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OCULAR MANIFESTATIONS OF PEDIATRIC INFLAMMATORY BOWEL DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background and aims: Ocular extraintestinal manifestations (O-EIMs) are known complications of Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBD-U). However, data on their prevalence in children are scarce and there are no clear recommendations on which follow-up should be offered. We aimed to review available data on O-EIMs in children.

Methods: In January 2018, we performed a systematic review of published English literature using PubMed and EMBASE databases using disease-specific queries.

Results: Fifteen studies (7467 patients) reported data on O-EIMs prevalence in children. Overall prevalence of O-EIMs was 0.62% - 1.82%. Uveitis was the most common O-EIM. Meta-analysis showed that children with CD are at increased risk of O-EIMs as compared with children with UC and IBD-U (OR 2.70, 95% CI 1.51-4.83). Five studies (357 patients) reported data on ophthalmologic screening in asymptomatic children: mild asymptomatic uveitis was identified in a variable proportion of patients (1.06%-23.1%), more frequently in male patients with CD and colonic involvement. No evidence of ocular complications from untreated uveitis was detected. Twenty-three case reports (24 patients) were identified.

Conclusions: Data on O-EIMs in children are scarce. Prevalence of O-EIMs is lower than in adults but may be underestimated because of the possibility of asymptomatic uveitis; however, the long-term significance of this condition is unknown. Children with CD may be at increased risk of O-EIMs. No recommendations on routine ophthalmological examination can be made but a low threshold for ophthalmologic referral should be maintained. Larger studies in pediatric IBD populations are needed.

Keywords: ocular; extraintestinal manifestations; eye; IBD; children.

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn disease (CD), ulcerative colitis (UC), and IBD-unclassified type (IBD-U), are chronic inflammatory disorders mainly affecting the gastrointestinal tract. They are associated with various extra-intestinal manifestations (EIMs), which affect approximately 10% to 40% of patients,[1–3] and may potentially involve almost any organ, even before gastrointestinal symptoms. Ocular EIMs (O-EIMs) have been recognized since the early descriptions by Crohn,[4] and are among the most common EIMs. Uveitis and episcleritis are among the most commonly reported conditions in adult patients, with a prevalence between 2% and 6% in large cohort studies,[3,5,6] but when a wider spectrum of ocular conditions is considered, a higher prevalence has been reported.[6–9] O-EIMs may be associated with potentially severe outcomes. Uveitis, in particular, is associated with ocular pain, photophobia, and blurred vision, and when untreated may lead to several ocular complications, including keratopathy, cataract, glaucoma, posterior synechiae, cystoid macular edema, and permanent vision loss. Other, rarer but potentially severe ocular manifestations in patients with IBD include retinal vasculitis, central retinal artery/vein occlusion, retrobulbar neuritis, keratopathy, and orbital myositis.

Data on O-EIMs prevalence and clinical course in children are scarce and there are no clear recommendations on which ophthalmologic investigations and follow-up should be offered, unlike other pediatric inflammatory disorders, such as Juvenile Idiopathic Arthritis, for which an ophthalmological screening schedule has been developed.[10] We aimed to review published data on the prevalence and clinical course of O-EIMs from observational studies in children with IBD, in order to better define their epidemiology and clinical characteristics, as well as possibly identifying clinical phenotypes that may be associated with a higher risk of ocular involvement.

METHODS

We performed a systematic review of O-EIMs in IBD children according to the MOOSE guidelines.[11] Search strategy: We searched PubMed and EMBASE databases for studies published from inception to January 31, 2018, using the following queries: [1] (uveitis OR scleritis OR episcleritis OR iritis OR iridocyclitis OR "pars planitis" OR choroiditis OR chorioretinitis OR retinitis OR papillitis OR ocular OR eye OR ophthalmologic OR ophthalmic OR orbital OR retinal OR optic OR dacryoadenitis OR keratopathy OR corneal OR conjunctivitis OR blepharitis OR cataract OR intraocular OR "visual acuity" OR blindness OR uveal OR lacrimal) AND (Crohn OR "ulcerative colitis" OR "inflammatory bowel disease"); [2] ("extraintestinal manifestation" OR "extra-intestinal manifestation" OR "extraintestinal manifestations" OR "extra-intestinal manifestations") AND (children OR pediatric) AND ("Crohn" or "ulcerative colitis" OR "inflammatory bowel disease").

Data selection: Two authors (GO, SN) independently reviewed search results and found a consensus on the articles to be included. Articles references were also considered for additional studies. To be analyzed, studies had to report original data on O-EIMs in children with IBD. We included observational studies, as well as case reports. Limits related to age (0-18 years) and languages (English) were applied. Abstracts and unpublished studies were not included. If studies contained data from both adult and pediatric IBD patients, data from the two populations had to be clearly discernible. When articles contained potentially relevant data but not fully reported, the authors were contacted by e-mail for further information. Only in two cases contacted authors were able to provide the requested information, which were therefore included in our review, while the other authors declared the inability to provide their complete data.

Meta-analysis: Mantel-Haenszel weighting and random effects models were used. Statistical heterogeneity across studies was measured using the Cochran chi-square test ($p < 0.1$ considered significant) and the I^2 statistic. Variance was evaluated by means of tau^2. All statistical tests were two sided using an α level of 0.05. Publication bias was assessed by funnel plot. The meta-analyses were conducted with the statistical software Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, 2014, Copenhagen, Denmark).

RESULTS

We retrieved 1499 and 264 articles from the query one and two, respectively. We excluded 1470 and 247 articles because they did not meet inclusion criteria. Seven articles were found through both queries. Four other articles were found through the reference list of the included articles. In conclusion, we selected 43 articles for the analysis (Figure 1).

Prevalence of O-EIMs in children: Fifteen studies, including a total of 7467 patients, reported the prevalence of symptomatic ocular complications in children (table 1).[12–24] Substantial heterogeneity was present among studies. Timing of data collection varied, as some studies included only O-EIMs present at IBD diagnosis while others also considered O-EIMs appearing during follow-up. Studies also differed for O-EIMs inclusion criteria, since some authors reported data only for uveitis, while others also included other O-EIMs (e.g. episcleritis, papilledema, corneal infiltrates), and other articles generically reported "ocular manifestations", without further details. Finally, the modality of O-EIMs ascertainment was poorly described or not reported in most studies, making comparative evaluation difficult to perform.

Overall prevalence of O-EIMs in IBD at diagnosis ranged from 0.62% (3/483 patients, Dimakou et al.) to 1.81% (1/55 patients, Abdul Aziz et al.). Prevalence during follow-up ranged from 0.69% (7/1009 patients, Dotson et al.) to 1.82% (6/329 patients, Greuter et al.). The largest available study (Jose et al.) reported data about the first EIM in a cohort of 1649 North-American children with IBD. Among 387 children with a first EIM, 7% (27/387) had an O-EIM; 52 and 13 out of 387 children developed also a second and a third one, respectively, yet data on these EIMs were not detailed and when contacted authors could not provide further information; however, an overall incidence rate for anterior uveitis of 0.18 per 100 patient-years was reported. This study was also the only one among larger studies that analyzed the prevalence of different types of O-EIMs, with uveitis being the most commonly reported condition (17 patients out of 27 with O-EIMs), followed by papilledema and corneal infiltrates (7 patients – aggregate data).

