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Nomenclature and diagnosis of seronegative coeliac disease and chronic non-coeliac enteropathies in adults: the Paris consensus

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ABSTRACT

Objective Differential diagnosis of villous atrophy (VA) without coeliac antibodies in adults includes seronegative coeliac disease (CD) and chronic enteropathies unrelated to gluten, ie. non-coeliac enteropathies (NCEs). There is currently no international consensus on the nomenclature and diagnostic criteria for these enteropathies. In this work, a Delphi process was conducted to address this diagnostic and clinical uncertainty.

Design An international task force of 13 gastroenterologists from six countries was recruited at the 16th International Coeliac Disease Symposium, Paris, 2019. Between September 2019 and July 2021, a Delphi process was conducted through mail surveys to reach a consensus on which conditions to consider in the differential diagnosis of VA with negative coeliac serology and the clinical diagnostic approaches required for these conditions. A 70% agreement threshold was adopted.

Results Chronic enteropathies characterised by VA and negative coeliac serology can be attributed to two main clinical scenarios: forms of CD presenting with negative serology, which also include seronegative CD and CD associated with IgA deficiency, and NCEs, with the latter recognising different underlying aetiologies. A consensus was reached on the diagnostic criteria for NCEs assisting clinicians in differentiating NCEs from seronegative CD. Although in adults seronegative CD is the most common aetiology in patients with VA and negative serology, discriminating between seronegative CD and NCEs is key to avoid unnecessary lifelong gluten-free diet, treat disease-specific morbidity and contrast poor long-term outcomes.

Conclusion This paper describes the Paris consensus on the definitions and diagnostic criteria for seronegative CD and chronic NCEs in adults.

WHAT IS ALREADY KNOWN ON THIS SUBJECT

⇒ Differential diagnosis of villous atrophy without coeliac antibodies in adults includes seronegative coeliac disease and chronic enteropathies unrelated to gluten, ie. non-coeliac enteropathies.

⇒ Standard nomenclature and diagnostic criteria for these enteropathies are currently lacking, thus representing a major limitation for clinicians and researchers dealing with these conditions.

WHAT THIS STUDY ADDS

⇒ The panel of experts reached a consensus on the definitions and diagnostic criteria for seronegative coeliac disease and chronic non-coeliac enteropathies in adults.

⇒ Differentiating seronegative coeliac disease from chronic non-coeliac enteropathies is key to avoid unnecessary lifelong gluten-free diet and contrast long-term morbidity and mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Uniformity in the definitions and diagnostic criteria for seronegative coeliac disease and non-coeliac enteropathies will be of value to clinicians caring for these patients, and it will ensure a more consistent approach to research in this field.

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INTRODUCTION

Small bowel villous atrophy (VA) is one of the histopathological manifestations in the spectrum of chronic enteropathy.[1–3] In the vast majority of cases, it is due to coeliac disease (CD), a chronic gluten-dependent enteropathy characterised by heterogeneous clinical manifestations, high prevalence and an increased mortality compared with the general population.[4–6]

In adults, the diagnosis of CD is based on VA and positive coeliac specific serology, that is, IgA endomysial (EmA), IgA tissue transglutaminase (tTA), and IgA and IgG deamidated gliadin peptides antibodies while on a gluten-containing diet.[4 5] Although the diagnosis of CD is straightforward in the vast majority of cases, diagnostic challenges can occur when VA is found in patients reporting GI symptoms and testing negative to coeliac specific antibodies.[1–3 7] The first step is to ensure that there have been no errors of inadequate sampling, collection or processing of either serum samples or duodenal

biopsies, the latter potentially resulting in incorrect orientation and evaluation of duodenal specimens; another key requirement is that the diet has not been gluten restricted prior to endoscopy.[1–3 7–9] Thereafter, the clinical scenarios characterised by VA and negative coeliac serology can be broadly attributed to two main clinical entities: CD presenting with negative antibodies and chronic enteropathies unrelated to CD and gluten ingestion, which we have defined as non-coeliac enteropathies (NCEs).[1–3]

