Volume 14, No 3 | International Journal of Radiation Research, July 2016

External human exposure and management immune system in pathogenesis of irritable bowel syndrome

M.R. Sheikh Sajjadieh

National Medical Academy for Post Graduate Education, Kiev, Ukraine

► ***A mini-review***

***Corresponding author:**
Dr. M.R. Sheikh Sajjadieh,
***Fax:** +380 44 3422718*
E-mail:
mohammad_esfahan@yahoo.com

Revised: Jan. 2015
Accepted: Nov. 2015

Int. J. Radiat. Res., July 2016; 14(3): 165-171

DOI: 10.18869/acadpub.ijrr.14.3.165

ABSTRACT

External exposed radiation may play an important role in pathogens of irritable bowel syndrome (IBS), although is thought to arise due to a combination of genetic and environmental factors. The result is dysregulated immune responses due to alteration in the gut microbiota population and the subsequent development of gut inflammation. It has recently been shown that the effect of ionizing radiation on T-cell lymphocytes might be a risk factor of IBS. This article tries to discuss the effects of low dose radiation on alternation in the population of beneficial members of the gastrointestinal tract flora. The result may be activated inflammatory response of mucosal immune status induced Toll like receptors. Lipopolysaccharides produced by most gram-negative bacteria of gastrointestinal tract play a role in the initiation and progress of the Toll like receptors in the intestines. Circulating cytokines and soluble receptors released by activated Th2 can regulate neuronal function via endocrine mechanisms. Disturbance of the cytokine-mediated interaction between cells may lead to neuronal dysfunction or sensory dysfunction, motor dysfunction, or both sensory and motor dysfunction in patient with IBS.

Keywords: *Irritable bowel syndrome, radiation, intestinal microbiota, immune system.*

INTRODUCTION

Irritable bowel syndrome (IBS) is commonly observed in regions with high natural radiation [1]. IBS is a disorder characterized most commonly by cramping, abdominal pain, bloating, constipation, and diarrhea that cannot be explained by structural abnormalities. Although IBS symptoms (visceral pain, increased gut permeability, motility alterations) are clearly established, the etiology of this pathology is loosely understood (table 1).

Recent interest has been directed toward to the potential role of intestinal microbiota in management of IBS. The human intestinal microbiota are composed of more than 1000 different bacterial species, and are essential for the development, function, and homeostasis of the intestine, and for individual health. The putative mechanisms that explain the role of microbiota in the development of IBS For the purpose of this review, special attention is given to irregular cooperation between the host immune system and alternate intestinal microbiota by natural radiation. In a healthy individual, intestinal colonization stimulates and regulates host immune system. Dysbiosis and impaired barrier functions are associated with several negative consequences; translocation of lipopolysaccharides (LPS) and whole microbial cells, accumulation of endotoxin in the body and hyper activation of the immune system, and in result preformed mediators release by immune cells. Circulating cytokines and soluble receptors also regulate neuronal function via endocrine mechanisms. Disturbance of the cytokine-mediated interaction between cells may lead to neuronal dysfunction or sensory dysfunction, motor dysfunction, or both sensory and motor dysfunction in patient with IBS.

Table 1. Criteria of IBS.

Irritable Bowel Syndrome	
Symptoms	• Abdominal pain or cramping • Alternating diarrhea and constipation • Abdominal bloating • Mucus present in the stools • Nausea
Categories	• Constipation-predominant • Diarrhea-predominant
Pathogenesis	Infection, Food intolerance, General diet, Emotional stress, Medications, Brain-gut signal problems, GI motor problems, Hypersensitivity, Genetics
Rome III Diagnostic Criteria	3 months associated with two or more of the following: • Improvement with defecation; and/or • Onset associated with a change in frequency of stool; and/or • Onset associated with a change in form (appearance) of stool.

Chronic radiation syndrome, definition, importance, pathogenesis definition

The main pathways leading to human exposure is external exposure from radionuclides deposited on the ground and the ingestion of contaminated terrestrial food products. Inhalation and ingestion of drinking water, fish, and products contaminated with irrigation water will be generally minor pathways [4]. The radiation dose received by a person depends on a number of factors, including the years over which exposure occurred; age at exposure; the amount of contaminated food and water consumed; the distance and direction lived from nuclear power plant, and the length of time lived there.

