Diagnosis and treatment

Non-celiac villous atrophy: More confusion or a new syndrome?∗

Atrofia vellositaria sin enfermedad celíaca: ¿un nuevo síndrome o más confusión?

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It is not unusual for clinicians, particularly for those working in gastroenterology, to find intestinal villus atrophy (IVA) in duodenal biopsies from patients treated with chronic diarrhoea. In most cases, this finding rules out the existence of coeliac disease (CD)1. CD is an autoimmune disease that mostly develops in genetically predisposed subjects carrying HLA-DQ2/DQ8. To obtain a definitive diagnosis of CD, it is necessary not just to have compatible clinical data, but also to assess other findings, among them: the presence of positive serology, mainly through the detection of IgA or IgG anti-transglutaminase antibodies; a compatible histology, standardised by means of the MARSH Classification2; and a clinical response to a gluten-free diet. The new immunohistochemistry and flow cytometry techniques that make it possible to characterise the predominant lymphocyte subpopulations located in the intestinal lamina propria have not been available for that long. Thanks to these techniques, we have been able to establish how the increase of TCR gamma-delta lymphocytes and the decrease of NK CD3+/CD7- lymphocytes are specifically associated with CD, thus facilitating the differential diagnosis of other diseases. These techniques are not available for every medical centre. In spite of the aforesaid, CD diagnosis is not always easy to obtain, since there is a small group of patients who have IVA and are responsive to a gluten-free diet but whose antibodies are negative, resulting in the creation of the increasingly widespread seronegative CD concept.

Even though CD is the most frequent cause of IVA, there are other less frequent processes that may trigger it (table 1), widening a range of diagnostic possibilities before this histological finding in the context of chronic diarrhoea. To date, there are no studies with a sufficient number of patients to allow us to establish which disorders most frequently trigger these symptoms. In many of these entities, IVA is a constant finding and is part of its diagnostic criteria. However, in others, IVA may be one of multiple histological expressions. This phenomenon, along with the heterogeneity of diseases associated with IVA and the absence of a unified record of those diseases, prevents us from knowing the exact incidence of this nosologic spectre that we have called villous atrophy with absence of coeliac disease.

The recent description of an enteropathy associated with a drug as frequently used as olmesartan has accentuated the interest in systematically establishing an appropriate differential diagnosis allowing us to set up the necessary steps to provide the most adequate treatment for the patient.

In view of all the aforementioned, and considering the diagnostic difficulty and the low incidence of some of these disorders, we have made a systematic review of medical literature to determine the main diagnostic and therapeutic characteristics of the most important entities presenting IVA, serology for negative CD, and lack of response to a gluten-free diet. We have excluded from the review some of the most frequent ones such as intestinal lymphoma, bacterial overgrowth or giardiasis, so as to focus on the less frequent conditions that, consequently, spark more controversy in terms of diagnosis and treatment.

Autoimmune enteropathy

Autoimmune enteropathy (AE) consists of severe and prolonged diarrhoea, with clinical and analytical criteria of malabsorption and substantial weight loss due to immunologically-mediated intestinal injury. AE is typically seen in children and young adults. The description of this condition is relatively new, since the first documented case described in children was in 1982, in adults in 1997, and it was not until 2007 when the diagnostic criteria

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Table 1
Most frequent causes of villus atrophy without coeliac disease.

<table>
<thead>
<tr>
<th>Drug-induced enteropathy</th>
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<tbody>
<tr>
<td>Autoimmune enteropathy</td>
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<tr>
<td>Tropical sprue</td>
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<tr>
<td>Giardiasis</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
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<tr>
<td>Eosinophilic gastroenteritis</td>
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<tr>
<td>Inflammatory bowel disease (Crohn's disease)</td>
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<td>Collagenous sprue</td>
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<tr>
<td>Bacterial overgrowth</td>
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<td>HIV enteropathy</td>
</tr>
<tr>
<td>Acute post gastroenteritis atrophy</td>
</tr>
<tr>
<td>Intestinal lymphoma</td>
</tr>
<tr>
<td>Peptic duodenitis</td>
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</tbody>
</table>

HIV: Human Immunodeficiency Virus.

proposed by experts from the Mayo Clinic, which we use nowadays, were established.10 Cases documented in medical literature are few, which makes it more difficult to set forth an epidemiological approach, although some authors indicate that it might account for 25% to 30% of the cases with unexplained chronic diarrhoea.11 AE is most frequent among children between one month and 5 years old, and, unlike other autoimmune diseases, its incidence seems to be higher among males.