A trend towards greater prevalence of O-EIMs in children with CD emerged from several studies yet this difference did not reach statistical significance, possibly because of the limited number of patients included in each study. We performed a meta-analysis to assess the risk of O-EIMs in children according to the different IBD diagnosis. We compared the prevalence of O-EIMs in children with CD versus children with UC and IBD-U; these two latter groups of patients were analyzed together because not all the studies differentiated between them. Only studies including both categories of patients were included in the meta-analysis to allow direct between groups comparison. Children with CD were found to be at increased risk of O-EIMs (odds ratio 2.70, 95% CI 1.51-4.83, $p = 0.0008$) (Figure 2). No significant heterogeneity was detected among studies as evaluated by Cochran's chi squared ($p = 0.96$) and I^2 statistic ($I^2 = 0\%$); nevertheless data on O-EIMs diagnosis criteria and patients' characteristics for each study were scarce or absent. Publication bias did not seem to

be relevant as evaluated by funnel plot (data not shown), yet the number of available studies was low.

Dotson et al. evaluated the association of O-EIMs with intestinal disease localization, presence of perianal disease, patient's age and sex, but no significant association was found. One study (Gower-Rousseau et al.) reported a remarkably high prevalence of uveitis during follow-up in children with UC (4 of 113 patients, 3.54%). However, this study was relatively small and was performed only in patients with UC. Greuter et al. also included data on timing of uveitis appearance in their population: 6 of 329 patients in their cohort had a diagnosis of uveitis, which occurred at a median time of approximately 7 years after IBD diagnosis, with one case preceding intestinal disease onset.[17] The same study group published also a separate sub-analysis of patients from the same database (the Swiss IBD Cohort Study) evaluated at 10 years (range 108-132 months) of follow-up.[25] After 10 years, age at IBD diagnosis did not appear to influence risk of uveitis, with similar incidence rates in patients with IBD diagnosis <10 years of age, <17 years of age, <40 years of age, and >40 years of age.

No study did provide information about the prevalence of O-EIMs according to the patients' ethnicity. Jose et al. included data on patients' ethnicity, reporting no difference on the overall risk of EIMs, but no information was available for O-EIMs.[12] Finally, few studies provided details about concurrent treatments: Dotson et al. observed a protective effect of treatment mesalamine/sulfasalazine, infliximab, and immunomodulators on the overall risk EIMs for patients with moderate to severe disease as compared to patients who had not received these treatments; no data, however, were specifically available for O-EIMs.[15]

Finally, Greuter et al. reported the effect of treatment with anti-TNF on uveitis: 2 patients out of 3 experienced uveitis improvement with treatment; however, in 2 patients uveitis appeared during anti-TNF treatment.

Screening for O-EIMs in children: Five studies (including 357 patients) reported data on small cohorts of asymptomatic children who underwent ophthalmological screening regardless of the presence of ocular symptoms.[22,26–29] Four studies (including 299 patients) included full ophthalmologic evaluation (table 2), while a fifth study (Tripathi et al.) evaluated only ocular side effects of corticosteroid treatment.

Studies reporting full ophthalmologic evaluation found asymptomatic uveitis (i.e. subclinical uveitis detected only by slit-lamp examination) in several children with IBD. Three studies (Daum et al., 1979; Hofley et al. 1993; Rychwalski et al., 1997) reported a prevalence of asymptomatic uveitis substantially higher than prevalence of O-EIMs from cohort studies: 4.1% (6/147 patients, Hofley et al.), 12.5% (4/32 patients, Rychwalski et al.), and 23.1% (6/26 patients, Daum et al.). More recently, Naviglio et al. reported a lower prevalence (1/94 patients, 1.06%) of uveitis in a sample of pediatric patients with IBD who had undergone ophthalmologic screening evaluation. In this study, only one patient was found to have asymptomatic anterior uveitis on screening slit lamp examination; the same patient also had a history of previous bilateral symptomatic (i.e. eye redness and discomfort) anterior uveitis 7 years before, at IBD onset. Uveitis had been treated with dexamethasone eye drops and had not recurred after. No other patient had a history of O-EIMs diagnoses. Furthermore, no patient had ocular signs of complications from previous, unrecognized uveitis at ophthalmologic evaluation.

Considering combined data from these four studies, a total of 299 patients were screened (180 CD, 117 UC, and 2 IBD-U). Asymptomatic uveitis was detected in 18/299 patients (4.86%) and was characterized as mild anterior uveitis in all patients. Asymptomatic uveitis was detected more frequently in CD (CD/UC = 17/1; prevalence in CD patients = 9.4%; prevalence in UC patients = 0.85%), adolescent (mean age 14.5 years), and male (M/F = 14/4) patients. Colonic involvement was prevalent (13 out of 14 patients for which data are

available). Presence of HLA-B27 was reported only by Daum et al. (1/6 patients). Intestinal disease activity was not related to ocular inflammation (active intestinal disease in 6/12 patients with uveitis; no data available from Daum et al.). In all cases of asymptomatic uveitis no specific treatment was deemed necessary. Data on short-term follow-up (4-12 months) are available only for patients reported by Daum et al and Naviglio et al.: uveitis resolved in 6/7 patients overall (1 patient was lost to follow-up); the long-term outcomes were not reported. Posterior subcapsular cataract, a known adverse effect of corticosteroid treatment, was detected in 6 patients (5 by Rychwalski et al. and one by Naviglio et al.), and in no patients from the other two studies (overall prevalence 6/299 patients, 2.0%).

A fifth study, by Tripathi et al., performed an ophthalmologic evaluation targeted at ocular side effects of corticosteroid treatment.[29] Fifty-eight pediatric patients with IBD treated with corticosteroids as well as 58 age-matched controls were evaluated. Most patients (38/58) had received corticosteroid treatment for more than a year (range 1-104 months). Posterior subcapsular cataract was detected in 12 patients (20.7%) and in none of the controls. Patients also had a significantly higher intraocular pressure (15.89 +/- 4.11 mmHg vs. 13.63 +/- 2.35 mmHg, $p < 0.001$), with 21 patients (36.2%) defined as “intraocular pressure responders" (intraocular pressure ≥20 mmHg, or change ≥ 6 mmHg between visits, or a difference ≥6 mmHg between the two eyes). Overall 30 patients (52%) had either cataract or abnormal intraocular pressure. Cataract risk was not correlated with the total dose of corticosteroids, duration of treatment, average daily dose or number of days on higher doses, while increased intraocular pressure was correlated with average daily dose in the last 30 days. At follow-up visits, performed at 3-18 months after initial evaluation, dose-related changes in ophthalmologic findings were observed. Notably, cataract regression was observed in two patients lowering the prednisone daily dose to less than 10 mg/day of prednisone. Similarly, increased ocular pressure responded to lowering of dose to less than 10 mg/day; on the other

hand, an increase in corticosteroid dose was associated with abnormal intraocular pressure in some patients with previously normal findings.