The differential diagnosis between forms of CD with negative serology and NCEs remains challenging, and patients with NCEs are frequently misdiagnosed as seronegative CD.[1–3 7 9 10] Reasons for this include the rarity of these enteropathies, the overlapping clinical and histopathological features and the lack of biomarkers for some of these conditions. Furthermore, widely accepted definitions and diagnostic criteria for most NCEs are still lacking. Although in adults seronegative CD is the most common aetiology of VA with negative coeliac serology,[1–3 11–15] discriminating between seronegative CD and NCEs is key to reduce diagnostic delay and avoid unnecessary lifelong gluten-free diet (GFD). Furthermore, accurate characterisation of NCEs ensures both appropriate management and a clinical perspective for our patients with regards to long-term morbidity and mortality.[9 11–14 16 17]

For all these reasons, there is an obvious need to find consensus on the nomenclature and diagnostic criteria for these enteropathies. Clear and widely applicable diagnostic criteria are necessary to avoid misdiagnoses, promote targeted management and facilitate future research on these conditions.

A multidisciplinary task force with specific expertise on the diagnosis and treatment of CD and NCEs was created to first identify the conditions responsible for VA with negative coeliac serology, and then propose definitions and diagnostic criteria. The panel of experts was recruited at the 16th International Coeliac Disease Symposium, Paris, France, 5–7 September 2019. The final diagnostic criteria are referred as 'the Paris consensus'. This task force focused on chronic conditions affecting adult patients. We excluded from our analysis transient VA as occurs with acute GI disorders (ie, viral/bacterial gastroenteritis), which can lead to a transient flat mucosa spontaneously healing over time. Paediatric conditions were outside the purposes of the present work.

METHODS

Recruitment of the panel of experts

Thirteen gastroenterologists from six Countries (Italy, the USA, the UK, Finland, France and New Zealand) were invited to participate by two of the authors (FB and AS) during and immediately after the 2019 Paris Symposium. The members of the task force have recognised international expertise on the diagnosis, clinical management and delivery of care for adult patients affected by various forms of CD and NCEs. Some of them have already participated to collaborative working groups on the definitions and diagnostic criteria of CD.[4 18–20] An external statistician was also enrolled to ensure unbiased management of experts' opinions and data analysis.

Development and phases of the Delphi process

After recruiting the panel of experts, a three-phase Delphi process was conducted between September 2019 and July 2021 to transform the opinions of each expert into a group consensus.[21 22] This was performed by means of repeated rounds of voting and discussion conducted through email with two primary aims: (1) to clarify and delineate the conditions that should be considered in the differential diagnosis of VA with negative coeliac serology, according to the current literature and to classify them into diagnostic categories; and (2) to provide definitions and diagnostic criteria for enteropathies voted in the first phase and for CD presenting with negative serology.

First phase: identification of conditions with VA and negative coeliac antibodies and classifications into diagnostic categories

Approaching the differential diagnosis of enteropathies characterised by VA and negative coeliac serology is complex, as the underlying causes described in the literature are extremely heterogeneous. Apart from CD presenting with negative serology, VA can be found also in chronic enteropathies unrelated to gluten ingestion, which are often misdiagnosed as seronegative forms of CD.[1–3 7–15] Interestingly, VA is the diagnostic hallmark for some of these NCEs, whereas for others, it is only one of the elements contributing to the entire clinical and histopathological picture. Nevertheless, when the clinical picture is dominated by severe malabsorption, these aetiologies fall within 'not to miss diagnoses'. Furthermore, there are some conditions reported in the literature as possible aetiologies of VA, for which a definitive consensus on their causal role is still lacking.

Panel members were asked to provide a list of enteropathies causing VA on the basis of the literature and their clinical experience and to vote to classify them in the following groups: (I) NCEs posing a problem of differential diagnosis with seronegative CD; (II) NCEs not posing a problem of differential diagnosis with seronegative CD due to the overall clinical and/or histopathological picture; and (III) conditions whose role in causing VA is unclear and therefore should not be taken into account in the differential diagnosis of VA with negative coeliac serology.

The threshold for agreement on this phase was set at ≥70% of all voting panellists. NCEs not reaching the required threshold were not further evaluated.

Enteropathies included in group I were the main object of the second phase of the Delphi process.

Second phase: diagnostic criteria for non-coeliac enteropathies characterised by VA and negative coeliac serology

NCEs included in group I on the first phase of voting were individually discussed through email survey to reach agreement on definitions and diagnostic criteria. For each enteropathy, members of the group were first asked to provide their set of diagnostic criteria and qualitative comments. These were collected and merged into a quantitative Excel spreadsheet, which was sent back to each panellist for the round of voting. Each member had to vote on whether diagnostic items were 'necessary', 'supportive' or 'irrelevant' for the diagnosis of a specific enteropathy. Criteria voted as necessary were those that had to be fully satisfied to make the diagnosis of a specific enteropathy. Criteria voted as supportive were those suggestive but not sufficient, if taken alone, to make a diagnosis. Irrelevant criteria had no diagnostic role.

