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Role of Chronic Inflammation in Developing Non-Thyroid Illness Syndrome in Symptomatic Patient with H.Pylori-Related Gastric Affection

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Abstract:

Background: Helicobacter pylori (H. pylori) infection is a common cause of chronic gastric inflammation and has been linked to systemic effects, including thyroid dysfunction. Non-thyroid illness syndrome (NTIS) is a thyroid hormone imbalance seen in systemic illness without intrinsic thyroid disease. This study aims to evaluate the role of chronic inflammation in the development of NTIS in symptomatic cases with H. pylori-related gastric affection. **Methods:** This prospective study included 100 adult cases with gastrointestinal symptoms and confirmed H. pylori infection via stool antigen testing. All cases received standard triple therapy (PPI, metronidazole, and amoxicillin). Thyroid function (free T3, free T4, TSH) and inflammatory markers (CRP, ESR, ferritin, IL-6) were assessed at baseline and after 6 months. NTIS was defined by FT3 <1.8 pg/mL and/or FT4 <0.9 ng/dL and TSH <0.35 μIU/mL. **Results:** NTIS was observed in 5% of cases. These cases showed markedly elevated inflammatory markers compared to NTIS-negative cases: ESR first hour (23.87 ± 8.72 vs. 20.14 ± 8.51 mm/hr, P = 0.017), ESR second hour (35.37 ± 9.38 vs. 29.05 ± 9.04 mm/hr, P = 0.028), CRP (33.04 ± 2.5 vs. 27.01 ± 2.08 mg/L, P = 0.004), ferritin (251.75 ± 78.07 vs. 239.09 ± 83.34 ng/mL, P = 0.012), and IL-6 (19.33 ± 5.41 vs. 17.05 ± 4.99 pg/mL, P = 0.048). Thyroid and inflammatory markers substantially improved after 6 months of therapy. **Conclusion:** Chronic inflammation due to H. pylori infection may contribute to NTIS development. Early identification and eradication may prevent systemic complications.

Keywords: Chronic Inflammation; Helicobacter pylori; Non-Thyroid Illness Syndrome.

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Introduction

Helicobacter Pylori (H. Pylori) infection is a widespread condition, estimated to impact approximately 50% of the global population, with prevalence rates exceeding 80% in certain regions of Asia [(1)].

In addition to its well-documented deleterious effects on the gastrointestinal tract, H. Pylori has been increasingly recognized as a contributing factor in the development of extra-gastric disorders such as coronary artery disease, metabolic syndrome, insulin resistance, and type 2 diabetes mellitus. Among these systemic associations, considerable attention has been directed toward exploring the relationship between H. Pylori infection and thyroid dysfunction, particularly autoimmune thyroid disorders (ATDs). Notably, previous investigations in this context have not imposed age-related inclusion criteria for study participants [(2)].

Age-related morphological and physiological changes in the thyroid gland predispose older adults to functional disturbances, which have been linked to adverse clinical outcomes, including increased hospitalization rates and mortality—emphasizing the vital importance of thyroid assessment in geriatric health management [(3)].

Age-related transcriptome profiling of the thyroid has demonstrated gene expression changes indicative of mitochondrial compromise and proteostatic imbalance [(4)].

Evidence-based international guidelines delineate therapeutic approaches tailored to the clinical spectrum of thyroid dysfunction, encompassing both clinical and subclinical presentations [(5)].

Prolonged inflammation driven by H. Pylori infection can elicit widespread autoimmune responses, implicating diverse tissues and organ systems [(6)].

Evidence suggests that the systemic immunoinflammatory response to H. Pylori infection may extend beyond the gastrointestinal tract, contributing to thyroid-related pathologies, including decreased serum free thyroxine, the presence of thyroid nodules, increased glandular volume, and ATD [(7)].

Notable associations have been identified between H. Pylori infection and the development of NTIS, a condition prevalent among critically ill cases and recognized for its negative implications on recovery trajectories and overall prognosis [(8)].

The current study aimed to evaluate the role of inflammation in developing NTIS in *H. Pylori* infected cases.

Patients and methods:

Patients:

This prospective investigation was conducted at Internal Medicine Department, Faculty of Medicine, Benha University on a sample consisted of 100 adult cases presenting with gastrointestinal symptoms and diagnosed with H.Pylori infection during the period from April 2023 to April 2024.

