Pernicious Anemia

Pernicious anemia (PA) is a megaloblastic anemia caused by a deficiency of vitamin B_{12} resulting from malabsorption. Impaired absorption is the result of defective intrinsic factor (IF) secretion. This is due to atrophy of the gastric mucosa caused by autoimmune reactions to gastric parietal cells and their products.

Virtually all patients will have gastric parietal cells antibody targeting antigens in the secretory canaliculi, which are the intracellular channels carrying hydrochloric acid into the gastric lumen and its major target is the α subunit of the proton pump (H^+, K^+, ATPase), an enzyme composed of two transmembrane components, the α and β subunits. In addition, there are at least two types of antibody against intrinsic factor: blocking and binding antibodies; the blocking type reacts with the combining site for vitamin B_{12} on IF and is found in most patients (over 70%), while the binding antibody reacts with other epitopes on IF (whether this is free or complexed to vitamin B_{12}) and is present in some 60% of pateints.

During the course of the digestion of foods containing B_{12}, the B_{12} becomes attached to a substance called intrinsic factor. Intrinsic factor is produced by parietal cells that line the stomach. The B_{12}-intrinsic factor complex then enters the intestine, where the vitamin is absorbed into the bloodstream. In fact, B_{12} can only be absorbed when it is attached to intrinsic factor.

In pernicious anemia, the parietal cells stop producing intrinsic factor. The intestine is then completely unable to absorb B_{12}. So, the vitamin passes out of the body as waste. Although the body has significant amounts of stored B_{12}, this will eventually be used up. At this point, the symptoms of pernicious anemia will develop.
Pernicious anemia occurs in equal numbers in both men and women. Most patients with pernicious anemia are older, usually over 60 years. Occasionally, a child will have an inherited condition that results in defective intrinsic factor.

Causes

Intrinsic factor is produced by specialized cells within the stomach called parietal cells. When these parietal cells shrink in size (atrophy), they produce less intrinsic factor. Eventually, the parietal cells stop functioning altogether. Other important products of parietal cells are also lessened, including stomach acid, and an enzyme involved in the digestion of proteins. Other conditions that interfere with either the production of intrinsic factor, or the body's use of B_{12}, include conditions that require surgical removal of the stomach, or poisonings with corrosive substances which destroy the lining of the stomach. Certain structural defects of the intestinal system can result in an overgrowth of normal

bacteria. These bacteria then absorb B_{12} themselves, for use in their own growth. Intestinal worms (especially one called fish tapeworm) may also use B_{12}, resulting in anemia. Various conditions that affect the part of the intestine (the ileum), from which B_{12} is absorbed, can also cause anemia due to B_{12} deficiency. These ileum-related disorders include tropical sprue, Crohn's disease, tuberculosis.

Symptoms

Symptoms of pernicious anemia and decreased B_{12} affect three systems of the body

- **The hematopoietic system** is harmed because B_{12} is required for the proper formation of red blood cells. Without B_{12}, red blood cell production is greatly reduced. Those red blood cells that are produced are abnormally large and abnormal in shape. Because red blood cells are responsible for carrying oxygen around the body, decreased numbers (termed anemia) result in a number of symptoms, including fatigue, dizziness, ringing in the ears, pale or yellowish skin, fast heart rate, enlarged heart with an abnormal heart sound (murmur) evident on examination, and chest pain.
- **The gastrointestinal system** include a sore and brightly red tongue, loss of appetite, weight loss, diarrhea, and abdominal cramping.
- **The nervous system** is severely affected when pernicious anemia goes untreated. Symptoms include numbness, tingling, or burning in the arms, legs, hands, and feet; muscle weakness; difficulty and loss of balance while walking; changes in reflexes; irritability, confusion, and depression.

