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Original Article

Does previous tuberculosis increase the risk of functional gastrointestinal disorders in children?

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ABSTRACT

Objective: Functional gastrointestinal disorders (FGIDs) encompass a range of chronic conditions of unknown etiology, including functional dyspepsia, irritable bowel syndrome, functional abdominal pain, and functional constipation. The exact pathogenic mechanisms behind tuberculosis (TB) are unclear. This study aimed to investigate whether children with previous TB are at an increased risk of developing FGIDs after completion of TB treatment.

Materials and **Methods:** A total of 35 patients diagnosed with TB (age range, 24 to 216 months) and 49 age- and sex-matched healthy controls were included in this retrospective study. Patients were evaluated for the presence of FGID symptoms after at least 6 months had passed after cessation of TB treatment, while the control group was assessed at the time of their first examination according to the Rome IV criteria.

Results: The overall prevalence of FGIDs was 42.9% (n=15) in the patient group versus 12.2% (n=6) in the control group. A significant difference was found between the groups in terms of the frequency of FGIDs and the diagnosis of functional abdominal pain ($p = 0.001$ and $p < 0.001$, respectively).

Conclusions: This study demonstrated a higher prevalence of FGIDs in children with a history of TB compared to healthy controls, supporting the hypothesis that FGIDs are more common in children with previous TB. Children with previous TB may be at an increased risk for FGIDs, possibly due to chronic inflammation and immune system alterations associated with TB, highlighting the need for ongoing assessment of GI health in this population.

Keywords: children, functional gastrointestinal disorders, tuberculosis.

INTRODUCTION

Functional gastrointestinal disorders (FGIDs), also known as disorders of gut-brain interaction, encompass a range of chronic, relapsing conditions of unknown etiology. The most common subtypes include functional dyspepsia, irritable bowel syndrome (IBS), functional abdominal pain, and functional constipation. Diagnosis and treatment of FGIDs are challenging because they do not cause any obvious structural or biochemical changes in the gastrointestinal (GI) system.[1] Low-grade inflammation plays a role in the pathogenesis of FGIDs. Disruption to the gut-brain axis, associated changes in GI microbiota and mucosal permeability, as well as abnormalities in mucosal defense mechanisms, are also involved in the disease process.[2-4]

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Tuberculosis (TB) is a preventable, chronic, inflammatory, and infectious disease caused by the *Mycobacterium tuberculosis (M. tuberculosis)* complex. After exposure to *M. tuberculosis* and subsequent deposition in the lungs, one of the following outcomes may occur: immediate clearance of the organism, immediate onset of active disease (primary disease), latent infection, and reactivation disease (onset of active disease years after a period of latent infection).[5] In children, TB most commonly manifests as pulmonary disease and/or intrathoracic adenopathy. Sites of extrapulmonary involvement include the lymph nodes, central nervous system (CNS), abdomen, and bones/joints.[6]

The exact pathogenic mechanisms behind TB are unclear. The time between aerosol droplets containing *M. tuberculosis* entering the body and disease onset varies among individuals. Studies have shown that *M. tuberculosis* causes persistent infection due to persistent inflammation, chronic antigen exposure, and chronic antigenic stimulation despite the induction of adaptive immune responses.[5] Low-grade, chronic inflammatory process induced by the inhalation of the aerosol droplets permanent or temporary changes in the gut microbiota following the development of TB, and GI changes associated with the therapeutic agents used suggest that FGID symptoms may be triggered in children with TB.[7-9]

The aim of this study was to investigate whether children with previous TB are at an increased risk of developing FGIDs after completion of TB treatment.

MATERIALS AND METHODS

This study has a retrospective design.

Sample selection

Forty-eight patients who received treatment for tuberculosis at our department between January 1, 2017, and November 1, 2021, were evaluated for FGID symptoms after at least six months had passed since the cessation of the TB treatment. For each patient, relevant information was obtained by reviewing their medical records retrieved from the hospital database and questioning their parents.

Inclusion and exclusion criteria

Patients with symptoms of organic GI disorders such as involuntary weight loss, significant vomiting, chronic diarrhea, bloody stools, fever, or a family history of inflammatory bowel disease, as well as those previously diagnosed with FGID were excluded from the study. Individuals with a history of any chronic rheumatic or endocrinological disease and/or those currently receiving any medications were also excluded.