Approval to conduct this research was granted by the Faculty of Medicine, Benha University's Research Ethics Committee (Approval Code: MS 26-2-2023). Informed consent was documented from all participants or their legal guardians. All necessary institutional permissions were obtained before the study began.

The diagnostic criteria for H. pylori infection included the presence of gastrointestinal symptoms (e.g., epigastric pain related to meals), positive H. pylori antibody in blood, positive stool antigen test, and normal abdominal ultrasound; H. pylori infection was confirmed by stool antigen detection [(9)].

Inclusion criteria encompassed cases over 20 years of age of both sexes diagnosed with H. pylori. Exclusion criteria comprised asymptomatic cases; those receiving NSAIDs; smokers; obese or overweight cases (BMI >25 kg/m²); patients experiencing emotional stress; diabetic cases; chronic diseases; other endocrine disorders (e.g., MEN); or chronic inflammatory conditions

Methods:

Every patient was subjected to laboratory test including: testing for H.pylori antibodies in serum, stool antigen detection, inflammatory markers (CRP, IL-6, ferritin, ESR), and thyroid function tests (T4, T3, TSH) [10].

NTIS was diagnosed based on serum FT3 <1.8 pg/mL and/or FT4 <0.9 ng/dL with TSH <0.35 μIU/mL [11].

Triple therapy included esomeprazole 40 mg twice daily, amoxicillin 1 g twice daily, and metronidazole 500 mg twice daily for 14 days, with only one treatment course administered [12].

Criteria for successful H. pylori eradication included a negative stool antigen test 4-6 weeks after therapy [13].

Radiological investigations including abdominal ultrasound [cases treated by standard triple therapy _H. Pylori eradication, Thyroid function done after eradication follow up for 6 months for recurrence of H. Pylori then thyroid function at 6 months].

Statistical analysis

Microsoft Excel 2016 (Microsoft Office Suite, USA) was utilized for data entry and coding, and statistical analyses were carried out using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics included mean ± standard deviation for continuous variables and frequencies with corresponding percentages for categorical variables.

Results:

Table 1 showed that the mean age was (35.93± 13.45) and as regard sex the percentage of male were (49 %) and female were (51 %).

Mean serum levels recorded were 2.82 pg/mL for free T3, 1.06 ng/dL for free T4, and 2.82 μIU/mL for TSH. Low free T3 was observed in 5% of cases, low free T4 in 3%, and reduced TSH in 2%. The prevalence of NTIS among the studied group was 5%. **Table 2**

Table 3, Figure 1 showed that NTIS cases were (5%) and negative cases were (95%).

Mean ESR (1st hour: ≤7 mm, 2nd hour: ≤15 mm), CRP, ferritin, and IL-6 levels were all substantially elevated in NTIS cases than in negative cases. **Table 4**

Mean freeT3, free T4 and TSH were increased after 6 months compared to before 6 months. Mean ESR first hour (up to 7mms) and ESR second hour (up to15mms) were decreased after 6 months compared to Before 6 months. CRP, IL-6, and ferritin levels demonstrated a statistically significant reduction at the 6-month follow-up compared to baseline measurements.

N.B. Normal reference ranges of thyroid function tests were as follows, TSH (0.35–6.5 mlU/ml); FT4 (.9–1.9 ngl/dl) and FT3 (1.8–4.6 pg/ml). Criteria for NTIS applied in our study were as follows: (1) FT3 level <1.8 pg/ml; and / or (2) FT4 level <0.9 ngl/dl, (3) TSH < 3.5 mlU/ml.

Table 1: Demographic data of the studied cases

		N=100
Age (years)		35.93± 13.45
Sex	**Female**	51 (51.0%)
	Male	49 (49.0%)

Data presents as mean ± SD or frequency (%).

Table 2: Thyroid function of the studied cases.

	N=100
Free T3 (pg/ml)	2.82± 1.1
Normal	95 (95.0%)
Low	5 (5.0%)
Free T4 (ng/dl)	1.06± .29
Normal	97 (97.0%)
Low	3 (3.0%)
TSH. (ulU/ml)	2.82± 1.63
Normal	98 (98.0%)
Low	2 (2.0%)

Data presents as mean ± SD or frequency (%), T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid-Stimulating Hormone.

Table 3: Prevalence of Non thyroid illness syndrome among the studied cases.

Categories	No. (%)
Non thyroid illness syndrome cases	5 (5%)
Negative cases	95 (95%)

Data presents as frequency (%).

