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Original Article

Screening For Hypothyroidism in Children with Celiac Disease

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Abstract *- Background: Celiac disease is one of the most prevalent autoimmune diseases affecting the digestive system, and elicited by gluten and related prolamines in genetically susceptible individuals, it is a common disease in Arab countries, CD patients are more likely to develop autoimmune diseases, especially hypothyroidism and the appearance of symptoms and signs often occurs late, which may lead to complications related to growth, puberty, mental performance, and metabolic disorders, so it is necessary to diagnose and manage early. Objective: The study aimed to assess the frequency of hypothyroidism in children diagnosed with celiac disease. Materials and Methods: An observational, descriptive, cross-sectional study was conducted over the period of three years (May 2021 - May 2024). Out of 699 patients who underwent upper gastrointestinal endoscopy for various reasons, including 56 children (32 girls and 24 boys) aged 1-16 years who were biopsy positive for celiac disease, thyroid stimulating hormone (TSH) testing was performed for all patients. Blood samples were obtained to measure free thyroxin (FT4) testing if TSH was elevated. Results: The mean TSH was 2.74±1.9 uIU/L. Nine children (16.1%) had elevated TSH levels, 7 children (12.5%) had low levels of FT4(overt hypothyroidism), and 2 children(3.6%) had normal levels of FT4(subclinical hypothyroidism). Conclusion: There is a real increase in the cases of hypothyroidism in children with celiac disease, so thyroid function in these patients must be periodically investigated.*

Keywords *- Celiac disease, Free thyroxin, Hypothyroidism, Thyroid stimulating hormone.*

1. Introduction

Celiac Disease (CD) is a systemic disorder elicited by gluten and related prolamines in genetically predisposed individuals and characterized by a variable combination of gluten-dependent clinical manifestations, enteropathy, and CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes. CD-specific antibodies comprise autoantibodies against TG2, Endomysial Antibodies (EMA), and antibodies against deamidated forms of gliadin peptides (DGP). (1)

It is one of the most prevalent autoimmune diseases affecting the digestive system 2.

The global prevalence of CD is about 1.4% depending on the seroprevalence rate and 0.7% depending on biopsy diagnosis, with wide geographic and racial differences, as it is less common in black individuals than in whites in the United States. (3)

Although it is a common disease in Arab countries, it has not been well studied, and most studies have been on a small scale. The prevalence rate in Syria was about 1.6%, according to Genetic Epidemiology. (4)

Celiac disease may manifest with typical symptoms such as vomiting, chronic diarrhea, abdominal pain and abdominal stretching, anorexia, or with atypical symptoms including constipation, failure to thrive, short stature, anaemia, depression, delayed puberty, and dermatitis. It may be silent where there are no symptoms. (5)

The European Society of Paediatric Gastroenterology and Nutrition recommends using serological tests as diagnostic criteria for CD. However, the gold diagnostic standard is the histological changes in the small bowel mucosa. A life-long gluten-free diet is an effective method to treat CD. (3)

CD patients are more likely to develop autoimmune diseases such as autoimmune Thyroid Disorder (TD), Type-I diabetes mellitus(T1DM), Addison's disease, rheumatoid arthritis, alopecia, and systemic lupus erythematous. (6)

The pathogenesis of the association between TD and CD is still unknown. However, several hypotheses have been proposed: The combination of one or more genes between the two diseases, continued exposure to gluten, and non-

adherence to the gluten-free diet leads to damage to the intestinal barrier and, thus, a systemic immune response. (7) the most common Autoimmune Thiroditis (AT) disorder is Hashimoto's disease, which is the most common cause of acquired hypothyroidism in children and adolescents (8)

As the symptoms and signs of hypothyroidism are not always obvious, Early diagnosis and treatment should be carried out to avoid complications related to growth, puberty, mental performance, and metabolic disorders, especially high blood cholesterol. (9)

This study aimed to assess the thyroid functions in Celiac Disease patients by measuring serum levels of Thyroid Stimulating Hormone (TSH) and free thyroxine (fT4).

2. Highlights

- Celiac disease is a common immune disease that is associated with other autoimmune diseases
- Hashimoto's disease is the most common cause of acquired immune hypothyroidism in children
- Symptoms and signs of hypothyroidism are not always obvious, so early diagnosis and treatment are required to avoid various complications

3. Methods and Patients

3.1. Study Population

After approval by the local research ethics committee, an observational descriptive cross-sectional study was conducted on children attending the gastroenterology clinic at Tishreen University Hospital, Syria, over a period of three years (May 2021 - May 2024). Out of 699 patients who underwent upper gastrointestinal endoscopy for different indications,63 were positive for celiac disease. The histopathological changes of small intestinal biopsies were graded according to a modified Marsh classification, where the result is considered positive if it is type 3a or more (10). The study population included 56 outpatient children (7) patients did not consent to the test) aged 1–16 years; 32 girls and 24 boys were enrolled, TSH was performed for all patients, and a blood sample was obtained for perform FT4 in case of high TSH To investigate thyroid function and diagnose hypothyroidism in these patients with biopsy-proven celiac disease.

The specimens were carried out in the laboratory of the University Hospital. Results were communicated to the parents. Those with hypothyroidism were referred to the pediatric endocrinology clinic for follow-up.

Overt hypothyroidism diagnosis was made if there was increased TSH and decreased FT4 levels and Subclinical hypothyroidism was diagnosed based on normal FT4 despite increased TSH levels.

The lower and upper limit values of the measurement method used in the biochemistry laboratory were accepted as the normal reference range for thyroid function tests (FT4: 0.61-1.48 ng/dL, TSH: 0.34-5.6 uIU/L).