The assessment of absorbed doses from external radiation sources requires knowledge of several factors that influence the dose estimates. These factors include the isotopic composition of the deposited radioactive fallout; whether the deposition was primarily due to wet or dry processes; the soil density and the rates of radionuclides migration into the soil; information about the subject's residence location and lifestyle; and information about the type of dwelling and the settlement in which it was located.

Long-lived radionuclides released to the environment will be present for longer times than short-lived nuclides. The external dose rate may be decreased mainly due to radioactive decay of the short-lived radionuclide [5].

During the following decade in Ukraine after Chernobyl accident, the external dose rate decreased because of the radioactive decay of ^{134}Cs and ^{137}Cs (half-life =30 years) and the migration of radio cesium into the soil. Afterwards, the external dose rate was mainly due to ^{137}Cs. In the long term, radio cesium becomes fixed within the soil matrix, and this results in a slow migration into the soil and correspondingly, in a slow decrease of the external dose rate.

The average annual dose and typical dose range worldwide from natural sources is 2.4 mSv per year. At very low radiation dose rates about 3-5 mSv per year, there is evidence of a chronic radiation syndrome affecting, in particular, the immune system [6].

Importance

Some evidence suggests that IBS is affected by the immune system [3, 7, 8, 9], a large body of literature showing that cytokines can influence the function of epithelial cells, smooth muscle, and enteric nerves and changes in the cytokine profile of these tissues could promote changes in secretion, permeability, motility, and sensitivity to generate symptoms in IBS [10].

External radiation exposure in Ukraine after the Chernobyl accident appears to be related mostly to changes in the immune status in Ukrainian children (table 2) [1, 11, 12, 36]. Soluble lymphokine derived of T-cell whose main bioactivity is to stimulate the activated T-cell (Th, Ts, and Tc) to reproduce continually and proliferate, is the key mediator in cell and humoral immunity and immune regulation. The balance between lymphokine and their receptors regulates the immune status. T-cell serves as the center in controlling cellular immune status that can affect directly the occurrence, development, and progression of immune status [13]. T-cell's regulating function is mainly performed by CD4 and CD8 T-cells. CD4 T cells can help B-cell to produce antibody and CD8 T cells can suppress B-cell to produce antibody. The stable balance between them keeps normal immune response of the organism. However, the role of signaling and regulatory pathways is unclear in the exposed populations; the findings of an earlier study on patient with IBS resistance in contaminated aria showed that elevated concentrations of IL-4 (produced by Th2) and reduced blood serum levels of IFN-γ (produced by Th1) [14].

Interaction between cytokines and their receptors leads to the activation of multiple signaling molecules, including the family of ″signal transducer and activator of transcription″ (STAT) proteins. Different STAT proteins are capable of regulating the activity of common signaling pathways used by many cytokines. Gamma radiation has been shown to reduce STAT-1 phosphorylation. In agreement, mRNA levels for IL-5 were only slightly increased by gamma radiation compared with non irradiation samples, suggesting that ionizing radiation induce a polarized Th2 response by interfering with STAT signals, thereby causing suppression of Th1 response [15]. On the other hand, after low dose radiation, the change observed might contribute to a shift in favor of Th1 differentiation [16, 17]. In patients with IBS increased levels of IL-4 were associated with alteration in cytokine release from Th2 cell type [18, 19]. This may cause enhancing Th2 immune responses [19, 20] and suppression of Th1 while decreasing in level of IFN-γ.

Table 2 Immune status measurement in patient with IBS exposed by ionizing radiation [1,11,12,14,36].