A total of 13 patients who did not attend follow-up examinations regularly, had chronic diseases, and were diagnosed with and treated for any FGID were excluded from the study. None of the TB patients in the study had FGID symptoms or follow-up before TB treatment. The control group consisted of children without any health problems as reported by their parents and did not meet the aforementioned exclusion criteria. Ultimately, the study population consisted of 35 patients with TB, aged between 24 and 216 months, and 49 age- and sex-matched healthy controls. The study flow diagram is presented in Figure 1.

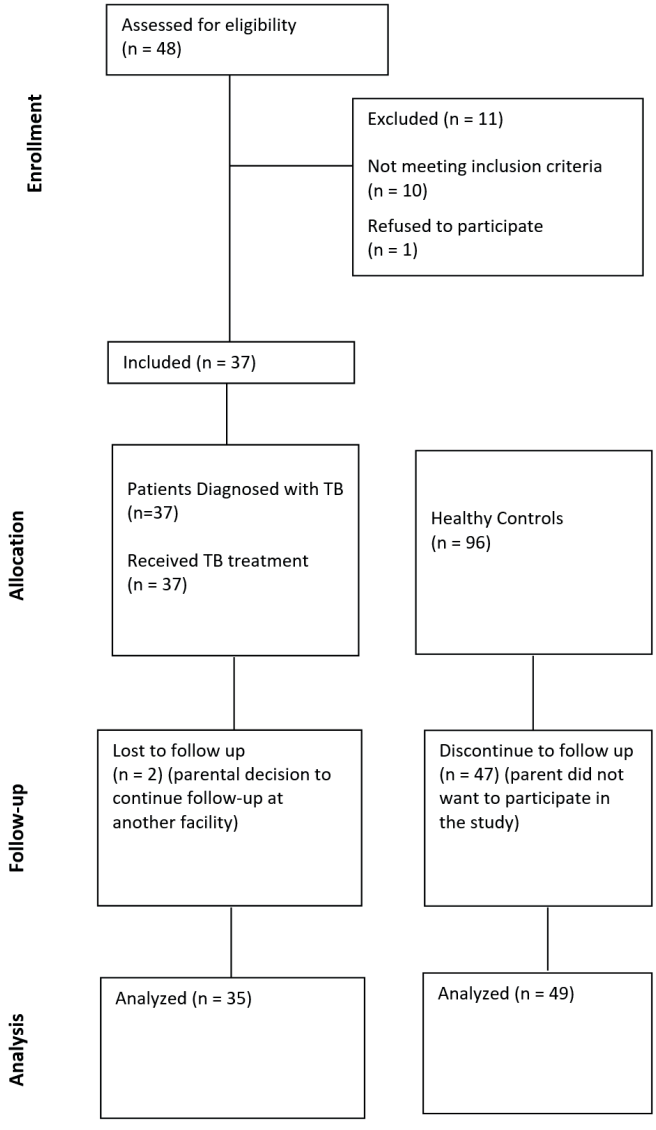

Figure 1. Flow diagram showing participants through each stage of the study

Patients were evaluated for the presence of FGID symptoms after at least 6 months had passed after completing TB treatment, while the control group was assessed at the time of their first examination according to the Rome IV criteria by experienced pediatricians.[10] The diagnosis of tuberculosis was established by reviewing the results of clinical, radiological, bacteriological, and histopathological examinations in patients suspected of having TB based on their history, physical examination, laboratory workup, and chest X-ray findings.[11] Among the laboratory parameters of the patients, white blood cell (WBC), platelet (PLT), lymphocyte and neutrophil counts, hemoglobin concentration, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level were noted. Data on patient sex, age at diagnosis, symptoms such as cough, fever, weight loss, areas of involvement, medications used for TB treatment, and total duration of treatment were also noted.

Diagnosis of Functional Gastrointestinal Disorders

We used the Rome IV criteria to diagnose FGIDs at study enrollment and at least six months after completing TB treatment. FGIDS were simply classified into three subcategories: functional nausea and vomiting disorders, functional abdominal pain disorders, and functional defecation disorders. These conditions were identified in both patient and control groups using specific diagnostic criteria for the subcategories, including functional dyspepsia, IBS, functional abdominal pain, and functional constipation.