Case reports: we retrieved 23 case reports/case series including 24 children with O-EIMs (table 3). Reported conditions included: central retinal vein/artery occlusion,[30–32] orbital myositis/orbital pseudotumor,[33–39] choroidal neovascular membrane,[40] nasolacrimal duct obstruction,[41] dacryoadenitis,[42] dry eyes syndrome,[43] cataract,[43] unilateral/bilateral uveitis,[44–46] episcleritis,[47] keratopathy/keratitis,[48,49] granulomatous conjunctivitis,[50] optic neuritis,[51] and recurrent neuroretinitis.[52] All patients presented with ocular symptoms when evaluated, including reduced visual acuity (even sudden vision loss), ocular pain/discomfort, redness, eyelid swelling, proptosis, photophobia, and diplopia. Considering all patients for which detailed information were available, more patients were males (M/F = 14/8) and had CD (CD/UC = 18/5). Mean age at O-EIM onset was 13 years (range 2-20 years). Five patients were diagnosed with ophthalmological conditions before IBD onset, while in 11 patients they were present at IBD diagnosis. When O-EIMs occurred after IBD onset, latency ranged from 2 to 8 years. Complete resolution was reported in most cases of inflammatory complications (i.e. uveitis, orbital myositis/pseudotumor, neuroretinitis, and optic neuritis), yet persistent visual impairment was reported in a 6-year-old boy with intermediate uveitis who had residual amblyopia despite resolution of uveitis.[46] Treatment included systemic steroids in almost all reported cases; methotrexate was used in one case of orbital pseudotumor, leading to resolution.[39] Vascular conditions (central retinal artery or vein occlusion, choroidal neovascular membrane) had a worse prognosis, with residual visual impairment in 3 out of 4 patients.

DISCUSSION

Data on ocular involvement in children with IBD are scarce and fragmented. Substantial heterogeneity among studies and several methodological issues currently limit the complete evaluation of this topic. Among cohort studies reporting prevalence of O-EIMs in children with IBD, inclusion criteria for O-EIMs were, in fact, highly variable, with some authors focusing only on selected conditions (e.g. uveitis) and others reporting the presence of "ocular manifestations" without further specification. Furthermore, criteria for the diagnosis of O-EIMs are not fully defined in most studies. Notwithstanding these limitations, data from cohort studies indicate a lower prevalence of ocular involvement in children (0.6-1.8%) than in adults (2-6%). Data on different types of O-EIMs are even scarcer, with only one report (Jose et al. 2009) showing different prevalence for selected ocular conditions (uveitis, papilledema, corneal infiltrates). According to this study, uveitis represents the most common O-EIM in children with IBD. Subtype and localization of uveitis were not indicated, yet in adult patients anterior uveitis (i.e. iritis/iridocyclitis) is predominant.[53] Data on prevalence of other O-EIMs such as episcleritis/scleritis or rarer conditions such as orbital myositis are not available, and only data from case reports are presented.

O-EIMs can affect both CD and UC patients, yet our meta-analysis showed that children with CD are at increased risk of O-EIMs as compared to other pediatric IBD, with an odds ratio of 2.70. No significant study heterogeneity was detected, yet, given the paucity of information available, we had to consider together in the analysis studies on EIMs at diagnosis and during the follow-up. Nevertheless, the evaluated outcome (prevalence of O-EIMs) was uniform, and there are no data from both pediatric and adult studies suggesting that timing of data collection timing may bias prevalence among different IBD subtypes (CD vs. UC vs. IBD-U). Hence we can assume that including both types of studies (at diagnosis vs. during follow

up) did not affect the relative risk analysis. In adult patients, O-EIMs are often considered to be more frequent in CD as compared to UC;[54] however, data from studies on adult patients are conflicting, with only some studies reporting a significantly increased prevalence of O-EIMs in CD patients, while in others the difference appears to be nonsignificant.[1,3,55,56]

Data on timing of O-EIMs in children are also scarce. Greuter et al. reported a median time of 7 years after IBD diagnosis for uveitis onset, although substantial variability was observed. Occurrence of O-EIMs before gastrointestinal symptoms onset is also possible, even though in a minority of patients; O-EIMs that have been reported to precede intestinal disease include uveitis and orbital myositis. Results from the largest study (Jose et al., 2009) indicate that the prevalence of uveitis increases with time (incidence rate: 0.18 cases per 100 patient-years). Herzog et al. reported no difference for uveitis rates according to age at IBD diagnosis when patients were evaluated after 10 years, possibly indicating that age at IBD onset does not influence uveitis risk per se.

Very little data are available also for correlation of O-EIMs with intestinal disease activity. While uveitis is classically considered to be unrelated to intestinal disease activity, some studies on adult patients actually found a significant correlation with disease activity in patients with CD (but not in UC).[1] Few studies specified concurrent treatments in IBD patients, which may possibly have an effect on the risk of O-EIMs during follow-up. Dotson et al reported a protective effect of immunomodulators and anti-TNF on the overall risk of EIMs in their cohort, yet no data were available for O-EIMs. While systemic immunomodulatory treatments could possibly reduce the risk of inflammatory O-EIMs, this relationship may not be straightforward. In fact, Greuter et al reported a good response of uveitis to anti-TNF antibodies in 2 out of 3 patients, yet the same Authors detected uveitis during anti-TNF treatment in other two patients.

We did not find evidence of a difference in prevalence of O-EIMs according to patients' ethnicity. No study provided information on patients' ethnicity as related to O-EIMs, yet among prevalence studies several world regions were actually included (North America, Western Europe, Turkey, Saudi Arabia, South Korea) and no difference in overall prevalence was observed. Jose et al. reported no significant association for patients' ethnicity with overall EIMs prevalence, but no specific data were available for O-EIMS. Another study, by Eidelwein et al., compared EIMs prevalence between white and African American children in North America.[57] This study, however, could not be included in the prevalence analysis because it did not show exact figures of the condition, stating only that uveitis prevalence was "less than 3%" in both groups of patients. Contacted authors also could not provide further information. Nonetheless, no difference in overall EIMs prevalence was reported. Similarly, White et al. found no difference in overall EIMs prevalence in African American children with IBD as compared to other ethnic groups; however, sub-analysis of different types of EIMs was not performed, nor could contacted authors provide further information.[58] Remarkably, data from adult patients seem to suggest that prevalence of uveitis may be higher in African American CD patients as compared to other ethnic groups.[59–61]

The recognition of subclinical uveitis by slit-lamp examination in screening evaluation in small samples of asymptomatic children with IBD raises concerns about under-diagnosis of a potentially invalidating condition. Three studies (Daum et al., 1979; Hofley et al. 1993; Rychwalski et al. 1997) showed a significantly increased prevalence of subclinical uveitis (4.1% - 23.1%) compared to that reported in cohort populations. It may be worth noting that these studies were performed more than 20 years ago (between 1979 and 1997), before the introduction of biologic anti-tumor necrosis factor alpha agents and the wider use of immune modulators, which allowed a better control of both gastrointestinal manifestations and EIMs.[62,63] The more recent report by Naviglio et al., while confirming the existence of

subclinical uveitis in children with IBD, indicated a lower prevalence (1.06%), in line with the prevalence from cohort studies. In all these studies, asymptomatic uveitis was anterior, confirming this as the most common type of uveitis associated with IBD in children, even though other types of uveitis (e.g. intermediate uveitis) are also possible.[46] Asymptomatic uveitis did not seem to correlate with intestinal disease activity. Interestingly, some clinical characteristics recurred among patients with asymptomatic uveitis: they were more commonly adolescent males with CD and with colonic involvement (13/14 patients). This may confirm CD patients are at increased risk of O-EIMs. Recent data have suggested that eye-specific autoreactive T cells may be activated in the gut from an antigen dependent cross-reaction on commensal microbiota.[64] Abnormal gut permeability in CD and increased density of microbiota in the colon could explain the increased risk of O-EIMs in these patients. However, the low number of cases does not allow to draw a general conclusion nor to identify other significant characteristics.

