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REVIEW ARTICLE

Diagnostic Delay in Crohn's Disease: Reality Today and Strategies to Overcome It

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ABSTRACT

Ulcerative colitis and Crohn`s disease are chronic inflammatory bowel diseases characterized by a chronic course, relapsing nature, and significant cumulative, irreversible bowel damage if adequate treatment is not introduced early. Over the last decades, we have witnessed an increase in the prevalence of inflammatory bowel diseases.

The diagnostic delay is the period from the onset of the first inflammatory bowel disease-related symptoms to the moment of diagnosis. The prognosis of inflammatory bowel disease patients largely depends on a timely diagnosis and early treatment. Diagnostic delay is more frequent in Crohn`s disease than in ulcerative colitis due to the presence of more unspecific symptoms and the lack of blood in the stools of some Crohn`s disease patients. Early Crohn`s disease is defined as a disease diagnosed within 18 months from symptom onset, without complications and previous treatment. In these patients, therapeutic goals, presently set on transmural healing, are easier to achieve than in those diagnosed with significant diagnostic delay that, according to the available data in the literature, varies from 2 months to several years. Diagnostic delay in Crohn`s disease patients depends on many risk factors that are not well-defined in the available literature. Early diagnosis, followed by early therapeutic intervention, has been proven to significantly reduce the risk of complications and the need for surgical treatment. Patient risk stratification and subsequent therapy choice during the early stages of Crohn`s disease improve patient long-term outcomes and allow the change of the natural course of the disease. Therefore, overcoming diagnostic delay in Crohn`s disease patients is one of the crucial tasks for the future.

A possible solution for diagnostic delay in Crohn`s disease patients is the development and implementation of efficient screening tools like the Red Flags Index and education of general practitioners to suspect possible Crohn`s disease and refer patients to gastroenterologists. There is a strong need for proper use of available biomarkers like fecal calprotectin and the development of new, more specific ones. Only when this problem is overcome will more Crohn`s disease patients receive proper therapy on time which will ultimately improve their long-term outcomes and quality of life.

Introduction

Ulcerative colitis (UC) and Crohn`s disease (CD) are chronic inflammatory bowel diseases (IBD) characterized by a relapsing nature and significant cumulative and potentially irreversible bowel damage if adequate treatment is not introduced early.[1,2] Over the last decades there has been a significant rise in both incidence and prevalence of IBD worldwide.[3,4,5] It is estimated that the prevalence of IBD in Europe is about 0.3% of the general population, resulting in almost 3 million IBD patients. Furthermore, in the last decades, a dramatic rise in IBD incidence and prevalence has occurred in world regions previously considered to be low prevalence like Asia, Africa, South America, and Southern and Eastern Europe.[3,5,6] It is estimated that by the year 2030 IBD prevalence in North America will have doubled, from two to four million patients. Given all of the above, it is expected that this phenomenon will significantly burden healthcare systems worldwide.[3-6] Nowadays one of the major problems in IBD patients, especially in ones with CD, continues to be diagnostic delay (DD), which contributes fairly to morbidity caused by disease complications, impairs patients' quality of life, and substantially increases costs and exerts additional pressure on healthcare systems.

In this article, we will review the literature to determine the duration, risk factors, and impact of DD in CD patients, and propose possible tools for reducing it. Only by overcoming the DD will more CD patients receive adequate therapy within the therapeutic window. This will ultimately improve the clinical outcomes of the disease and enhance the patients' quality of life.

Definition of diagnostic delay in IBD

The diagnostic delay is the period from the onset of the first IBD-related symptoms to the moment of IBD diagnosis. This period is further divided into two periods according to some authors:

- The first period known as ***help-seeking or patient-related delay*** is the time between the first IBD-related symptoms and the first physician consultation.
- The second period known as ***physician-related delay*** is the period from the first physician consultation to the definite IBD diagnosis.[7,8]

This initial division is important because the first step in overcoming diagnostic delay should be understanding if DD is more patient- or physician-related in order to create more efficacious tools for overcoming it. In the available literature, there is no conclusive information about the exact cause of DD. While Vavricka et al. report significantly longer help-seeking delay for CD patients compared to UC ones[8], Nguyen reports a longer physician-related interval for CD patients than for UC ones[9]. Walker et al., on the other hand, suggest that both patient-related and physician-related DD is longer in CD than in UC patients.[10] The differences could be attributed to a difference in healthcare systems and availability of gastroenterologists, but also to cultural and ethnic diversity that could influence patient-related delay.

