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Co-morbid Psychiatric Disorders in Patients with Irritable Bowel Syndrome Attending Gastroenterology and Psychiatry OPD in Tertiary Centre

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Abstract— Background*: Irritable bowel syndrome [IBS] is a chronic psycho-physiological disorder. It is considered to be the most common functional gastrointestinal disorder, and about 50-90% of IBS patients have associated psychiatric co-morbidity.* ***Aim and Objectives****: To assess and compare the socio-demographic profile and co-occurring of the psychiatric co-morbidity between the groups of patients with IBS and health controls.* ***Methods and materials****: A Cross sectional comparative study was conducted during the period of June 2017 to May 2018. A total of 100 individuals (50 patients with IBS and 50 health controls) who fulfilled the inclusion and exclusion criteria were interviewed using a semi-structured interview schedule consisting of socio-demographic profile, Rome IV criteria to assess Symptoms and severity of irritable bowel syndrome, the Mini screen, PHQ-15,HAM-D, and HAM-A. The ICD-10 diagnostic criterion was used for the psychiatric disorder. The statistical test such mean, SD, and Chi-squire test and t-test were used to compare the groups. The data was analyzed using SPSS IBM version 23 software.* ***Results****: Mean age of our patients with IBS and healthy controls was 30.30±10.570 and 27.28±8.887 years, respectively. Males outnumbered females in our cases as well as their controls. There were common psychiatric disorders such as major depression, generalized anxiety disorders and mixed depression, social phobia, agora phobia, OCD, panic disorder and anorexia nervosa especially among patient with IBS. Co-occurrence of psychiatric disorders especially major depression, GAD, and mixed depression-anxiety was found significantly high ($p<0.05$) among patient with IBS compared to the healthy controls.* ***Conclusions****: Majority of the patient with IBS were found with psychiatric co-morbidity compared to the health controls.*

Keywords— *Psychiatric Co-morbidity, gastro-intestinal disease, depression, anxiety disorders, stress.*

I. INTRODUCTION

Irritable Bowel Syndrome (IBS) is a chronic illness of gastro-intestinal (GI) system characterised by generalized or localized pain, constipation, diarrhoea and urgency. [1] It is one of the most common GI disorders having community prevalence of 1.1-29.2%. [2-5] It constitutes nearly half of the patients attending gastroenterology department. [6-8]

Review of relevant literature reveals that 50% of patients with IBS have one or more somatic disorder and some IBS patients also meet the diagnostic criteria of functional gastrointestinal disorder [9]. According to recent meta-analysis by Ford et al, there is an overlap between functional dyspepsia and IBS [10]. Asian studies have also emphasized overlap between functional dyspepsia and IBS. [11] Apart from somatic or other functional gastrointestinal disorders, 54-94% IBS patients have co-morbid psychiatric disorder. [9, 12-15]

According to some studies, patients with IBS make two to three times more hospital visits than age matched controls and about 80% of these visits are for non-intestinal complaints. [16-18] There is dearth of studies regarding somatic and psychiatric co-morbidities in Asian population. The treatment of IBS includes psychotherapy alone or in combination with psychotropic drugs. Cognitive behaviour therapy has been found to be most beneficial among psychotherapeutic interventions. [19] Some studies suggest that low dose tricyclic antidepressants (TCA) leads to overall improvement in IBS symptoms. [20]

Majority of literature on psychiatric co-morbidities in IBS patients is from Western studies and since socio-cultural differences play major role in manifestation of psychosomatic illness and also there is scarcity of studies from India and in best of our knowledge there has not been any study on IBS from Eastern part of Uttar Pradesh. Therefore, our aim was to strengthen the current literature.

Aim and Objective:

1. Comparative study of socio-demographic profiles of patients having IBS with co-occurring psychiatric disorder and healthy control.
2. Study psychiatric co-morbidities in patients with IBS, visiting psychiatry and gastroenterology OPD.

II. MATERIALS AND METHODS

The present study was conducted in the Department of Psychiatry, Institute of Medical Sciences, Banaras Hindu University, from September 2017 to May 2018.

Sample Size and Sample Selection

There were a total of 100 individuals (50 patients with IBS and 50 healthy controls) included in the present study.