Clinical implications of asymptomatic uveitis are unclear. In fact, most cases were diagnosed as mild uveitis, and both Daum et al. and Naviglio et al. reported spontaneous resolution of ocular inflammation without specific treatments, suggesting asymptomatic uveitis in children with IBD may be transient and self-limiting. Remarkably, no studies detected evidence of ocular complications from previous unrecognized uveitis, suggesting this type of ocular manifestation may not be aggressive or lead to complications, at least in children with IBD. This is in sharp contrast with asymptomatic uveitis associated with other pediatric chronic inflammatory disorders, such as juvenile idiopathic arthritis-associated uveitis, which has a high potential for ocular complications and visual impairment.[65] Nevertheless, natural history of asymptomatic uveitis in IBD is poorly known, therefore definitive conclusions cannot be drawn. Notably, several treatments used in IBD are also effective for uveitis, therefore uveitis

may also benefit from systemic treatments used to control intestinal disease. New studies are needed to outline specific phenotype risk and orientate proper follow-up for these patients. Iatrogenic ocular complications, mainly corticosteroid-induced posterior subcapsular cataract and increase of intraocular pressure, should also always be considered in children with IBD receiving corticosteroids. Available data on this complication come mostly from the case-control study by Tripathi et al. The majority of children (52%) developed either cataract or alteration of intraocular pressure; however, this study was performed mainly on children receiving long-term corticosteroid treatment, an eventuality that has now become less frequent, as corticosteroids are considered more as a "bridge therapy". There are few data in medical literature defining timing and dose-related risk of corticosteroid-induced ocular complications in children. It is now well recognized that there is a high inter-individual variability in sensitivity to ocular adverse effects of corticosteroids, with some patients free of ocular complications after years of corticosteroid treatment, while in others they may develop rapidly (even as soon as after two weeks of treatment).[66] Data from adult patients seem to indicate that the overall risk is dose- and time-related, even though a "safe dose" does not seem to exist.[67] Notably, corticosteroid-induced complications, especially increased intraocular pressure, did respond to dose lowering to less than 10 mg/day of prednisone in the study by Tripathi et al., yet we have not enough data to consider this as a "safe" dose. Therefore, at present, a precise threshold for corticosteroid dose or treatment duration to guide ophthalmological evaluation cannot be clearly defined. In the study by Tripathi et al. the risk of cataract was not correlated to treatment duration or steroid dose, while the risk of abnormal intraocular pressure was associated to the average dose in the previous 30 days. It may be possible therefore to consider that this is an adequate timing for alterations of intraocular pressure to develop, therefore, it could be reasonable to suggest that in children in whom systemic corticosteroid are considered for longer periods of time and not as a "bridge

therapy" (i.e. in whom tapering and suspension are not programmed after one month) an ophthalmologic evaluation, including intraocular pressure measurement, should be considered after one month of therapy. Timing for subsequent evaluations should be decided by the referral ophthalmologist, as there are no data to guide patient management. It is noteworthy that in the study by Tripathi et al. some patients with a previously normal ophthalmologic evaluation developed complications after a significant increase in their daily corticosteroid dose, therefore this should also be taken in consideration in guiding follow-up. All these recommendations are based on low/moderate quality evidence (one case-control study), and therefore their strength should be considered as weak. Patients on very long-term corticosteroid treatment (i.e. continuative treatment for several months/years), however, are at high risk of ocular complications and a strict ocular follow-up should be offered.

Available case reports of O-EIMs define a wide array of ocular conditions that have been reported in children with IBD. However, for some of them it is currently not possible to determine whether they were simply coincidental, though similar manifestations have been reported in adult patients. Presenting symptoms varied widely, from mild ocular redness or discomfort to complete loss of visions, highlighting the need not to underestimate ocular complaints in these patients. Reported O-EIMs can be roughly classified in inflammatory and vascular conditions. The first group includes uveitis, episcleritis, orbital myositis/pseudotumor, dacryoadenitis, and optic neuritis. Orbital pseudotumor, which identifies any inflammatory enlargement of intraorbital structures elements,[68] despite being a rare condition, was one of the most commonly reported O-EIMs in case reports. While the clinical manifestations may vary widely depending on the structures affected, they often included ocular/orbital pain, diplopia, ophthalmoplegia, proptosis, eyelid swelling, and reduced visual acuity. Almost all cases involving an inflammatory O-EIM resolved with treatment, which usually included systemic corticosteroids.

Among vascular conditions we identified reports on both retinal artery or vein occlusion, and choroidal neovascular membrane; these complications may also share an inflammatory pathogenesis, possibly due to retinal vasculitis, which has been associated with IBD in adults.[69] In most cases, vascular conditions resulted in some residual visual impairment despite treatment. Notably, also among case reports there was a preponderance of children with CD (CD/UC = 18/5), thus possibly confirming a greater incidence of O-EIMs in CD patients.

In conclusion, available data indicate that prevalence of O-EIMs in children is lower than in adult patients, yet children with CD seem to be at increased risk as compared to other groups of patients. Prevalence of O-EIMs in children may be underestimated in consideration of the possibility of asymptomatic uveitis, which has not been described in adults.[70] The significance of this condition, however, is unclear, as all reported cases were mild and self-limiting, with no evidence of ocular complications from underdiagnosis. Nevertheless, data on natural history of this manifestation and long-term follow-up are lacking. It has been recently suggested that annual screening eye examination should be considered in all children with IBD;[71] however, this is often not performed in clinical practice, nor it is possible to define the cost-benefit ratio of such an approach. Currently, the paucity of data on O-EIMs in children does not allow to draw clear conclusions on which ophthalmologic follow-up should be provided. An option may be to perform ophthalmologic evaluation at IBD diagnosis in order to have a baseline reference, yet we cannot provide any evidence for this suggestion. On the other hand, we recommend that a low threshold for ophthalmologic referral should be maintained in all children with IBD, both at the diagnosis and during follow-up. Available data, in fact, show that most children with O-EIMs presented some ocular signs or symptoms, therefore ocular complaints should never be dismissed, and both health care providers and patients/care givers be instructed about the increased risk of ocular complications in children

with IBD. Since available data indicate a higher incidence of O-EIMs in children with CD, especially if colonic involvement is present, this subset of patients may be considered at higher risk of O-EIMs in clinical practice, but further studies on larger groups of patients are needed. Finally, patients receiving systemic corticosteroids for more than brief periods may probably benefit from ophthalmologic evaluations, including intraocular pressure measurement. A strict follow-up should be offered in patients receiving long-term corticosteroid treatment, as these children are at increased risk for iatrogenic ocular complications.

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References

1. Vavricka SR., Brun L., Ballabeni P., Pittet V., Prinz Vavricka BM., Zeitz J., et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol* 2011;**106**(1):110–9. Doi: 10.1038/ajg.2010.343.

2. Isene R., Bernklev T., Høie O., Munkholm P., Tsianos E., Stockbrügger R., et al. Extraintestinal manifestations in Crohn's disease and ulcerative colitis: results from a prospective, population-based European inception cohort. *Scand J Gastroenterol* 2015;**50**(3):300–5. Doi: 10.3109/00365521.2014.991752.

