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Research Article

Detection of *Cytomegalovirus* in Patients with Inflammatory Bowel Diseases in Iraq

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I N F O

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A B S T R A C T

Introduction: Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders of the gastrointestinal tract caused by interactions between genetic, environmental, immunological, and microbial factors.

Objective: To study the association of Cytomegalovirus in a sample of Iraqi patients with inflammatory bowel diseases

Methodology: The study included 160 patients, of which, 80 were diagnosed with IBD by a specialist in gastroenterology and 80 were apparently healthy subjects. Stool samples were collected from all participants and were prepared for detection of CMV PP65 by ELISA. The molecular method (real-time PCR) was used to detect the DNA of each pathogen.

Results: Twenty-five patients with IBD had a significantly high level (8.44 pg/ml) of CMV as compared to the control group. The results showed that there was no significant correlation between CMV PP65 and the signs and symptoms of IBD patients (smoking, UC severity, bloody diarrhoea, abdominal pain, biological therapy, behaviour, or CD location). CMV real-time copy quantity was significantly correlated with smoking, bloody diarrhoea, abdominal discomfort, and biological therapy, but not with UC extent, behaviour, or CD location, as determined by molecular real-time PCR.

Conclusion: There is a possible role of CMV in the pathogenesis of IBD in patients in Iraq. The biological treatment given to patients with IBD seems to reduce the CMV level.

Keywords: Inflammatory Bowel Disease, *Cytomegalovirus,* Ulcerative Colitis, Crohn's Disease

Introduction

A persistent inflammatory illness with an unknown cause is called Inflammatory Bowel Disease (IBD). Crohn's Disease (CD) and Ulcerative Colitis (UC) are the two main clinical forms of IBD that have been identified.[1] These illnesses vary in terms of their histology, location, and distribution of inflammatory lesions.[2] CD can be distinguished from UC on the basis of the following features:

- Development of fistulae, which are caused by burrowing ulcers, and stricture formation in the gastrointestinal tract
- More frequent systemic manifestations and extra-intestinal complications, such as fever, weight loss, malaise, and rheumatologic diseases
- Presence of granulomas in the pathological presentation[3]

These are clinically diverse illnesses with a range of phenotypic, clinical, and demographic characteristics. To compare the illness features over time and space, various phenotypes must first be classified. Additionally, it could increase the likelihood of discovering genotype–phenotype correlations and perhaps provide a molecular explanation for both diseases.[4] In Crohn's disease, the areas of inflammation are dispersed unevenly and affect the whole gut from the mouth to the anus. Asymmetrical inflammation that affects the entire intestinal wall from the mucosa to the serosa can be transmural and can cause secondary problems such as fistulas, abscesses, and stenosis. Small superficial ulcerations and occasional non-caseating granulomas are seen histologically, according to observations.[2] Depending on the age of onset, the anatomical localisation of the inflammation, and disease behaviour, the disease phenotypes might be categorised in accordance with the Montreal classification as shown in Table 1.

Table 1.Montreal Classification of Crohn's Disease (2006) (Modified from the Vienna Classification)[5]

Variables	Characteristics
Age of diagnosis (years)	
A1: < 16	Colonic localisation in most cases, high family aggregation and genetic susceptibility
A2: 17–40	Frequent and extensive inflammation from the upper GI tract to the colon
A3: > 40	Colonic localisation in most cases
Localisation (L)	
L1: Ilea	30% of CD patients; Basic clinical manifestations: stenosis, nausea, vomiting, abdominal pain, loss of weight, and fever; less aggressive diarrhoea than in colonic localisation
L2: Colonic	20% of CD patients; One or several affected areas between the cecum and rectum, but mainly the colon; abundant diarrhoea, bleeding, abdominal pain, and loss of weight; correlates with perianal disease and extraintestinal manifestations
L3: Ileocolonic	40% of CD patients; Localisation and clinical manifestations of L1 and L2
L4: Upper GI tract	5% of CD patients; Proximal ileum, jejunum, duodenum, stomach, oesophagus or oropharynx can be affected; heterogeneous clinical manifestations depending on the exact localisation
Behaviour (B)	
B1: Inflammatory	(Not stricturing-not penetrating) Superficial ulcerations and inflammation; abdominal pain and diarrhoea
B2: Stricting	Presence of stenosis and fibrosis; nausea, vomiting, pain and abdominal distension; cases often refractory; occasional surgical intervention; low recurrence
B3: Penetrating	Perforation; often formation of fistulas and abscesses; surgery necessary; high recurrence

Ulcerative Colitis

It is a kind of IBD that affects only the colon. In 95% of cases, the rectum is affected, with varying degrees of proximal extension. With the exception of a few uncommon instances including toxic megacolon, inflammation in contrast to CD is limited to the mucosa and has a continuous distribution of varied intensity. Bleeding, oedema, and ulceration are symptoms of UC. Histological characteristics include goblet cell depletion, crypt abscesses, deformation of the

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mucosal glands, and acute and chronic inflammation by polymorphonuclear leukocytes and mononuclear cells. Faeces with blood and mucus together with lower abdominal cramps are the most typical digestive symptoms. Depending on how far the inflammation has spread anatomically, the disease is sub-classified as shown in Table 2.