A dedicated round of voting was set up for each NCE. Responses to each round of voting were emailed back by each panellist to the statistician of the group in order to maintain an unbiased and anonymous approach. Feedbacks were aggregated by the statistician and shared with the group after each round. A diagnostic item was taken into account either when at least 70% of the panellists voted it as 'necessary for the diagnosis', or 0% voted as 'irrelevant for the diagnosis'. After analysing the votes,

Table 1 List of enteropathies with villous atrophy and negative coeliac serology evaluated by the consensus group and divided into diagnostic categories.

Spectrum of CD presenting with negative serology	NCEs posing problems of differential diagnosis with seronegative forms of CD	NCEs not posing problems of differential diagnosis with seronegative forms of CD	Conditions not to consider as causes of villous atrophy
► Seronegative CD. ► CD associated with IgA deficiency. ► CD associated with CVID. ► Dermatitis herpetiformis.* ► GFD already started. ► Immunosuppressants.	► Autoimmune enteropathy. ► CVID. ► Tropical sprue. ► Giardiasis. ► Indolent $CD4^+$ T cell lymphoma. ► Idiopathic villous atrophy.	► Type 1 EATL. ► Type 2 EATL. ► Crohn's disease. ► HIV enteropathy. ► Iatrogenic enteropathies.† ► Eosinophilic enteritis.	► Peptic duodenitis. ► NSAIDs enteropathy. ► *Helicobacter pylori* infection.

Threshold for agreement was set at ≥70% of voting panellists.
*Patients affected by dermatitis herpetiformis without any specific circulating antibodies have also been identified.[80]
†Iatrogenic causes include drug-induced enteropathy (angiotensin II receptor blockers particularly olmesartan, azathioprine, micophenolate mophetile, methotrexate and chemotherapy), transplanted small intestine, radiotherapy and graft-versus-host disease.
CD, coeliac disease; CVID, common variable immunodeficiency; EATL, enteropathy associated T-cell lymphoma; GFD, gluten-free diet; NCEs, non-coeliac enteropathies; NSAIDs, non-steroidal anti-inflammatory drugs.

a description of the proposed diagnostic criteria was drafted by two of the authors (AS and FB) and sent to the other group members to obtain their final approval. Diagnostic items not meeting an agreement after the first round of voting remained unsolved.

Third phase: nomenclature and diagnostic criteria for CD presenting with negative coeliac serology

Although it has long been known that CD can present with negative serology, the term seronegative CD has been adopted, over the years, to refer to different and heterogeneous clinical scenarios.[23–25] This has generated confusion on whether the term seronegative CD defines a single clinical entity or a clinical spectrum of different conditions sharing a common clinical and pathogenetic background.[26] Therefore, a first round of voting was conducted to assess the existence of different forms of seronegative CD. Based on the results of this first round, a second round of voting was conducted to define the diagnostic criteria for the conditions identified in the first round. We adopted the same methodological approach used for the definitions and diagnostic criteria of NCEs in phase 2, meaning that diagnostic items were considered either when 70% of panellists voted a specific criterium as 'necessary for the diagnosis', or 0% voted as 'irrelevant for the diagnosis'.

RESULTS

Table 1 shows the list of aetiologies contemplated in this work. Chronic conditions to consider in the differential diagnosis of enteropathies with VA and negative coeliac serology include the different forms of CD presenting with negative serology, NCEs posing problems of differential diagnosis with seronegative CD (group I) and NCEs not posing problems of differential diagnosis with CD (group II). Conditions with insufficient evidence for causing VA were also identified (group III). Online supplemental table 1 shows the list of enteropathies for which the established threshold for agreement was not reached.[27–34] For these conditions, a diagnostic category (as per table 1) could not be assigned.