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Group 1: IBS Patients

The present study consisted of 50 patients who fulfilled the criteria for study. These were recruited from the Gastroenterology department, Institute of Medical Sciences, Banaras Hindu University. Diagnosis of IBS was made by gastroenterologist in OPD, according to ROME IV criteria [21] and patients were classified into constipation predominant IBS (IBS-C), diarrhea predominant IBS (IBS-D), mix of the 2 symptoms (IBS-M) and IBS unsubtype (IBS-U). All subjects were between age of 18 to 60 years and were diagnosed with IBS in past 3 months and gave informed consent before enrolling in study. We excluded patients with history of hematochezia, malena, weight loss > 5% in past 1month, age more than 60 years, history of carbohydrate intolerance, celiac disease, abuse of laxatives or antidiarrheal agents. Patients with history of any systemic disease or metabolic disorder, chronic medical disorders, abnormal complete blood count and Erythrocyte Sedimentation Rate were also excluded.

Group 2: Controls

Fifty healthy relatives of the patients visiting outpatient department were recruited as controls. Controls were matched with respect to age and gender. Only healthy adults between 18 to 60 years, who gave informed consent, were included in this study. We excluded patients suffering from chronic medical and surgical conditions.

Ethics Committee approval was obtained from the Institutional Ethics Committee.

Data Collection

1) *Socio-demographic status:* The details of socio-demographic were recorded on socio-demographic sheet. Detail of biochemical investigations and physical examination were done of all cases and controls. The socio-economic class was established by Kuppuswamy's scale [22] .
2) *Symptoms and severity of irritable bowel syndrome*: We used Rome IV criteria [21] for diagnosing and classification of IBS. The severity of IBS was assessed using irritable bowel severity scoring system. The irritable bowel severity scoring system evaluates primarily the intensity of IBS symptoms during a 10-day period: abdominal pain, distension, stool frequency and consistency, and interference with life in general. The IBS-SSS calculates the sum of these 5 items each scored on a visual analog scale from 0 to 100. Patients were classified on the basis of cumulative scores into mild IBS (severity score 75-175), moderately severe IBS (score 175-300) and severe IBS (score> 300). [23]
3) *Assessment of psychiatric co-morbidities*: Patients were assessed using the Mini International Neuropsychiatric Interview Schedule Plus [24, 25], Physical Health Questionnaire 15 [PHQ-15] [26], Hamilton Anxiety Rating Scale [HAM-A] [27], Hamilton Depression Rating Scale [HAM-D]. [28]

Statistical Analysis: Statistical analysis was done by using SPSS software version 23.0. The Simple statistical analysis using Chi Square test, t test, p value for significance and correlation coefficient were used for the analysis of data. [29]

III. RESULTS

The mean age of the patient with IBS was 30.30±10.57 years and the mean age of controls was 27.28±8.88 years. The proportion of the male respondents in both study groups was comparatively higher than females. Most of the patients (52%) were married in the IBS group but in controls, the majority of them were unmarried (52%). Nearly one-third of the respondents in both study groups belong to rural areas. Most of the patients were living in joint families (58%), but in controls, an equal number of the respondents were living in both family types (nuclear 50% and joints 50%). Most of the patients (40%) and controls (44%) were from the lower middle class of socioeconomic status. The majority of the patients with IBS were solely vegetarian (36%) but in the control group, most of them were predominantly vegetarian (58%).

TABLE 1: Socio-demographics

Socio-demographic characteristics	IBS Patients [n=50]		Control [n=50]		P value
	F	%	F	%	
Mean age (In years)	30.30±10.57		27.28±8.88		0.125
Gender					
Male	38	76	34	68	0.373
Female	12	24	16	32	
Marital status					
Married	26	52	24	48	0.689
Unmarried	24	48	26	52	
Domicile					
Urban	13	26	10	20	0.496
Rural	37	74	40	80	
Type of family					
Nuclear	21	42	25	50	0.422
Joint	29	58	25	50	
Socio-Economic Status					
Upper Middle Class	3	6	3	6	
Middle Class	19	38	13	26	
Lower Middle Class	20	40	22	44	0.568
Lower Class	8	16	12	24	
Dietary habits					
Solely Vegetarian	18	36	19	38	
Predominantly Vegetarian	30	30	29	58	0.978
Predominantly Non Vegetarian	2	4	2	4	

Table 2 shows that majority of our patients (56%) had diarrhea predominant IBS (IBS-D), respectively constipation predominant IBS-C (32%), 2 patients (4%) had mixed type of IBS (IBS-M), and 4 patients had unclassified type of IBS (IBS-U).