3. Karmiris K., Avgerinos A., Tavernaraki A., Zeglinas C., Karatzas P., Koukouratos T., et al. Prevalence and Characteristics of Extra-intestinal Manifestations in a Large Cohort of Greek Patients with Inflammatory Bowel Disease. *J Crohns Colitis* 2016;**10**(4):429–36. Doi: 10.1093/ecco-jcc/jjv232.

4. Crohn BB. Ocular lesions complicating ulcerative colitis. *Am J Med Sci* 1925;**169**:260–7.

5. Hopkins DJ., Horan E., Burton IL., Clamp SE., de Dombal FT., Goligher JC. Ocular disorders in a series of 332 patients with Crohn's disease. *Br J Ophthalmol* 1974;**58**(8):732–7. Doi: 10.1136/bjo.58.8.732.

6. Cury DB., Moss AC. Ocular manifestations in a community-based cohort of patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2010;**16**(8):1393–6. Doi: 10.1002/ibd.21180.

7. Yilmaz S., Aydemir E., Maden A., Unsal B. The prevalence of ocular involvement in patients with inflammatory bowel disease. *Int J Colorectal Dis* 2007;**22**(9):1027–30. Doi: 10.1007/s00384-007-0275-1.

8. Taleban S., Li D., Targan SR., Ippoliti A., Brant SR., Cho JH., et al. Ocular

Manifestations in Inflammatory Bowel Disease Are Associated with Other Extra-intestinal Manifestations, Gender, and Genes Implicated in Other Immune-related Traits. *J Crohn's Colitis* 2016;**10**(1):43–9. Doi: 10.1093/ecco-jcc/jjv178.

9. Felekis T., Katsanos K., Kitsanou M., Trakos N., Theopistos V., Christodoulou D., et al. Spectrum and frequency of ophthalmologic manifestations in patients with inflammatory bowel disease: A prospective single-center study. *Inflamm Bowel Dis* 2009;**15**(1):29–34. Doi: 10.1002/ibd.20584.
10. Cassidy J., Kivlin J., Lindsley C., Nocton J., Section on Rheumatology., Section on Ophthalmology. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics* 2006;**117**(5):1843–5. Doi: 10.1542/peds.2006-0421.
11. Stroup DF., Berlin JA., Morton SC., Olkin I., Williamson GD., Rennie D., et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**(15):2008–12.
12. Jose FA., Garnett EA., Vittinghoff E., Ferry GD., Winter HS., Baldassana RN., et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2009;**15**(1):63–8. Doi: 10.1002/ibd.20604.
13. Card TR., Langan SM., Chu TPC. Extra-Gastrointestinal Manifestations of Inflammatory Bowel Disease May Be Less Common Than Previously Reported. *Dig Dis Sci* 2016;**61**(9):2619–26. Doi: 10.1007/s10620-016-4195-1.
14. Castro M., Papadatou B., Baldassare M., Balli F., Barabino a., Barbera C., et al. Inflammatory bowel disease in children and adolescents in Italy: data from the pediatric national IBD register (1996-2003). *Inflamm Bowel Dis* 2008;**14**(9):1246–52. Doi: 10.1002/ibd.20470.
15. Dotson JL., Hyams JS., Markowitz J., LeLeiko NS., Mack DR., Evans JS., et al.

Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. *J Pediatr Gastroenterol Nutr* 2010;**51**(2):140–5. Doi: 10.1097/MPG.0b013e3181ca4db4.

16. Dimakou K., Pachoula O., Panayotou I., Stefanaki K., Orfanou I., Lagona E., et al. Pediatric inflammatory bowel disease in Greece: 30-years experience of a single center. *Ann Gastroenterol* 2015;**28**(1):81–6.
17. Greuter T., Bertoldo F., Rechner R., Straumann A., Biedermann L., Zeitz J., et al. Extraintestinal Manifestations of Pediatric Inflammatory Bowel Disease: Prevalence, Presentation, and Anti-TNF Treatment. *J Pediatr Gastroenterol Nutr* 2017;**65**(2):200–6. Doi: 10.1097/MPG.0000000000001455.
18. Cakir M., Unal F., Dinler G., Baran M., Yuksekkaya HA., Tumgor G., et al. Inflammatory bowel disease in Turkish children. *World J Pediatr* 2015;**11**(4):331–7. Doi: 10.1007/s12519-015-0042-2.
19. Gower-Rousseau C., Dauchet L., Vernier-Massouille G., Tilloy E., Brazier F., Merle V., et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. *Am J Gastroenterol* 2009;**104**(8):2080–8. Doi: 10.1038/ajg.2009.177.
20. Martinelli M., Giugliano FP., Russo M., Giannetti E., Andreozzi M., Bruzzese D., et al. The Changing Face of Pediatric Ulcerative Colitis. *J Pediatr Gastroenterol Nutr* 2017:1. Doi: 10.1097/MPG.0000000000001833.
21. Saadah OI. Childhood onset of Crohn disease: Experience from a university teaching hospital in Saudi Arabia. *Ann Saudi Med* 2012;**32**(6):596–602. Doi: 10.5144/0256-4947.2012.596.
22. Naviglio S., Parentin F., Nider S., Rassu N., Martelossi S., Ventura A. Ocular Involvement in Children with Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2017;**23**(6):986–90. Doi: 10.1097/MIB.0000000000001079.

23. Lee YA., Chun P., Hwang EH., Mun SW., Lee YJ., Park JH. Clinical Features and Extraintestinal Manifestations of Crohn Disease in Children. *Pediatr Gastroenterol Hepatol Nutr* 2016;**19**(4):236–42. Doi: 10.5223/pghn.2016.19.4.236.

24. Abdul Aziz D., Moin M., Majeed A., Sadiq K., Billoo AG. Paediatric inflammatory bowel disease: Clinical presentation and disease location. *Pakistan J Med Sci* 2017;**33**(4):2–6. Doi: 10.12669/pjms.334.12926.

25. Herzog D., Fournier N., Buehr P., Rueger V., Koller R., Heyland K., et al. Age at disease onset of inflammatory bowel disease is associated with later extraintestinal manifestations and complications. *Eur J Gastroenterol Hepatol* 2018:1. Doi: 10.1097/MEG.0000000000001072.

26. Daum F., Gould HB., Gold D., Dinari G., Friedman AH., Zucker P., et al. Asymptomatic transient uveitis in children with inflammatory bowel disease. *Am J Dis Child* 1979;**133**(2):170–1.

27. Hofley P., Roarty J., McGinnity G., Griffiths AM., Marcon M., Kraft S., et al. Asymptomatic uveitis in children with chronic inflammatory bowel diseases. *J Pediatr Gastroenterol Nutr* 1993;**17**(4):397–400.

28. Rychwalski PJ., Cruz OA., Alanis-Lambreton G., Foy TM., Kane RE. Asymptomatic uveitis in young people with inflammatory bowel disease. *J Am Assoc Pediatr Ophthalmol Strabismus* 1997;**1**(2):111–4. Doi: 10.1016/S1091-8531(97)90009-4.

29. Tripathi RC., Kipp MA., Tripathi BJ., Kirschner BS., Borisuth NS., Shevell SK., et al. Ocular toxicity of prednisone in pediatric patients with inflammatory bowel disease. *Lens Eye Toxic Res* 1992;**9**(3–4):469–82.