Diagnostic criteria for non-coeliac enteropathies posing problems of differential diagnosis with seronegative CD

These enteropathies are characterised by a variable degree of duodenal VA unresponsive to a GFD, negative coeliac serology and malabsorption of different severities. For some of these enteropathies, the availability of specific biomarkers may facilitate the differentiation from seronegative CD. This group includes autoimmune enteropathy, enteropathy associated with common variable immunodeficiency, tropical sprue, giardiasis, CD4 + indolent T cell lymphoma and idiopathic VA. Drug-induced enteropathies were initially considered for this section. However, the consensus of the group was that most drug-induced enteropathies can be easily identifiable, and for this reason, this category is discussed under the section 'non-coeliac enteropathies not posing problems of differential diagnosis with seronegative coeliac disease'.

Autoimmune enteropathy

Autoimmune enteropathy (AE) is a very rare enteropathy described first in children and then in adults.[35–40] Based on the votes of our consensus, the following criteria must be satisfied for the diagnosis of autoimmune enteropathy:

1. Severe malabsorption symptoms (chronic diarrhoea, weight loss, nutritional deficiencies and electrolyte imbalance) unresponsive to any dietary restriction.[35 36]
2. Frank VA unresponsive to any dietary restriction.[35 36]
3. IgA/IgG positive enterocyte antibodies (indirect immunofluorescence on human/monkey jejunum).
4. Negative coeliac serology.
5. Exclusion of other causes of VA.

The following criteria were considered supportive for the diagnosis:

1. History of associated autoimmune conditions.
2. Clinical response to immunosuppressive treatments.
3. Deep crypt lymphocytosis and/or plasma cells infiltration, neutrophilic cryptitis±crypt microabscesses and lack/decrease of Paneth cells on duodenal histology.
4. Positive serum anti-AIE 75KD antibodies (ELISA) or non-organ specific autoantibodies.

HLA typing is irrelevant for the diagnosis of autoimmune enteropathy. Finally, no consensus was found for the following items: absence of severe immunodeficiencies, diagnostic role of serum antigoblet cells antibodies, involvement of other sites of the GI tract and some duodenal histopathological features. These histopathological aspects, for which also the current literature provides very discordant data, include intraepithelial lymphocytes count, crypt hyperplasia and crypt apoptotic bodies, lack of gamma-delta T cells and depletion of goblet cells.[37 38 41–45]

Enteropathy associated with common variable immune-deficiency

Common variable immune-deficiency (CVID) is one of the most common forms of primary immune-deficiencies, and the GI tract is frequently involved in these patients.[46 47] Although it has been long recognised that CVID can be associated with VA,[48] the prevalence of frank VA in CVID and its causes remain poorly understood. Although giardiasis and other GI infections are major causes for CVID enteropathy, intestinal lesions are heterogeneous and can also occur in the absence of any apparent infection. Our consensus focused on these non-infectious forms of VA. The possible association between CVID and CD was also discussed.

The following criteria were considered necessary for the diagnosis of enteropathy associated to CVID:

1. Presence of GI symptoms regardless from their severity (from sporadic diarrhoea to a frank malabsorption syndrome).
2. Diagnosis of primary CVID according to European and American societies for immunodeficiency.[49]
3. VA.
4. Exclusion of other causes of VA, including *Giardia lamblia* and other GI infections.

The following criteria were considered supportive, although not sufficient, for the diagnosis of CVID enteropathy:

1. Duodenal intraepithelial lymphocytosis.
2. Increased inflammation of the *lamina propria*.
3. Crypt apoptotic bodies.
4. Graft versus host disease-like lesions.

HLA typing was considered irrelevant for the diagnosis of enteropathy associated to CVID. A consensus was not reached on the diagnostic relevance of the following clinical and histopathological features, which reflects the uncertainty reported in the literature. These include association with microscopic colitis and IBD, association with lymphocytic gastritis and atrophic gastritis, mucosal depletion of plasma cells, follicular/nodular lymphoid hyperplasia, Crohn's-like lesions/granulomas, eosinophilic infiltrate and cryptic abscesses/neutrophilic infiltrate.[50–59] The authors of this consensus agreed to evaluate these features on a case-by-case basis.

The clinical dilemma of CD associated with common variable immune deficiency

Although the coexistence of CVID and CD in patients with VA was historically reported in the literature,[50–52] this appears to be a very rare event. According to our votes, the major criterion confirming the diagnosis of CD in CVID is the histological and clinical response to a GFD.

Criteria excluding the diagnosis of CD in CVID include:

1. Lack of response to a gluten-free diet.
2. Negative HLA-DQ2/DQ8 typing.

The following criteria were considered unable to confirm or exclude the diagnosis of CD in CVID: extension of intestinal lesions to different parts of the small bowel, crypt hyperplasia, intraepithelial lymphocytes (IELs) increase, increased inflammation of the *lamina propria*, crypt apoptotic bodies, HLA-DQ2 and/or DQ8 positive. Finally, the role of mucosal TTG deposits in CVID has not been substantiated so far.

