF were also associated with PI-IBS [69].

Diagnosis: [70]

Initial assessment

Gastroenterologist should consider following symptoms for at least 6 months:

1. Abdominal pain
2. Bloating
3. Change in bowel movement

If the patients are suffering with possible IBS symptoms should be asked if they have any of the following 'red flag' indicators.

1. Weight loss
2. Rectal bleeding
3. Ovarian cancer
4. Change in bowel habbit to looser and/or more frequent stools continue for more than 6 weeks in a patients who are aged over 60 years.

The following four symptoms must be considered, only if the patients have abdominal pain or associated with altered bowel frequency or stool form.

1. Alteration in stool passage
2. Abdominal distension, tension or hardness
3. Symptoms made worse by eating
4. Passage of mucus.

Diagnostic Criteria

There are following test should be considered

1. Full blood count
2. Erythrocyte sedimentation rate
3. C-reactive protein
4. Antibody testing for coeliac disease (endomysial antibodies or tissue transglutaminase).

Pharmacological management

Following pharmacological strategies are helpful in the management of IBS.

1. Antispasmodic medication for those patients who are having IBS.
2. Use of laxatives for the treatment of constipation in patients with IBS, but people should be discouraged from taking lactulose

3. Follow up people taking linaclotide after 3 months [71].
4. Loperamide should be the first choice, as anti-motility agent for diarrhoea in those patients which have IBS.
5. Patients with IBS should be advised through clinicians how to adjust their doses of laxative or antimotility agent according to the clinical response.
6. Use of tricyclic antidepressants (TCAs) as second-line treatment for people with IBS if laxatives, have been failed. Initiate the treatment with a low dose (5–10 mg equivalent of amitriptyline), taken once at night.
7. Use of selective serotonin reuptake inhibitors (SSRIs) for patients with IBS only if TCAs have been failed.

Conclusion

Spastic colon is a syndrome which suffered by both the brain and the intestine. Stress is not only prime factor, to institute the IBS to patients. As per above discussion various somatic factor are responsible for IBS institution to the patient. One good way to fight with stress is cognitive behavior therapy. Even if the patients succeed in reducing their stress, some of their symptoms may last for a long time. The therapeutic goal is not a symptom free state but self-control of symptoms.

Bibliography

1. Pimentel M., *et al*. "Report from the multinational Spastic colon initiative 2012". *Gastroenterology* 144 (2013): 1-5.
2. Lovell RM., *et al*. "Global prevalence of and risk factors for Spastic colon. a meta-analysis". *Clinical Gastroenterology and Hepatology* 10.7 (2012): 712-721.
3. Dekel R., *et al*. "The use of psychotropic drugs in Spastic colon". *Expert Opinion on Investigation Drugs* 22. 3 (2013): 329-339.
4. Patel P., *et al*. "Spastic colon is significantly associated with somatisation in 840 patients, which may drive bloating". *Alimentry Pharmacology and Therapeutics* 41.5 (2015): 449-458.
5. Chey W., *et al*. "Spastic colon A Clinical Review". *Journal of American Medical Association* 313.9 (2015): 949-958.
6. Guilera M., *et al*. "Balboa A and Mearin F: Bowel habit subtypes and temporal patterns in Spastic colon". *The American Journal of Gastroenterology* 100.5 (2005): 1174-1184.
7. Osler W. "The principles and practice of medicine: designed for the use of practitioners and students of medicine". New York: Daniel Appleton and company (1892).
8. Corney RH., *et al*. "Physical symptom severity, psychological and social dysfunction in a series of outpatients with Spastic colon". *Journal of Psychosomatic Research* 34 (1990): 483-491.
9. Locke GR., *et al*. "Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study". *The American Journal of Gastroenterology* 99 (2004): 350-357.
10. Koloski NA., *et al.* "The brain-gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study". *Gut* 61 (2012): 1284-1290.
11. Kellow JE., *et al*. "Altered small bowel motility in Spastic colon is correlated with symptoms". *Gastroenterology* 92 (1987): 1885-1893.
12. Chey WY., *et al*. "Colonic motility abnormality in patients with Spastic colon exhibiting abdominal pain and diarrhea". *The American Journal of Gastroenterology* 96 (2001): 1449-1506.
13. Whitehead WE., *et al.* "Spastic colon: physiological and psychological differences between diarrhea-predominant and constipation predominant patients". *Digestive Disease and Science* 25 (1980): 403-113.
14. Fukudo S., *et al*. "Impact of corticotrophin releasing hormone on gastrointestinal motility and adrenocorticotrophin hormone in normal controls and patients with Spastic colon". *Gut* 42 (1998): 845-849.
15. Camilleri M., *et al*. "Prospective study of motor, sensory, psychologic, and autonomic functions in patients with Spastic colon". *Clinical Gastroenterology and Hepatology* 6 (2008): 772-781.
16. Barbara G., *et al*. "Mechanisms underlying visceral hypersensitivity in Spastic colon". *Current Gastroenterology Report* 13 (2011): 308-315.
17. Whitehead WE., *et al*. "Tolerance for rectosigmoid distension in Spastic colon". *Gastroenterology* 98 (1990): 1187-1192.
18. Mertz H., *et al*. "Altered rectal perception is a biological marker of patients with Spastic colon". *Gastroenterology* 109 (1990): 40-52.
19. Prior A., *et al*. "Anorectal manometry in Spastic colon: differences between diarrhoea and constipation predominant subjects". *Gut* 31 (1990): 458-462.
20. Posserud I., *et al*. "Altered rectal perception in Spastic colon is associated with symptom severity". *Gastroenterology* 133 (2007): 1113-1123.

