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MINIREVIEWS

Non-invasive diagnosis of Crohn's disease: All that glitters is not gold

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Abstract

Crohn's disease (CD) is associated with occurrence of inflammation in the digestive tract. Diagnosing intestinal bowel diseases can be difficult because bowel disease can be tricky as it does not have unique symptoms. Endoscopy and histopathological tests play a crucial role in the diagnosis and management of inflammatory bowel diseases. Various techniques can be used to diagnose CD. Nevertheless, the diagnosis of CD mostly requires having patients in the hospital. During the SARS-CoV-2 pandemic, that might not be very feasible, as minimizing contact is essential, but can an alternative diagnosis technique be enough to provide a definitive diagnosis?

Key Words: Crohn's disease; Inflammatory bowel disease; Diagnosis; Noninvasive; Histopathology; Overdiagnosis

Core Tip: Diagnosing intestinal bowel diseases can be difficult because bowel disease can be tricky as it does not have unique symptoms. Endoscopy and histopathological tests play a crucial role in the diagnosis and management of inflammatory bowel diseases. However, various techniques can be used to diagnose Crohn's disease.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition that affects any part of the gastrointestinal tract, and is characterized by the development of fistulas or strictures[1]. The incidence of CD varies around 5/100000, a figure that is associated with residence in urban areas[2]. CD has nonspecific symptoms and commonly shared symptoms with other intestinal bowel diseases, such as ulcerative colitis. This makes the diagnosis of CD challenging with many patients, especially those with mild and moderately severe disease. The diagnosis of CD is based on various clinical, histological, and laboratory findings. Histopathology can be used as a confirmatory method for diagnosing CD along with imaging modalities. Additionally, diagnostic modalities are used either for disease severity evaluation or for monitoring the response to treatment[3]. However, histopathology is not always accessible, and even reaching the site of inflammation for taking biopsies is not always feasible. Differentiation from other causes of small intestine inflammation (*e.g.*, lymphomas, Behçet disease, and tuberculosis) is crucial as immunosuppression induced by CD therapies may aggravate those conditions and result in additional, unnecessary risk of serious adverse events. This highlights the necessity of having various procedures to confirm the diagnosis of CD. Recently, numerous useful tools and techniques have emerged. However nowadays, under this austere environment, an accurate technique with minimal patient contact is extremely important, but high accuracy with a definitive diagnosis also remains vital.

HISTOPATHOLOGICAL TESTING

The presence of non-caseating granuloma could confirm the diagnosis in the setting of a typical clinical presentation. Biopsies may be taken during upper endoscopy (including a portion of the jejunum), colonoscopy (including the terminal part of the ileum), and during surgical exploration in complicated cases. However, inflammation may not be accessible by upper endoscopy or colonoscopy, especially if surgical exploration is not indicated. This hinders taking a biopsy, makes it less convenient, and requires using an alternative modality.

DEVICE-ASSISTED ENTEROSCOPY

The use of device-assisted enteroscopy (DAE) is mandatory when the biopsy location is unapproachable[4]. DAE has an outstanding advantage of allowing deeper intubation of the small intestine. However, it is of limited availability due to a prolonged examination time and carries an increased risk of perforation, especially in the situation of markedly inflamed ulcerated mucosa. Most DAEs are performed in tertiary hospitals, and limited availability results in frequent long queues that delay the diagnosis of such cases.

VIDEO CAPSULE ENDOSCOPY

Video capsule endoscopy (VCE) is the least invasive technique compared with the others. It is now taking on a more prominent role in the detection of small intestinal lesions and monitoring disease progression. With its increased availability, straightforward interpretation, high-quality imaging, simplicity, and most importantly, noninvasiveness of the procedure, VCE has become a highly recommended modality in the European Crohn's and Colitis Organization guidelines[5]. Nevertheless, the inability of taking biopsies, relatively high cost, and the fear of retention when in doubt of strictures have limited its use. Esaki *et al*[6] conducted a nationwide case-control study that illustrated the presence of distinctive

signs for CD that may ease the diagnosis without the need to biopsy. The signs include cobblestoning (a cobblestone appearance), many longitudinal ulcers and erosions, and circumferential and longitudinal diminutive lesions[7].