Tropical sprue

Tropical sprue is a chronic condition, which has been known for many years.[60] It should be suspected in patients presenting with malabsorption syndrome, a certain degree of VA (most often mild) with intraepithelial lymphocytosis and a medical history of living in or travelling to tropical countries (particularly regions of South Asia, Southeast Asia, Africa and South America falling within the Tropics) for at least 2 months and in poor hygienic conditions. Exclusion of other causes of VA is mandatory as well as prompt clinical and histological response to a course of antibiotics. Biochemical abnormalities such as low folate responding to supplements, low vitamin B12 with possible megaloblastic anaemia and deficiency of fat-soluble vitamins can be supportive elements to the diagnosis. HLA typing has no diagnostic role.

No consensus was found on whether in tropical sprue ileal involvement is more pronounced than duodenal involvement and whether this can be used as a diagnostic criterion.

Giardiasis

Giardiasis is an infestation due to *Giardia lamblia* (also known as Giardia *duodenalis* or *intestinalis*), a flagellated intestinal protozoan.[61] Clinical picture is highly variable ranging from a severe malabsorption syndrome to asymptomatic. In the clinical setting of VA with negative coeliac antibodies and a clinical picture with malabsorption, giardiasis must be considered and thoroughly investigated. Nevertheless, clinical suspicion of giardiasis can be prompted by less severe clinical scenarios such as IBS-like symptoms. In order to confirm the diagnosis, at least one of these tests is necessary:

- Positive Giardia specific stool antigens.
- Identification of trophozoites on formalin-fixed paraffin-embedded H&E stained duodenal specimens and/or on the duodenal aspirate.
- Direct identification of cysts/trophozoites in fresh faeces.
- Specific Giardia PCR.

Clinical response to a course of antibiotics further confirms the diagnosis

HLA typing does not have any relevance for the diagnosis, but it might be helpful in patients with borderline tTA to exclude CD. Although it is well known that giardiasis can be found in patients affected by CVID, IgA deficiency and CD, this panel of authors did not reach a consensus on the necessity of ruling out these conditions in patients with VA due to *Giardia lamblia*. So, the decision on whether or not to investigate other causes of VA is to be taken on a case-by-case basis.

Small bowel indolent CD4$^+$ T-cell lymphoma

Small bowel indolent CD4 +T-cell lymphoma is a rare non-Hodgkin's lymphoma primarily involving the small bowel.[62] This type of lymphoma is quite often mislabelled as type 2 refractory CD given the persistence of VA and malabsorption despite a GFD and the clonal phenotype of intraepithelial lymphocytes.[62] Clinical picture prompting the suspicion of indolent CD4$^+$ T-cell lymphoma is characterised by long-lasting malabsorption syndrome with malnutrition unresponsive to a GFD. Duodenal VA is mandatory for diagnosis, after excluding all the other causes of VA.

Diagnosis is based on immunohistochemistry showing diffuse infiltration of the epithelium and/or expansion of the *lamina propria* by small/medium CD3$^+$CD4$^+$ T cells and presence of monoclonal rearrangement for beta-TCR and/or gamma-TCR on duodenal biopsies. Increased CD3$^+$CD4$^+$ intraepithelial/*lamina propria* lymphocytes on flow cytometry are also diagnostic.

No consensus was found on the necessity of performing a bone marrow biopsy, further endoscopic/radiological exams to assess involvements of other GI tracts, or molecular diagnostics for STAT3-JAK2 fusions.[63] Therefore, the decision whether to perform these investigations should be decided on a case-by-case basis and based on local availability.

Idiopathic villous atrophy

IVA is a very recently recognised and still poorly defined chronic clinical entity characterised by frank VA unresponsive to a GFD, negative coeliac serology and in which all the known causes of VA have been thoroughly excluded.[12 17]

Duodenal intraepithelial lymphocytosis was voted as supportive for the diagnosis of IVA. HLA typing is helpful only to rule out CD, when negative for coeliac haplotypes. Other aspects of IVA still need to be elucidated, as no consensus was found on the diagnostic relevance of the following clinical and histopathological elements: degree of malabsorption syndrome at presentation, family history for CD, medical history of autoimmunity including dermatitis herpetiformis, possible involvement of other portions of the gastrointestinal tract, role of mucosal deposits of IgA TTG and timing for histological reassessment of duodenal histology.

