A Silent or Hypo-symptomatic Disease Can Erupt: Acute Presentations of Celiac Disease

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Abstract Celiac disease is a multi-organ disorder which is highly variable in its clinical expression, presenting multiple enteric and extraintestinal manifestations. However, most of treating physicians and dieticians regard celiac disease as a chronic, gradually evolving, asymptomatic or hypo-symptomatic entity. The present mini-review aims to screen the literature for acute presentations of celiac disease and to increase the awareness of the medical communities, for such a possibility. It appears that the disease can present acutely in multiple symptomatic, phenotypic and laboratory pictures. The acute presentation involves mainly the gastrointestinal tract and adjacent organs like liver and gallbladder, however, extraintestinal and remote organs presentations can occur.

Keywords: celiac disease, acute, presentation

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1. Introduction

Celiac disease (CD) is an autoimmune disorder elicited in genetically predisposed individuals by the consumption of gluten-containing grains (i.e. wheat, barley, rye and oat) or ingredients of them. It is generally accepted that CD affects approximately 1-1.5% of Western populations, whereby in Northern European countries like Sweden, Finland and Ireland the incidence is higher, thus fitting the North to South incidence gradient [1]. Even in the Far East, where rice is the main staple food, increased incidence of CD is being reported. In India, for example, the prevalence of CD in the general pediatric population attending a tertiary care hospital of North India mounted to 1%. [2] and the question: can we avert the impending epidemic of CD in India? This is highly vindicated [3]. China, however, presents a comparable incidence to the Western world only in high risk populations, but in the normal population it is much lower, not reaching even 0.5%. [4, 5]. In recent years, an increasing number of CD patients have been identified even in the Middle East and North Africa, where it was historically considered to be an extremely rare disorder [6]. Co-localization of gluten consumption, HLA-DQ2 and -DQ8 genotypes frequency and CD incidence reinforce the genetic and environmental interplay in CD progression [7].

In fact, CD is actually a multi-organ disorder which is highly variable in its clinical expression, presenting multiple enteric and extraintestinal manifestations [8]. For these reasons the diagnosis is often delayed.

Currently, we are witnessing a diffused ongoing endemic of CD of great scale. Epidemiological data provides strong evidence of a steady rise of the disease throughout Westernized societies over the last six decades [1]. The reasons for this worldwide surge in CD incidence are multiple and debatable (Table 1).

Table 1. Summary of the potential explanation for CD incidence surge [1,9,10,11,12]

| Suggested raison for the increased incidence of celiac disease |
|---------------------------------------------------------------|
| Increased prolamins intake                                    |
| Higher gluten content in modern wheat                         |
| Higher toxicity of gluten in modern wheat                     |
| Gluten is autoimmunogenic                                      |
| Gluten is potentially detrimental to humankind                |
| Increased production of wheat per hectare                     |
| Increased environmental inducers of CD: stress, infections    |
| Associate dysbiome                                            |
| Increased intestinal permeability by processed food additives  |
| Increased public and professional awareness                    |
| Improved serological diagnosis                                |
| Skipping intestinal biopsy as per ESPGHAN 2012 new criteria    |

Moreover, some patients have no symptoms at all despite the presence of characteristic intestinal lesions, while various atypical clinical manifestations and asymptomatic forms of CD means that most cases remain un- or misdiagnosed, with a 1:7 ratio of diagnosed to undiagnosed cases [13]. This has led to the concept of a “CD iceberg”, with only the “tip” of the cases being seen [14]. Furthermore, undiagnosed CD patients cannot receive timely treatment, and will have an elevated risk for developing secondary autoimmune disorders (type 1 diabetes, Hashimoto thyroiditis, Addison's disease, autoimmune hepatitis, etc.)
stunted growth, osteoporosis/osteopenia, infertility, increased morbidity and mortality as well as various malignancies [14].

Epidemiologically, it has been shown that the classic intestinal clinical picture of malnutrition, chronic diarrhea and nutritional deficiencies are disappearing and extraintestinal presentations are emerging. Skin, endocrine, skeletal, hepatic, hematological, thrombophilic, gynecological, fertility-related, dental, obesity, neurological and behavioral abnormalities are often described [15,16,17]. Today, we are witnessing an epidemiological shift in the disease phenotype toward a more advanced age, and increased prevalence of latent, hypot-symptomatic or asymptomatic behavior [15]. All these changes make the diagnosis of the disease more difficult and the reliance on symptomatology more remote. Most of treating physicians and dieticians regard CD as a chronic, gradually evolving, unnoticed, asymptomatic or hypot-symptomatic entity. In such a case, quite frequently, acute presentations are not considered and do not lead to bringing up CD as a possibility. The present review aims to screen the literature for acute presentations of CD and to increase the awareness of the medical communities for such a possibility.

