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Research Article

Ocular Disorders in Patients with Idiopathic Inflammatory Bowel Disease Under Methotrexate

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Received: December 24, 2017; **Published:** January 22, 2018

Abstract

Background: Patients with Inflammatory Bowel Disease (IBD) may show often various intraintestinal and extraintestinal disorders. Patients treated with methotrexate experience quite often ocular disorders that need special attention.

Aim: The aim of the current study was to record ocular disorders in patients with IBD treated with methotrexate.

Methodology: Twenty nine patients that fulfilled inclusion criteria were enrolled and were followed in four departments of North-western Greece.

Results: The cohort (n = 29) comprised, 11 females and 18 males. Ulcerative colitis (UC) was diagnosed in 14 patients and Crohn's disease (CD) in 15 patients. Visual acuity examination revealed that left eye was more frequently affected. In funduscopic evaluation, maculopathy and pigmental disorders were evident in one patient each. Anterior eye examination showed that 10.4% (n = 3) of patients suffered from cataract and 20,6% (n = 6) Posterior Chamber Intraocular Lens (IOL) bilateral.

Conclusion: Patients with IBD in general but also those treated with methotrexate may suffer from significant ocular disorders, a finding that underscores the need for systematic ophthalmologic follow-up.

Keywords: *IBD; Crohn's Disease; Ulcerative Colitis; Ocular Disorders; Methotrexate*

Abbreviations

IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn's Disease; BCVA: Best Corrected Visual Acuity; IOP: Measurement of Intraocular Pressure; BUT Test: Break-Up Time Test

Introduction

Inflammatory bowel disease (IBD) is a chronic disorder of the gastrointestinal system that has two different phenotypes – Ulcerative Colitis (UC) and Crohn's Disease (CD) - with usually overlapping pathological and clinical characteristics. IBD occurs quite often in several areas of the modern world [1,2] with UC having a greater incidence compared to CD (9 - 12/100,000 vs 6 - 8/100,000 people in the general population) [3]. In Mediterranean countries including Greece, the occurrence of IBD in first relatives of patients does not exceed 7% in adults [4] and 8.5% in children [5]. Furthermore, CD seems to occur quite often in Northwestern Greece (mean annual incidence $1.6/10^5$ inhabitants), even though these numbers are much lower compared to Northern European Countries [6,7].

Clinical manifestations of IBD refer to intestinal (e.g. pain, inflammation, obstruction, fever, diarrhea etc) and extra-intestinal disorders (e.g. dermatological, ocular, myoskeletal, hematological etc) [8]. Ocular disorders as part of the IBD range from simple mild ocular symptoms and signs to extremely severe conditions and are more frequent in CD (10 - 13%) compared to UC (5%) [9].

Methotrexate stands among the medications used in IBD. Methotrexate inhibits conversion of folic acid to its active metabolite affecting thus the synthesis of DNA which is related to the anti-inflammatory and immunosuppressive action of this medication (leading to cellular apoptosis) [10]. It has been previously shown that methotrexate is effective in corticosteroid-dependent patients suffering from CD [11]. However, the use of methotrexate has been associated with several side effects including stomatitis, nausea, lung toxicity, diarrhea, loss of hair and mild leucopenia [9,12]. Methotrexate has been used to treat ocular manifestations of IBD including episcleritis, scleritis, uveitis, keratitis, conjunctivitis, increase in intraocular pressure and glaucoma [8]. On the other hand, important ocular side effects of methotrexate occur in both adults and children. After methotrexate use sub retinal alterations may heal but corneal damage, macular edema and cotton wool spots appear in both eyes and could be irreversible [13]. Intravenous administration of methotrexate results in clinically significant levels inside the aqueous humor [14]. Methotrexate has been also associated with the appearance of other ocular manifestations such as decreased vision and field constriction, granular pattern and dye leakage from the vessels and disc, intraretinal hemorrhages and retinal detachments, aggravating ocular irritation, retinopathy and cataract [8,15-17].