A classification of different forms of IVA was recently proposed.[17] This included type 1 IVA characterised by transient VA resolving spontaneously within 6–12 months; type 2 IVA, characterised by persistent non-clonal VA with excellent long-term prognosis; finally, type 3 IVA is characterised by persistent VA, the finding of aberrant T cell populations or persistent gamma-TCR mono clonality, or a medical history of lymphoproliferative disorders. However, in the present work, a consensus was reached only for type 1 IVA, a chronic enteropathy that should be differentiated from acute and self-limiting forms of enteropathy with variable degree of villous blunting likely due to acute infective gastroenteritis.[64 65]

Future research directions may consider the possibility of evaluating the clinical applicability of HLA-gluten tetramers and specific biopsy anti-TTG2 deposit for the differential diagnosis between IVA and forms of refractory CD.[25 66]

Non-coeliac enteropathies not posing problems of differential diagnosis with seronegative CD

These enteropathies are characterised by a variable degree of duodenal VA and a malabsorption syndrome of varying severity. Their diagnosis is usually prompted by a suggestive personal and pharmacological history and typical clinical or histopathological clues, which increase the pretest likelihood of the diagnosis. Particular attention should be deserved to medication-induced enteropathies which, despite being the second most common aetiology for VA with negative coeliac antibodies in adults, can still be overlooked.[2 9 67] Patients with a medication-induced enteropathy seen in a coeliac centre have been frequently mislabelled as having seronegative CD unresponsive to a GFD.[2 7 9 67 68] While awareness on the issue of medication induced enteropathy has been increasing among coeliac experts, particularly since the discovery of olmesartan-associated enteropathy in 2012,[68] there is still a need to improve knowledge for general gastroenterologists and other medical specialists on this topic. Table 2[67–79] shows the major clues guiding the differential diagnosis for each enteropathy included in this group.

Finally, a list of enteropathies for which the established threshold for agreement was not reached is provided in the supplementary section (online supplemental table 1).[27–34] So, these conditions could not be assigned to any of the diagnostic categories contemplated in table 1.

The clinical spectrum of CD presenting with negative serology

In the absence of a shared consensus, controversies have surrounded the use of the term seronegative CD, which has been adopted to refer to a wide variety of clinical and histopathological conditions. Uncertainties still exist on whether this term should refer to a single clinical entity, or a spectrum of different forms of CD. In this regard, whether to consider positive coeliac IgG based serology in the context of IgA deficiency as seronegative CD, or instead as a conventional form of CD associated with IgA deficiency has been hugely debated.[1–3 9 12–15 23–26 67]

The present consensus agreed on the existence of different forms of CD presenting with negative serology. Primarily, seronegative CD, which should be considered separately from CD, associated with selective IgA deficiency. Second, CD with negative serology has been reported in up to 30% of patients with biopsy-proven dermatitis herpetiformis[4 26 80] and rarely also in patients affected by CVID (discussed in the section on CVID previously).[50–52] Finally, there are two heterogeneous groups of patients, which can present with negative coeliac serology at time of serological testing, which the present consensus agreed to consider as conventional forms of CD rather than seronegative. They include: (1) patients presenting with negative serology if they already are on a GFD or immunosuppressive therapies at time of serological testing. These patients restore their positive serological response if they are challenged with gluten or if immunosuppressants are withdrawn[9 26]; (2) patients with VA but discrepancies between tTA and EmA results (ie, borderline/low titre positive tTA with negative EmA or vice versa). These last two groups

Table 2 Clinical clues guiding the diagnosis of enteropathies not posing problems of differential diagnosis with seronegative coeliac disease

