# THE RELEVANCE OF THE CASE STUDY METHOD FOR INVESTIGATING RARE DISEASES ON THE EXAMPLE OF GLUTEN ENTEROPATHY

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**Abstract**

*Case study has been gaining importance as a method of research which is especially efficient for educational purposes. The aim of the current paper is to shed light on its particular relevance when studying rare diseases on the example of a gluten enteropathy case.*

*The case which is reviewed is that of a 22 year old woman, having dyspeptic syndrome of the lower gastrointestinal tract (20 day-diarrhea), consummative syndrome, abdominal-pain syndrome, and heavy anemic syndrome. Blood tests showed early phase of DIC syndrome, combined with thalassemia minor and iron deficiency anemia, serological tests showed extremely high level of antibodies specific for gluten enteropathy, histological results from duodenal biopsy of video gastroscopy, barium sulfate x-ray diagnosis of the gastrointestinal tract and Contrast CT scan abdominal investigation supported the diagnose. The patient has gluten enteropathy, showing the polymorphism of the disease.*

**Keywords:** *case study method, gluten enteropathy, polymorphism of the disease*

## 1. INTRODUCTION

Case study has been gaining importance as a method of research which is especially efficient for educational purposes. The aim of the current paper is to shed light on its particular relevance when studying rare diseases on the example of a gluten enteropathy case.

Gluten enteropathy is a type of chronic enteritis, characterized by subtotal atrophy of the intestinal mucosa as a result of autoimmune reaction toward gluten (a protein contained in barley, wheat, rye and oats). Gluten enteropathy is a very often cause for malabsorption syndrome in Europe, England, North America, and Scandinavian peninsula, and it is characterized by chronic diarrhea, secondary endocrine, coagulation and vitamin disorders. If not diagnosed on time, it can lead to death, otherwise effective treatment exists, but patients need to keep a special diet during all their lives.

## 2. GLUTEN ENTEROPATHY: KEY FACTS AND SPECIFICITIES

### *2.1. Heredity*

It is proved that intolerance toward gluten is genetically determined by the following factors:

- The frequency of the disease is increased in the families of patients;
- Gluten enteropathy is associated with DR3, CW7, DR3/AW 24, BW 59 haplotype and there is an increased frequency of HLA-B8 antigen in approximately 80% of the patients, compared with 20% of the population as a whole. In the different families the disease can be inherited in autosomal recessive or autosomal dominant way;
- There is a gene that encodes the existing of specific B-lymphocyte surface antigen in 70% of the patients versus 6 % of the non-inflicted;
- Gene over the 14-th chromosome that encodes a part of the heavy chain of IgG and determines the response with anti-gliadin IgG antibodies;
- Gene that encodes a gliadin receptor over the surface of the enterocyte and the lymphocyte.

It is considered that in that way the patient inherits receptors for gliadin over the enterocyte and B-lymphocyte surface which enables the capture of gluten from the intestinal mucosa and activates B-lymphocyte.

*2.2. The role of gluten*

Gluten is a toxic substance for the intestinal mucosa of genetically prone people and is a result of the alcoholic extract of wheat. The toxic substance of gluten is being produced by hydrolysis of trypsin and pepsin in the stomach and in the intestinal mucosa. It is compounded by peptides with different molecular weight. In patients with gluten enteropathy the toxic substance for the intestinal mucosa is the alcohol-soluble fraction (gliadin), whereas the alcohol non-soluble fraction (glutenin) is harmless. Upon electrophoresis gliadin is divided into 4 fractions - α, β, γ, ω. All of them are toxic for the mucosa, but the most toxic is the alpha-fraction. It is considered that the toxicity of the gluten is a result of the side carbohydrate chain in the molecular structure and the removal of this chain diminishes toxicity. The first intake of gluten sensitizes the enteral epithelial cells but the second one induces Arthus phenomenon and disorders become visible 6-12 hours later.