In terms of its physiopathology, the most widely approved theory indicates that an enterocyte antigenic interaction with a probable genetic susceptibility prompts them to express, on their surface, HLA type II molecules, which naturally appear only in antigenic cells, thus activating CD4 and CD8 T cells. They would generate direct damage on the intestinal mucosa, eliminating goblet cells and enterocytes. It is within this context that both IgG anti-enterocyte and anti-goblet cell autoantibodies appear, and they can be identified in plasma by means of immunofluorescence methods. Although it might be appealing to identify them in a diagnosis, they are estimated to be present in just 50% of AE cases. Moreover, these autoantibodies have also been identified in other enteropathies such as allergy to cow-milk proteins or inflammatory bowel disease, which reduces its specificity. It is currently not altogether clear what the true role played by autoantibodies in AE is, despite the fact that they might be more of an immune reaction to enteric damage than its causative agent.12

The extra intestinal condition in AE might affect organs such as the kidneys, the liver or the lungs, as well as systems such as the haematopoietic, musculoskeletal and endocrine. In this way, cases of hypothyroidism, nephrotic and nephritic syndromes, haemolytic anaemia, interstitial pneumopathy, periporal fibrosis, and atopic dermatitis have been described, and it has been associated with other diseases or autoimmune epiphphenomena such as autoimmune pancreatitis, autoimmune hepatitis, rheumatoid arthritis and vitiligo, among others.13

AE is part of genetic syndromes that tend to develop during childhood, like IPEX syndrome (I: immunodysregulation; P: polyendocrinopathy; E: enteropathy; X: X-linked), caused by the mutation of FOXP3 gene, or APECED syndrome (polyglandular syndrome type 1), caused by the mutation of the AIRE gene.14 These syndromes, potentially lethal and only diagnosed in children, demonstrate the importance of genetics in the pathogenesis of AE.

Although histological alterations will be found more frequently in the duodenum, with total or partial atrophy of intestinal villi and lymphoplasmocytic infiltration in the lamina propria, there may be less specific histological findings in other organs such as the stomach (atrophic gastritis, absence of oxyntic cells and intestinal metaplasia) or the colon (lymphocytic infiltrate).10

To establish a diagnosis, we follow the criteria proposed by experts from the Mayo Clinic,10 which includes 2 necessary parameters, such as the presence of chronic diarrhoea and the exclusion of other causes of enteropathy, particularly CD. The presence of autoantibodies is indicative but not necessary for diagnosis since they will only be present in 50% of patients with AE. In Table 2, a differential diagnosis between EA and CD is established.

Since the diagnosis of AE tends to take longer to establish, in general we see very undernourished patients; therefore, the first and most important therapeutic step that must be taken must be to provide adequate nutrition by means of enteral feeding and even parenteral feeding if the patient does not tolerate the former. The other important element in this treatment is glucocorticosteroids, with the possibility of administering methylprednisolone in 1 mg/kg/day or similar doses. Due to their systemic side effects, it has been suggested that budesonide 9 mg/day might be used, in 3 doses of 3 mg by mouth, mainly with an ileocolic effect; considering that the condition tends to affect the digestive tract in its entirety, some authors suggest that in order for the drug to have an effect on the entire small intestine, the first 3 mg dose of the day should be administered in the morning with food and chewed before swallowing, the second 3 mg dose should be administered at noon also with food but without the need to chew, and finally, the last 3 mg dose should be administered at night, with the entire capsule.10 In patients refractory to reducing or discontinuing the glucocorticosteroid treatment, immunosuppressant drugs can be used, but due to the lack of experience in their use for treating this disease, it is not possible to recommend which drug and dose to use, since each clinician should make that decision on a case-by-case basis, based on the side-effect pattern of these drugs, and on his or her own experience with each one of them.

Collagenous sprue

Collagenous sprue (CS) is a chronic-type diarrhoea caused by food malabsorption in patients with IVA, and a subepithelial collagen band detected by means of the duodenum biopsy. Although this condition was first described in 1947,15 it was not until 1970 that the first histological diagnosis was established.16 However, and despite the extended use of the term, we did not find more than 120 reported cases in medical literature after reviewing it extensively. This might be due to the debate, persisting to date, as to whether CS is an entity in itself, or whether it is part of the CD spectrum. Those defending the first option state that they are 2 conditions where treatment, evolution and histology are different; however, in the face of an absence of commonly accepted diagnosed criteria and considering that up to 30% of CD cases present a small collagen band (less than 5 μm), it might lead us to believe that it is part of the refractory CD range. Although it has been suggested that it might be a paraneoplastic manifestation of tumours from other levels, the immunomediated hypothesis seems to be the most probable one, since up to 70% of CS cases present associated autoimmune diseases and response to glucocorticosteroids in these patients has been demonstrated. CS is more frequent in middle-aged and elderly females, and very unusual in children.19