Type of enteropathy	Clinical and laboratory features	Histological/molecular features on duodenal biopsy	Diagnostic tests
EATL (type 1 and type 2)[68]	Severe malabsorption, abdominal pain, fever, bleeding, obstruction and/or perforation; type 1 most commonly associated to CD, unlike type 2.	Aberrant T cells population on IHC or flow cytometry; TCR monoclonality on PCR.	Inflammatory markers, abdomen CT/PET scan, capsule endoscopy, bone marrow aspirate and haematological consultation.
Drug induced*[67 69–73]	Severe malabsorption, often with abrupt onset and suggestive pharmacological history.	VA undistinguishable from CD, increased eosinophilic count, preserved neuroendocrine cells.	Duodenal biopsy and drug withdrawal.
Chemotherapy[74]	Severe malabsorption and suggestive oncological history.	VA undistinguishable from CD, *lamina propria* fibrosis.	Duodenal biopsy.
Radiotherapy[75]	Severe malabsorption and history of radiotherapy.	*Lamina propria* fibrosis.	Duodenal biopsy.
GVHD[76]	Severe malabsorption and history of bone marrow transplantation.	Crypt cell necrosis and loss of epithelium.	Duodenal biopsy.
HIV enteropathy[77]	Known history of AIDS, presence of opportunistic infections.	Decrease CD4+ T lymphocytes and increase in CD8+ T lymphocytes.	HIV test.
Eosinophilic gastroenteritis[78]	History of atopy and allergies, after exclusion of parasites.	Massive eosinophilic infiltration on duodenal biopsy.	Duodenal biopsy and peripheral hyper-eosinophilia.
Crohn's disease[79]	Bloody diarrhoea, abdominal pain, fever, elevated CRP, ESR and faecal calprotectin.	Aftous ulcers and granulomas.	Colonoscopy+biopsy, duodenal biopsy, entero-MRI.

*This includes angiotensin II receptor blockers particularly olmesartan, azathioprine, micophenolate mophetile and methotrexate.
CD, coeliac disease; CRP, C reactive protein; -EATL, enteropathy associated T-cell lymphoma; ESR, erythro-sedimentation rate; GVHD, graft-versus-host disease; IHC, immunohistochemistry; PCR, polymerase chain reaction; TCR, T-cell receptor; VA, villous atrophy.

of patients are very commonly encountered scenarios in clinical practice and frequently causes of diagnostic mistakes.[9]

Seronegative CD and CD associated with IgA deficiency

The following criteria must be satisfied to make a diagnosis of both seronegative CD and CD associated to IgA deficiency:

1. VA, crypt hyperplasia and an increased intraepithelial lymphocytes count, on correctly oriented duodenal specimens, recovering on a GFD.
2. Necessity of performing diagnostic investigations before starting the patient on a GFD or immunosuppressive therapy as they may lead to false negative serology.
3. Exclusion of all the other causes of VA, which means to assess normal levels of immunoglobulins, negative enterocyte antibodies, negative stool parasites/HIV testing/tuberculosis, absence of iatrogenic causes for VA and no history of travelling to/residing in the tropics.
4. Evidence of HLA typing showing specific coeliac haplotypes, that is, DQ2.5 (DQA1*0501, DQB1*0201), HLA-DQ8 (DQA1*03, DQB1*0302), HLA-DQ2.2 (DQA1*0201, DQB1*0202) or HLA-DQ7.5 (DQA1*05, DQB1*0301).

In equivocal cases, reintroduction of gluten in the diet can be necessary to induce reoccurrence of intestinal lesions and symptoms in order to confirm the diagnosis. Although dosage and duration of diagnostic gluten challenge have not been standardised yet, at least 10 g of gluten/day for 6–8 weeks have been suggested.[12 81] HLA typing should always be performed in equivocal cases of VA with negative coeliac serology, as it still has a role in discriminating seronegative CD from NCEs. Although, in Caucasian populations, up to 30%–40% of people carry the HLA-DQ2 or DQ8 haplotypes, a negative HLA typing excludes seronegative CD.[1–5 7]

A clinical picture with severe malabsorption, associated autoimmune disorders, family history of CD and biopsy-proven dermatitis herpetiformis can be supportive of the diagnosis, but they are not sufficient to make a diagnosis of seronegative CD in the absence of the necessary diagnostic criteria. Similarly, when available, small-bowel mucosal transglutaminase 2-specific IgA deposits can support the diagnosis of seronegative CD and may be helpful to discriminate from other NCEs in patients with normal serum IgA levels.[25]

Finally, in a patient with negative IgA coeliac antibodies who fulfil these diagnostic criteria (ie, flat duodenal mucosa recovering on a GFD and coeliac HLA), the finding of selective IgA deficiency (total serum IgA level <5–7 mg/dL) ± positive IgG coeliac serology will allow differentiation between seronegative CD and CD associated to IgA deficiency. It has been shown that in patients with IgA deficiency sensitivity of IgG tTA and IgG deamidated gliadin peptides antibodies outperform IgG EMA (91% vs 82% vs 76%).[82]