	Patient with IBS (mean)	Normal range (mean)
Radiation activity		
Cs-137 (µci)	50,48	286,
Cellular immune system		
CD3%	51	61
CD4%	26	39
CD8%	22	18
CD4:CD8	1.3	2.2
Humoral immune status		
CD22%	25	20
IgG g/L	13.1	12.1
IgM g/L	1.4	1.1
IgA g/L	1.8	1.2
IgE (ng/ml)	162	101
Innate immune status		
CD16%	18	16
Phagocyte activity %	65	73
Circulating immune complex	48.5	25.8
Monocyte%	3.3	3.5
Neutrophil%	48	56
Cytokine status		
IL-4 (pg/ml)	5.0	3.3
IFN-γ(pg/ml)	48.5	50.8
Clinical symptoms		
Diarrhea %	34	5
Constipation %	31	3
Abdominal pain %	95	-

PATHOGENESIS

The gastrointestinal tract harbors a huge diversity of aerobic and anaerobic bacteria that interact in a complex ecosystem. This microflora comprises 400 to 500 metabolically active bacterial species, which have a pronounced impact on the host's intestinal function and health [21]. Intestinal bacteria can be grouped into species that have detrimental effects on the host and species that have beneficial effects. The

detrimental effects include diarrhea, infections, liver damage, carcinogenesis, and intestinal putrefaction [22], stimulation of the immune system, improvements in the digestion and absorption of essential nutrients, and vitamin synthesis are examples of the protective effects brought about by the intestinal microbiota [23]. Microorganisms of the genera *Bifidbacterium* and Lactobacillus perform a variety of functions important for the host's health. Whereas microorganisms of the genus Bacteroides have beneficial as well as detrimental effects [24] by producing acetic and lactic acids, which lower intestinal pH, which prevents the development of yeasts as like as *Candida albicans* [25]. In addition, they can stimulate cells of the immune system, inducing the production of IL-12 by macrophages and B cells [26].

Gastrointestinal dysbiosis is often the result of broad-spectrum antibiotic use, radiation therapy or exposure, stress, dramatic changes in altitude, ingestion of different organisms, or changes in diet. Occasionally, usually suppressed components of the indigenous microflora can allow potential pathogens or toxinogenic strains to colonize and to multiply thus causing diarrhea, flatulence, or different variations of colitis [27]. Cremon *et al.* showed that the intestinal flora of patients with diarrhea predominant IBS diverged significantly not only from controls but also from the other IBS subgroups, the results by them further support the hypothesis that intestinal microbial flora has a role in IBS pathophysiology, and foster the idea that abnormal microbiota may act by triggering local and systemic immune responses linked to symptom generation [28].

Hill discussed the influence of intestinal bacterial-derived signals on immune cell function and the mechanisms by which these signals modulate the development and progression of inflammatory disease[29]. Ionizing radiation is known to increase the development of irritable bowel syndrome [1] by harm the beneficial members of the gastrointestinal tract flora [2] (table 3), whereas others have been implicated on the homeostasis of the immune system [1, 11, 12], and change in cytokine secretion status and to drive a Th2-biased immune response and may lead this resulting in IBS symptom [14].

Recent research has demonstrated that higher levels of pro-inflammatory and lower level of anti inflammatory cytokines may be a risk factor for IBS or may make the response different from others. Santhosh *et al.* showed that there are polymorphism differences in cytokine genes between patients with IBS and healthy controls [30].

Table 3. Population of bacteria in caecal contents in patient with IBS [2].

Organisms	Number of bacteria (log CFU/g caecal contents)	
	Normal range (mean)	Patient with IBS (mean)
Enterobacter .sp	1.05	2.93
Enterococcus .sp	7.41	6.15
Lactobacillus. sp	6.71	5.24
Bifidbacterium .sp	8.57	6.0

This has led to a low grade inflammatory state which causes gut sensory motor dysfunction resulting in IBS symptoms [10] and has led to the hypothesis that cytokines may lead this resulting in IBS symptoms, it may be represented that polymorphisms cytokine genes resulting in higher level of pro-inflammatory and lower level of anti-inflammatory cytokines may be a risk factor for IBS or may make the response different from others [30].

Recent controversy

A prevalent theory, derived from hypotheses that were first postulated by Metchnikoff a century ago, proposes that individual members of the microbiota might influence the balance between pro-inflammatory and regulatory host responses and that alterations in the composition of the microbiota could jeopardize host immune responses and promotes the development of various inflammatory disorders. The intestinal microbiota is able to influence the balance between pro inflammatory and regulatory responses and to denote an altered reaction as may be characterized by an

immediate onset of symptoms in patient with irritable bowel syndrome (IBS) [21,22,24,25].