Diagnosis

Tests that may be used to diagnosis pernicious anemia include

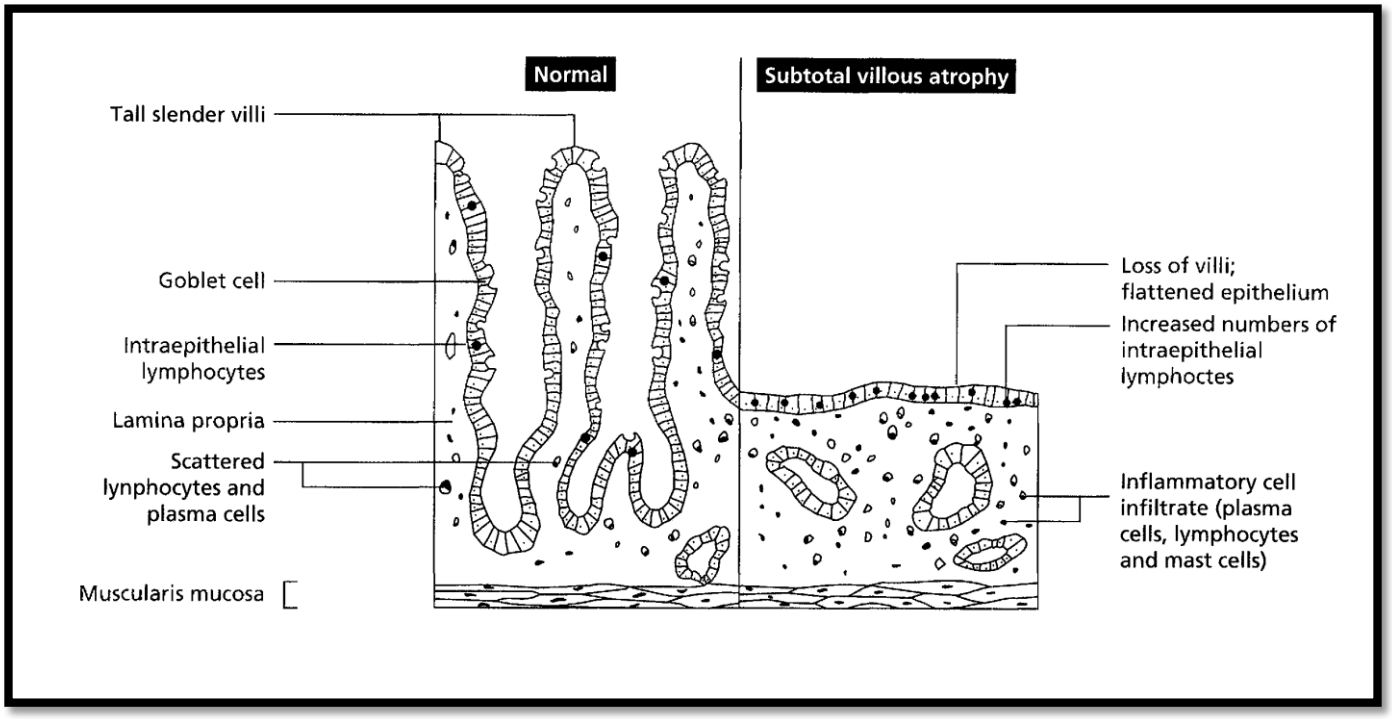
- Blood smear reveals abnormally large red blood cells.
- White blood cells and platelet counts may also be decreased in number.
- Reticulocyte count will be low in number.
- Serum vitamin B_{12} level will be low.
- Schilling test, in this test, a patient is given radioactive B_{12} under two different sets of conditions: once alone, and once attached to intrinsic factor. Normally, large amounts of B_{12} are absorbed through the intestine, then circulate through the blood, and enter the kidneys, where a certain amount of B_{12} is then passed out in the urine. When a patient has pernicious anemia, the dose of B_{12} given by itself will not be absorbed by the intestine, so it will not pass into the urine. Therefore, levels of B_{12} in the urine will be low. When the B_{12} is given along with intrinsic factor, the intestine is able to absorb the vitamin. Urine levels of B_{12} will therefore be higher.

- Immunology, specifically anti-parietal cell antibody (APCA) and intrinsic factor antibody (IFA). APCAs bind to the alpha- and beta-subunits of the membrane-bound H(+)/K(+)-ATPase. In contrast, IFAs bind directly to intrinsic factor, blocking its ability to bind vitamin B12 and can be detected by means of immunofluorescence, enzyme-linked immunosorbent assay - currently the most commonly used method, and radioimmunoprecipitation assay (RIA). APCA can be found in 85-90% of patients with PA. Their presence is not sufficient for diagnosis, because they are not specific for PA as they are also found in the circulation of individuals with other diseases. APCA are more prevalent in the serum of patients with T1D, autoimmune thyroid diseases, vitiligo, celiac disease. So that a combination of PCA and IFA testing was the optimal strategy for the evaluation of patients with suspected PA.