In children with acute lymphoblastic leukemia and non-Hodgkin's lymphoma following multiple regimens of chemotherapy including intrathecal methotrexate with systemic corticosteroids and preventive cranial radiotherapy, a decreased excretion of methotrexate in the eye was observed [17].

Aim of the Study

The aim of the current study was to investigate the ocular manifestations in IBD patients treated with methotrexate.

Material and Methods

Study Population

Currently we enrolled patients with IBD from Northwestern Greece who were followed-up in the Gastroenterology Department of the University Hospital of Ioannina, the Gastroenterology Group of Northwestern Greece and the Ophthalmology outpatients' department of the University Hospital of Ioannina. Clinical history and metabolic data of all patients were extracted from the IBD database that is kept since 1980.

Diagnosis of IBD

The diagnosis of IBD was based on clinical, radiographic, endoscopic and histological criteria. In the current study we enrolled exclusively patients that fulfilled the diagnostic criteria for CD or UC at least twice within 6 months. In patients diagnosed with UC the extent of disease was recorded at the time of the maximum intestinal involvement: pancolitis (involvement of the entire colon or proximal to the transverse colon), left-sided colitis (no involvement proximal to the splenic turn) or proctitis (no involvement proximal to the rectum or the last 15 cm of the colon).

Patients followed in the above mentioned departments suffered from IBD and were treated with methotrexate (n = 53), 34 of whom were men and 19 women. Out of the 53 patients approached for ophthalmological screening tests 29 patients were actually examined (response rate 55%).

Protocol of Ophthalmological Tests

Patients that were enrolled in the study visited the outpatient's department following telephone contact. Ophthalmological Tests were performed between 29/10/2012 - 27/11/2012.

Ocular related symptoms were recorded in detail as well a previous history of ocular disease. Two experienced ophthalmologists consecutively examined the patients blinded to each other findings. Accordingly any disagreement in diagnosis was discussed until a final consensus was reached. All IBD patients underwent a complete ophthalmological testing including visual acuity with the use of Snellen optotypes, slit-lamp examination of the anterior ocular department and measure of the intraocular pressure with the use of a Goldman tonometer.

Ophthalmological examination for each patient is as follows:

1. Best Corrected Visual Acuity (BCVA) in each eye
2. Slit lamb examination of anterior segments of the eye
3. Measurement of Intraocular Pressure (IOP)
4. Fundoscopy under mydriasis.

Funduscopic examination was performed with the use of 3-mirror Goldman lens following pupillary dilation and complemented with colored photography of the fundus. Angiography with Fluorescein was based on the photography of the fluorescence of the substance within the fundus vessels. Infusion of fluorescein dilution 10% rapidly within 4 - 6 seconds was followed by the photography of the fundus. Testing of the eye dryness was assessed by the use of breakup time test - BUT test, Rose Bengal, και Schirmer tests. The diagnostic cut-off for dry eye for each of these tests was defined as follows: 1) Break-up time test (BUT test): The tear film was stained with fluorescein dye 1% and the interval between a complete blink and the appearance of the first randomly distributed black dry spot, hole, or streak in the precorneal fluorescein layer was evaluated. The observation was made with the blue light of the slit lamp. Abnormal was considered to be a value below 10 seconds. 2) Rose Bengal: We "divided" the eye into 3 segments: nasal conjunctiva, cornea, and temporal conjunctiva.

Based on the density and area occupied by the dye, we graded each area on a scale from 0–3 and added the scores. Abnormal were values > 3. 3) Schirmer test: performed with the use of absorbent paper strips placed in the interpalpebral conjunctiva. We asked patients to keep their eyes closed for 5 minutes. Values lower than 5.5 mm/5 minutes were considered abnormal. Patients were followed up at least every 6 months. In each of the cases the patient was informed afterwards of the result of the examination and was given appropriate therapy or instructions for follow-up in the outpatient clinic.

Ethical Considerations

All patients gave their signed consent for their participation in the current study (IBD study cohort). Anonymity of all patients' data was preserved during the entire study period.

Statistical Analysis

Continuous variables were described as means ± SD when they were normally distributed or as median with maximal and minimal range for observations not normally distributed. A x2 analysis was used when comparing frequencies. P value < 0.05 (2-tailed) was considered significant. For all calculations we used the SPSS 12.0 working package (Chicago, IL).