For the diagnosis of functional dyspepsia, one or more of the following symptoms must be observed at least 4 times a month in the last 2 months: postprandial fullness, early satiety, epigastric pain, or burning not associated with defecation. Patients are diagnosed with IBS if they experience recurrent abdominal pain at least 4 days per month, associated with two or more of the following: symptoms related to defecation, changes in the frequency and appearance of stools, and symptoms that persist even after resolution of constipation. According to the Rome IV criteria, episodic or persistent abdominal pain must occur at least 4 times per month for at least 2 months in the absence of sufficient criteria for other functional abdominal pain disorders. Additionally, functional constipation is diagnosed when a patient meets two or more of the following criteria at least once a week for at least one month, with insufficient criteria for IBS: two or fewer defecations per week, fecal incontinence more than once a week, retentive posturing, history of painful or hard bowel movements, large fecal mass in the rectum, and large diameter stools.

For all FGID diagnoses, symptoms must not be attributable to any other medical condition after appropriate evaluation.[10]

Statistical analysis

All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY). Categorical variables were reported as numbers and percentages, while continuous variables were summarized as median and interquartile range (IQR). Chi-square and Fisher's exact tests were used to compare categorical variables between the groups. The between-group age difference was analyzed using the Mann-Whitney U test among continuous variables. The statistical significance level was set at 0.05 for all tests.

Ethics statement

This study has been approved by the Adıyaman University Non Interventional Clinical Research Ethics Committee (approval date 24.05.2022, number 2022/5-16). Written informed consent was obtained from the participants.

RESULTS

The patient group comprised 35 children with a median age of 11.5 years (IQR,5.75-14). Among them, 42.9% (n=15) were male and 57.1% (n=20) were female. The control group consisted of 49 children with a median age of 8 years (IQR, 3-12.2), 57.1% (n=28) of whom were male and 42.9% (n = 21) were female. No significant difference was found between the groups in terms of age (p = 0.115) or sex (p = 0.197).

Of the patients diagnosed with TB, 65.7% (n=23) had pulmonary tuberculosis, 22.9% (n = 8) had tuberculous lymphadenitis, 8.6% (n = 3) had gastrointestinal tuberculosis, 2.9% had (n = 1) had tuberculous meningitis. TB treatment was completed in all patients at least six months prior to the study. None of the patients had laboratory and/or clinical findings suggesting relapse or treatment failure during post-treatment follow-up. The patients' Laboratory workup results and clinical characteristics are shown in Table 1.

Initial TB treatment was administered as a combination of three (RHZ) or four (RHZE) drugs, including rifampin, isoniazid, and pyrazinamide, with or without ethambutol. After two months of initial treatment, maintenance treatment with rifampin and isoniazid was commenced. For each patient, the duration of treatment was determined based on the area and extent of involvement, as well as the results of clinical, radiological, and bacteriological examinations. The minimum duration of treatment for all patients was six months.

In the patient group (n=35), the median (IQR) time elapsed since the cessation of TB treatment was 8 (6-12) months. When the

Table 1. Laboratory and clinical data of the patient group at the time of diagnosis	
Variables	
CRP** (mg/dL)	39 (20-68)
ESR** (mm/h)	37 (27.5-59)
WBC** (103/uL)	14,500 (9675-18,100)
Hb** (g/dL)	11 (10-12)
Neutrophils** (103/uL)	9745 (5450-13,000)
Lymphocytes** (103/uL)	4670 (2975-5600)
Presence of cough, n (%)	23 (65.7%)
Presence of fever, n (%)	27 (77.1%)
Presence of weight loss, n (%)	27 (77.1%)
Pulmonary tuberculosis, n (%)	23 (65.7%)
Tuberculous lymphadenitis, n (%)	8 (22.9%)
Gastrointestinal tuberculosis, n (%)	3 (8.6%)
Tuberculous meningitis, n (%)	1 (2.9%)
Treatment duration (months)*	8.57 ± 1.65
Type of treatment	
Triple treatment, n (%)	8 (22.9%)
Quadruple treatment, n (%)	27 (77.1%)

* mean± SD (standard deviation)
** median (IQR)
WBC: White Blood Cell, Hb: Hemoglobin, PLT: Platelet Count, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein.