Celiac disease

Celiac disease (CD), an immune-mediated mucosal disorder primarily affecting the small intestine in genetically susceptible individuals, is triggered by the ingestion of dietary gluten. Gluten is the alcohol-soluble protein component of the cereals wheat, rye and barley. It is composed of 2 major protein fractions: glutenin and gliadin; most of the toxic activity exerted by gluten in CD is due to gliadin.

It is, also known as celiac sprue, gluten-sensitive enteropathy, non-tropical sprue, characterized by inflammation leading to injury to the mucosal lining of the small intestine, including villous atrophy with crypt hyperplasia, intraepithelial lymphocytosis, and subsequent nutrient malabsorption.



The disorder is a multifactorial condition, originating from the interplay of genetic and environmental factors. The necessary environmental trigger is gluten, timing of gluten introduction into the diet could play a role in pathogenesis, since initial exposure to wheat, barley, or rye in the first 3 months of life or after the 7th months proved to be related to an increased risk of CD. Breast-feeding could have a protective effect, since introduction of gluten to the infant's diet when infant is still at the age of being breastfed has markedly reduced the risk of celiac disease. While, the genetic predisposition has been identified in the major histocompatibility complex region on chromosome 6p21, with over 90% of CD patients expressing human leukocyte antigens HLA DQ2 and the remaining celiac patients express DQ8.Some infectious agents could increase the risk of celiac disease, like repeated

infection with rotavirus, the most common cause of childhood gastroenteritis, represent an independent risk factor for celiac disease in genetically susceptible individuals. Some drugs can have a role in enhancing a person's susceptibility to gluten, a course of interferon alfa could activate celiac disease in predisposed people.

Clinical features

The clinical manifestations of CD vary markedly with the age of the patient, the duration and extent of disease, and the presence of extraintestinal pathology. Depending on the features at the time of presentation, together with the histologic and immunologic abnormalities at the time of diagnosis, CD can be subdivided into the following clinical forms.

1. Classical (typical) form

The so-called typical form of CD is present characteristically between 6 and 24 months of age. Symptoms begin at various times after the introduction of weaning foods containing gluten. Infants and young children typically present with chronic diarrhea, anorexia, abdominal distension, abdominal pain, poor weight gain or weight loss and vomiting. Malnutrition can be severe if the diagnosis is delayed. Behavioral changes are common and include irritability.

2. Atypical forms

An increasing number of patients, especially at an older age, are being diagnosed with CD without having typical gastrointestinal manifestations but there are various extraintestinal manifestations present such as dermatitis herpetiformis, anemia, osteoporosis, autoimmune hepatitis, dental enamel defects, recurrent aphthous stomatitis, epilepsy, and neuropathy. Serology for CD is positive and bioptic findings confirm the diagnosis.

3. Silent form

Silent celiac disease patients are those who are asymptomatic but small intestinal biopsy show villous atrophy. Silent cases are detected by population screening and screening of first degree relatives of celiac disease, 10% of whom are found to have CD. Serological tests are positive in them.

4. Latent form

Latent (or "potential") form is asymptomatic patients, with a normal or minimally abnormal mucosa. These individuals have a genetic susceptibility to CD and may also have positive autoimmune serology.

Refractory celiac disease (RCD) is defined by persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet (GFD) for at least 6–12 months in the absence of other causes of non-responsive treated celiac disease and overt malignancy

Celiac disease prevalence is increased in at-risk conditions such as family history of celiac disease, autoimmune diseases, especially type1diabetes (T1D) and thyroiditis, IgA deficiency, and some genetic syndromes.

Immunopathogensis

Celiac patients present with a complex immunological reaction to ingested gluten encompassing both innate and adaptive immunity and leading to progressive inflammation and severe destruction of the mucosal lining of the small bowel.