30. Vayalambrone D., Ivanova T., Misra A. Nonischemic Central Retinal Vein Occlusion in an Adolescent Patient with Ulcerative Colitis. *Case Rep Ophthalmol Med* 2011;**2011**:1–2. Doi: 10.1155/2011/963583.

31. Falavarjani KG., Parvaresh MM., Shahraki K., Nekoozadeh S., Amirfarhangi A. Central retinal artery occlusion in Crohn disease. *J Am Assoc Pediatr Ophthalmol Strabismus* 2012;**16**(4):392–3. Doi: 10.1016/j.jaapos.2012.03.004.

32. Lapsia S., Meyer R., Abazari A., Usmani K., Gathungu G. Bilateral Central Retinal Vein Occlusion in a patient with Ulcerative Colitis and Antiphospholipid Antibody Syndrome. *J Pediatr Gastroenterol Nutr* 2016;**62**(3):e25-6. Doi: 10.1097/MPG.0000000000000404.

33. Young RS., Hodes BL., Cruse RP., Koch KL., Garovoy MR. Orbital pseudotumor and Crohn disease. *J Pediatr* 1981;**99**(2):250–2. Doi: 10.1016/S0022-3476(82)80214-X.

34. Camfield PR., White M., Warner HA., Lythgoe C. Orbital pseudotumor and Crohn disease. *J Pediatr* 1982;**101**(1):157–8. Doi: 10.1016/S0022-3476(82)80214-X.

35. Weinstein JM., Koch K., Lane S. Orbital pseudotumor in Crohn's colitis. *Ann Ophthalmol* 1984;**16**(3):275–8.

36. Squires RH., Zwiener RJ., Kennedy RH. Orbital myositis and Crohn's disease. *J Pediatr Gastroenterol Nutr* 1992;**15**(4):448–51.

37. Durno CA., Ehrlich R., Taylor R., Buncic JR., Hughes P., Griffiths AM. Keeping an eye on Crohn's disease: orbital myositis as the presenting symptom. *Can J Gastroenterol* 1997;**11**(6):497–500.

38. Tan JHT., Arkachaisri T., Das L., Chu HP. Orbital pseudotumour as a presentation of paediatric ulcerative colitis. *Singapore Med J* 2014;**55**(10):169–71. Doi: 10.11622/smedj.2014149.

39. Vargason CW., Mawn L a. Orbital Myositis as Both a Presenting and Associated Extraintestinal Sign of Crohn's Disease. *Ophthal Plast Reconstr Surg* 2015;**XX**(Xx):1. Doi: 10.1097/IOP.0000000000000475.

40. Thomas BJ., Emanuelli AA., Berrocal AM. Unilateral Choroidal Neovascular

Membrane as a Herald Lesion for Crohn's Disease. *Ophthalmic Surgery, Lasers Imaging Retin* 2014;**45**(1):62–5. Doi: 10.3928/23258160-20131220-10.

41. Greninger DA., Yoon MK., Bloomer MM., Keyser R., Kersten RC. Extraintestinal Crohn disease causing bilateral nasolacrimal duct obstruction. *Ophthal Plast Reconstr Surg* 2012;**28**(2):e55-6. Doi: 10.1097/IOP.0b013e318222e47c.
42. Rafiei N., Tabandeh H., Hirschbein M. Bilateral dacroadenitis associated with acute Crohn's disease. *Eye (Lond)* 2006;**20**(12):1372–3. Doi: 10.1038/sj.eye.6702205.
43. Mrugacz M., Sredzińska-Kita D., Cyrta-Jarocka E., Bakunowicz-Lazarczyk A. Dry eye syndrome and cataract as ocular manifestations of Crohn's disease. *Klin Oczna* 2005;**107**(7–9):509–10.
44. Paroli MP., Spinucci G., Bruscolini A., La Cava M., Abicca I. Uveitis preceding Crohn's disease by 8 years. *Int Ophthalmol* 2011;**31**(5):413–5. Doi: 10.1007/s10792-011-9470-8.
45. Girardin M., Waschke KA., Seidman EG. A case of acute loss of vision as the presenting symptom of Crohn's disease. *Nat Clin Pract Gastroenterol Hepatol* 2007;**4**(12):695–8. Doi: 10.1038/ncpgasthep0982.
46. Symeonidis C., Matsou A., Tzetzi D., Dermenoudi M., Brazitikos P., Mataftsi A. Amblyopia due to intermediate uveitis as the presenting symptom of Crohn's disease in a 6-year-old boy. *J AAPOS* 2017:1–3. Doi: 10.1016/j.jaapos.2017.07.218.
47. Read RW., Weiss AH., Sherry DD. Episcleritis in childhood. *Ophthalmology* 1999;**106**(12):2377–9. Doi: 10.1016/S0161-6420(99)90520-1.
48. Fasci-Spurio F., Thompson A., Madill S., Koay P., Mansfield D., Satsangi J. Sight-threatening keratopathy complicating anti-TNF therapy in Crohn's disease: a case report. *Inflamm Bowel Dis* 2014;**20**(1):E2-3. Doi: 10.1097/01.MIB.0000436952.88522.77.

49. Seo JK., Yeon KM., Chi JG. Inflammatory bowel disease in children--clinical, endoscopic, radiologic and histopathologic investigation. *J Korean Med Sci* 1992:221–35. Doi: 10.3346/jkms.1992.7.3.221.

50. Blase WP., Knox DL., Green WR. Granulomatous conjunctivitis in a patient with Crohn's disease. *Br J Ophthalmol* 1984;**68**(12):901–3. Doi: 10.1136/bjo.68.12.901.

51. Barabino AV., Gandullia P., Calvi A., Vignola S., Arrigo S., Marco R De. Sudden blindness in a child with Crohn's disease. *World J Gastroenterol* 2011;**17**(38):4344–6. Doi: 10.3748/wjg.v17.i38.4344.

52. Shoari M., Katz BJ. Recurrent neuroretinitis in an adolescent with ulcerative colitis. *J Neuroophthalmol* 2005;**25**(4):286–8. Doi: 10.1097/01.wno.0000189827.69634.7d.

53. Taylor SRJ., McCluskey P., Lightman S. The ocular manifestations of inflammatory bowel disease. *Curr Opin Ophthalmol* 2006;**17**(6):538–44. Doi: 10.1097/ICU.0b013e3280109461.

54. Vavricka SR., Schoepfer A., Scharl M., Lakatos PL., Navarini A., Rogler G. Extraintestinal Manifestations of Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2015;**21**(8):1982–92. Doi: 10.1097/MIB.0000000000000392.

55. Zippi M., Corrado C., Pica R., Avallone EV., Cassieri C., De Nitto D., et al. Extraintestinal manifestations in a large series of Italian inflammatory bowel disease patients. *World J Gastroenterol* 2014;**20**(46):17463–7. Doi: 10.3748/wjg.v20.i46.17463.

56. Greenstein AJ., Janowitz HD., Sachar DB. the Extra-Intestinal Complications of Crohn's Disease and Ulcerative Colitis: a Study of 700 Patients. *Medicine (Baltimore)* 1976;**55**(5):401–12. Doi: 10.1097/00005792-197609000-00004.