According to Segal et al., the reasons for DD may be divided into two subsets: (1) individual, confined to the patient, and (2) public-related. Those confined to the patient include a lack of awareness of IBD and the way the disease presents, a lack of recognition of symptoms, embarrassment associated with symptoms like diarrhea, hematochezia, or perianal discomfort, and avoidance of healthcare services. Public-related reasons may be a lack of public awareness of IBD, referral bias, overburdened diagnostic services, and others.[11] Further investigation is needed in order to clarify factors influencing DD, although available data already points out that both patients and physicians should be educated in order to reduce DD in CD patients.

One of the main reasons for DD is the variable clinical presentation in IBD patients. Main symptoms, including abdominal pain, changes in bowel habits, weight loss, fatigue, fever, and rectal bleeding, can often mislead both patients and physicians, especially when symptoms are mild. Adding the possibility of various extraintestinal manifestations of IBD, most commonly affecting joints, eyes, and skin, the correct IBD diagnosis becomes even more difficult if IBD is not suspected initially. According to some studies IBD symptoms are often attributed to other conditions like irritable bowel syndrome (IBS), gastrointestinal infections, or haemorrhoids.[7,8,12,13] Another contributing factor to DD in IBD is the insufficient specificity of available biomarkers used in IBD diagnosis, including fecal calprotectin (fCAL). Namely, fCAL specificity is too low making it difficult to recommend its wide everyday use.[14-16] For instance, fCAL has been proven to be a sensitive marker of gut inflammation. Calprotectin represents about 60% of cytosolic proteins in neutrophil granulocytes and macrophages. In the case of inflammation, leukocytes migrate to the gut and degrade in later phases of the inflammatory process. In that instance, calprotectin concentration in the stool is proportionate to neutrophil migration to the gastrointestinal tract and correlates to inflammatory burden.[17,18] However, fCAL levels are proven to vary greatly between different localizations of CD. Some studies show that in

endoscopically active ileal disease fCAL levels are significantly lower than in endoscopically active colonic or ileocolonic disease.[19,20] Gesce et al. found fCAL levels of 297 ± 81 mcg/g in endoscopically active ileal CD while fCAL values in active ileocolonic and colonic disease were 1523 ± 97 mcg/g. This study also identified patients with large ulcers in the ileum without fCAL values elevation.[19] Adding to that unspecific clinical presentation of ileal CD, it becomes obvious that more efforts should be made in order to develop more efficient biomarkers for diagnosing CD.

Duration of diagnostic delay in Crohn`s disease patients

The duration of diagnostic delay in IBD varies greatly between different studies and ranges from 2 months to 8 years. All available studies agree on the fact that DD is significantly longer in CD than in UC. The main underlying cause is attributable to the fact that bloody stools are a hallmark of diagnosis in all UC patients, while hematochezia is present only in a subset of CD patients, namely those with colonic localization of disease. Patients experiencing rectal bleeding are far more likely to consult a physician shortly after its onset due to fear and discomfort this symptom often causes, and physicians are also more likely to order further diagnostic tests in this case. For instance, in the Korean observational cohort study, the median interval from the first IBD-related symptoms to a physician visit for CD patients with DD was 739 days, while in UC patients with DD, it was 409 days. Also, the median interval from the first physician visit to diagnosis was significantly longer for CD patients with DD, 150 days compared to only 10 days for UC patients. In this study, the median DD for UC patients was 2.4 months while it was 6.2 months for CD patients.[21] Another reason for longer DD in CD patients is that CD symptoms are far more variable and can sometimes be very mild, leading to a lack of clinical suspicion and a prolonged diagnostic workup.[7,8] In a large Swiss cohort study[8], the median DD for UC patients was 4 months, while it was 9 months for CD patients. Similar results were reported by others. Novacek reported a median DD of 3 months for UC patients, and 6 months for CD patients among Austrian patients,[22] while in Italy median DD for UC patients was only 2 months compared to 7.1 months for CD patients.[12] (Table 1.)