Table 2.Montreal Classification of the Extent of Ulcerative Colitis (UC) (2006)[6]

Extent	Anatomy
E1: Ulcerative proctitis	Involvement is limited to the rectum (that is, the proximal extent of inflammation is distal to the rectosigmoid junction).
E2: Left-sided UC (distal UC)	Involvement is limited to a proportion of the colorectum distal to the splenic flexure.
E3: Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure.

The human *cytomegalovirus* (HCMV) is one of the most common causes of gastrointestinal infections in people with IBD.[7] The Herpesviridae family's *Cytomegalovirus* (CMV) causes a typical viral infection in people, with infection rates ranging from 40% in developed nations to 100% in underdeveloped nations.[8] It is known that after the primary infection, this virus maintains a long-lasting, persistent infection in the host, frequently in a latent form that may be identified in several cell types.[9] Among IBD cases that combine colon inflammation and long-term immunosuppressive medication, both of which might reactivate latent CMV, HCMV infection is of special interest.[10] It is crucial to distinguish CMV colitis from an IBD flare-up in immunosuppressed patients with IBD since untreated CMV infection in such patients might develop into fulminant colitis, which may need colectomy or may result in death.[11] Although numerous studies have demonstrated a link between severe steroid–refractory IBD and CMV infection,[12,13] international guidelines from the American College of Gastroenterology (ACG) and the European Crohn's and Colitis Organisation (ECCO) advise that CMV colitis should be excluded in patients with acute steroid resistance before increasing treatment dosage.[14]

Materials and Methods

This study aims to investigate the association of *Cytomegalovirus* with inflammatory bowel disease in a cohort of Iraqi patients. The research employed traditional methodologies, quantitative ELISA, and PCR techniques to analyse stool samples.

Inclusion Criteria

- Patients who were older than 18 years of age and had been diagnosed with inflammatory bowel disease

Exclusion Criteria

- Patients who possessed or had previously possessed any form of malignancy
- Patients who had been diagnosed with other conditions such as diabetes mellitus (DM), thyroid problems, congenital adrenal illness, renal diseases, or any congenital or hereditary metabolic disorders
- Three categories of women who were either pregnant or lactating
- Patients who were currently receiving treatment with antibiotic, antiparasitic, and antiviral medications
- There was an absence of Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Human Immunodeficiency Virus (HIV) in the given context

Sample Collection

Stool samples were collected from all participants using disposable gloves. Plastic spoons were used to transfer small quantities of the specimen to pre-labelled, clean, and dry plastic containers with locked cups. The samples were stored in a cold box and were processed within three hours of the storage time. Sometimes, it did not require any storage, but rather work was done directly on the sample. A total of 160 patients (80 patients with IBD diagnosed by a specialist in gastroenterology and 80 apparently healthy subjects) were included in this study conducted from December 2022 to the end of March 2023 in Al-Imamain Al-Kadhimain Medical City, Iraq. The study was performed in the laboratories of the Microbiology Department in the College of Medicine, Al-Nahrain University and was approved by the Institutional Review Board of the College of Medicine, Al-Nahrain University (under number 239 and dated 30/7/2019).

Serology

CMV was detected by ELISA technique using sandwich ELISA to detect PP65 CMV Ag in the stool of all patients using a commercially available kit (Sunlong, China).

DNA Extraction

DNA was extracted from the stool samples using the Geneaid Presto Stool DNA Extraction Kit (Taiwan, Catalogue Number: STLD100). The manufacturer's instructions were followed.

Molecular Technique

The technique of real-time quantitative polymerase chain reaction (qPCR) was employed to amplify the DNA of *Cytomegalovirus* (CMV) in faecal specimens. The final reaction volume of CMV was 21 µl, as indicated in Table 3. The determination of the annealing temperature was performed subsequent to the optimisation of the polymerase chain reaction (PCR) (Table 4).