Recent research has shown that a trade-off is established between the host immune system and the bulk of the microbiota in patients with IBS have imbalance between the microbiota affected by natural radiation and changed immune response, suggested a causative role for dysbiosis in lack of Th1 responsiveness with enhanced Th2 function [2, 14].

Future remarks: is IBS an allergic disease?

Endotoxins are integral components of the outer membrane of Gram-negative bacteria, composed of proteins, lipids, and lipopolysaccharides (LPS). LPS, which is responsible for most of the biological properties of bacterial endotoxins, is known to have exceptionally strong ability to induce inflammation via the so called Toll-like receptors 2 (TLR2) and 4 (TLR4) which appear to be key regulators of the innate response system. LPS produced by most gram-negative bacteria of microbiota play a role in the initiation and progress of the TLRs in the intestines and presented by M cells and dendritic cells to CD4+ Th2 cells. An interesting study showed, TLR4-deficient or antibiotic-treated mice showed an increased Th2-type skewing of cytokine responses compared with control mice [31]. TLR2 and TLR4 can drive a Th2-biased immune response [32]. Signaling by TLR2 in APCs and expression of specific cytokines were suggested to favor Th2 responses [33-35]. It seems to be necessary to conduct a study regarding to TLR signaling and Th2 responses in pathogenesis of IBS. This may be due to intestinal dysbiosis, change in product of LPS, activates M cells and dendritic cells primarily through TLR2 or TLR4-dependent signaling. Furthermore, LPS product may be causes a pronounced Th2 bias, evidenced by T cell expression of depended cytokines. However, this hypotheses in pathogenesis of IBS is similar to the influences of susceptibility to food allergy. Therefore, an adequate clinical examination in the management of IBS should not focus only on the main complaints but might consists of a thorough examination of immune status, dysbiosis and laboratory panel of allergic disease. Figure 1 summarizes the involvement of immune response to radiation which may lead to IBS.

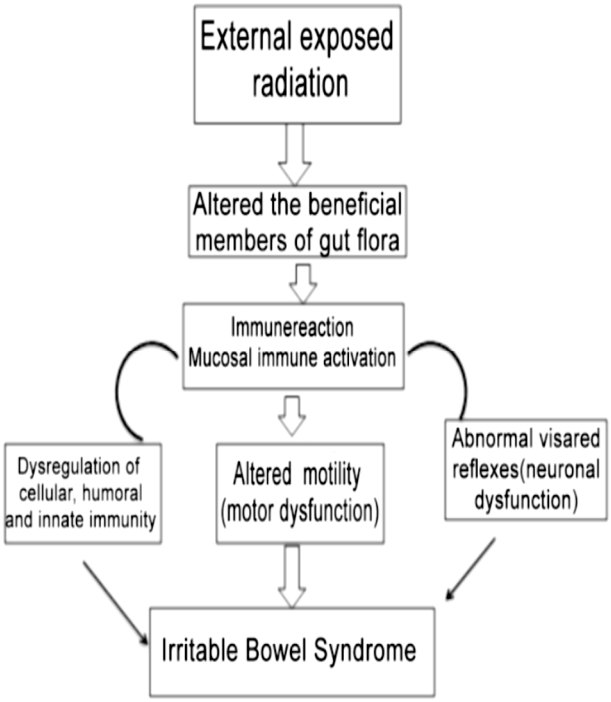

Figure 1. Possible immune response to radiation leading to Irritable Bowel Syndrome.

CONCLUSION

This review demonstrate that intestinal dysbiosis affect by natural radiation, a relatively understudied IBS pathogenesis, mediated the regulation of immune system via the TLR/ Th2 pathway. The mechanism by which intestinal dysbiosis induces inflammation and symptom of IBS are poorly understood. This phenomena may be explained by the LPS activation of important intracellular signaling pathways involved in inflammatory response. The main effects of these products is an available evidence that nervous system dysfunction may occur which may lead to sensory dysfunction, motor dysfunction, or both sensory and motor dysfunction.

Conflict of interest: *Declared None*.

