Celiac Disease: An Underrecognized Concern in Women's Health

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Abstract: Celiac disease (Celiac disease, CD) is a kind of autoimmune bowel disease caused by dietary gluten in genetically susceptible individuals, also known as non-tropical inflammatory fatty diarrhea (Non-tropical sprue), wheat gum bowel disease (Glutenenteropathy), idiopathic fatty diarrhea (Idiopathicsteatonhea), gluten mainly exists in wheat and other crops, including rye, barley, oats, etc. All foods produced and processed from these cereals, such as bread, cakes, biscuits, and beers, contain gluten. The components of gluten include gluten (glutenin) and alcohol-soluble gluten (alcohol-soluble protein, prolamine). Immune response, born in the small intestine, has increased significantly in the past five decades, especially in the last decade, but overall, it remains an underestimated problem in women's health.

Keywords: celiac disease; female health; autoimmune liver disease

1. Introduction

Celiac disease is an autoimmune intestinal disease induced by the intake of gluten-containing cereals (wheat, barley, and rye) and their products. The disease can lead to intestinal mucosal damage, such as intraepithelial lymphocytic infiltration in the small intestine, villous atrophy, and crypt hyperplasia. Clinically, the main manifestations are gastrointestinal symptoms such as abdominal pain, diarrhea, and parenteral symptoms caused by secondary malnutrition, which Sometimes also coexist with autoimmune diseases such as type 1 diabetes and autoimmune thyroiditis. It has seriously affected the safety and quality of life of patients. Therefore, understanding the disease of CD in China is of great significance for prevention, treatment, and health management.

2. Current status of CD research worldwide

In recent years, research on CD has become increasingly intensive worldwide, and the seroprevalence rate of milk diarrhea in the general population is 1.4% [1]. Meanwhile, the CD seropositivity varies significantly between continents. The serological results meta-analysis showed that CD antibody seroprevalence was 1.1% in the African population, 20 and 1.8% in the Asian population, and the global pooled prevalence of biopsy-confirmed CD was 07% according to the current meta-analysis [2]. In Africa, the prevalence of biopsy-proven CD is 0.5%, while in Europe, biopsy-proven CD is up to 0.8% by gender-based differential prevalence of 0.4% in men and 0.6% in women [3]. Analysis of biopsy-diagnosed milk diarrhea incidence in children and adults showed a CD prevalence of 0.5% in adults and 0.9% in children [4]. There is a significant difference in the prevalence of breast diarrhea in adults, which is higher than in adults.

Clinical workers in Asia are also gradually realizing that CD is not only occurring in European and American countries. In Asia, studies on CD started late, and there are few population-based studies and search data in high-risk groups. Asia is a continent with high demographic diversity, and Asians themselves differ significantly in race, genetic makeup, dietary habits, and other key factors affecting the incidence of CD. In recent years, journal articles and publicity on CD have increased, indicating that the awareness and vigilance of Asians have increased in the past decade. A meta-analysis showed an overall seroprevalence of 1.6% in Asia and a biopsy-confirmed overall incidence of 0.5% ^[5]. The incidence was not statistically different between adults and children but not between men and women, with higher CD rates in women than in men.

The incidence of CD varies between different Asian countries because the pathogenesis-related HLA-

DQ 2 / HLA-DO 8 haploid occupies different populations in other countries, and it is also associated with the distinct types of wheat consumption in various countries. In Asia, the prevalence of CD may also vary by country due to differences in dietary habits and the proportion of people susceptible to HLA haplotypes. Previous studies suggest that the proportion of HLA-DQ 2 / HLA-DQ 8 haploid population and the incidence of CD with gastroenterologists, other experts, and primary care doctors increasingly understanding of the disease, based on wheat diet content gradually increased, detection of CD more and more widely, it is expected that the incidence of CD in many Asian countries will increase, Asian women and men prevalence differences. Still, the difference is far less than that of European and American countries. The reason may be that there is less research data and significant heterogeneity. Multienter collaborative population-based prevalence studies (domestic and international) will help not only assess the prevalence of CD in Asian countries but also understand the complex interactions between genetic and environmental factors in the pathogenesis of CD.