2. Acute Presentations of Celiac Disease

Contrary to the accepted scientific and medical communities impression, CD can present acutely, in multiple symptomatic, phenotypic and laboratory pictures. More so, it is considered as a “1000 faces disease” with a very wide range of presentations, including acute ones. Table 2 lists some of them.

It is quite obvious that CD is not only a chronic, gradually evolving, unnoticed, asymptomatic or hypot-symptomatic entity. It can present acutely, involving mainly the gastrointestinal tract and adjacent organs like liver and gallbladder, notably, extraintestinal and remote organs presentations were also described.

3. Discussion

The present mini-review opens a hatch, showing that CD can present acutely, thus adding an additional aspect to the celiac clinical kaleidoscope. In view of the routine belief that CD presents mainly in a hypo- or asymptomatic ways, the health providing care teams should be aware of such acute presentations in a chronic disease like CD. Such a wide view might increase the diagnostic rate, impact the diagnosed/undiagnosed ratio and might advance initiation of gluten withdrawal.

It will be difficult or unethical to study the acute effects of gluten consumption, in vivo, on CD high risk people. Ex-vivo gluten application on gluten-free diet intestinal biopsy, bypass the obstacle. Many ex-vivo, in vitro models were described, using human originated intestinal cell-lines or CD patients small bowel mucosal biopsies [41,42]. We know nowadays that gluten or gliadin, when incubated with primary cultures of CD patients on gluten-free diet, induces morphological as well as immunological aberrations. Cytokine release, autoantibodies secretions, increased CD25+ cell density, MHC class I chain-related gene A expression were reported [43,44]. Applying genetic bioinformatics, it was shown that important dysfunction of pathogenic networks related to cell to cell communications, intracellular signaling, ubiquitin-proteasome system, cell cycle and apoptosis and extracellular matrix modulation resulted from acute gliadin effects on mucosal biopsies of CD patients, while on gluten withdrawal [45].

Those ex-vivo, acute effects of gluten/gliadin that are manifested during the first 48 hours of incubation, give us some mechanism hints whereby CD can manifest in an acute clinical presentations. Additionally, the black box of the mucosal events occurring during accidental gluten exposure is unknown. Unravelling the pathogenesis of acute presentation of CD, might open new comprehensive picture of key events contributing to CD initiation and progression.

Table 2. Summary of acute presentations of celiac disease

| Acute presentation/manifestation                  | Organ involved          | Reference |
|--------------------------------------------------|-------------------------|-----------|
| 1 Iron deficiency anemia                         | blood                   | 18        |
| 2 Folate deficiency anemia                       | blood                   | 19        |
| 3 Watery diarrhea                                | gastrointestinal        | 20        |
| 4 Profound diarrhea and weight loss              | gastrointestinal        | 21        |
| 5 Celiac crisis                                  | Multi-organ             | 21-25     |
| 6 Electrolyte imbalance                          | blood                   | 22-25     |
| 7 Hepatitis                                      | liver                   | 23        |
| 8 Hepatic failure                                | liver                   | 26        |
| 9 Intestinal Intussusception/invagination        | intestine               | 27-30     |
| 10 Cholecystitis, lithiasis                      | gallbladder             | 31, 32    |
| 11 Quadriplegia                                  | neurological             | 24, 25    |
| 12 Status epilepticus, encephalopathy           | neurological             | 33        |
| 13 Malabsorption                                 | intestinal              | 34        |
| 14 Malnutrition                                  | intestinal              | 35,36     |
| 15 Infections                                    | Liver, urinary tract    | 23, 37    |
| 16 After pregnancy                               | Gynecological           | 38, 39    |
| 17 Colonic pseudo-obstruction                    | Gastrointestinal-colon  | 40        |
4. Conclusions
Contrary to the accepted scientific and medical communities impression, CD can present acutely, in multiple symptomatic, phenotypic and laboratory pictures. More so, it is considered as a “1000 faces disease” with a very wide range of presentations, including acute ones. The acute presentation involves mainly the gastrointestinal tract and adjacent organs like liver and gallbladder, however, extraintestinal and remote organs presentations can occur. The genetic as well as the environmental factors that contribute to an acute presentation in a CD patient await further exploration.

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