Table 1. Difference of DD between UC and CD patients in different countries

Country	DD in UC patients (months)	DD in CD patients (months)
Switzerland[8]	4	9
Italy[12]	2	7
Austria[22]	3	6
USA[9]	3	9
France[23]		5
Romania[24]	1	5
Korea[25]	2,4	6,2

One of the first big cohorts evaluating DD in CD patients was a Swiss study published in 2012 by Vavricka et al. who came up with a median DD of 9 months for CD patients, while one-quarter of patients had DD longer than 24 months.[8] Comparable results were reported from the USA where Nguyen et Al. anayzed 110 patients with CD and reported a median DD of 9,5 months. In their study, 25% had DD longer than 26 months.[9]

Some cohort studies worldwide reported shorter DD for CD patients. In the Austrian cohort, the median DD was 6 months, and ranged from 2 to 23 months.[22] The French study reported a median DD of 5 months,[23] the Italian multicentre study found the median DD to be 7,1 months,[12] the Romanian national cohort reported median DD to be 5 months, while in three-quarters of CD patients, DD was less than 18 months,[24] and in the UK median DD was 4 months.[10]

However, other national studies have reported significantly longer DD for CD patients. For example, in one Korean study, the mean DD was 16 months,[25] in the Indian study the average DD was 18 months,[26] and in Chinese patients, there are reports of an average DD of almost 29 months.[27]

Recent data has been systematized in a big review by Cross et al., who analysed 31 studies, of which 23 were cohort and 8 were cross-sectional, including almost 13.000 CD patients in whom DD was adequately defined. They concluded that the overall delay ranged from 2 to 26.4 months and that most of the patients (75% of them) had median DD ranging from 2 to 12 months.[7]

This heterogeneous duration of DD can possibly be attributed to differences in the study design but can also be associated with differences in healthcare systems in different countries. The CD was considered to be a disease a lot more prevalent in Europe and America compared to Asia. Nowadays, as previously mentioned, there is a significant rise in

the prevalence of CD in Asia, resulting in less aware, less prepared, and less experienced healthcare systems and the public in general, leading to longer DD in those regions.

Changes in diagnostic delay duration over time

Only two studies compared the duration of DD over time. An Italian study analyzed a total of 3392 IBD patients, further divided into the historical cohort (1955-1984) and the modern cohort (1985-2014). They found no significant difference in the duration of DD in CD or UC patients among the two groups. However, the authors report as a promising finding the fact that nowadays there are fewer IBD patients with long DD, which is defined as a duration of DD lasting longer than 24 months. This also indirectly proves that there is a true rise in the incidence and prevalence of CD in Europe and not a rise caused by a reduction of non-detected cases due to increased awareness and improved diagnostic tools for IBD.[12] Conversely, a study conducted in Mexico revealed a noteworthy 24,9% reduction in the duration of DD over the last four decades. This decline can be attributed to the considerable advancements in diagnosing and managing CD in regions not traditionally affected by IBD. These improvements were necessitated by the rising incidence of IBD in these regions in recent years.[28]

Risk factors for diagnostic delay in Crohn`s disease patients

A variety of possible risk factors was evaluated in an aim to identify the ones that contribute to DD. Different authors evaluated such factors as age at diagnosis, gender, localization of disease, perianal disease, presence of complicated disease at diagnosis, presence of endemic diseases in different regions, extraintestinal manifestations, positive family history for CD, educational level, smoking, NSAIL uptake, urban or rural place of living, private or public insurance, presence of concomitant upper gastrointestinal (GI) disease, season of symptom onset, previous medical history and others.