3. Epidemiological Analysis

Celiac disease is a chronic autoimmune bowel disease induced by genetically susceptible individuals who consume gluten-containing grains (wheat, barley, wheat, and naked wheat) and their products. It affects the health of 1% of the world's population and is on the rise. Patients with various clinical symptoms of CD and no apparent symptoms are easily "misdiagnosed" and "missed diagnosis," and there is a serious "iceberg" phenomenon. In recent years, several CD cases have been reported, suggesting that CD disease increases and is far more common than expected. However, the primary data on the epidemiology of CD are lacking, with only a few data on the incidence of CD in the female population.

In contrast, the research on the susceptibility gene characteristics of CD in the female population is almost blank. CD is a complex immune-mediated chronic intestinal disease, and the prevalence of CD has increased annually in recent years. In Western countries, studies have shown that the prevalence of positive serological test results is about 1%, and the prevalence of tissue biopsy diagnosis is about 0.6% ^[6]. The CD was once recognized as a rare disease in China. However, in recent years, CD-related studies have been reported in China, and serological surveys in many regions show that the prevalence of Chinese women is about 1% -4.9% ^[7]. All these suggest that CD is expected in the Chinese female population. The CD has a broad spectrum of clinical manifestations and involves various systems throughout the body and intestinal manifestations. The foreign literature confirmed that patients with CD intestinal performance increased significantly. About 62% of adults are diagnosed with CD with intestinal manifestations, such as iron deficiency anemia, osteoporosis, thyroid disease, vitamin D deficiency, mental illness, and a wide range of nervous system abnormalities. This study also showed that about 87% of CDs have other diseases [8], higher than the foreign data, which may be related to the small sample size and poor representativeness.

The current study showed that 36% of the female CD patients had neurological manifestations, and the proportion of CD patients in this study increased significantly to about 74% [9]. Different from foreign studies, this may be related to the small sample size, racial difference, and regional difference distribution after CD combined with neurological manifestations. As there is no relevant epidemiological study in China, there is a debate about whether routine screening for CD is necessary for patients with unexplained neurological manifestations, but the high prevalence results of this study support screening for CD. Due to the small sample size in this study, further sample size is needed to study the epidemiological characteristics of CD with neurological manifestations.

4. Diagnosis and management of CD disease conditions

(1) Extraintestinal and non-intestinal disease or symptoms in patients with autoimmune signs of celiac disease

A recent retrospective cohort study showed that 62% of women with CD had parenteral manifestations at diagnosis^[10]. This chapter showed that of twenty-nine female patients with autoimmune diseases, 49% had parenteral symptoms. Among them, insomnia, anxiety, and depression were the most common symptoms, followed by autoimmune thyroiditis and stillbirth or miscarriage in women. In addition, a skin rash was often present in the diagnosis (13.79%)^[11]. So far, the diagnosis and treatment of dermatitis herpetiformis have not been conducted in some areas, so we suspect that such patients may have both celiac disease and dermatitis herpetiformis. In addition to the rash, anemia was common in patients with autoimmune signs of celiac disease (13.79%)^[12]. Parenteral symptoms associated with CD

usually involve multiple systems, including neurological symptoms: headache or migraine; mental illness: fatigue, anxiety, depression, etc.; skin diseases: dermatitis herpetiformis; oral symptoms: recurrent oral ulcer, missing enamel; skeletal system: osteoporosis, arthritis or arthralgia; endocrine diseases: autoimmune endocrine diseases (thyroid disease, type I diabetes, etc.); reproductive system diseases: amenorrhea, infertility, etc.; blood system diseases: anemia. Therefore, Western physicians recommend CD screening for people with extraintestinal symptoms. At present, what needs to be solved is to improve physicians' awareness of various clinical manifestations of CD so that more CD patients can be treated in time and reduce the occurrence of other complications.

(2) Clinical symptoms of the digestive tract in patients with autoimmune symptoms of CD disease

Patients with autoimmune signs of breast diarrhea also had clinical manifestations (gastrointestinal symptoms) and asymptomatic symptoms (gastrointestinal polyps) and had a similar prevalence in the two female groups (1.28%.1.23%) [13]. However, the asymptomatic patients here are women with gastrointestinal polyps, so the true prevalence of CD in the asymptomatic female population should be further studied based on the general female population. In Western countries, patients with diarrheal irritable bowel syndrome or dyspepsia have a higher prevalence than (> 1%) in the general female population, so such patients are usually examined for milk diarrhea. The study showed that the prevalence of autoimmune signs of CD in patients with diarrhea, poor tolerance, and nausea or vomiting was higher than that in the general Western female population (> 2%vs.1%) [14], especially in patients with poorvolume performance. In addition, the prevalence of autoimmune signs of celiac disease in the underweight group was significantly higher than that in other groups (5.69%> 1.02%, p <0.01) [15]. Therefore, screening for CD is recommended for patients with diarrhea, poor appetite, nausea (vomiting), and unexplained weight loss are indicated.