REFERENCES

1. Sheikh Sajjadieh MR, Kuznetsova LV, and Bojenko VB (2010) Affects of ionizing radiation on T-cell population lymphocyte: A risk factor of irritable bowel syndrome. *Toxicology and Industrial Health,* ***26:*** *323–330*.
2. Sheikh Sajjadieh MR, Kuznetsova LV, Bojenk VB (2012) Dysbiosis in Ukrainian children with irritable bowel syndrome affected by natural radiation .*Iran J Pediat,* ***22:*** *364-368*.
3. Ohman L, Isaksson S, Lindmark AC, Posserud I, Stotzer PO, Strid H (2009) T-cell activation in patients with irritable bowel syndrome. *American Journal of Gastroenterology,* ***104:*** *1205–1212*.
4. Sanchez AL, Walters CB, Singleton DL, Wood NH, Mondon K (1999) Food ingestion doses from artificial radionuclides in Cumbrian diets, ten years post Chernobyl. *Journal of Environmental Radioactivity,* ***46:*** *301–317*.
5. Golikov V, Balonov M, Jacob P (2002) External exposure of the population living in areas of Russia contaminated due to the Chernobyl accident. *Radiation and Environment Biophysics,* ***41:*** *185–193*.
6. Akleyev A, Veremeyeva GA, Silkina LA, Vozilova AV (1999) Long term hemopoiesis and immunity status after chronic radiation exposure of red bone marrow in humans. *Central European Journal of Occupational and Environmental Medicine,* ***5:*** *113–129*.
7. Chadwick VS, Chen W, Shu D (2002) Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology,* ***122:*** *1778-1783*.
8. Dunlop SP, Jenkins D, Neal KR, Naesdal J, Borgaonker M, Collins SM, Spiller RC (2003) Randomized, double-blind, placebo-controlled trial of prednisolone in post infectious irritable bowel syndrome. *Aliment Pharmacol Ther,* ***18:*** *77-8*.
9. Van Der Veek PP, Van Den Ber M, De Kroon YE (2005) Tumor necrosis factor-alpha and interleukin 10 gene polymorphisms in irritable bowel syndrome. *American Journal of Gastroenterology,* ***100:*** *2510–2516.*
10. Collins SM (1996) The immunomodulation of enteric neuromuscular function: implications for motility and inflammatory disorders. *Gastroenterology,* ***111:*** *1683–1699*.
11. Sheikh Sajjadieh MR, Kuznetsova LV, Bojenko VB (2010) Low internal radiation alerts innate immune status in Ukrainian children with clinically of irritable bowel syndrome. *Toxicol Ind Health,* ***26:*** *525-31*.
12. Sheikh Sajjadieh MR, Kuznetsova LV, Bojenko VB (2011) Effect of cesium radioisotope on humoral immune status in Ukrainian children with clinical symptoms of irritable bowel syndrome related to Chernobyl disaster. *Toxicol Ind Health,* ***27:*** *51-6*.
13. Lotze MT and Finn OJ (1991) Recent advance in cellular immunology: implications for immunity to cancer. *Immunology Today,* ***11:*** *190 -194*.
14. Sheikh Sajjadieh MR, Kuznetsova L, Bojenko V (2012) Cytokine status in Ukrainian children with irritable bowel syndrome residing in a contaminated area. *Iran J Immunol,* ***9:*** *248-53*.
15. Han SK, Song JY, Yun YS, Yi SY (2002) Gamma irradiation-reduced IFN-γ expression, STAT1 signals, and cell-mediated immunity. *J Biochem Mol Biol,* ***35:*** *583-9*.
16. De Kruyff RH, Fang Y, Umetsu DT (1995) IL-4-based helper activity of CD4+ T cells is radiation sensitive. *Cell Immunol,* ***2:*** *248-56*.
17. Sun Y and Liu S (1998) Change in mRNA level of TNF-alpha and IL-1beta in mouse peritoneal macrophage after whole body Xirradiation. *Radiation Protection,* ***18:*** *119-25*.
18. Pons I, Gras G, Courberand S, Benveniste O, Dormont D (1997) Consequences of gamma-irradiation on inflammatory cytokine regulation in human monocytes/ macrophages. *Int J Radiat Biol,* ***71:*** *157-66*.
19. Field EH, Rouse TM, Gao Q, Chang B (1997) Association between enhanced Th2/Th1 cytokine profile and donor T-cell chimerism following total lymphoid irradiation. *Hum Immunol,* ***52:*** *144-54*.
20. Kremer IB, Hilkens CM, Sylva-Steenland RM, Koomen CW, Kapsenberg ML, Bos JD, Teunissen MB (1996) Reduced IL-12 production by monocytes upon ultraviolet-B irradiation selectively limits activation of T helper-1 cells. *J Immunol,* ***157:*** *1913-8*.
21. Berg RD (1996) The indigenous gastrointestinal microflora. *Trends Microbiol,* ***4:*** *430-5*.
22. van der Waaij D (1982) Colonization resistance of the digestive tract: Clinical consequences and implications. *J Antimicrob Chemother,* ***10:****263-70*.
23. Gibson GR and Roberfroid MB (1995) Dietary modulation of the human colonic microflora: introducing the concept of prebiotics. *J Nutr,* ***125:****1401- 12*.
24. Salminen S, Bouley C, Boutron-Ruault M-C (1998) Functional food science and gastrointestinal physiology and function. *Nutr Soc,* ***80:*** *48-71*.
25. Lidbeck A and Nord CE (1993) Lactobacilli and the normal human anaerobic microflora. *Clin Infec Diseases,* ***16:*** *181-7*.
26. Hessle C, Hanson LA, Wold AE (1999) Lactobacilli from human gastrointestinal mucosa are strong stimulators of IL -12 production. *Clin Exp Immunol,* ***116:*** *276-82*.
27. Reuter G (2001) The Lactobacillus and Bifidobacterium microflora of the human intestine: composition and succession. *Curr Issues Intest Microbiol,* ***2:*** *43-53*.
28. Cremon C, Carini G, De Giorgio R, Stanghellini V, Corinaldesi R, Barbara G (2010) Intestinal dysbiosis in irritable bowel syndrome: etiological factor or epiphenomenon? *Expert Rev Mol Diagn,* ***10:****389-93*.
29. Hill DA and Artis D (2010) Intestinal bacteria and the regulation of immune cell homeostasis. *Annu Rev Immunol,* ***28:*** *623-67*.
30. Santhosh S, Dutta AK, Samuel P, Joseph AJ, Ashok Kumar J, Kurian G (2010) Cytokine gene polymorphisms in Irritable bowel syndrome in Indian population—a pilot case control study. *Trop Gastroenterol,* ***31:****30-3*.
31. Bashir ME, Louie S, Shi HN, Nagler-Anderson C (2004) Toll-