AGE AT DIAGNOSIS

There is data suggesting that longer DD is associated with younger patients (less than 40 years old at the time of diagnosis). The longer DD in younger CD patients results from the physician-related part of DD.[8] Others failed to confirm this finding and suggest that older patients are at greater risk for DD.[12,22,25] A possible explanation for these contradictory findings is that the symptoms of CD can overlap with irritable bowel syndrome (IBS) symptoms which can result in a tendency of physicians to underestimate the need for further diagnostic workup since functional disorders are usually more frequent than organic ones in the young population. On the other hand, in other studies, shorter DD in younger patients was attributed to the more aggressive biology of CD resulting in a poor quality of life and an earlier seeking of medical help.[12,22,25]

GENDER

Only one Spanish study found the female gender to be a risk factor for longer DD among CD patients. They found that the average duration of DD in females was 12.6 months compared to 4.5 months in males. The clinical presentation of CD was similar in both sexes. The main reason for the longer diagnostic delay was the more common occurrence of misdiagnosis in female patients. Attributing the symptoms of CD to IBS in females due to the higher prevalence of this condition in women could be the explanation behind this phenomenon. Moreover, CD symptoms were in some cases contributed to gynaecologic conditions. Gender inequities leading to delayed diagnosis or misdiagnosis were found on all levels of the healthcare system.[29] Other studies did not find gender to be a risk factor for DD.[8,9,12,22-24]

LOCALIZATION OF DISEASE

Ileal localization of the disease was found to be a significant risk factor for DD, largely attributable to the ileal CD presenting with mild and unspecific symptoms, including abdominal pain, less frequent diarrhea, and absence of rectal bleeding. This often leads to delayed physician consults. Isolated ileal CD is often misdiagnosed as IBS or some other functional GI disease, but also diagnostic tests are postponed and done late because of a lack of clinical suspicion.[8,9,24]

PERIANAL DISEASE

Surprisingly, the presence of perianal disease seems to be a risk factor for DD in CD patients according to some studies.[7,25] This could be due to the embarrassment around complaining of perianal discomfort. Other reasons could be associated with physicians misdiagnosing this condition as benign ones like anal fissures or hemorrhoids. On the other hand, Schoepfer et al. didn't find an association between perianal disease and DD. A possible explanation for this is that perianal symptoms make a large proportion of patients seek medical help faster because of impaired quality of life.[30]

COMPLICATED DISEASE AT THE TIME OF DIAGNOSIS

Paradoxically, complicated disease at the time of diagnosis was also found to be a risk factor for long DD in CD patients according to one study. This could

be explained by the fact that the stenosing disease is often clinically silent, causing mild and unspecific symptoms like abdominal pain, until complications including ileus and/or perforation occur, leading to urgent surgical treatment. The presence of internal fistulas can also be asymptomatic until intraabdominal abscess occurs followed by severe abdominal pain and fever.[12]

PRESENCE OF ENDEMIC DISEASES

One of the risk factors for DD in CD patients is the presence of endemic diseases in some regions. In India and other regions endemic for tuberculosis (TB) infection, there is frequent DD in CD because of diagnostic dilemmas between intestinal tuberculosis (ITB) and CD. Results from diagnostic procedures are often inconclusive, thus TB therapy is initiated as a result of the high prevalence of ITB. This leads to long DD, which delays the start of specific CD therapy.[26] Dilemmas in differential diagnosis also occur in regions endemic for protozoal infestation causing diarrheal syndrome, between CD and infectious etiology.[28]

EXTRAINTESTINAL MANIFESTATIONS

The presence of extraintestinal manifestations (EIM) can also lead to DD in CD patients, according to data published by Vavricka et al. EIMs contribute fairly to the heterogenicity of CD symptoms, and in a setting of mild GI complaints can mislead physicians from CD diagnosis. This emphasizes the importance of educating physicians such as dermatologists, rheumatologists, and ophthalmologists to suspect CD and direct patients at risk to gastroenterologists.[8,23]

FAMILY HISTORY OF INFLAMMATORY BOWEL DISEASE

Some studies show that patients with no family history of IBD are at a greater risk for DD than patients with positive family history. The logical explanation for this is that those patients have more awareness and knowledge about CD, which leads to better recognition of symptoms and faster physician consultation.[27]