(3) Analysis of different neurological performance of CD

Studies have shown that the frequency of neurological manifestations in CD is all called headache, peripheral neuropathy, ataxia, and epilepsy. Some foreign studies have shown that compared with the general population, the prevalence of CD patients with recurrent headaches has doubled, and the risk of headache in CD patients compared with non-CD patients in studies is higher compared with foreign data. Now, I think the cause of headache may be CD patients with gluten intake caused by impaired immune response and pro-inflammatory cytokines imbalance, induced vascular tension disease, may also be caused by long-term malabsorption of vitamin B12, folic acid, magnesium, potassium, calcium, lack of elements and low serotonin level, leading to headache attacks. Considering that the study subjects are all from the digestive department, long-term gastrointestinal diseases lead to nutrition absorption disorders, which are more likely to cause folic acid, and vitamin and iron deficiency, which is more likely to cause headaches.

Studies have shown that CD patients have lower hemoglobin, magnesium, potassium, and calcium ions than non-CD patients, proving that CD patients are prone to anemia and iron deficiency and are more likely to have headache manifestations. As presented in the Ramin Niknam et al. study, headache was the most common neurological manifestation in CD patients, which agrees with the present study. At present, a foreign Mate analysis shows that the prevalence of female headaches in CD patients is 26% [16]. About 65% of CD patients in the study have headaches, which is higher than the data from foreign studies—considering that more than half of the patients in the case group included in this study had anemia, mental disorders, autoimmune diseases, etc., which will increase the probability of headache.

A retrospective study comparing neuropathy risk in 28232 CD patients with 139473 age and sexmatched controls showed that the risk of peripheral neuropathy increased by 2.5 times in CD patients than the general population and in CD patients compared to non-CD patients than foreign data. It is currently thought to be caused by the presence of anti-neuronal antibodies, and there are also reports of neuropathy due to vitamin B12 deficiency resulting from malabsorption in CD patients. In this study, CD patients were complicated with multiple food allergies, which is not excluded to be related to the effect of food antigens on neurons. Therefore, CD patients with multiple food intolerances may be more likely to have peripheral neuropathy, leading to high data, and vitamin deficiency is not excluded as a cause of peripheral neuropathy. The present study shows significant variation in the prevalence of peripheral neuropathy, from about 0% to 39% [17], Consistent with this study. In addition to the tingling and numbness in the distal limb, EMG can also improve the evaluation of nerve damage. Studies have shown that the clinical manifestations of CD patients with peripheral neuropathy can occur before or after neuro parenchymal damage and in asymptomatic CD patients. Therefore, CD screening should be timely for unknown EMG abnormalities or tingling and numbness in the distal limb. Mearns et al. showed that the

prevalence of CD ataxia varies from 0% to 6% [18]. Consistent with the present study, although ataxia was a common neurological problem in some studies, it was the least frequent neurological manifestation in our results.

A foreign study showed that the majority of ataxia in CD patients, 69%, was mild [19]. Patients can walk without assistance, which may lead to information bias in evaluating the patient's condition. The exact mechanism of its nerve damage is not precise. Most think the cerebellar Purkinje antibody cross-reaction mediates between cells and gluten peptide. Gluten protein intake can damage the cerebellum, thus affecting gait and muscle coordination. Fine control of random movement will also be damaged, and part of the damage may be irreversible. Therefore, even if the proportion of this study is small, attention should be paid to such diseases. Epilepsy is one of the common neurological manifestations of CD, and some studies have shown that the prevalence of epilepsy in CD patients is increasing, with the prevalence ranging from 1% to 5% [20]. The prevalence of epilepsy in female CD patients is 1.8 times that of the general population [21]. There was no epilepsy among non-CD patients in the study, and no comparison could be made. Because the study subjects in this control group were all derived from the gastroenterology department, the possibility of epilepsy is minimal, and there is a chance of bias in medical treatment.