57. Eidelwein AP., Thompson R., Fiorino K., Abadom V., Oliva-Hemker M. Disease presentation and clinical course in black and white children with inflammatory bowel

disease. *J Pediatr Gastroenterol Nutr* 2007;**44**(5):555–60. Doi: 10.1097/MPG.0b013e3180335bb3.

58. White JM., O'Connor S., Winter HS., Heyman MB., Kirschner BS., Ferry GD., et al. Inflammatory Bowel Disease in African American Children Compared With Other Racial/Ethnic Groups in a Multicenter Registry. *Clin Gastroenterol Hepatol* 2008;**6**(12):1361–9. Doi: 10.1016/j.cgh.2008.07.032.

59. Basu D., Lopez I., Kulkarni A., Sellin JH. Impact of race and ethnicity on inflammatory bowel disease. *Am J Gastroenterol* 2005;**100**(10):2254–61. Doi: 10.1111/j.1572-0241.2005.00233.x.

60. Nguyen GC., Torres EA., Regueiro M., Bromfield G., Bitton A., Stempak J., et al. Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic whites: Characterization of a large North American cohort. *Am J Gastroenterol* 2006;**101**(5):1012–23. Doi: 10.1111/j.1572-0241.2006.00504.x.

61. Hou JK., El-Serag H., Thirumurthi S. Distribution and manifestations of inflammatory bowel disease in Asians, Hispanics, and African Americans: a systematic review. *Am J Gastroenterol* 2009;**104**(8):2100–9. Doi: 10.1038/ajg.2009.190.

62. Löfberg R., Louis E V., Reinisch W., Robinson AM., Kron M., Camez A., et al. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: Results from CARE. *Inflamm Bowel Dis* 2012;**18**(1):1–9. Doi: 10.1002/ibd.21663.

63. Peyrin-Biroulet L., Van Assche G., Gómez-Ulloa D., García-Álvarez L., Lara N., Black CM., et al. Systematic Review of Tumor Necrosis Factor Antagonists in Extraintestinal Manifestations in Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2017;**15**(1):25–36.e27. Doi: 10.1016/j.cgh.2016.06.025.

64. Horai R., Zárate-Bladés CR., Dillenburg-Pilla P., Chen J., Kielczewski JL., Silver PB.,

et al. Microbiota-Dependent Activation of an Autoreactive T Cell Receptor Provokes Autoimmunity in an Immunologically Privileged Site. *Immunity* 2015;**43**(2):343–53. Doi: 10.1016/j.immuni.2015.07.014.

65. Heiligenhaus a., Niewerth M., Ganser G., Heinz C., Minden K. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. *Rheumatology (Oxford)* 2007;**46**(6):1015–9. Doi: 10.1093/rheumatology/kem053.

66. Malgarinos G., Giannakoulopoulou E., Mastrangelis A., Cheracakis P., Fouskas J., Georgopoulos F., et al. Cataract development as a complication of corticosteroid treatment in a young patient with ulcerative colitis. *Ann Gastroenterol* 2006;**19**(4):358–9.

67. Skalka HW., Prchal JT. Effect of corticosteroids on cataract formation. *Arch Ophthalmol (Chicago, Ill 1960)* 1980;**98**(10):1773–7.

68. Katsanos A., Asproudis I., Katsanos KH., Dastiridou AI., Aspiotis M., Tsianos E V. Orbital and optic nerve complications of inflammatory bowel disease. *J Crohns Colitis* 2013;**7**(9):683–93. Doi: 10.1016/j.crohns.2012.09.020.

69. Matsuo T., Yamaoka a. Retinal vasculitis revealed by fluorescein angiography in patients with inflammatory bowel disease. *Jpn J Ophthalmol* 1998;**42**(5):398–400. Doi: 10.1016/S0021-5155(98)00022-7.

70. Verbraak FD., Schreinemachers MC., Tiller A., van Deventer SJ., de Smet MD. Prevalence of subclinical anterior uveitis in adult patients with inflammatory bowel disease. *Br J Ophthalmol* 2001;**85**(2):219–21. Doi: 10.1136/bjo.85.2.219.

71. DeFilippis EM., Sockolow R., Barfield E. Health Care Maintenance for the Pediatric Patient With Inflammatory Bowel Disease. *Pediatrics* 2016;**138**(3):e20151971. Doi: 10.1542/peds.2015-1971.

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Table 1: Studies reporting prevalence of O-EIMs in IBD children (ordered by population size)

	N. of IBD patients	O-EIMs considered	Timing of data collection	O-EIMs prevalence	O-EIMs prevalence according to IBD type		
					CD	UC	IBD-U
Jose et al. (2009)	1649	Uveitis, Papilledema, Corneal infiltrates	During follow-up (only first-appearing EIMs)	1.63% (27/1649)	-	-	-
Card et al. (2016)	1594	Uveitis	During follow-up	1.63% (26/1594)	2.07% (21/1014)	0.86% (5/580)	-
Castro et al. (2008)	1576	Ocular manifestations, not better specified	At diagnosis	1.07% (17/1576)	1.73% (11/635)	0.74% (6/810)	0% (0/131)
Dotson et al. (2010)	1009	Uveitis	During follow-up	0.69% (7/1009)	0.82% (6/728)	0.36% (1/281)	-
Dimakou et al. (2015)	483	Ocular manifestations, not better specified	At diagnosis	0.62% (3/483)	0.60% (1/167)	0.37% (1/267)	2.04% (1/49)
Greuter et al. (2017)	329	Uveitis	During follow-up	1.82% (6/329)	2.9% (5/173)	0.64% (1/156)*	
Duricova et al. (2017)	158	Uveitis	At diagnosis	1.27% (2/158)	-	1.27% (2/158)	-
Cakir et al. (2015)	127	Uveitis	At diagnosis	1.57% (2/127)	3.4% (1/29)	1.1% (1/90)	-

Gower-Rousseau et al. (2009)	113	Uveitis	During follow-up	3.54% (4/113)	-	3.54% (4/113)	-
Martinelli et al. (2017)	111	Uveitis	During follow-up	1.80% (2/111)	-	1.80% (2/111)	-
Saadah (2012)	96	Uveitis, Keratitis	At diagnosis	2.11% (2/96)	2.11% (2/96)	-	-
Naviglio et al. (2017)	94	Uveitis	During follow-up	1.06% (1/94)	2.17% (1/46)	0% (0/46)	0% (0/2)
Lee et al. (2016)	73	Uveitis	During follow-up	1.37% (1/73)	1.37% (1/73)	-	-
Abdul Aziz (2017)	55	Uveitis	At diagnosis	1.81% (1/55)	10% (1/10)	0% (0/34)	0% (0/11)

* aggregate data (UC+IBD-U)

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Table 2: Studies reporting full ophthalmological screening in children with IBD

	N. patients	Asymptomatic uveitis			Cataract
		Overall	CD	UC	
Daum et al. (1979)	26	23.08% (6/26)	31.58% (6/19)	0% (0/7)	0%
Hofley et al. (1993)	147	4.08% (6/147)	6.19% (6/97)	0% (0/50)	0%
Rychwalski et al. (1997)	32	12.50% (4/32)	16.67% (3/18)	7.14% (1/14)	15.63% (5/32)
Naviglio et al. (2017)	94	1.06% (1/94)	2.17% (1/46)	0% (0/46)	1.06% (1/94)
Total	299	4.86% (18/299)	9.44% (17/180)	0.85% (1/117)	2.00% (6/299)