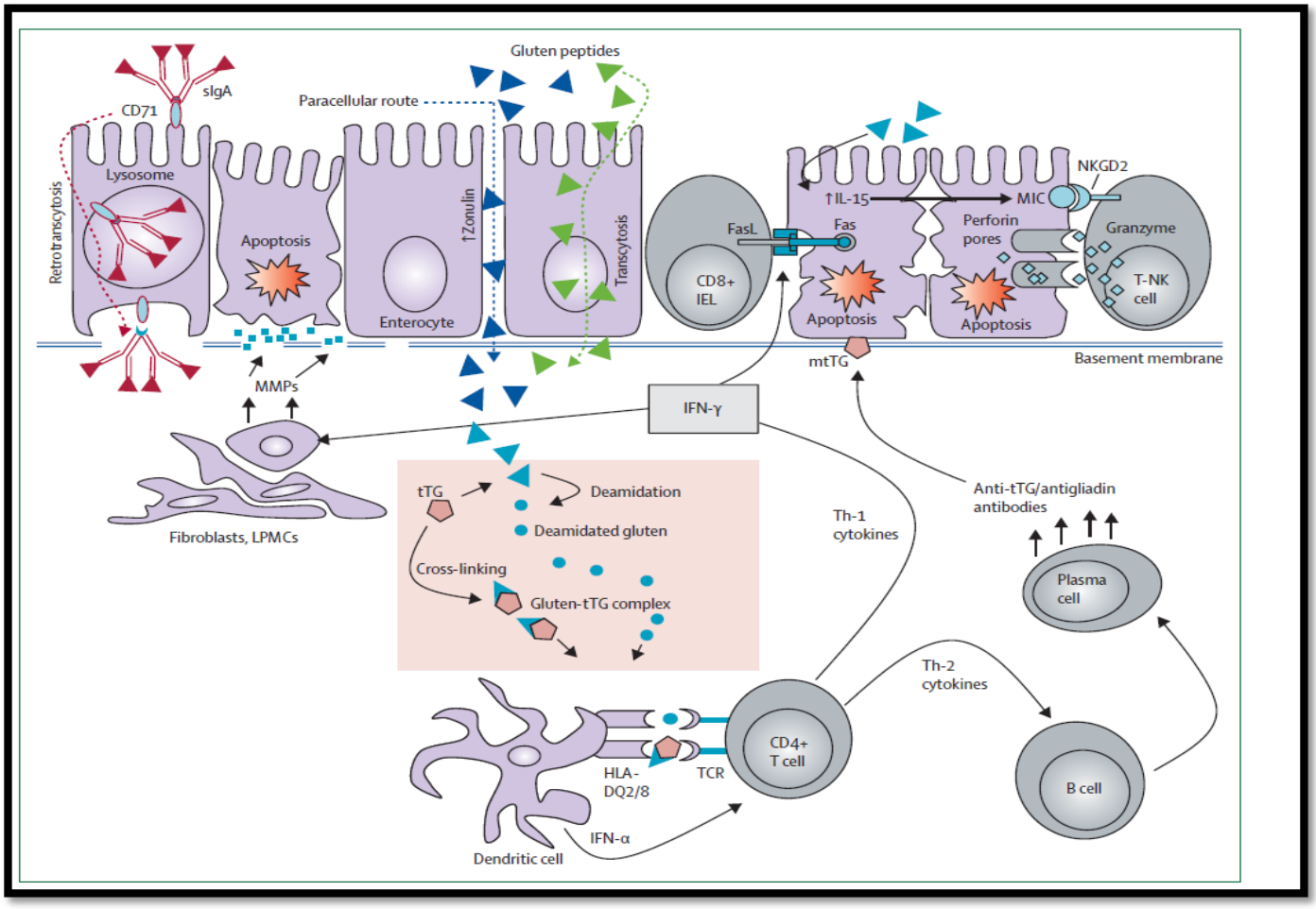


Figure: Mechanisms of mucosal damage in celiac disease.

Diagnosis

1. Small intestine biopsy

The most relevant feature of the disease was histological change, and histology became the gold standard for diagnosis. The diagnosis required three small bowel biopsies-the first during the gluten containing diet, which had to show "flat" mucosa; the second, during gluten free diet which showed improvement in villous structure, and the third, at gluten challenge 2 years later which had to show histological relapse.