The classic triad of epilepsy was CD, bilateral occipital lobe calcification, and seizures. One of the epilepsy patients in this study was a young female patient with a previous history of epilepsy for ten years. The perfect head MRI showed no occipital calcification, and the current condition control is fair. Studies have confirmed that patients diagnosed with CD before the age of twenty have the highest risk of future epilepsy, and women with CD also have a significantly higher risk of epilepsy. Therefore, CD-specific antibody serological markers should be examined for epilepsy patients with unknown etiology, and early diagnosis and treatment may improve the efficacy of antiepileptic therapy.

(4) Association analysis of CD combined with neurological performance

The correlation analysis of CD patients with combined neurological manifestations has not been reported in China. This study performed a Logistic regression analysis of two subgroups of patients, which suggested that older age, female gender, and anemia were associated with the appearance of neurological manifestations in the univariate Logistic regression analysis. In the multivariate logistic regression analysis, age varied in the univariate analysis. After multivariate analysis, it was not statistically significant, demonstrating that women and anemia were independent risk factors for developing neurological manifestations in CD patients.

Foreign literature shows that the number of CD patients is higher in women than men. In some studies, the male-to-female ratio was 1:439 in adults ^[22]. In our research, most of the subjects were also female. In this study, we found a significant association between females and the neurological manifestations of CD, consistent with the study by Cavusoglu et al.. However, Aksoy et al. seventeen did not identify any statistical significance between gender and neurological performance, which is divergent and confirmed by further studies.

CD can occur at all ages, especially in children and patients> 20 years, 3 matching the age of onset in our analyzed patients. In our study, the mean age of patients with neurological manifestations was significantly higher than that in the group without neurological manifestations, with a significant difference between the two groups [23]. It agrees with the study of Mearns et al. four, which may be generated due to the long duration of the disease, late elimination of gluten protein in the diet, more complex and diverse diet, or different susceptibility to immune diseases. However, age in this study is not an independent risk factor for CD and the neurological system, and there are still contradictions about the correlation between age and CD and the neurological system, which requires further research and discussion. The study also found that the hemoglobin level of CD patients with neurological manifestations was significantly lower than that of CD patients without neurological manifestations, and the hemoglobin value of CD patients with neurological manifestations was lower than the average hemoglobin level, indicating a statistical difference between the two.

Anemia is the most common parenteral manifestation of CD, iron deficiency is the most common cause, and the primary mechanism of iron deficiency anemia in CD is related to malabsorption because the proximal duodenum is the leading site of iron absorption. The severity of iron malabsorption is associated with the degree of slight intestinal atrophy. Recent foreign studies showed that the prevalence of iron deficiency anemia among CD patients is between 12% and 82% [24]. The prevalence of CD in iron deficiency anemia was 3.2%B439-4, whose patients were more female, consistent with this study [25]. In this study, seven of seventeen experimental patients developed iron deficiency anemia, and one of 6 CD without neurological manifestations developed iron deficiency anemia. CD patients with

neurological manifestations were likelier to develop iron deficiency anemia B443.44^[26]. Therefore, it can be considered that CD patients have an increased risk of iron deficiency anemia, which can easily lead to neural tissue damage and brain hypoxia, resulting in neurological manifestations.

CD with neurological performance compared with neurological CD patients, longer duration, higher serum anti-tTG value, and low-density lipoprotein values for vitamin B12, folic acid, thyroid hormone, magnesium, potassium, and calcium, the current existing studies show that the duration and the size of serum anti-tTG value is not associated with CD neurological performance P1^[27]. Studies have shown that CD patients are more likely to have dyslipidemia, high levels of thyroid stimulating hormone, Ion, vitamin D, and folic acid deficiency, and high blood lipid may lead to an increased incidence of cardiovascular and cerebrovascular diseases^[28], Ion, vitamin D, and folic acid deficiency are also more likely to show neurological manifestations. This study shows no correlation between these indicators and the neurological performance of CD, which is related to the small sample size collection and poor representativeness. Therefore, we must expand the sample size for further research and proof.