One of the main characteristics of CS is the presence of a patchy area in the digestive tract, even affecting the colon and causing collagenous colitis. The histological study of the duodenum shows total or subtotal intestinal villus atrophy, normally presenting crypt hypoplasia, establishing a difference between CS and CD. Nonetheless, the histological finding that defines CS is the presence of a fibrous collagen band with thickness of more than 5 μm, although in most patients, this may exceed 15 μm.20

Treatment is very controversial, since we have neither clinical trials nor long-term controlled studies. However, considering that there are documented cases of CS patients who have responded to a gluten-free diet, it seems reasonable to start treatment by suspending gluten. If there was no clinical response to a gluten-free
diet, corticosteroids such as methylprednisolone administered at an initial dose of 1 mg/kg/day and then at a descending rate may resolve up to 80% of CS cases. There is no consensus on how to approach cases that are either dependant or refractory to glucocorticosteroids, but for those where the clinical and analytical impact is significant, the recommendation may be to undergo an intestinal transplant.

**Common variable immunodeficiency**

Common variable immunodeficiency (CVID) is a heterogeneous group of immunological disorders whose common denominator is the inability of B lymphocytes to adequately synthesize immunoglobulins. Clinical manifestations are very diverse, including a marked propensity to develop recurrent respiratory infections, gastrointestinal disorders, high incidence of autoimmune diseases, and a higher risk to develop lymphoreticular neoplasias. This type of immunodeficiency is the most frequent in Spain, after the selective deficit of IgA. It is generally diagnosed during the second and third decades of life, and there is no distribution difference according to gender.

Characteristic laboratory findings shall be a marked decrease in immunoglobulin levels, and a normal, or slightly lower, count of T and B lymphocytes.

The most common symptom in the digestive tract is diarrhoea, present in up to 60% of patients, with malabsorption data in 20%–30% of cases. A frequent complication and, in itself, a cause of IVA is giardiasis. In patients with CVID, infection by Giardia lamblia tends to cause damage and extensive atrophy of the intestinal mucosa. Besides the infection by Giardia lamblia, it is not unusual, however, to find other parasite infections such as those caused by Cryptosporidium and Strongyloides, which also lead to a similar clinical condition.

From a histological viewpoint, CVID is characterised by presenting an IVA pattern in the duodenum, with absence of plasma cells in the lamina propria, which confirms the diagnosis and makes it possible to establish differences with CD (Table 2). Another characteristic anatopathological finding is nodular lymphoid hyperplasia, which will also be present both in the stomach and colon, and that is not pathognomonic of this disease, since it can be frequently found in healthy adults. Cases of colitis histologically similar to Crohn's disease or ulcerative colitis have been described, along with others that are even indistinguishable regarding findings described for graft-versus-host disease, with marked apoptosis and lymphocytosis in the intestinal crypts. The main difference between these entities is the absence of plasma cells that are characteristic of CVID.

It is important to know that, besides the intestinal condition that characterises CVID, these patients have a higher propensity to suffer oncological diseases such as intestinal lymphoma or gastric and colic adenocarcinoma.

The treatment of choice should be intravenous infusion of gamma globulins. Nonetheless, when it comes to establishing a definitive diagnosis and treatment, it should be borne in mind that CD can also be associated with CVID, since the villous atrophy present in these patients may, at times, be due to the presence of CD and, thus, should respond to a gluten-free diet.

**Table 2**

<table>
<thead>
<tr>
<th>Differential diagnosis for rare causes of intestinal villus atrophy.</th>
<th>CD</th>
<th>AE</th>
<th>CS</th>
<th>CVID</th>
<th>DE</th>
<th>EG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Any</td>
<td>Children and young adults</td>
<td>Adults</td>
<td>Second-third decade</td>
<td>Adults</td>
<td>Third-fourth decade</td>
</tr>
<tr>
<td><strong>Association with autoimmune diseases</strong></td>
<td>Possible (30%)</td>
<td>Very frequent</td>
<td>Frequent</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Response to gluten-free diet</strong></td>
<td>Good</td>
<td>Null</td>
<td>Null</td>
<td>Null</td>
<td>Null</td>
<td></td>
</tr>
<tr>
<td><strong>Duodenal biopsy</strong></td>
<td>Villus atrophy and crypt hyperplasia</td>
<td>Villus atrophy and crypt hyperplasia</td>
<td>Villus atrophy and absence of plasma cells</td>
<td>Villus atrophy</td>
<td>Villus atrophy</td>
<td></td>
</tr>
<tr>
<td><strong>T gamma-delta cells</strong></td>
<td>Increased</td>
<td>Normal</td>
<td>Normal or increased</td>
<td>Normal</td>
<td>Normal or increased</td>
<td></td>
</tr>
<tr>
<td><strong>Serology/immunoglobulins</strong></td>
<td>Anti-transglutaminase and antiendomysial antibodies</td>
<td>Anti-enterocyte and anti-goblet cell antibodies (50%)</td>
<td>They might present antiendomysial antibodies</td>
<td>Decrease of every Ig</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastric and colic microscopic condition</strong></td>
<td>In frequent</td>
<td>Possible (80% respond)</td>
<td>Possible (80% respond)</td>
<td>Possible</td>
<td>Possible</td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Response to steroids/immunosuppressants</strong></td>
<td>Good with diet</td>
<td>Bad</td>
<td>Variable</td>
<td>Good</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**AE:** Autoimmune Enteropathy; **CD:** Coeliac Disease; **DE:** Drug-induced Enteropathy; **CS:** Collagenous Sprue; **EG:** Eosinophilic Gastroenteritis; **CVID:** Common Variable Immunodeficiency; Ig: Immunoglobulin.
From a histological viewpoint, it might be indistinguishable from CD, although it typically starts with an substantial clinical and laboratory impact, presenting total or subtotal villus atrophy and an increase of intraepithelial lymphocytes in duodenum biopsies. Other findings, however, such as those overlapping with CS, or an isolated increase of intraepithelial lymphocytes might be the only anatomopathological findings for this entity.