Conditions not clearly associated with VA

There are several conditions listed in the literature as possible causes of VA. For some of these conditions, the evidence in favour of their causal role for VA is poor and almost exclusively anecdotal. Their relevance in clinical practice is unknown. The present consensus aimed to identify whether these conditions had to be taken into account in clinical practice. Based on the clinical experience of each panellist, this consensus concluded that non-steroidal anti-inflammatory drugs use, *H. pylori* infection and peptic duodenitis do not cause VA. Therefore, these aetiologies should not be considered in the differential diagnosis of VA with negative coeliac antibodies.

Conditions for which a consensus was not found

The panel of experts failed to find a consensus for the assignment to a specific diagnostic category for the enteropathies listed in online supplemental table 1. A discussion on the diagnostic criteria for these conditions is not provided, but some relevant elements for the diagnosis are provided in online supplemental table 1. Nevertheless, the authors agreed on considering these conditions in the differential diagnosis of VA with negative coeliac antibodies on a case-by-case basis.

DISCUSSION

Chronic enteropathies characterised by VA and negative coeliac serology represent a group of heterogeneous conditions, often with a poor prognosis, and for which diagnostic challenges are common.[1–3 7–17] Some of these enteropathies such as seronegative CD[26] and autoimmune enteropathy have been known for years,[35–40] whereas others such as enteropathy due to olmesartan and other angiotensin II receptor blockers were discovered more recently.[68 70] Difficulties in the differential diagnosis of these enteropathies lie in their rarity and the lack of unanimous standard diagnostic criteria. By recruiting panellists with decennial international expertise in the field, who worked in accordance with a rigorous methodological approach, the present paper provided the first consensus on the definitions and diagnostic criteria of enteropathies characterised by VA and negative coeliac serology. This paper also identified the conditions not to be considered in the differential diagnosis of VA with negative coeliac serology. Finally, we have proposed a terminology for the heterogeneous clinical spectrum of CD presenting with negative serology, and we have agreed on considering CD associated with IgA deficiency and seronegative CD as two separate entities. We would like to point out that, while CD associated with selective IgA deficiency may not technically be considered as 'seronegative' CD, the present consensus agreed to include it in the spectrum of CD presenting with negative serology given the clinical relevance of this condition and to provide more complete clinical guidance.

A Delphi process with a minimum threshold of 70% for agreement[21 22] was conducted first to identify conditions to consider in the differential diagnosis of VA with negative coeliac serology, and then to propose specific diagnostic criteria. For the voting phases on the diagnostic criteria of each enteropathy, we adopted an agreement threshold of ≥70% for items being 'relevant' and 'supportive' for the diagnosis, and items that received a 0% of voting for being 'irrelevant for the diagnosis' were also taken into account. This procedure was chosen a priori to prioritise a clinical-based approach and guarantee that relevant opinions by a small group of experts on rare disorders were not dispersed. Overall, taking into consideration that very recent consensus statements in gastroenterology were based on a threshold agreement between 70% and 80%[83–86] and that a universally agreed percentage for shared consensus does not exist for the Delphi,[21 22] we believe our results are acceptable.

Despite its novelty, our work has some limitations. First, despite generally high agreement, some clinical and histopathological aspects of these rare enteropathies failed to be precisely defined. This is the case for some histopathological features of autoimmune enteropathy and CVID.[37 38 41–45 50–59] While we certainly acknowledge that our group of experts did not include pathologists and immunologists, our work was primarily focused on clinical gastroenterology practice, and authors involved in this consensus published exhaustive research on the histopathological features of both CVID and autoimmune enteropathy (AE).[37 38 42 44 45 50 52] Therefore, we believe that the outputs and recommendations from our Delphi process reflect a growing

understanding of these rare conditions, and the elements lacking a consensus should be areas considered for future research. Particular emphasis should be dedicated to translational research investigating the pathogenetic and molecular aspects of seronegative enteropathies, which were not discussed in the present consensus, as no papers have specifically addressed this issue so far. Finally, a systematic review of the literature was not performed since no specific diagnostic criteria had been previously established.

We hope that the nomenclature and diagnostic criteria proposed in this paper will bring a methodological uniformity among clinicians caring for patients with seronegative enteropathies and encourage new developments in the clinical management and research perspectives on these disorders.

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