There are different mechanisms of toxic action of gluten over the intestinal mucosa:

1. The existing of specific peptidase deficiency in the intestinal mucosa as a result of which gluten could not be hydrolyzed fully and correctly;
2. It is supposed that there is initial disturbance in the glycoprotein structure of the enterocyte membrane and in such a way there is possibility the gliadin to be connected (like the lectin) with this glycoprotein on the enterocyte surface, inducing toxicity;
3. The immunologic theory of the pathogenesis of the disease is the most accepted one, and according to it, gluten enteropathy is a result of a pathologic immune reaction towards gluten. The evidence for this theory is associated with:
    - The described upper HLA antigenes that determine hereditary transmission of a certain type of pathologic immune response;
    - Very good results from corticosteroid therapy;
    - Changed level of serum immunoglobulins. Selective IgA deficiency is found in 1 to 50-70 patients with gluten enteropathy which is 10 times more often than the level in the population as a whole. IgM deficiency exist in 60% in the non-treated patients;
    - Presence of circulating antibodies in the blood. Anti gliadin and Anti gluten IgG antibodies are being found in the serum in 1/3 of the patients versus 5% in healthy people. Anti reticulin antibodies could be found in ¾ of the patients. Anti-tissue transglutaminase and anti-DGP are specific for the disease;
    - Intestinal mucosa and intestinal secretion. An increased number of immunoglobulin synthesizing cells, and plasmatic cells producing IgM and IgG, are found in the intestinal mucosa. In adults prolonged antigen stimulation induces the exhaustion of the first line of mucosa defensive cells (IgA secreting cells). That is why in adults their number is smaller at the expense of a second line situated deeper in the mucosa of defensive cells (IgM and IgG secreting cells) In infants IgA secreting cells are a larger number. Increased is also the number of the other cells of the inflammatory response-macrophage cells, mastocytes.
    - Gluten enteropaty and other autoimmune diseases:
        - Endocrine diseases - Hashimoto's thyroiditis, Diabetes mellitus, type 1, Addison's disease;
        - Pulmonary diseases - Fibrosing alveolitis, Allergic alveolitis, Sarcoidosis;
        - Hepatic diseases - Chronic active hepatitis, Primary biliary cirrhosis;
        - Rheumatoid diseases - Rheumatoid arthritis, Lupus erythematosus, Periarteritis nodosa;
        - Dermatological diseases - Vitiligo, Vasculitis, Selective IgA deficiency, Atopic disease;

- Other-Ulcerative colitis, Pernicious anaemia.

- Cellular immune response: the diminished number of peripheral T lymphocytes in non-treated patients as a result of transudation through the damaged intestinal mucosa is very characteristic.

In a nutshell it can be said that gluten joins up with the receptor onto the enterocyte and lymphocyte surface, sensitizing the lymphocytes and thus increasing lymphokine production, which on its part, injures the epithelial cells in the type of cell-mediated cytotoxicity. The sensitized lymphocytes migrate through the Thoracic duct in the main circulation; turn back in the intestinal lamina propria, where they undergo pathological transformation in immunoglobulin secreting plasmatic cells. As a result there is increased secretion of immunoglobulins (anti gluten antibodies) with the production and deposition of antigen-antibody complexes with gluten specificity into the intestinal mucosa which cause enterocyte damage.