Table 3: Case reports on ocular complications in children with IBD

1st author, Year	Ocular signs and symptoms	O-EIM diagnosis	IBD	O-EIM onset (y)	IBD onset (y)	Sex	IBD localization	Other EIMs	Therapy	Outcome
Symeonidis (2017)	Low visual acuity	Unilateral intermediate uveitis	CD	6	6 (after 5 months)	M	Terminal ileum	Arthritis	Systemic steroids	Resolved uveitis, persistent amblyopia
Lapsia (2016)	Low visual acuity	Bilateral central retinal vein occlusion	UC	19	17	M	ND	ND	Enoxaparin Bevacizumab Colectomy	Improved visual acuity
Vargason (2015)	Eyelid swelling	Orbital myositis	CD	15	15	M	Terminal ileum	ND	Systemic steroids Methotrexate	Resolved
Tan (2014)	Ocular pain and swelling	Bilateral orbital pseudotumor	UC	2	2	F	Pancolitis	Arthritis Vasculitis	NSAIDs	Resolved
Thomas (2014)	Low visual acuity	Unilateral choroidal neovascular membrane	CD	13	15	M	ND	ND	Intravitreal bevacizumab	Stabilized
Fasci-Spurio (2014)	Low visual acuity	Bilateral rosacea-like keratopathy	CD	16	16	M	Pancolitis	EN Acne rosacea	Anti-TNF discontinuation	Resolved
Falavarjani (2012)	Low visual acuity	Unilateral central retinal artery occlusion	CD	9	5	M	ND	ND	None	Optic nerve atrophy
Greninger (2012)	Epiphora Enlarged lacrimal sacs	Bilateral granulomatous dacryocystitis	CD	16	13	M	Ileocolonic	Granulomatous cheilitis	External dacryocysto-rhinostomy	ND

Barabino (2011)	Bilateral visual loss	Optic neuritis	CD	11	11	M	Stomach, duodenum, colon	ND	Systemic steroids	Resolved
Paroli (2011)	Bilateral ocular pain redness	Bilateral anterior uveitis, optic disc edema	CD	4	12	M	ND	EN, Arthritis Aphthous stomatitis	Topical and systemic steroids	Resolved
Vayalambrone (2011)	Low visual acuity	Nonischemic central retinal vein occlusion	UC	16	16	F	ND	ND	ND	Improved visual acuity
Girardin (2007)	Low visual acuity Photophobia	Bilateral anterior uveitis	CD	17	17	M	Stomach, duodenum, ileocolonic	ND	Topical steroids	Resolved
Rafiei (2006)	Bilateral upper eyelid swelling	Bilateral dacryoadenitis	CD	10	10	F	Ileum, colon	Arthralgia, Aphthous stomatitis	Systemic steroids	Resolved
Mrugacz (2005)	Low visual acuity, ocular pain, redness, photophobia, foreign body sensation	Dry eyes, bilateral posterior subcapsular cataract	CD	11	4	F	ND	ND	Hyaluronan eye drops (tears substitute)	Dry eye syndrome resolved; stable cataract
Shoari (2005)	Low visual acuity, Ocular pain	Recurrent neuroretinitis	UC	14	17	M	Pancolitis	ND	Systemic steroids	Improved visual acuity
Read (1999)	ND	Episcleritis	ND	16	ND	M	ND	ND	ND	ND
Durno (1997)	Proptosis, Periorbital swelling	Orbital myositis	CD	12	13	F	Stomach, duodenum ileocolonic	ND	5-ASA	Resolved
Squires (1992)	Orbital pain Diplopia	Unilateral orbital myositis	CD	20	12	M	Ileocolonic	ND	Systemic steroids	Resolved

Seo (1992)	ND	Keratitis	CD	ND	ND	ND	ND	ND	ND	ND
	ND	Chronic conjunctivitis	UC	ND	ND	ND	ND	ND	ND	ND
Blase (1984)	Bilateral eye redness	Granulomatous conjunctivitis	CD	13	13	M	Rectum	ND	Systemic steroids	Resolved
Weinstein (1984)	Ocular pain, Diplopia, Ptosis	Unilateral orbital pseudotumor	CD	17	17	F	Colon	ND	Systemic steroids	Resolved
Camfield (1982)	Ocular pain, Photophobia	Bilateral orbital pseudotumor	CD	15	15	F	Terminal ileum	ND	Systemic steroids	Resolved
Young (1981)	Ocular pain, Proptosis, Diplopia	Bilateral orbital pseudotumor	CD	14	14	F	Terminal ileum	ND	Systemic steroids, Bowel resection	Resolved

ND: no data; NSAID: non-steroid anti-inflammatory drug; EN: erythema nodosum; 5-ASA: mesalamine

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Figure legends

Figure 1

Flow chart of systematic literature search and selection process for systematic review

Figure 2

Forest plot for prevalence of O-EIMs among children with IBD

Figure 1

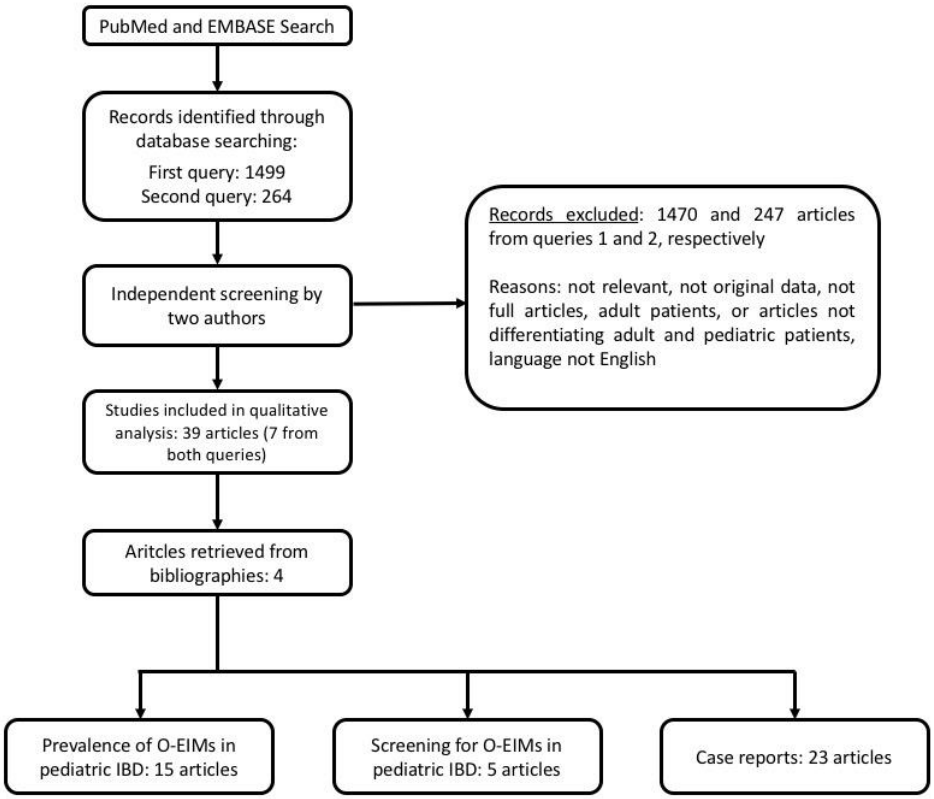

Figure 2