Table 4: Comparison between Non thyroid illness syndrome cases and Negative cases regarding (ESR, CRP, Ferritin and IL6).

	Non thyroid illness syndrome	Negative cases	t.test	P. value
ESR first hour (up to 7mms)	23.87± 8.72	20.14± 8.51	1.362	**0.017***
ESR second hour (up to15mms)	35.37± 9.38	29.05± 9.04	0.151	**0.028***
CRP	33.04± 2.5	27.01± 2.08	1.5	**0.0 4***
Ferritin	251.75± 78.07	239.09± 83.34	0.658	**0.012***
IL6	19.33± 5.41	17.05± 4.99	-.603-	**0.048***

Data presents as mean ± SD or frequency (%). ESR: erythrocyte sedimentation rate, IL6: Interleukin 6, CRP: C-reactive protein, *: significant as P value ≤ 0.05

Table 5: Relation between (thyroid functions, ESR, CRP, IL6 and Ferritin) and follow up after 6 months among non-thyroid illness syndrome.

	Before 6 months	after 6 months	Paired sample t.test	P. value
Free T3 (pg/ml)	2.2±.62	3.86± .740	6.3	**0.001***
Free T4 (ng/dl)	1.09± .39	1.64± .240	7.6	**0.038***
TSH. (ulU/ml)	1.92±.83	3.80±1.15	9.1	**0.014***
ESR first hour (up to 7mms)	23.87± 8.72	4.40± 1.71	0.754	**0.000***
ESR second hour (up to15mms)	35.37± 9.38	8.18± 1.47	0.858	**0.000***
CRP	33.04± 2.5	3.70± 1.09	0.958	**0.002***
IL6	19.33± 5.41	4.10± 2.01	-.603-	**0.007***
Ferritin	251.75± 78.07	78.00± 19.23	0.758	**0.000***

Data presents as mean ± SD or frequency (%). T3: Triiodothyronine, T4: Thyroxine, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, IL6: Interleukin 6, *: significant as P value ≤ 0.05

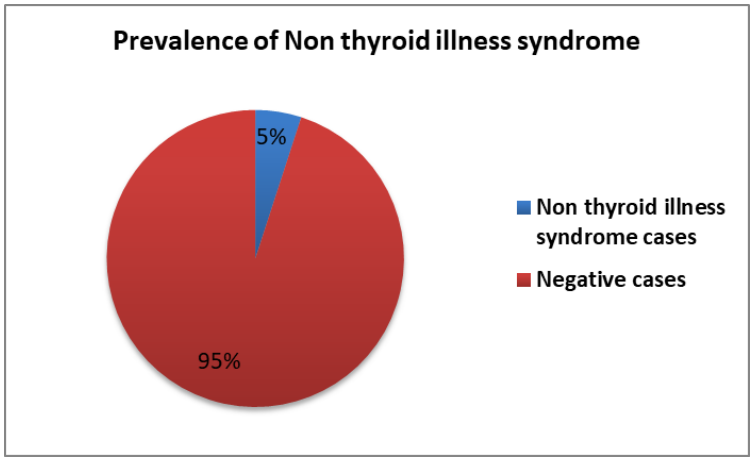

Figure 1: Prevalence of Non thyroid illness syndrome among the studied cases.

Discussion:

In the current study, cases treated by triple therapy of PPI& metronidazole & amoxicillin in (100%). With eradication about 64% of the study cases. In harmony with the findings of Shiota et al. [14] clarithromycin-based triple therapy has been shown to eradicate approximately 77% of H. pylori infections in the United States; however, its efficacy is strongly influenced by local rates of clarithromycin resistance.