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Table 3.Mixture of PCR Working Solution for Detection of CMV in IBD Patients and Healthy Controls

Component	Volume (µl)
GoTaq® qPCR Master Mix (2X)	10
Forward primer (20X)	0.5
Reverse primer (20X)	0.5
Supplemental CXR reference dye	0.2
DNA template	4.0
Nuclease-free water	5.8
Total volume	21.0

Table 4.PCR Programme for Amplification of Cytomegalovirus by Thermal Cycler

S. No.	Steps	Temperature (˚C)	Time	No. of Cycles
1	Initial Denaturation	94	6 minutes	1
2	Denaturation	94	40 seconds	35
3	Annealing	56	45 seconds	
4	Extension	72	1 minute	
5	Final extension	72	10 minutes	1

Primers: The primers were designed according to reference sequences in the National Center for Biotechnology Information (NCBI) database. They were synthesised and lyophilised by Alpha DNA Ltd. (Canada) (Table 5).

Table 5.Sequences and Product Size of Cytomegalovirus Gene

Virus	Nucleotide Sequences (5' → 3')		Products bp
CMV	F	AGACGTTAGCAGCTGGTCGT	240
	R	TCACCCACACGGTAGAATCA	

Statistical Methods

The statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 24 and a Microsoft Excel worksheet. All data were tested for normality of distribution using the Shapiro–Wilk test. The categorical data were described as count and percentage and the chi-square test was used for the estimation of association with study groups. The probability values below 0.05 were considered significant.

Results

The study showed that in the patient group, the mean age was 34 years and males (55%) were more than females (45%). There were no significant differences between the patient and control groups with reference to their age and gender as shown in Table 6. *Cytomegalovirus* was detected quantitatively by ELISA. It revealed significant differences between the two groups as shown in Table 7.

Table 6.Distribution of Inflammatory Bowel Disease Patients and Controls by Gender and Age Range

Demographic Data			Study Groups		p Value
			IBD	Control	
Age (years)	(Mean ± SD)		34.21 ± 10.16	33.47 ± 11.06	0.778^{NS}
	(Min–Max)		19–57	18–70	
Gender	Female	n	36	42	0.215
		%	45.0	52.5	
	Male	n	44	38	
		%	55.0	47.5	

NS: Not significant

Table 7.Quantitative ELISA for Cytomegalovirus

Pathogens		Study Groups		p Value
		IBD	Control	
CMV (pg/ml)	Median	8.44	3.54	< 0.001
	5th percentile	4.81	1.74	
	95th percentile	12.24	6.73	

NS: Not significant

There was no statistically significant association between the CMV values for Crohn's disease and ulcerative colitis as shown in Table 8.

Table 8.Quantitative ELISA for Cytomegalovirus in IBD Patients

-		IBD		p Value
		Crohn's disease	Ulcerative colitis	
CMV (pg/ml)	Median	8.97	8.40	0.069^{NS}
	5th percentile	4.81	5.67	
	95th percentile	12.83	11.47	

NS: Not significant

Cytomegalovirus was detected quantitatively by the molecular method. This revealed significant differences between IBD patients and controls as shown in Table 9.

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Smoking, severity of UC, bloody stools, abdominal pain, biological therapy, behaviour, and CD location were not observed to be significantly associated with *Cytomegalovirus* (ELISA) in IBD patients. The molecular approach showed a strong association between the CMV real-time copy number and symptoms like stomach discomfort, smoking, bloody diarrhoea, and biological therapy, but not with symptoms like UC severity, CD location, and behaviour (Table 10).

Table 10.Association of Signs and Symptoms of IBD Patients with Cytomegalovirus

Signs and Symptoms		CMV (pg/ml)			CMV (copy/ml)		
		Median	Percentile		Median	Percentile	
			5th Percentile	95th Percentile		5th Percentile	95th Percentile
Abdominal pain	Absent	8.44	4.78	12.83	676.36	20.29	5698.30
	Present	8.39	4.81	11.59	225.15	19.90	1258.36
p value		0.837^{NS}			< 0.001		
Smoking	No	8.43	4.81	12.21	650.15	40.59	2587.30
	Yes	8.83	4.81	12.28	225.15	19.90	901.30
p value		0.608^{NS}			0.001		
Bloody diarrhoea	Absent	8.51	5.94	11.59	450.36	20.10	998.36
	Present	8.43	4.76	12.83	666.60	43.86	6589.30
p value		0.684^{NS}			0.050		
Biological therapy	No	8.44	4.81	12.28	568.83	20.29	2587.30
	Yes	8.28	5.94	11.04	134.58	19.90	505.30
p value		0.688^{NS}			0.038		
Behaviour	B2	8.43	4.81	10.83	386.56	19.90	907.63
	B1	9.20	4.81	12.83	476.36	20.89	2000.30
p value		0.297^{NS}			0.207^{NS}		
UC extent	E1: Ulcerative proctitis	8.31	5.67	12.21	650.15	20.29	2587.30
	E2: Left-sided UC	9.22	8.51	9.98	78.60	66.87	8096.30
	E3: Extensive UC	7.56	3.98	9.56	504.64	34.93	5698.30
p value		0.091^{NS}			0.676^{NS}		
CD location	L1: Ileal	8.43	5.95	12.94	682.48	40.79	998.36
	L2: Colonic	8.51	6.67	10.83	442.48	19.90	789.36
	L3: Ileocolonic	9.57	4.79	12.55	350.87	20.00	2293.80
p value		0.521^{NS}			0.486^{NS}		