(5) Infertile women and those suffering from CD disease

In developed countries, no less than 10% of the population of childbearing age suffer from infertility $^{[29]}$. When people are unable to reproduce without using contraception for 6 – 12 months, they are often diagnosed with infertility, depending on several factors, such as age. Women with recurrent abortions are also considered infertile (ACOGI 2016). Couples seek various treatments when they wish to have children, such as surgery or artificial insemination. The average couple spends about \$10,000 on assisted reproductive technology (Assisted Reproductive Technology, ART). However, almost one-third of the pregnancy loss is due to an undiagnosed and treatable disease. When we compared the serum sex hormone levels of female CD patients, the mean FSH (4.37 \pm 2.46 IU / ml) in female CD patients was like female healthy controls (4.92 \pm 2.35 IU / ml) $^{[30]}$, Clearly in Yemeni female CD patients, their infertility is independent of their serum FSH level. However, there were significantly low estradiol levels of 40.7 \pm 30.8 IU / ml in the CD patient group $^{[31]}$, While estradiol in healthy controls was 137.1 \pm 76.66 IU / ml $^{[27]}$. In addition, there were significantly low progesterone levels of 1.2 \pm 1.15 IU / ml in the CD patient group $^{[32]}$, Whereas the progesterone level in the healthy controls was 6.4 \pm 4.38 IU / ml $^{[33]}$.

Hypogonadism refers to a deficiency of reproductive hormones. Progesterone changes the endometrium from proliferative to secretory, while estradiol promotes the development of secondary sexual characteristics in women. In this study, there was no change in serum FSH levels, and progesterone and estradiol levels were decreased in Yemeni female CD patients, indicating that infertility in Yemeni female CD patients may be related to the reduced progesterone and estradiol levels. The decreased progesterone and estradiol levels were not associated with the pituitary damage caused by autoimmunity. They may be related to the decrease in cholesterol synthesis and absorption caused by intestinal epithelial damage caused by autoimmunity in CD patients.

(6) Frequency of susceptibility genes for CD

The study found that the frequency of the HLA-DQ 2 antigen and DQB 1 * 0201 alleles in northern China were higher than that in southern China, and the frequency of the DQB 1 * 0201 allele was higher in north China than in south China. Further subgroup analyses also showed the same results, with minor inconsistency only when comparing the differences of DQB 1 * 0201 in Han Chinese and minority women because the DQB 1 * 0201 allele distribution varied significantly in northern and Southern minority women, at 16.63% and 4.5%, respectively [34]. In the subgroup analysis, if the north data exceeds the south, the value of the minority will increase or decrease, and the difference between the DQB 1 * 0201 allele in the south and the north will not occur. According to the geographical distribution of gene frequencies, DQB shows that one * 0201 is more common in women in Xinjiang Uygur Autonomous Region living in northwest China, reaching 22.04% [35]. In southwest China, it is rare, only 2.89% [36]. Based on a comparative study of allele frequencies at multiple loci in China it showed that ethnic minorities living in northwest China are most genetically affected by Caucasians but less by southerners. In the European population, the DQB 1 * 02 allele frequency was 19.7% [37], Like the frequency of the DQB 1 * 02 gene (22.04%) in the Xinjiang population, explaining why DQB 1 * 02 is more common in northern China than in southern China.

There are exceptions, as the Jing people living in Guangxi Province in southern China had a high DQB 1 * 02 allele frequency, while the Qinghai Tu and Ningxia Hui people from northern China had a low DQB 1 * 02 allele. In addition, this study found that the gene frequencies of Han women and ethnic women living in the same region were similar, indicating that there is gene migration between Han women and ethnic minority women, which is consistent with the study results of Du Ruofu et al., who found that the gene characteristics of Han population in different regions were close to the local ethnic

minorities.

5. Conclusion

CD is known as a "pretender" because it often lacks typical intestinal symptoms, combined with different comorbidities, making the diagnosis and treatment of CD difficult. Over the past decade, our understanding of CD has improved dramatically, and CD is increasingly being diagnosed after recognizing the comorbidities and parenteral manifestations of the disease. The bio-psychosocial-social medicine model has surpassed the traditional medical model, emphasizing that in addition to disease diagnosis and treatment, we should also pay attention to the importance of psychological and social factors in diagnosing and treating diseases. Human health and disease are biological processes and psychological and social factors. Therefore, it is imperative for all clinicians to understand CD from the overall level of biology, psychology, and society and to attach importance to the connection between CD and mental and psychological diseases.

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