SMOKING

A Romanian study suggests that smoking is also a risk factor for DD. One explanation for this is that smokers often belong to marginalized groups, have more trouble with health insurance, and restricted access to healthcare systems. On the other hand, smokers have a more aggressive CD phenotype, according to previous studies.[24] Other studies failed to demonstrate the influence of smoking on DD in CD.[8,9,12,22,23]

TYPE OF HEALTH INSURANCE

The main aim of the Mexican study on DD in 214 CD patients was to evaluate if there is a difference between CD patients with public and private health insurance regarding DD. The authors reported a significant difference between these two groups. Namely, patients with public health insurance had DD in 37.9%, while those with private insurance had DD in 23,4%.[28] An Austrian study with 830 CD patients included reported similar findings.[22] This could be due to the high pressure public health systems withstand nowadays, leading to the later referral of patients to gastroenterologists.

CONCOMITANT UPPER GASTROINTESTINAL DISEASE

Concomitant upper GI disease such as peptic ulcer has also proven to be a risk factor for DD in CD patients according to one study.[25] The explanation for this is that some of the GI symptoms caused by CD are in those cases contributed to preexisting GI disease, and no diagnostic procedures are undertaken, leading to DD.

SEASON OF DIAGNOSIS

Interestingly, one study suggested that DD was more likely to occur if symptoms of CD occurred during the summer months. This is explained by more GI tract alimentary infections during summer, which leads to a greater risk that CD is mistaken for infection.[24]

PREVIOUS MEDICAL HISTORY

Considering previous medical history, one study suggests that patients with earlier diagnosis of IBS or psychiatric conditions such as depression are at greater risk for DD of CD.[13]

LEVEL OF EDUCATION

The level of education was also found to differ among DD and non-DD groups of patients in two studies. Novacek et al. reported that patients with higher levels of education are at a greater risk for DD,[22] which was not supported by the data published by Li and al. who reported that patients with lower education levels are the ones at higher risk for DD.[27] For the higher education level group, the explanation could be that they are under greater work pressure, and are more concerned about missing workdays, leading to ignoring symptoms and delaying physician consults. People with lower education level could be less informed and aware of CD, which leads to underestimation of symptoms and delays in health service visits.

None of the studies found significant differences between urban and rural areas, and NSAIL or oral contraceptive uptake was not found to be

significantly different between DD and non-DD groups.

Impact of diagnostic delay in Crohn`s disease

To fully understand the impact of DD, one needs to understand the natural course of CD. As previously stated, CD is characterized by a chronic course and relapsing nature. In the past, CD was seen as an intermittent disease, but nowadays it is more than clear that it is progressive. The uncontrolled inflammatory phase of the disease causes chronic damage to the bowels which leads to fibrotic changes. After that, complications such as stenosis and fistula formation can occur.[24,30,31] Once the fibrosis of the bowel walls has occurred, there is no available therapeutic option that would be able to reverse it. All the available drugs can only impact the natural course of the disease during the active inflammation phase.[32] There is even evidence that bowel wall damage happens very early in the course of the disease. One study suggests that the cumulative risk for complication occurrence was 18.6% in the first 90 days from diagnosis, and 22% at 1 year.[31] Across a 20-year span of the disease, the rates of inflammatory, stenosing, and penetrating disease were found to be 12%, 18%, and 70%, respectively, as indicated by several studies. In the 20-year interval from CD diagnosis, most patients (70-80%) will need surgical treatment at least once.[24,32] Other studies show a cumulative risk of 34% at year 5 and 51% at year 20 after diagnosis for the occurrence of stenosing and penetrating complications.[33] To appropriately quantify the bowel damage in CD, the Lemman score was developed. It reflects damage severity, extent, reversibility, progression, and localization that is evaluated by imaging diagnostic modalities, and also takes into account previous surgical resections. It is proven by some studies that patients with longer DD have higher scores of the Lemman index.[31,33]