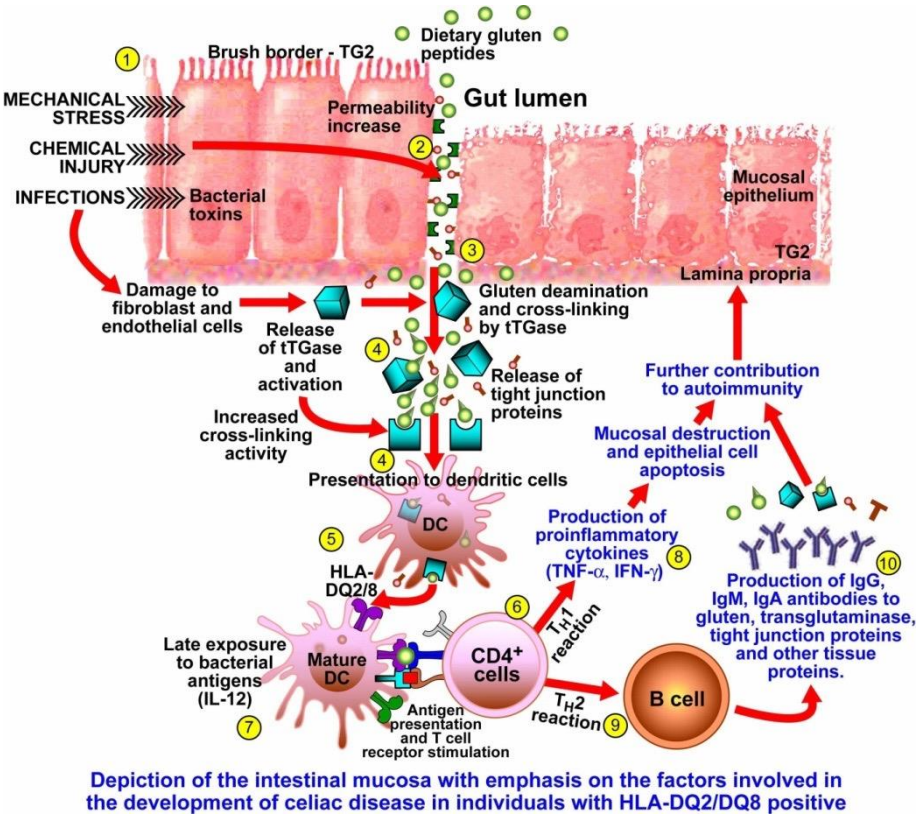



**Fig. 1.** Intestinal mucosa

*2.3. Clinical manifestaion*

Gluten enteropathy can manifest itself in any age with higher frequency in women. In infants the beginning is between 1st and the 5th year, more often during the second year. In adults the beginning of the disease is between the third and fourth decade. As it has been already underlined above, the disease has a wide spectrum of clinical manifestations and it is very important for us to search not only for the typical symptoms of the upper gastrointestinal tract, but syndromes of disorders of other organs and systems in the human body. That is why it is relevant to acknowledge that there is an "iceberg'' of Gluten enteropathy morbidity in the world and that is why the real frequency of the disease could never be known exactly.

*2.4. Diagnose*

Diagnose is put under the criteria of the ESPHGAN 1970, or:

1. Malabsorption syndrome as a result of subtotal atrophy of the intestinal mucosa.
2. Clinical improvement and morphologic recovery after non gluten diet.
3. Morphologic relapse, with or without clinical relapse after secondary gluten consumption.

*2.5. Treatment*

Treatment of the disease is complex and different in each patient. The first and extremely important thing is keeping a lifelong gluten-free diet. In such a way the patients may diminish the risk of malignant transformations as a result of constant antigen stimulation of the intestinal mucosa. The diet must be linked to enzyme deficiency and allergic intolerance. Patients can consume corn flour, rice flour, fruits, fruit juices, vegetables. The proteins in the diet need to be of animal and milk origin, the fats need to be vegetable. When there is steatorrhea, diminishing the fats with chiefly using triglycerides of the medium chain fatty acids is needed. In severe cases the gluten-free diet is combined with parenteral application with fluid and electrolyte solutions, vitamins, blood transfusions, blood plasma, folic acid. When this treatment is ineffective, corticosteroids must be used. In patients with collagenous sprue treatment with corticosteroids could not be effective enough and starting immunosuppressive therapy (Imuran) is needed.

*2.6. Prognosis*

Prognosis in patients with gluten enteropathy is not very optimistic. Spontaneous regression of the disease is very rare. If not treated, the disease proceeds in periods of remissions and exacerbations, and sometimes in the form of the so-called coeliac crisis with 10 to 30% mortality. When starting gluten-free diet clinical improvement occurs soon - in 10-15 days, morphological improvement later - after 1-2 years, in some cases after 3 years. Given all these specific features, and as gluten enteropathy is a precancerous condition, making very strict periodical endoscopic, histological, X-ray investigations of the upper gastrointestinal tract is extremely important.