TABLE 2: Frequency of IBS type

IBS Type	Frequency	%
IBS-D	28	56
IBS-C	16	32
IBS-M	2	4
IBS-U	4	8
Total	50	100

Table 3 shows that there some common co-morbid psychiatric disorders such as major depression, generalized anxiety disorder, mixed anxiety depression, social phobia, agora phobia, OCD, panic disorder and anorexia nervosa were found in both study groups. There were a significant difference found in the prevalence of major depression

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(p<0.05), generalized anxiety disorder (p<0.05) and mixed depression (p<0.05) between both study groups. Patient with IBS were found highly vulnerable group for psychiatric disorders compared to controls.

TABLE 3: Psychiatric co-morbidities in IBS patients and controls (N=50 in each groups)

Psychiatric Disorders	IBS Patients		Controls		χ^2	P-value
	F	%	F	%		
Major Depression	13	26	4	8	4.536	**0.033**
Generalized Anxiety Disorder	10	20	2	4	4.640	**0.031**
Mixed anxiety depression	11	22	2	4	5.659	**0.017**
Social phobia	3	6	1	2	0.260	0.609
Agoraphobia	2	4	1	2	0.344	0.557
OCD	2	4	0	0	0.510	0.475
Panic disorder	1	2	0	0	1.010	0.314
Anorexia nervosa	1	2	0	0	1.010	0.314
Absent	7	14	40	80		

Table 4 Patients were asked through interview about various domains of stress in their life. This table shows that most of IBS patients had physical stress, which was pertaining to worry about their physical symptoms. In IBS group 12 (24.00 and in control group 1 (2.0) had physical stress. Occupational stress was related to profession and it was found in 12 patients in IBS group. Among all familial stress was least, significant correlation was observed between stress and both groups ($\chi2$ =71.009; p= <0.001).

TABLE 4: Type of Stress Vs Group (N=50 in each groups)

Type of stress	IBS Patients		Control	
	F	%	F	%
Physical Stress	12	24	1	2
Financial Stress	11	22	1	2
Family Stress	2	4	0	0
Occupational Stress	12	24	0	0
Educational Stress	8	16	1	3
Absent	5	10	47	94
$\chi2$ =71.009; p= <0.001				

IV. DISCUSSION

Irritable Bowel Syndrome (IBS) is a chronic illness related to the gastrointestinal system, some previous studies in western countries had shown that about 50-90% patients with IBS suffer from any type of co-morbid psychiatric disorders. [30] The present study was conducted to assess and compare the co-occurring psychiatric disorders between two study groups; IBS patients and healthy controls. Mean age in our study was 30 years in IBS group and 27 years in control group. Most of the study population belonged to rural area with lower middle socio-economic status. This can be explained as this study was done in Eastern part of Uttar Pradesh, which is catchment area consisting of population with low socio-economic status and rural background. Both groups were matched equally with respect to age, gender, marital status, dietary habits, domicile, type of family and socio-economic status, as difference between both groups were insignificant.

Wessely S et al. suggested that same IBS patient can be diagnosed with summarization emphasizing that these disorders share a common underlying path physiology [31]. In our study male outnumbered than female nearly 76% male and 24% female were belong to IBS group which is comparable to study done by Prashant Singh et al. in 2012 (73% males and 27% females) [33]. Although there were somatic and functional disorders found high in females. [33] The most common reason for this difference in the ratio of male and female patients with IBS is that there is a lack of awareness about it in the community in the eastern part of Uttar Pradesh and other reasons are like low socioeconomic status and illiteracy. Therefore a number of patients don't contact the professionals who are specialists to treat such types of disorders. [34-36]

In the present study, most of the IBS patients were either predominantly vegetarian or solely vegetarian and only a few numbers of the patients were non-vegetarian. There are very few studies concerning dietary habits in IBS, although in our study we did not find any statistical difference between cases and controls.

The findings of the present study indicated that the co-occurrence of co-morbid psychiatric disorders was comparatively high among patients with IBS compared to the healthy controls. There were common psychiatric problems such as major depression, generalized psychiatric and mixed anxiety-depression found significantly high in the IBS group. Other psychiatric disorders such as social phobia, agoraphobia, OCD, panic disorder, anorexia nervosa were found more common in the IBS group compared to the control group. Our findings are in accordance with other Indian studies [32, 37] where overall prevalence of psychiatric disorders was around 80%. While western studies report 40-60% overall prevalence of psychiatric disorders in IBS patients [38, 39]. Other Indian studies have also reported high prevalence of major depression [32, 37] as well as generalized anxiety [34]. This difference could be attributable to socio-demographic differences, as it has been observed that psychiatric disorders manifest more as somatic symptoms in developing countries and IBS being one of its somatic manifestations [40].