NS: Not significant, B: Behaviour

Discussion

Inflammatory bowel disease (IBD) has the potential to impact individuals across many age groups, although it frequently manifests itself in the age range of 15–30 years. The mean age of the patient group in the current investigation aligns with these findings since it was determined to be 34 years. In relation to the topic of sex, it is noteworthy that both males and females have the potential to develop IBD, and there exists no substantial disparity in the overall prevalence of this condition between the two sexes. Molodecky and his team conducted a comprehensive review and meta-analysis, which indicated a marginal prevalence of males in Crohn's disease, a form of IBD, and a small prevalence of ulcerative colitis in females, another type of IBD.[15] The findings of this investigation revealed a minimal disparity in the prevalence of affected males compared to females.[16] The first case report of HCMV linked to UC was published in 1961, which prompted researchers to wonder if the CMV found was the main factor in the patient's decline or merely a side effect of ulcerative colitis, debility, and the therapeutic use of adrenal cortical steroids. The literature on IBD has started to address this question in the last 50 years.[17] In

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the past, immunocompromised patients with symptoms of CMV disease have included neonates, people who had organ transplants, people who had the HIV virus, and people taking immunosuppressive drugs.[18,19] Additionally, numerous case reports have documented the discovery of CMV in patients with severe IBD who did not respond to conventional immunosuppressive medication.[20,21] So, CMV levels were found to be significantly different between the IBD patients and the control group in this investigation. The results of the molecular PCR experiment corroborated these findings.

CMV is frequently seen in the GI tract, but whether it is a causal agent or an opportunistic infection in IBD is still up for debate. It has been shown that 30% of CD patients have CMV infection, compared to only 8% of controls. Patients with IBD who are found to have CMV also tend to have more advanced disease and more problems. Patients with active IBD are at a higher risk for developing CMV colitis. A higher risk of surgery, lengthier hospital stays, and premature deaths have all been associated with it.[22] According to a study conducted by Rahier et al., the prevalence of CMV colitis was observed to be 7% among patients with severe disease of ulcerative colitis (UC), but it was only 0.5% among those with mild-to-moderate disease. The potential association between CMV and IBD in patients could be attributed to the effects of immunosuppressive medications, rather than CMV being a main aetiological factor for the development of the disease.[23] Association according to the type of IBD revealed no significant difference in the possible association with the type of IBD, Crohn's disease or ulcerative colitis. This may reflect that the possible mechanism(s) for induction of the disease process is the same for both. So the effect of CMV was seen more through the results seen in Table 9. The level of the virus measured by ELISA showed no significant differences for all signs and symptoms listed in Table 10. The molecular measuring by PCR showed that most of the signs and symptoms mentioned were significant and only the behaviours, extent and location were non-significant. The significant data regarding high CMV DNA level is associated with less abdominal pain but bloody diarrhoea and more smoking. This explained that the CMV virus exacerbates the disease process of IBD patients, but an interesting finding is the high level of DNA copy number of CMV in relation to IBD not using the biological treatment and this may reflect a possible cause and effect manoeuvre as the results showed low copy DNA number of the CMV in treated IBD patient.

The level of the virus measured by ELISA showed no significant difference for all signs and symptoms listed in Table 10. Molecular measuring by PCR showed that most of the signs and symptoms mentioned were significant, and only the behaviour, UC extent, and CD location were non-significant. The presence of elevated levels of CMV DNA has been found to be correlated with a decrease in abdominal pain accompanied by bloody diarrhoea, as well as an increase in smoking behaviour. This study elucidated the role of the CMV virus in exacerbating the disease progression of patients with IBD. Notably, a significant finding was the observation of a high level of CMV DNA copy number in IBD patients who did not receive biological treatment. This observation suggests a potential cause-and-effect relationship, as the results demonstrated a lower copy number of CMV DNA in IBD patients who underwent treatment. The utilisation of Polymerase Chain Reaction (PCR) for the identification of *Cytomegalovirus* (CMV) in patients holds the potential for enhancing treatment strategies and preventing future occurrences. As is widely recognised, the Polymerase Chain Reaction (PCR) has been employed in various medical domains pertaining to the identification of clinical pathogenesis associated with infectious diseases and other perilous genetic conditions, such as cancer.[24–38]

Conclusion

The study showed that there is a possible role of CMV in the disease process of IBD and CMV level is reduced in patients with IBD who have received biological treatment.

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Conflict of Interest: None

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