Results and Discussion

53 patients were finally enrolled(with the actually ocular examined (n = 29) out of whom 64.1% (n = 34) were men and 35.9% (n = 19) were women. The mean age of the participants was 53,3 ± 14,4 years (range 28 - 85 years). Accordingly 69.8% (n = 37) suffered from CD, 28.3% (n = 15) from UC and 1.9% (n = 1) from undefined colitis. In relation to gender, men were more frequently suffering from both phenotypes of the disease (Table 1). Most of the participants were diagnosed with IBD after 1990 and more specifically after 2000 (Figure 1). Age at diagnosis of IBD was more frequent in decades 41 - 50 and 51 - 60 years old (Figure 2).

	Male	Women
Crohn's Disease	22	15
Ulcerative Colitis	12	3
Non-Specific Colitis	0	1

Table 1: *Correlation of patients with sex.*

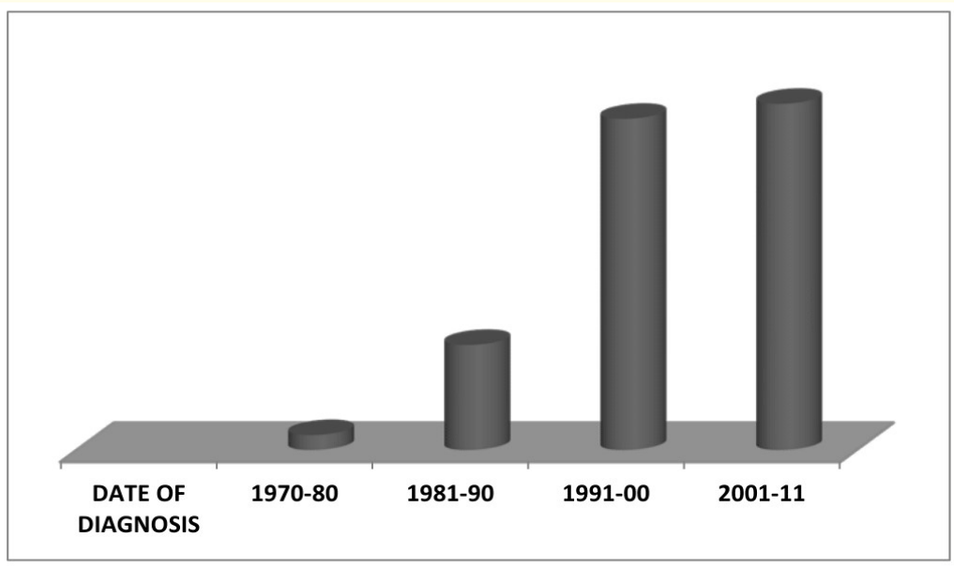

Figure 1: *Time of Diagnosis of the Disease (IBD).*

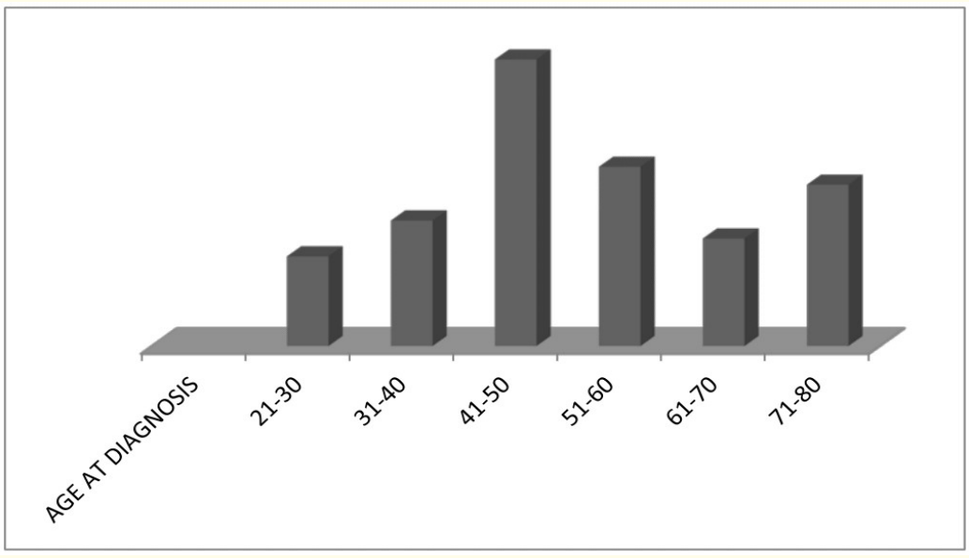

Figure 2: *Age of Patients at Diagnosis.*