Furthermore, our centre is a tertiary care centre where patients are referred from lower centres as well as from remote rural areas with low socio-economic background. This contributes to psychological distress, subsequently increasing psychiatric co morbidity as well. Also, severity of functional GI disorders increases the likelihood of having co-morbid psychiatric illness [41].

The present study also found that a number of patients with IBS were suffering from stressors such as physical, educational, financial, occupational, and family stress. And the results also revealed that there was a significant difference in the probability of having stress between both groups. These findings are similar to the findings of some previous studies conducted in other countries. [42, 43]

V. LIMITATIONS

This study was conducted at a tertiary care centre, where cases with severe forms of illness are referred which could lead to overestimation of psychiatric co-morbidity. The sample size was very small and the data was collected from

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only one centre, therefore the result of the present study may not be generalized for whole population.

VI. CONCLUSION

Findings of the present study indicates that majority of the patient with IBS were found with co-morbid psychiatric disorders comparatively higher than healthy controls. There were a significant difference found in the co-occurrence of psychiatric disorders such as major depression, generalized anxiety disorder and mix anxiety depression between IBS patients group and the healthy control group.

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REFERENCES

[1] Corney RH, Stanton R. Physical symptom severity, psychological and social dysfunction in a series of outpatients with irritable bowel syndrome. J Psychosomatic Res 1990;34:483-491.
[2] Talley NJ, Zinsmeister AR, Van Dyke C, Melton LJ. Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology 1991;101:927-934.
[3] Jones R, Lydyard S. Irritable bowel syndrome in the general population. BMJ 1992;304:87-90.
[4] Saito YA, Locke GR, Talley NJ, Zinsmeister AR, Fett SL, Melton LJ 3rd. A comparison of the Rome and Manning criteria for case identification in epidemiological investigations of irritable bowel syndrome. Am J Gastroenterol 2000;95:2816-2824.
[5] Oshima T, Miwa H. Epidemiology of functional gastrointestinal disorders in Japan and in the world. J Neurogastroenterol Motil 2015;21:320329
[6] Harvey RF, Salih SY, Read AE. Organic and functional disorders in 2000 gastroenterology outpatients. Lancet 1983;1:632-634.
[7] Ferguson A, Sircus W, Eastwood MA. Frequency of "functional" gastrointestinal disorders. Lancet 1977;2:613-614.
[8] Fielding JF. A year in out-patients with the irritable bowel syndrome. Ir J Med Sci 1977;146:162-166
[9] Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology 2002;122:1140-1156.
[10] Ford AC, Marwaha A, Lim A, Moayyedi P. Systematic review and meta-analysis of the prevalence of irritable bowel syndrome in individuals with dyspepsia. Clin Gastroenterol Hepatol 2010;8:401- 409.
[11] Gwee KA, Bak YT, Ghoshal UC, et al. Asian consensus on irritable bowel syndrome. J Gastroenterol Hepatol 2010;25:1189-1205.
[12] Chakraborti SK, Dey BK, Ghosh N, Chaudhury AN, Guha Mazumder DN. Objective evaluation of psychological abnormality in irritable bowel syndrome. Indian J Gastroenterol 1996;15:43-45.
[13] Kumano H, Kaiya H, Yoshiuchi K, Yamanaka G, Sasaki T, Kuboki T. Comorbidity of irritable bowel syndrome, panic disorder, and agoraphobia in a Japanese representative sample. Am J Gastroenterol 2004;99:370-376.
[14] Lydiard RB, Fossey MD, Marsh W, Ballenger JC. Prevalence of psychiatric disorders in patients with irritable bowel syndrome. Psychosomatics 1993;34:229-234.
[15] Walker EA, Gelfand AN, Gelfand MD, Katon WJ. Psychiatric diagnoses, sexual and physical victimization and disability in patients with irritable bowel syndrome or inflammatory bowel disease. Psychol Med 1995;25:1259-1267
[16] Levy RL, Whitehead WE, Von Korff MR, Feld AD. Intergenerational transmission of gastrointestinal illness behavior. Am J Gastroenterol 2000;95:451-456.