The degree of the intestinal lesion is defined on the basis of the widely used Marsh-Oberhuber classification, it ranges from type 0 (Marsh 0) to Marsh type 4:

- **Type 0** concerns the normal stage of the small bowel mucosa.
- **Type 1 or infiltrative lesion** comprises normal mucosal architecture in which the villous epithelium is infiltrated by small, non mitotic intraepithelial lymphocytes and it is characteristically present in first-degree relatives of children with celiac disease.
- **Type 2, or hyperplastic lesion,** consists of a type 1 lesion with enlarged crypts.
- **Type 3or destructive lesion** is synonymous with the typical flat mucosa of CD and it is subclassified according to the different degrees of villous atrophy present: Marsh type 3a, with partial villous atrophy; Marsh type 3b, in the presence of subtotal villous atrophy; and Marsh type 3c, when total villous atrophy is present.
- **Marsh type 4 or hypoplastic lesion** (total villous atrophy with crypt hypoplasia) represents the extreme end of the gluten-sensitivity spectrum and an irreversible lesion is present in some adult CD patients whose small bowel mucosa is unresponsive to gluten withdrawal: the so-called refractory CD.

2. Serology tests

Serologic testing is primarily used to identify symptomatic or at-risk individuals who need to undergo biopsy. Because of their high sensitivity and specificity, serologic tests are excellent for screening asymptomatic at-risk individuals; they also can be used for monitoring dietary compliance.

- Anti-gliadin antibodies (AGA) are not specific for CD as they are also found in healthy individuals and patients with other gastrointestinal diseases such as gastritis, gastroenteritis and irritable bowel syndrome, except in children younger than 2 years of age, in whom anti-gliadin antibodies measure is more sensitive test**.** IgG-

AGA is very sensitive but less specific, and IgA-AGA is less sensitive but more specific. Their use in combination can give results of a high detection rate. Several methods have been used to analyze AGA, but currently ELISA is the most used method.

- Anti-endomysial antibodies (EMAs) are used as the "gold standard" for CD screening because of their high sensitivity and specificity. The test was developed in the early 1980s and rapidly gained use as part of "a celiac panel" by commercial labs in combination with AGA IgG and IgA. IgA-EMA and IgG-EMA are measured by indirect immunofluorescence, using tissue sections from either monkey esophagus or human umbilical cord [140]. Its major drawbacks are false negatives in young children, and in the hands of an inexperienced laboratory because of the subjective nature of the test. Also IgA-EMA give false negative in patients with IgA deficiency.
- Anti-tissue transglutaminase (tTG) antibodies are more specific have shown to be correlated with mucosal damage and are used widely in CD screening**.** IgG-tTG and IgA-tTG were used in combination as a screening test for celiac disease to assess IgA deficiency. ELISA is the most used method to analyze tTG**.** However, it represents an improvement over the antiendomysial antibody assay because it is inexpensive, rapid and easy to perform**.**
- Anti-reticuline antibody is best detected by an indirect immunofluorescent method using unfixed cryostat sections of rat liver and kidney as antigens. IgA class reticulin antibodies react with connective tissue fibers and are found in 60% of celiac disease patients. IgG class reticulin antibodies are occasionally found in other disease states, especially bullous dermatoses and in some normal subjects.

3. Genetic testing

Up to 95% of patients with celiac disease are positive for HLA-DQ2, and most of the remaining patients are positive for HLA-DQ8. . However, these alleles are also found in 40% of the general population. Although HLA-DQ2 and HLA-DQ8 are necessary in the disease process, they alone are not sufficient for celiac disease to develop. HLA testing has a high negative predictive value and can be useful in certain situations, such as when a diagnosis is unclear, when serologic testing or biopsy is performed in patients on a gluten-free diet, or in determining which family members to screen for celiac disease.

Treatment

The only proven treatment for celiac disease is strict and life-long adherence to a gluten-free diet. All food and drugs that contain gluten from wheat, rye, barley, and their derivatives must be eliminated because even small amounts can be harmful.