## 3. GLUTEN ENTEROPATHY CASE REPORT

A 22-year-old woman arrived in our clinic with 20 days complaints of 4-5 times a day of diarrheal stools, including during in the night (twice) without pathological components in the stools, accompanied with abdominal cramps, malaise, strong weakness and easy weariness during common physical effort, without temperature, with significant vaginal flow. The complaints started a few hours after the patient had eaten an ice-cream. After consultation with her doctor (general practitioner), treatment with symptomatic antidiarrheal and enzyme medicines started, but without effect. She lost 5-6 kilos of her weight in 2 days, her relatives saw that she was very pale and after she collapsed, she was transported with emergency in our clinic for diagnosing and consequent treatment. Family history revealed that the mother had anemia. The patient denied having allergic reactions towards foods and medicines. She had no other diseases.

The examinations and tests done on the patient are summarized below:

- Physical examination: In our clinic the patient was in very bad condition, with astheno-adynamia, pale and subicterus skin and mucosa, dry and yellow-coated tongue, without lymphadenomegalia, cardiovascular system - RR 90 / 60, pulse 110 / min., without pathological sounds, abdomen - meteoristical, palpatory not painful, hastened peristaltic, without hepatosplenomegaly.
- Laboratory tests: RBC 5.28; Hgb 77, MCV 58.3, Hct 0.308, Ret. 0.8, WBC 5.9, Sg 59.6, Eo 0.4, Ba 0.3, Mo 6.2, Ly 30.2, Plt 392; haptoglobin 0.41, Coombs (-), Blood group ‘’A’’ Sedimentation rate 2; ser. Fe 3.3; T. prot.-78, Alb.-43; fib. 1.33, T. bil.-39.3; Dir. bil,.-14.3; gluc.-5.0; chol-1.9; HDL-chol.-0.42; TG 1.06; PT 41; Aptt 28.7; DD >0.20; Antithrombin III 208%, Factor VIII 127.6; Factor IX 33; Free Hgb 36.55; IgA 2.71; IgG 13.3; IgM 1.44; Na-145; K-4.2; Cl-97; Haemoculture

(-); Leishmaniasis blood test(-); Urea 2.7; crea 50, Ur. Ac.-231, ASAT 47; ALAT 25; amyl.-25; AP 220; HBDH 110; LDH 330; GGT 28; CRP<5; Afp 2.13; CEA 4.26; Ca 19-9 96.5; Ca 72-4 15.2; ferritin 54.7; coprogram stool tests-negative; Candida alb. (+); parasites test in the stools (-); Cl. Difficile (-); urine-normal; antiGliadin IgA 105.9 (>18 positive), antiGliadin IgG 38.7 (>24 positive), antiendomysial antibodies (AEA) IgA /+/, anti Ttg IgA 88.2 (>12 positive);

- ECG - Indifferent type, sinus rhythm, ST depressions in II, III, Avl.
- Abdominal Ultrasound: normal.
- Pulmography: Chronic bronchitis.
- Barium sulfate x-ray diagnosis of the gastrointestinal tract: 3 hours after taking the contrast there are depots of contrast substance type "snow storm'' along the jejuna wrinkles - a sign of larger quantity of mucous substance. The contrast reaches ileum in the pelvis. Normal terminal ileum.
- Contrast Abdominal CT scan: the small and large bowels are very bloated, filled in liquid and forming hydroaerial levels.
- Invasive investigations: video gastroscopy: oesophagus - normal view. stomach - a lot of bile in the lumen, duodenum: pale duodenum mucosa-taken biopsy. Histological examination: duodenum with chronic inflammation in which there are predominantly lymphocytes, plasmocytes, plenty of caliciform-like cells and Paneth cells, subtotal atrophy of the mucosa. Histological view is related to Gluten enteropathy.