In the present study, the mean freeT3 level was 2.82 pg/ml, freeT4 was 1.06 ng/dl, and TSH was 2.82 ulU/ml. This study shows that 5% of studied cases had low freeT3, 3% of studied cases had low freeT4, 2% of studied cases had low TSH. The prevalence of NTIS in this study was 5%. In partial concordance with the findings of Sun et al. [15] NTIS was identified in 30 out of 210 cases (14%) who experienced acute medical conditions and required hospitalization during a five-year follow-up period. Importantly, the prevalence of NTIS was substantially higher among individuals with H. Pylori infection relative to those without (17.1% vs. 5.6%, P = 0.001). Furthermore, multivariate logistic regression analysis revealed that H. Pylori infection remained an independent predictor of NTIS after adjusting for age, hemoglobin level and APACHE II score (OR = 3.497, P = 0.003). In agreement with Sun et al., [15] explained relationship between Higher Prevalence of NTIS in cases with Active H. Pylori Infection by investigating the link between NTIS and interleukin were markedly higher in NTIS cases. Silva et al., [16] evaluated the relationship between H. Pylori infection and ATD in children. In contrast to some adult data, they did not find an association between H. Pylori status and ATD in children. However, the frequency of H. Pylori positivity was low overall but did increase with older age, suggesting the role of this infection in autoimmunity may differ between pediatric and adult populations. A noteworthy observation in the study was the 34.90% prevalence of H. pylori infection detected in children with congenital hypothyroidism. Moreover, serum T3 levels were lower in H. Pylori-positive children compared to negative cases, indicating the infection impacts thyroid hormone balance. But TSH and T4 levels were unchanged, implying the underlying hypothalamic-pituitary-thyroid axis function remains intact. Overall, this study implies H. Pylori may disrupt thyroid function in infected children despite not clearly driving higher autoimmunity rates as seen in adults.

Conversely, other investigations [17, 18] reported no substantial differences in serum thyroid hormone concentrations or thyroid autoantibody levels between

individuals with and without H. Pylori infection. Additionally, the presence of H. Pylori did not appear to elevate the risk of ATD among cases presenting with dyspeptic symptoms [18]. Contrary to these findings, Triantafillidis et al. [19] demonstrated a substantial discrepancy in serum FT4 concentrations between H. Pylori-positive and -negative individuals (1.04 ± 0.2 ng/dL vs. 1.17 ± 0.3 ng/dL, P = 0.025), suggesting a potential endocrine influence of the infection in healthy populations.

These findings are inconsistent with those reported by Larizza et al. [20] , who investigated thyroid disorders in a pediatric population and identified a notable association between ATD and H. Pylori positivity. The authors suggested that ATD in childhood may represent an early manifestation of the disease, with its development potentially requiring prolonged infection duration and/or the presence of additional risk factors. The interplay between genetic predisposition and environmental influences was proposed as a key contributor to the pathogenesis of ATD in children [21].

It is conceivable that the systemic inflammatory response induced by chronic H. Pylori infection may contribute to broader physiological effects, potentially triggering adaptive mechanisms similar to those observed in NTIS.

Supporting the observations of Papamichael et al. [22] evidence indicates that persistent H. Pylori infection can incite inflammation in organs outside the gastrointestinal tract, particularly targeting the endocrine system. However, the comparable distribution of H. Pylori infection, irrespective of CagA strain status, in both Hashimoto's thyroiditis cases and control groups, challenges the notion of a definitive etiological link [17].

In pediatric populations, H. Pylori infection is linked to heightened secretion of inflammatory cytokines, particularly those involved in the innate immune response. Notably, TNF-α levels tend to be elevated to a greater extent in infected children compared to adults [23].

This study findings indicated a 5% prevalence of NTIS among the study population. In a five-year study, Sun et al.[15] observed that 30 out of 210 cases (14%) developed NTIS during episodes of acute illness requiring hospitalization. The condition was markedly more prevalent among H. Pylori-positive individuals (17.1%) compared to those without the infection (5.6%, P = 0.001).

In the current study, CRP levels were substantially elevated in NTIS cases. This aligns with other studies, such as Martocchia et al. [24], which found elevated CRP in NTIS cases.

In the present study, ESR and Ferritin levels were substantially higher in NTIS cases. Contradicting our results, Lee et al. [25] analyzed the relationship between NTI severity and inflammatory parameters such as ESR and CRP, and observed no substantial variations in ESR values across the comparison groups.

In this study, IL-6 levels were markedly higher in NTIS cases. In agreement with Wajner et al. [26] demonstrated the importance of IL-6 in NTIS, supporting this study's findings.

This study is limited by its small sample size, single-center design, lack of a control group, which may limit the findings' generalizability and depth. Larger, multi-center studies with a control group are recommended to confirm these results.

Conclusion:

A potential inflammatory pathway may underline the association between H.pylori infection and NTIS. This underscores the crucial role of systemic inflammation in NTIS development among infected cases and highlights the clinical importance of detecting and addressing H. pylori in cases with gastrointestinal manifestations to lower the likelihood of NTIS.

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Author contribution

Authors contributed equally to the study.

Conflicts of interest

The authors declare that no Conflicts of interest.

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