The diagnosis of CD was based on serologic testing of celiac-specific antibodies (antitransglutaminase IgA, or IgG in patients with IgA deficiency) and confirmed by multiple duodenal mucosal biopsies.

3.2. Statistical Analysis

The data were analyzed using the Statistical Package for Social Science (SPSS) software version 25 with a 95% CI and a margin of error of 5%. The qualitative variables are expressed as a percentage, while the quantitative variables are represented by an average ± SD. A value of P less than 0.05 is considered significant. The inferential statistics were calculated using the prevalence rate.

4. Results

The study included 56 participants, with 32 (57.1%) girls and 24 (42.9%) boys with an average age of 7.76±3.9 years. The mean TSH was 2.74±1.9 uIU/L, and the mean FT4 was 0.44±0.3 ng/dL (Table 1). Hypothyroidism was present in 9 (16.1%) of children with celiac disease, and there were 7 cases of overt hypothyroidism and 2 cases of subclinical hypothyroidism (Table 2).

Table 1. Laboratory investigations for thyroid function test (n=56)

TSH (mIU/L)	2.74±1.9
FT4 (ng/dL)	0.61-1.48

Table 2. Hypothyroidism in the study group

Hypothyroidism	N=			Percentage (%)	
Yes	9	Overt	7	16.1	12.5
		Subclinical	2		3.6
No	47			83.9	
Total	56			100	

4. Discussion

Celiac disease is an autoimmune disorder caused by dietary gluten in genetically susceptible individuals, and there are new diagnoses largely as a result of increased awareness, better diagnostic tools, and real potential increases in occurrence. (11)

CD is closely associated with autoimmune endocrine disorders, particularly autoimmune thyroid disease (12) Autoimmune Thyroiditis (AT) disorders are multigene and factors caused by immune system dysfunction; the most common of them is Hashimoto's disease. It occurs in 3% of children aged 6-18 years, with an increased incidence in

females. It is characterized by the appearance of anti-thyroid peroxidase antibody (TPO-Ab) and/or anti-thyroglobulin antibody (TG-Ab), which leads to infiltration of lymphocytes in the thyroid gland, then fibrosis and increased tissue hardness. (13)

Ashok et al 14 found that genetic background is the primary mechanism of association between celiac disease and autoimmune thyroid disorders as the common genes are Human leukocyte Antigen (HLA-B8, HLA-D3, HLA-DQ2, HLA-DQ8), the gene encoding Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), Interleukin 18(IL-18), Interferon-gamma (IFN-Y).

Based on the high association between celiac disease and Autoimmune Polyendocrine Syndrome (APS), the European Society proposes screening for T1DM and thyroid disorders at diagnosis and then re-evaluating thyroid function every two years in patients without thyroid disorders. (15)

In our study, the Mean age was 7.76±3.9 years with children. There were 24 (42.9%) males and 32 (57.1%) females; the mean TSH was 2.74±1.9mIU/l, and the mean FT4 was 0.44±0.3. Hypothyroidism was present in 9 (16.1%) of children with celiac disease, and this result is high compared to other studies in Turkey, Italy, and Iran (16-17-18)

Sahin et al. (16) reported in Turkey that the prevalence of hypothyroidism was 9.4%; this may be due to the fact that all patients were following a gluten-free diet, as the study by Oderda et al. (19) suggests that the duration of exposure to gluten may be a risk factor for the development of autoimmunity.

The prevalence of hypothyroidism in Ansaldi et al. (17) study in Italy was 8.1%; the same percentage (8.1%) was also found in Niknam et al. (18) study in Iran; this may be due to differences related to genetics and diagnostic thresholds.

In ZEESHAN et al. (20) study in Pakistan, the prevalence of hypothyroidism was 38.3%, which is a high percentage compared to our study. This may be due to racial differences. Also, the delay in diagnosing celiac disease may be an important reason as the patients belong to poor and middle-income families, and most of them are from urban areas and have illiterate mothers.

The prevalence of 16.1% of hypothyroidism in our study is believed to be due to delays in diagnosing celiac disease and the autoimmune diseases associated with it. Due to the lack of adherence to a free gluten diet by a large number of patients due to its high cost and the economic crisis in Syria, we also were not able to perform antibodies, which does not confirm the immune mechanism of all patients. The differences in prevalence rates are also due to genetic and ethnic differences. It should also be mentioned that children who have subclinical hypothyroidism with high levels of thyroid antibodies have a greater risk of converting to overt hypothyroidism (21).

5. Conclusion

CD is a common disease and has a higher association with autoimmune diseases, including hypothyroidism, and the rates of hypothyroidism can increase later with time, therefore. periodic follow-up is necessary for early diagnosis and treatment, thus avoiding various complications.

6. Limitations of the Study

Some limitations of this study should be acknowledged, including the need for a broader test, such as performing autoimmune thyroid antibodies and determining genetic patterns.

Ethical Approval

Ethical approval was obtained from the Scientific Research Directorate at Tishreen University, according to Decision No. 4145, as well as signed informed consent from the participants' parent.

Consent

Written informed consent was obtained from the participants' parents for publication of this study. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author Contribution

N.I. contributed to data interpretation, writing the paper, and performing an extensive literature review. A.C. and Y.Z. contributed as mentors and reviewers for this study.

Guarantor

Dr. Elein Saker

Data availability statement

There were not any datasets generated during and/or analyzed during the current study that are publicly available, available upon reasonable request data sharing is applicable to this article.

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