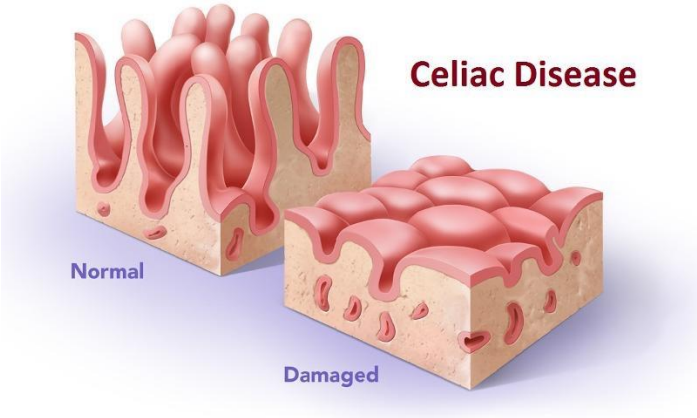



**Fig. 2.** Celiac disease manifestations

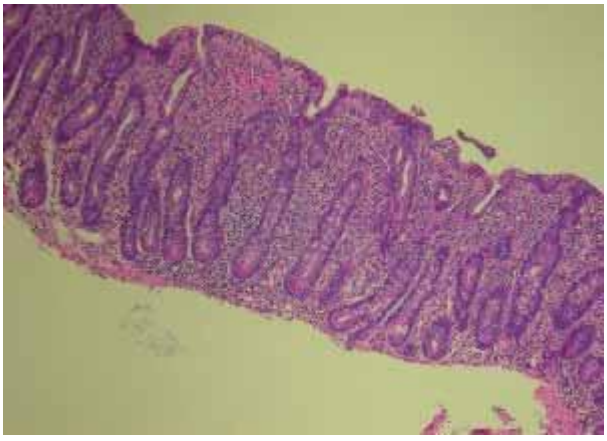


**Fig. 3.** Celiac disease from another perspective

Consultative examinations:

1. Specialist in infectious diseases - 20 day diarrhea with normal stool tests (including Cl. Difficile (-), afebrile, without information of consuming suspicious food, without accompanying diseases. There are no signs of acute infectious disease.
2. Obstetrician - TVUE (Transvaginal ultrasound investigation) - normal. Microbiological tests- Candida alb. (+). Treatment with Polydynax vaginal globules.
3. Hematologist - 5 times: Early phase of DIC syndrome, compounded with Thallassemia minor and iron deficiency anemia. Therapy: Plasma 400cc each day, Vit. K in case with PT <15% , Erythrocyte concentrate in case with Hgb <80g./ l.

The suggested treatment includes the following: Ringer, Venofer, Enterol, Smecta, Ceftriaxon, Metronidazol, Erythrocyte concentrate 1 bank, Plasma-11 banks, Nystatin, Kreon 25 000E, Potassium chloride in 5% 500cc Ser. Glucose, Ins. Actrapide, Human albumin, Vit. K.

## 4. CONCLUSION

Using case reports to present rare diseases with specific manifestations are a very useful method to illustrate facts related to them to students in medical universities. Theoretical framework is needed containing general knowledge of the disease and its manifestations, but when a particular case is examined, a lot more insight is gained by the students as they can see in practice the application of what they have studied in textbooks.

With this case report we would like to underline and illustrate that gluten enteropathy is a lifelong disease which leads to multisystem disturbances, some of which could be fatal. As symptoms persist, applying very strict clinical, laboratory and endoscopic control is of vital importance in order to prevent further fatal complications.

In the case of our young patient the autoimmune processes have been induced probably by stress and dietary factors. After she has been put to a strict gluten free diet the complaints continued to persist. That is why peroral corticosteroid therapy was started with Dehydrocortison 40mg., gradually reducing the daily dose to 10mg. Further diminishing the dose to 7.5mg. dehydrocortison led to reactivation of the autoimmune process and it was necessity to increase the dose to 40mg. daily. At that dose (10mg.) the patient was asymptomatic, but histological disturbances persisted when examining the patient by video gastroscopy with multiple enteral biopsy. Autoantibodies showed tendency to normalize (Anti Gliadin IgA 24.0; Anti endomysium IgA /+/; Anti tTg IgA 60.6 (03.2015).

Case study method have proven to be particularly useful in presenting cases similar to the above one and identifying the right treatment which could then be applied to other patients with symptoms like the ones presented in the report.

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