21. van der Veek., *et al*. "Symptom severity but not psychopathology predicts visceral hypersensitivity in Spastic colon". *Clinical Gastroenterology and Hepatology* 6 (2008): 321-328.

22. Mertz H., *et al*. "Regional cerebral activation in Spastic colon and control subjects with painful and nonpainful rectal distension". *Gastroenterology* 118 (2000): 842-848.

23. Accarino AM., *et al*. "Attention and distraction: effects on gut perception". *Gastroenterology* 113 (1997): 415-422.

24. Elsenbruch S., *et al*. "Patients with Spastic colon have altered emotional modulation of neural responses to visceral stimuli". *Gastroenterology* 139 (2010): 1310-1319.

25. Houghton LA., *et al*. "Towards a better understanding of abdominal bloating and distension in functional gastrointestinal disorders". *Neuro Gastroenterology and Motility* 17 (2005): 500-511.

26. Houghton LA., *et al*. "Relationship of abdominal bloating to distension in Spastic colon and effect of bowel habit". *Gastroenterology* 131 (2006): 1003-1010.

27. Tremolaterra F., *et al*. "Intestinal tone and gas motion". *Neurogastroenterology and Motility* 18 (2006): 905-910.

28. Accarino AM., *et al*. "Abdominal distension results from caudoventral redistribution of contents". *Gastroenterology* 136 (2009): 1544-1551.

29. Gasbarrini A., *et al*. "1st Rome H2-Breath Testing Consensus Conference Working Group. Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference". *Alimentry Pharmacology and Therapeutics* 29.1 (2009): 1-49.

30. Serra J., *et al*. "Impaired transit and tolerance of intestinal gas in the Spastic colon". *Gut* 48 (2001): 14-19.

31. Shepherd SJ., *et al*. "Dietary triggers of abdominal symptoms in patients with Spastic colon: randomized placebo-controlled evidence". *Clinical Gastroenterology and Hepatology* 6 (2008): 765-771.

32. Biesiekierski JR., *et al*. "Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial". *The American Journal of Gastroenterology* 106 (2011): 508-514.

33. Vazquez-Roque MI., *et al*. "A controlled trial of gluten-free diet in patients with Spastic colon-diarrhea: effects on bowel frequency and intestinal function". *Gastroenterology* 144 (2013): 903-911.

34. Simrén M., *et al*. "Rome Foundation Committee. Intestinal microbiota in functional bowel disorders: a Rome foundation report". *Gut* 62 (2013): 159-176.

35. Jeffery IB., *et al*. "A Spastic colon subtypes defined by species-specific alterations in faecal microbiota". *Gut* 61 (2012): 997-1006.

36. Tana C., *et al*. "Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in Spastic colon". *Neurogastroenterology and Motility* 22 (2010): 512-519.

37. Camilleri M., *et al*. "Measurement of serum 7 alpha-hydroxy-4-cholesten-3-one (or7alphaC4), a surrogate test for bile acid malabsorption in health, ileal disease and Spastic colon using liquid chromatography-tandem mass spectrometry". *Neurogastroenterology and Motility* 21 (2009): e734-743.

38. Wong BS., *et al*. "Increased bile acid biosynthesis is associated with Spastic colon with diarrhea". *Clinical Gastroenterology and Hepatology* 10 (2012): 1009-1015.

39. Montagnani M., *et al*. "Absence of dysfunctional ileal sodium-bile acid cotransporter gene mutations in patients with adult-onset idiopathic bile acid malabsorption". *Scand Journal of Gastroenterology* 36 (2001): 1077-1080.

40. Walters JR., *et al*. "A new mechanism for bile acid diarrhea: defective feedback inhibition of bile acid biosynthesis". *Clinical Gastroenterology and Hepatology* 7 (2009): 1189-1194.

41. Spiller RC., *et al*. "Increased rectal mucosa enteroendocrine cells t lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric Spastic colon". *Gut* 47 (2000): 804-811.

42. Marshall JK., *et al*. "WEL Investigators. Intestinal permeability in patients with Spastic colon after a waterborne outbreak of acute gastroenteritis in Walkerton, Ontario". *Alimentry Pharmacology and Therpeutics* 20 (2004): 1317-1322.