MAGNETIC RESONANCE ENTEROGRAPHY

Magnetic resonance enterography (MRE) recently became a commonly used diagnostic tool for CD following development of explicit criteria of evaluation and the emergence of the magnetic resonance index of activity (MaRIA). MaRIA is an improved scoring system that provides a more accurate evaluation of the disease insult to the intestines and the detection of complications, making MRE an essential tool for assessing the patient's condition[8]. Although MRE avoids the operator-dependent bias associated with abdominal ultrasound of the bowel, it has a few drawbacks. The process of the procedure may not be tolerated by the patient and the availability of the machine and the experience of the operator and interpreter may be limited[9,10].

LABORATORY TESTS

CD can be suspected by classical clinical symptoms and signs, involving either the gut or extraintestinal manifestations. From the time of the presentation of the patient and throughout the patient journey, a few laboratory tests aid the process of evaluation. During the diagnosis phase and on follow-up, C-reactive protein, calprotectin, complete blood cell counts, and ferritin, are regularly requested and are proven to correlate with disease activity[11]. Vitamin D deficiency, positive anti-*Saccharomyces cerevisiae* antibodies, low albumin, and the presence of red blood cells and pus in the stool analysis may point to the state of gastrointestinal inflammation. All these tests can provide a better insight to the physicians. In addition to the chance of raising doubts of the CD diagnosis, the tests can also be used to evaluate disease activity and monitor the response to treatment[12,13].

Apart from the guidelines and the current literature recommendations, to gain extra time until the CD diagnosis is proven and when the treating physician is in doubt, many physicians tend to start a trial treatment and judge the response. This trial treatment includes initiation of glucocorticoids in lower than recommended doses for treatment of active CD. However, although we may encounter this in our regular practice, to our knowledge, its benefit was never proven in a scientific publication. The concept of a steroid trial was borrowed from rheumatologist and dermatologist treatment of suspected immune disorders, and when patients with inflammatory bowel disease present with extraintestinal manifestation.

DIAGNOSIS DURING CORONAVIRUS DISEASE 2019

During the early months of the coronavirus disease 2019 (COVID-19) pandemic, healthcare services for nonemergency patients were less accessible. Endoscopy was reserved for those who had alarming signs only. We recently noticed an increase of patients referred with a diagnosis of CD without histopathological evidence. Their evaluation had been completed by either MRE or by other endoscopic modalities, and many of those patients were falsely misdiagnosed[14]. Hence the need of a confirmatory technique is vital, and the specificity and sensitivity of each available technique are compared in Table 1. The comparison shows that VCE is the leading diagnostic modality and has the potential to meet current needs[15].

CONCLUSION

To conclude, the healthcare system has been under severe stress from the current pandemic. COVID-19 has resulted in restrictions on asking patients to go to the hospital and to limit and avoid prolonging the time spent there. Patients need to agree to very precise procedures and only for crucial emergencies. CD is not characterized by specific symptoms and can be mistaken for other bowel disorders because of shared

Table 1 Accuracy of currently used diagnostic modalities

Tool	Ref.	*n*	Sensitivity	Specificity
VCE	Monteiro *et al*[7]	36	90%	100%
MRE (MaRIA)	Roseira *et al*[9]	84	90%	98%
CRP	Mosli *et al*[13]	2499	49%	92%
Calprotectin	Rokkas *et al*[12]	2822	82.4%	72.1%

The modalities used in each study and the number of cases that were recruited in each are shown. Sensitivity and specificity were calculated on that basis. The study by Rokkas *et al*[12] using calprotectin had the largest number of patients but reported the lowest specificity. On the other hand, Monteiro *et al*[7] who used video capsule endoscopy had the highest sensitivity and specificity. CRP: C-reactive protein; MaRIA: Magnetic resonance index of activity; MRE: Magnetic resonance enterography; VCE: Video capsule endoscopy.

symptoms. Various well-established imaging modalities used in diagnosing CD. However, as they can be a bit risky, using safe, combined techniques could be our go-to at this time. Having a confirmed diagnosis is of ultimate importance to provide the right treatment. The diagnosis of CD is sometimes not accessible because of the need for histopathologic confirmation before initiation of treatment. Histopathology has limitations both in occasional difficulty in taking a biopsy and in a tentative diagnosis. In the aspect of the guarantee of the high diagnostic value of other modalities, such as MRE and VCE, combining both of them and supporting them with laboratory tests may decrease the need for histopathology in diagnosing CD. Future research may fulfil this strong demand by developing a model for noninvasive diagnoses of CD. The potential of having a noninvasive technique could not only be promising for the time being, but also more comfortable and less stressful for patients compared with regular biopsies and other invasive techniques.

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