Therapeutic targets in CD have evolved over time. In the past, the conventional step-up therapeutic approach was used, and the goal was set at clinical remission, but evolving evidence that patients with no symptoms can still have disease progression and risk of complication forced us to come up with new ones. Currently, the treat-to-target strategy is recommended along with the tight control approach. In 2021 STRIDE II (The Selecting Therapeutic Targets in Inflammatory Bowel Disease Endpoints) was published based on experts' consensus. In STRIDE II there are short, intermediate, and long-term targets. The short-term targets include clinical and symptomatic remission, intermediate ones include biomarkers normalization and normal growth and development in children with CD. Long-term goals include mucosal healing, the absence of disability, and a normalized quality of life. In the next period, it is expected that the ultimate goal could be transmural healing in CD as many studies show that achieving transmural healing reduces rates of hospitalizations, steroid use, therapy escalation, and surgery.[34-36] Another term frequently used when speaking about treatment targets in CD is deep remission. Deep remission is defined as complete clinical remission in combination with complete endoscopic remission and it has been proven to reduce the risk of complications in CD patients.[23,37]

Recent studies have emphasized the importance of early diagnosis, followed by early intervention and disease control in order to change the natural history of CD to improve patients' clinical outcomes in the first place, and also quality of life. The efforts were made to define early CD, and international consensus proposed 'The Paris Definition for Early Crohn's disease'. They defined early CD as a disease diagnosed within 18 months from the onset of symptoms, with no previous treatment with thiopurines, methotrexate, or biologics, and without previous complications.[25,32-34]

In the past, the conventional step-up approach was used in the treatment of CD patients. This means that therapy was escalated to biologics only when there was no clinical response to corticosteroids and/or immunomodulators (thiopurines, methotrexate). Nowadays, there is a significant amount of evidence suggesting that a top-down approach is more effective in achieving deep remission, thus improving long-term clinical outcomes, and preventing disease progression and complications.[25,32,35,36,38] SONIC trial reports results in favour of top-down early intervention since it showed improved results for patients treated with combination therapy with infliximab and azathioprine that was started during early CD.[32] Similarly, in EXTEND study deep remission was achieved at a higher rate in patients who were started on adalimumab during the early CD phase.[37] Peyrin-Biroulet et al. confirmed that starting immunomodulators and biologics for non-complicated disease during early CD reduces the need for later surgery.[39]

Given all of the above, it is clear that diagnostic delay is a significant risk factor for unfavourable clinical course in CD patients, significantly increasing the risk for disease complications and surgery.[7,8] Nygen et al. suggest that every six months of diagnostic delay increase the risk of complication

and intestinal stricture occurrence by 16% and 17%.[9] Cohort study came to the conclusion that increased surgery rates are seen in Swiss CD patients with diagnostic delay.[30] This was confirmed by an Indian study where it was found that patients with diagnostic delay duration over 18 months had a higher rate of stenotic complications and subsequent need for surgical treatment.[26] A French study showed that patients with late CD diagnosis had a significantly higher risk for early surgical treatment.[38] Only one Chinese study found no link between DD and increased risk for surgery, although they found that patients with DD had a higher risk for stenosis, internal fistulas, and perianal disease.[25]

Diagnostic delay, by causing uncontrolled disease, the occurrence of complications, and the need for surgery increases costs and burdens healthcare systems. The need for hospitalizations, a decrease in productivity at work, and the use of new expensive drugs can also be attributed to diagnostic delay, further increasing costs.[28]

Patient risk stratification, adequate therapy choice, and sequencing done during the early stage of the disease improve patient long-term outcomes and allow us to change the natural course of the disease.[32]

Tools for shortening diagnostic delay

In the past various molecules were studied as potential biomarkers for early CD diagnosis. Serological antiglycan antibodies directed against various microbial carbohydrate epitopes, such as *anti-Saccharomyces cervisiae antibodies (ASCA), anti-chitobiose antibodies (ACCA) and anti-laminaribioside antibodies (ALCA),* were used, but none of them have proven to be useful and today they are not recommended for routine CD screening.[40]