[17] Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci 1993;38:1569-1580.
[18] Vandvik PO, Wilhelmsen I, Ihlebaek C, Farup PG. Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications. Aliment Pharmacol Ther 2004;20:1195-1203.
[19] Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology 2003;125:19-31.
[20] Rahimi R, Nikfar S, Rezaie A, Abdollahi M. Efficacy of tricyclic antidepressants in irritable bowel syndrome: a meta-analysis. World J Gastroenterol 2009;15:1548-1553.
[21] Lacy, B.E.; Mearin, F.; Chang, L.; Chey, W.D.; Lembo, A.J.; Simren, M.; Spiller, R. Bowel Disorders. Gastroenterology 2016, 150, 1393–1407.
[22] Shaikh Z et al. Int J Community Med Public Health. 2017 Apr;4 [4]:997-999
[23] Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. 1997 Apr;11 [2]:395-402.
[24] Amorim P. Mini International Neuropsychiatric Interview [MINI]: validation of a short structured diagnostic psychiatric interview. Revista Brasileira de Psiquiatria 2000;22:106-115.
[25] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini International Neuropsychiatric Interview [M.I.N.I]: the development and validation of structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 [suppl 20]:22-33
[26] Kroenke K, Spitzer RL, Williams JB . The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. 2002 Mar-Apr;64 [2]:258-66.
[27] Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55
[28] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
[29] IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.
[30] Fukudo S , Kaneko H, Akiho H, et al. Evidence-based clinical practice guidelines for irritable bowel syndrome. J Gastroenterol 2015;50:11-30.
[31] Wessely S, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? Lancet 1999;354:936-939
[32] Singh P, Agnihotri A, Pathak MK, et al. Psychiatric, somatic and other functional gastrointestinal disorders in patients with irritable bowel syndrome at a tertiary care center. J Neurogastroenterol Motil 2012;18:324331.
[33] Haug TT, Mykletun A, Dahl AA. The association between anxiety, depression, and somatic symptoms in a large population: the HUNT-II study. Psychosom Med 2004;66:845-851
[34] Weiss BD, Hart G, Pust RE. The relationship between literacy and health. J Health Care Poor Underserved. 1991 Spring;1[4]:351-63.
[35] Yoko Furuya, Naoki Kondo, Zentaro Yamagata, Hideki Hashimoto, Health literacy, socioeconomic status and self-rated health in Japan, *Health Promotion International*, Volume 30, Issue 3, September 2015, Pages 505–513, https://doi.org/10.1093/heapro/dat071
[36] https://www.census2011.co.in/census/state/uttar+pradesh.html
[37] Yuman Kawoos, Zaid A Wani, Showkat A Kadla, Irfan A Shah, Arshad Hussain, M Maqbool Dar, Mushtaq A Margoob, and Kouser Sideeq. Psychiatric Co-morbidity in Patients with Irritable Bowel Syndrome at a Tertiary Care Center in Northern India. J Neurogastroenterol Motil, Vol. 23 No. 4 October, 2017.
[38] Hausteiner-Wiehle C, Henningsen P. Irritable bowel syndrome: relations with functional, mental, and somatoform disorders. World J Gastroenterol 2014;20:6024-6030. 34. Toner BB, Garfinkel PE, Jeejeebhoy KN. Psychological factors in irritable bowel syndrome. Can J Psychiatry 1990;35:158-161.
[39] Toner BB, Garfinkel PE, Jeejeebhoy KN. Psychological factors in irritable bowel syndrome. Can J Psychiatry 1990;35:158-161.
[40] Barsky AJ. Assessing the new DSM-5 diagnosis of somatic symptom disorder. Psychosom Med 2016;78:2-4.
[41] Jafari P, Asadollahi Z, Moini M, Seyed Mirzaie M. Health related quality of life in Iranian patients with irritable bowel syndrome: reliability and validity of the persian version of the IBS-QOL. Iran Red Crescent Med J 2013;15:723-728

[42] Boroujerdi L, Shih W, Presson AP, Naliboff BD, Mayer EA, Chang L. Sa1416 Perceived Stress is Higher in IBS Than Healthy Controls and Correlates With IBS Severity Over Time. Gastroenterology. 2012 May 1;142(5):S-299.

[43] Sato N, Suzuki N, Sasaki A, Aizawa E, Obayashi T, Kanazawa M, Mizuno T, Kano M, Aoki M, Fukudo S. Corticotropin-releasing hormone receptor 1 gene variants in irritable bowel syndrome. PloS one. 2012;7(9).