TB patients were divided into two subgroups, those with or without a FGID, the median time elapsed since TB treatment discontinuation was 9 (6-12) and 8 (7-11) months, respectively. No significant difference was observed between the subgroups (p = 0.973).

The frequencies of FGIDs and their subtypes in the study population are shown in Table 2. The overall prevalence of FGIDs was 42.9% (n=15) in the patient group and 12.2% (n=6) in the control group. A significant difference was found between the groups with respect to the overall frequency of FGIDs (p = 0.001). The frequency of functional abdominal pain was higher among the patients (34.3%, n=12) versus controls (2%, n=1), with a significant difference between the groups (p<0.001). There was no statistically significant difference between groups for other FGID subtypes.

DISCUSSION

In this study investigating whether children diagnosed with TB show an increased frequency of FGIDs after cessation of treatment, it was found that FGIDs were more common in patients with previous TB than in healthy controls.

In TB, phenotypic and genetic variation of the bacteria, as well as the interaction between the bacteria and their hosts, can affect the disease progression.[12] Although TB typically affects the lungs, abdominal TB accounts for about 5 percent of all TB cases. Clinical signs of abdominal TB may include fever, weight

Table 2. Frequency of functional gastrointestinal disorders in patient and control groups			
	Patients (n=35)	**Controls (n=49)**	**p**
Age (years)-median (IQR)	11.5 (5.75-14)	8 (3-12.2)	p = 0.115
Sex, n (%)			p = 0.197#
Male	15 (42.9%)	28 (57.1%)	
Female	20 (57.1)	21 (42.9%)	
FGID, n (%)			p = 0.001#
Yes	15 (42.9%)	6 (12.2%)	
No	20 (57.1%)	43 (87.8%)	
Cyclic vomiting, n (%)	1 (2.9%)	0 (0.0%)	p = 0.417*
Functional dyspepsia, n (%)	2 (5.7%)	2 (4.1%)	p = 0.556*
Irritable bowel syndrome, n (%)	2 (5.7%)	0 (0.0%)	p = 0.171*
Functional abdominal pain, n (%)	12 (34.3%)	1 (2%)	p <0.001*
Functional constipation, n (%)	4 (11.4%)	3 (6.1%)	p = 0.316*

FGID: Functional gastrointestinal disorders
Using Chi-square test, *Using Fisher's exact test.

loss, abdominal pain, bloating, ascites, hepatomegaly, diarrhea, intestinal obstruction, and abdominal mass.[13]

FGIDs are a collection of chronic or recurrent gastrointestinal symptoms that occur in the absence of a known underlying structural or biochemical abnormality. Currently, it is believed that low-grade and/or chronic inflammation, disruptions to the GI microbiota, changes in mucosal permeability, and impaired mucosal defense mechanisms are responsible for the pathogenesis of FGID.[2-4,14]

Although the reported prevalence of FGIDs varies across studies, Vernon-Roberts et al.[15] found a median prevalence of 22.2% (range 5.8-40%) in children up to four years of age and 21.8% (range 19-40%) in children aged four to eighteen years. In a study, Alonso-Bermejo et al.[16] reported that the annual frequency of FGIDs based on the Rome IV criteria was 32.4% in children under 16. In our study, the median frequency of FGIDs was higher compared to previous reports, with 42.9% (n=15) of the patients and 12.2% (n=6) of the controls being diagnosed with an FGID, and the difference between the groups was significant (p=0.001).

In many parts of the world, the prevalence of TB is much higher in males than in females.[17] On the other hand, FGIDs are more common in females than in males.[18] Our study findings show both similarities and contrasts with the existing literature in terms of sex distribution in TB and FGIDsin terms of sex distribution. Contrary to the literature, 42.9% (n = 15) of the patients diagnosed with TB were male, and 57.1% (n = 20) were female. However, consistent with the literature, 40% (n = 6) of the patients who developed any FGID were male and 60% (n =9) were female.

Functional dyspepsia, IBS, functional constipation, and functional abdominal pain are the most common manifestations of FGIDs in children.[19] In our study, among FGIDs, functional abdominal pain was the most common in the patient group (34.3%, n=12), while cyclic vomiting was the least frequent (2.9%, n=1). By comparison, functional constipation was the most prevalent FGID in the control group, diagnosed in 6.1% (n=3) of the controls. Statistical analysis revealed a significant difference in the frequency of functional abdominal pain between the patients and controls (Table 2).