like receptor 4 signaling by I ntestinal microbes influences susceptibility to food allergy. *J Immuno,* ***172:*** *6978–6987*.

32. Dillon SA, Agrawal T, Van Dyke G, Landreth L, McCauley A, Koh C, Maliszewski S (2004) A Toll-like receptor 2 ligand stimulates Th2 responses in vivo, via induction of extracellular signal-regulated kinase mitogen-activated protein kinase and c-Fos in dendritic cell. *J Immunol,* ***172:*** *4733–4743*.
33. Re F and Strominger JL (2004) IL-10 released by concomitant TLR2 stimulation blocks the induction of a subset of Th1 cytokines that are specifically induced by TLR4 or TLR3 in human dendritic cells. *J Immunol,* ***173:*** *7548–7555*.
34. Redecke V, .Ha¨cker H, Datta SK, Fermin A, Pitha PM, Broide DH, Raz E (2004) Cutting edge: activation of Toll-like receptor 2 induces a Th2 immune response and promotes experimental asthma. *J Immunol,* ***172:*** *2739–2743*.
35. Wenink MH, Santegoets KC, Broen JC, van Bon L, S. Abdollahi R, Popa C, R Huijbens R, Remijn T, Lubberts E, van Riel PL, van den Berg WB, Radstake (2009) TLR2 promotes Th2/Th17 responses via TLR4 and TLR7/8 by abrogating the type I IFN amplification loop. *J Immunol,* ***183:*** *6960–6970*.
36. Sheikh Sajjadieh MR , Kuznetsova LV, Bojenko VB (2009) Effect of ionizing radiation on development process of T-cell population lymphocytes in Chernobyl children. *Int J Radiat Res,* ***7****: 127-133*.