From those patients who underwent the ophthalmological examination (n = 29), 11 were women and 18 were men, UC was reported in 14 patients and CD in 15 patients too (2 patients reported allergies in medications), while 42% were currently smoking (Table 2). Visual acuity was measured and it was reported that in the left eye patients showed lower values (Figure 3). From the examination of the anterior parts of the eye, 10.4% (n = 3) of the patients were diagnosed with cataract, 20.6% (n = 6) Posterior Chamber Intraocular Lens (IOL) bilateral, while 69% (n = 20) had normal findings. From the funduscopic examination, maculopathy was diagnosed in one patient, pigmentation disorders in one patient while the rest had normal findings. Intraocular pressure was measured (normal values 10-20 mmHg) and results showed that only 31% (n = 9) of the patients had normal values (Table 3).

Sex	**N**	**%**
Male	18	42
Female	11	38
Disease		
UC	14	48
CD	15	52
Age		
Smoking		
Yes	11	38
No	18	42
Place of Residence From Source		
0 - 20 Kilometres	15	52
20 - 100 Kilometres	9	32%
100 - 150 Kilometres	3	10%
> 150 Kilometres	2	6%
Allergy		
Aspirin	1	3,4%
Ciprofloxacin	1	3,4%
CD phenotype		
Inflammatory	9	
Stenotic	3	
Penetrating	1	
inf+sten	6	
inf+ pen	7	
sten+pen	1	
inf+sten+ pen	3	