Fecal calprotectin (fCAL) is one of the most commonly used biomarkers for diagnosis and follow-up of IBD patients. However, studies have shown that fCAL is not specific enough since it can be elevated in many other gastrointestinal diseases and conditions. According to some studies, it has a decent negative predictive value at a threshold set at 70 to 100 mcg/g, so its potential role could be excluding IBD in patients with IBS at the primary care level. [14,15] Similarly, Menees et al. found in their study that none of the biomarkers are reliable enough to discriminate between IBD and IBS. They only suggest that values of C reactive protein below 1 g/ml and fCAL below 40 mcg/g can exclude IBD in patients with IBS symptoms.[16] In recent years there have been some novel promising biomarkers including prostaglandin E, anti-αvβ6 antibody, oncostatin M, and microRNA, but further studies are needed to evaluate reliability in making CD diagnosis.[41]

One of the most promising tools for early CD diagnosis is the Red Flag Index (RFI). RFI was developed from a literature review and consensus of 12 IBD experts. Out of 21 items, the authors identified 8 key ones to include in the questionnaire so as to help physicians in primary and secondary healthcare to identify symptoms and signs that might raise suspicion of CD diagnosis before any diagnostic algorithm is even commenced. It is simple and easy to use, it is not time-consuming, and it might lower the costs of healthcare systems and improve the chances of DD reduction. The result of 8 points or more in this questionnaire would mean that the patient should shortly be appointed to the gastroenterologist and endoscopic and radiological workup. Those symptoms and signs are non-healing or complex perianal fistula or abscess or perianal lesions, first-degree relative with confirmed IBD, weight loss (5% of usual body weight in the last 3 months), chronic abdominal pain (longer than 3 months), nocturnal diarrhea, mild fever in the last 3 months, no abdominal pain 30-45 minutes after meals, predominantly after vegetables and no rectal urgency. In the initial evaluation of RFI, results were very promising. It had a sensitivity and specificity of 94%, a positive likelihood ratio was 15,1, and a negative likelihood ratio was 0,06.[37] However, in a real-world setting, RFI had a sensitivity of 50%, specificity of 58%, positive predictive value of 4%, and negative predictive value of 97%. A combination of RFI and fCAL, where RFI was 8 and more, and fCAL was above 250 mcg/g, has shown excellent results. Sensitivity was 100%, specificity was 72%, positive predictive value was 21%, and negative predictive value was 100%. This study has proven that a combination of fCAL and RFI is a legitimate method for CD screening in primary and secondary care.[42]

Another attempt for coping with DD was a CalproQuest, a questionnaire that contained 8 questions, of which 4 were considered major criteria, and 4 were considered minor criteria. The CalproQuest was considered positive if more than or equal to two major criteria or one major criterion and two minor criteria were answered positively. CalproQuest was supposed to increase the pre-test probability for a positive fCAL (value above 50 mcg/g) that would allow physicians in primary care to determine whether patients with gastrointestinal complaints should be tested for fCAL value. Two studies were conducted regarding this matter. The

first study proved that CalproQuest was feasible, but the second study showed that the sensitivity and specificity of CalproQuest for detecting patients with fCAL levels above 50 mcg/g and patients with positive IBD diagnosis were not good enough.[43,44]

One study shows that knowledge and awareness in the general population about IBD is poor. Only 32% of subjects interviewed in one study could answer what Crohn's disease is. It has also been concluded that higher educated people and those from urban areas have more knowledge about CD.[45] Another study emphasizes that more effort is necessary to increase awareness and knowledge in the general population about IBD, especially about CD and the various ways it can present. This could be done through media campaigns and the involvement of the whole community.[11]

Conclusions

Diagnostic delay in CD patients, unfortunately, remains our reality. Therefore, overcoming diagnostic delays in CD patients represents one of the crucial tasks in years to come. More studies need to be conducted to better understand risk factors for DD. A solution for diagnostic delay in CD patients is the development of more efficient screening tools like the Red Flags Index and the education of general practitioners to suspect possible CD patients and refer them to gastroenterologists. Furthermore, there is a strong need for proper use of available biomarkers like fecal calprotectin and the development of new, more specific ones. Only when this problem is overcome will more CD patients be able to receive proper therapy in the therapeutic window which will ultimately improve their clinical outcomes and quality of life.

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