Clinically, it is characterised by severe diarrhoea, with intestinal malabsorption that does not respond to a gluten-free diet and that disappears between 1-2 weeks after the drug was suspended.

To establish its diagnosis, it is not necessary to obtain a histological confirmation of healing, which is achieved after many months, and it could be enough just to demonstrate a clinical response, obtaining symptom resolution once the drug has been suspended (fig. 1).

**Eosinophilic gastroenteritis**

Eosinophilic gastroenteritis (EG) is a rare disease that can affect the entire digestive tract, from the oesophagus to the rectum, though the organ that is most frequently involved is the stomach, followed by the proximal tracts of the small intestine. It is characterised by the presence of a large number of eosinophils in the gastric or intestinal mucosa and the peripheral blood, with no other disease accounting for it. It is generally diagnosed during the third and fourth decades of life, with a slight preference for the male gender. However, its epidemiological approach is very complex due to the scarce casuistry published to date, with less than 300 cases, and its longest series consisting of 31 patients.

The most-widely accepted physiopathological theory is the one stating that EG could be the result of a hypersensitivity reaction. The presence of eosinophilia and elevated IgE levels in many patients supports this theory. Besides, it has also been proved that up to 50% of EG patients had a history of asthma, eczema, or another clinical allergy. Many inflammatory molecules have been described, among them, interleukin 3, interleukin 5, and eotaxin, which may perpetuate the eosinophilic inflammatory infiltration that these patients have in their digestive tract.

Symptoms are quite varied and they differ regarding condition stage and its predominant location. In most patients, symptoms are present for years and are quite varied, ranging from dysphagia, if the condition is predominantly oesophagus, diarrhoea, with loss of fat (steatorrhea) and proteins, and symptoms of severe intestinal pseudo-obstruction in those patients with a mostly enteric condition. This disease may also present chronic abdominal pain, growth retardation or amenorrhea in adolescent patients. Cases with subserosa damage may start by presenting ascites with elevated eosinophils in peritoneal fluid.

To establish a diagnosis, patients must have gastrointestinal symptoms and an eosinophil infiltration in the digestive tract, but other causes of eosinophilia, such as parasitic infections or hyper-eosinophilic syndrome, should be discounted. It is important to know that eosinophilia is present in 20%-80% of patients; therefore, its absence does not exclude the diagnosis and, hence, it is not part of the necessary criteria. An increase of eosinophils in the duodenum lamina propria will be histologically demonstrated (more than 50 per field), with crypts hyperplasia and atrophy of intestinal villus. Other typical findings will be the presence of fibrosis and an eosinophil cationic protein deposit.

Glucocorticosteroids are the initial treatment of choice for these patients, with an approximate response rate of 90%. However, the absence of clinical trials and long-term controlled studies prevents making recommendations on treatment duration and maintenance dose. The use of other drugs, such as cromolyn sodium or montelukast (stabilizer of mast cells membrane), has been suggested, with no clear usage indications established to date. Since EG has always been associated with the presence of food allergies, it seems reasonable to do skin tests using common allergens and, in case of positive results, remove them from the patient’s diet.

Summing up, IVA is frequently seen in patients with chronic diarrhoea, and is not always associated with CD, particularly in those patients with negative antibodies who do not respond to a gluten-free diet. Obtaining a complete medical history must be insisted upon, listing all of the drugs that the patient is taking, even those he has been taking for years. The presence of autoimmune diseases may be indicative of enteropathies, such as CS or AE. A medical
Conflict of interest

The authors declare that there are no conflicts of interest.

References


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