Table 2: *Demographic Data.*

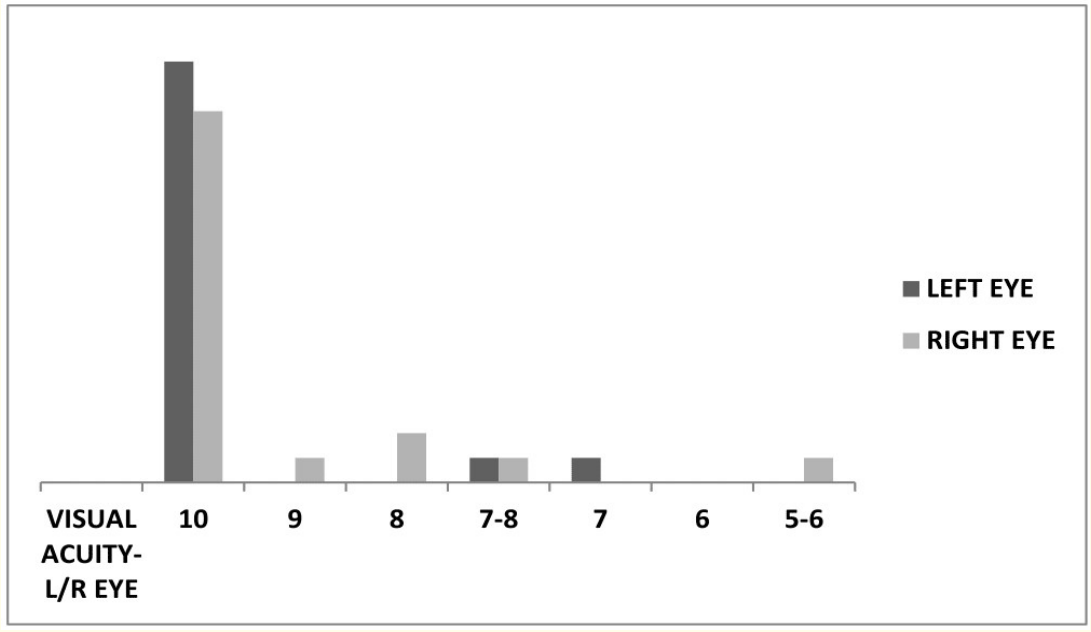

Figure 3: *Visual Acuity.*

Normal	IOP 10/10	IOP 14/12	IOP 12/12	IOP 14/13	IOP 14/14	IOP 12/14	IOP 14/15	IOP 15/15	IOP 16/16	IOP 16/16	IOP 15/17	IOP 16/17	IOP 17/16	IOP 17/17	IOP 20/20
9	2	1	2	1	1	1	1	3	2	1	1	1	1	1	1

Table 3*: Intraocular Pressure.*

Our study is the first attempt to investigate IBD patients treated with methotrexate in Northwestern Greece. This study was feasible, given that IBD patients were fully documented in the institutions from which the data was collected and also excellent collaboration between them. Patients participated in the study, despite the difficulty of access and long distance from the reference clinics. There was a difference in gender distribution, given that there were more male patients than women who had IBD and were treated with methotrexate in contrast with literature, where IBD appears to be more common in females [17]. The explanation for this is that in our study, we include patients treated with methotrexate only and not all patients with IBD who were monitored in reference clinics. In contrast to other studies our population was consisted mainly of male subjects considering the fact that IBD is more common on female subjects [18,19].

Literature shows that methotrexate may be a therapeutic approach of IBD in specific cases and our study focused on this group of patients who received this medicine. In literature, is documented that administration of methotrexate can cause significant side effects [8,11,17,18]. The patient taking methotrexate may manifest reduced vision, ocular pain and non arteritic ischemic optic neuropathy. Methotrexate related ocular toxicities consist of peri-orbital edema, ocular pain, blurred vision, conjunctivitis, and non-arteritic ischemic optic neuropathy. The optic neuropathy has been linked to folate deficiency. Folate supplementation must co-administered with methotrexate to minimize its adverse effects and may prevent from optic neuropathy. When this condition is recognized, the nerve damage can be reserves if methotrexate is stopped and appropriate folate supplementation is administered promptly [8,15,16].

In the majority of our patients visual acuity was normal but there wasn't available previous measurements of visual acuity to compare. However, this visual acuity check was performed during the standard control of patients. Several studies report that IBD patients may experience ophthalmic complications more often than other populations [20,21]. Because ophthalmic manifestations of patients with IBD may not be specific or absolutely relevant to the disease, a baseline ophthalmology examination and systematic follow-up is necessary [21,22].

The occurrence of cataract was 10,4% in our study was similar as in other studies. Ophthalmic complications such as cataracts in patients with IBD may also be associated with administration of corticosteroids and immunosuppressant's such as methotrexate [22,26]. A 20,6% had Posterior Chamber Intraocular Lens (IOL) bilateral. Two patients had abnormal fundoscopy. The one of them had maculopathy and the other one had a non-specific disturbance in the pigmentation of retinal pigment epithelium. Similar findings have been reported by other studies, in IBD patients treated with methotrexate.

A significant finding was that only 31% of patients had normal values of intraocular pressure. This finding is in accordance with findings from other studies [8,15-20].

Conclusions

Patients with IBD and more specifically those treated with methotrexate may develop serious ocular disorders. In the current study ocular involvement was frequent but no severe complications were observed. The systematic follow-up of patients with IBD requires a thorough examination of all systems and more specifically of the eyes in order to prevent future complications as a result of the disease itself or the treatments of the disease; several ocular disorders such as uveitis and scleritis may precede the diagnosis of IBD. On the other hand, many patients with IBD do not recognize the risk of ocular disorders as part of the IBD itself and hence the training of these patients is equally vital for their systematic follow-up. Larger studies are needed to confirm our findings and define their clinical relevance.

Conflicts of Interest

There is no conflict of interest of any of the Authors.

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Volume 5 Issue 2 February 2018