43. Rao AS., *et al*. "Urine sugars for in vivo gut permeability: validation and comparisons in Spastic colon-diarrhea and controls". *American Journal of Physiology Gastrointestinal and Liver Physiology* 301 (2011): G919-928.

44. Martínez C., *et al*. "Diarrhoea predominant Spastic colon: an organic disorder with structural abnormalities in the jejunal epithelial barrier". Gut 62 (2013): 1160-1168.

45. Piche T., *et al*. "Impaired intestinal barrier integrity in the colon of patients with Spastic colon: involvement of soluble mediators". *Gut* 58 (2009): 196-201.

46. Vanuytsel T., *et al.* "Psychological stress and corticotrophin-releasing hormone increase intestinal permeability in humans by a mast-cell dependent mechanism". *Gut* (2013): 305-690.

47. Vivinus-Nébot M., *et al.* "Combination of allergic factor scan worsen diarrheic Spastic colon: role of barrier defects and mast cells". *American Journal of Gastroenterology* 107 (2012): 75-81.

48. Rodriguez LA., *et al*. "Increased risk of Spastic colon after bacterial gastroenteritis: cohort study". *British Medical Journal* 318 (1999): 565-566.

49. Spiller R., *et al*. "Postinfectious Spastic colon". *Gastroenterolog* 136 (2009): 1979-1988.

50. Villani AC., *et al.* "Genetic risk factors for post-infectious Spastic colon following a waterborne outbreak of gastroenteritis". *Gastroenterology* 138 (2010): 1502-1513.

51. Barbara G., *et al*. "The immune system in Spastic colon". *Journal of Neurogastroenterology and Motility* 17 (2011): 349-359.

52. Barbara G., *et al*. "Mast cell-dependent excitation of visceral-nociceptive sensory neurons in Spastic colon". *Gastroenterology* 132 (2007): 26-37.

53. Cenac N., *et al*. "Role for protease activity in visceral pain in Spastic colon". *Journal of Clinical Investigation* 117 (2007): 636-47.

54. Buhner S., *et al*. "Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with Spastic colon". *Gastroenterology* 137 (2009): 1425-1434.

55. Steck N., *et al*. "Bacterial proteases in IBD and IBS". *Gut* 61 (2012): 1610-1618.

56. Barbara G., *et al*. "Activated mast cells in proximity to colonic nerves correlate with abdominal pain in Spastic colon". *Gastroenterology* 126 (2004): 693-702.

57. Gershon MD. "5-Hydroxytryptamine (serotonin) in the gastrointestinal tract". *Current Opinion in Endocrinology, Diabetes and Obesity* 20 (2013): 14-21.

58. Camilleri M. "Pharmacology of the new treatments for lower gastrointestinal motility disorders and Spastic colon". *Clinical Pharmacology and Therpeutics* 91 (2012): 44-59.

59. Shekhar C., *et al*. "Rome III functional constipation and Spastic colon with constipation are similar disorders within a spectrum of sensitization, regulated by serotonin". *Gastroenterology* 145 (2013): 749-757.

60. Atkinson W., *et al*. "Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant Spastic colon". *Gastroenterology* 130 (2006): 34-43.

61. Coates MD., *et al*. "Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and Spastic colon". *Gastroenterology* 126 (2004): 1657-1664.

62. Cremon C., *et al.* "Intestinal serotonin release, sensory neuron activation, and abdominal pain in Spastic colon". *American Journal of Gastroenterology* 106 (2011): 1290-1298.

63. Levy RL., *et al*. "Spastic colon in twins: heredity and social learning both contribute to etiology". *Gastroenterology* 121 (2001): 799-804.

64. Camilleri M., *et al*. "Serotonin-transporter polymorphism pharmacogenetics in diarrhea predominant Spastic colon". *Gastroenterology* 123 (2002): 425-432.

65. Gonsalkorale WM., *et al*. "Interleukin 10 genotypes in Spastic colon: evidence for an inflammatory component". *Gut* 52 (2003): 91-93.

66. Camilleri M., *et al*. "Neuropeptide S receptor induces neuropeptide expression and associates with intermediate phenotypes of functional gastrointestinal disorders". *Gastroenterology*.138 (2010): 98-107.

67. Wong BS., *et al*. "Klothoβ variant mediates protein stability and associates with colon transit in Spastic colon with diarrhea". *Gastroenterology* 140 (2011): 1934-1942.

68. Zucchelli M., *et al*. "Association of TNFSF15 polymorphism with Spastic colon". *Gut* 60 (2011): 1671-1677.

69. Swan C., *et al*. "Identifying and testing candidate genetic polymorphisms in the Spastic colon (IBS): association with TNFSF15 and TNFα". *Gut* 62 (2012): 985-994.

70. National Institute for Health and Care Excellence. "Spastic colon in adults: diagnosis and management of Spastic colon in primary care 2008". (2015).

71. National Institute for Health and Care Excellence. "Spastic colon in adults: diagnosis and management of Spastic colon in primary care 2015". (2015).

Volume 3 Issue 2 February 2019