Our study demonstrated that both the overall frequency of FGIDs and the prevalence of functional abdominal pain were higher in TB patients than in controls. Additionally, our study diagnosed 3 (8.6%) patients with gastrointestinal TB. Considering that there is some overlap in symptoms of gastrointestinal TB and FGIDs, especially concerning abdominal discomfort and changes in bowel movements, these three patients were evaluated more attentively for proper differentiation. One of these patients did not have any FGID symptoms, the second patient had IBS and cyclic vomiting, and the third patient had functional constipation. These patients were evaluated approximately one year after completion of TB treatment. Of note, after TB treatment, these three patients no longer exhibited any symptoms or signs present at the time of diagnosis. Based on these results, we concluded that the observed conditions were more likely associated with FGIDs rather than the residual effects of previous TB. Our findings support the hypothesis that FGIDs are more common in patients with a history of TB than in healthy controls.

Studies have shown that infections of the GI tract, nonspecific inflammation, exacerbations of IBD, celiac disease, rheumatic, autoimmune, and some inflammatory diseases may cause FGIDs.[20-22] Paula et al. showed that extra-intestinal infections may also trigger FGIDs. They suggested that this could be due to changes in the GI tract induced by a previous GI infection (e.g., alterations in cytokine production) and/or the use of antibiotics that modify the gut microbiota, both of which can trigger symptoms .[23]

In many countries, patients with TB are not followed for extended periods after treatment, resulting in limited data on the extent of long-term complications of the disease and their impact on children. In a study by Igbokwe et al.[24], it was reported that a small number of patients receiving conservative treatment for GI TB may experience permanent sequelae, such as recurrent adhesive obstructions, in the following years. However, the same study also noted that none of the long-term and/or permanent sequelae caused by other types of TB were related to the gastrointestinal system. This information is crucial for differentiating between GI TB and FGIDs to avoid confusion due to overlapping symptoms of these conditions.

A review of the literature revealed that the relationship between previous TB and FGIDs has not been thoroughly investigated. At present, it is not known exactly how long the inflammatory state and the changes in the immune system associated with TB persist or when they subside or resolve. Moreover, long-term antibiotic treatment for TB can lead to changes such as immune system dysregulation, altered mucosal permeability, abnormal mucosal defense mechanisms, inappropriate activation of the host immune system, and microbiota plasticity.[23] Due to the interaction of all these TB-related factors with host-related factors, patients with a history of TB may be susceptible to the development of FGIDs. To our knowledge, there is no other study in the literature focusing on the relationship between previous TB and susceptibility to FGIDs.

While attributing FGID symptoms to TB or its treatment after 6 months might seem indirect, several plausible mechanisms exist. Firstly, TB treatment often involves a prolonged course of antibiotics. Antibiotics can disrupt the normal gut flora, potentially leading to conditions like antibiotic-associated diarrhea or IBS. Disruptions in the microbiome can last long after the antibiotics have been stopped, contributing to FGID symptoms. Secondly, some of the drugs used to treat TB, such as rifampin or isoniazid, can cause GI side effects like nausea, diarrhea, or abdominal pain. Even after the drugs are discontinued, there might be lingering effects or sensitivity. Also, TB can cause significant inflammation in the GI tract, especially if the infection was extrapulmonary or gastrointestinal involvement. After the treatment, residual inflammation or immune system changes might contribute to ongoing FGID symptoms. Some GI symptoms might not appear immediately after the treatment but could develop over time as the body continues to recover and adjust from the effects of the illness and its treatment.

Limitations

The main limitations of this study are the relatively small sample size and its retrospective design. Future studies should investigate the underlying mechanisms linking TB with FGIDs and explore potential preventive or therapeutic strategies.

CONCLUSION

Our study supports the hypothesis that patients with previous TB are more likely to develop FGIDs than healthy controls. Children with previous TB may be at an increased risk for FGIDs, possibly due to chronic inflammation and immune system alterations associated with TB, highlighting the need for ongoing assessment of GI health in this population. Healthcare providers should be aware of the increased risk of FGIDs in children with a history of TB and implement appropriate monitoring and management strategies.

Ethical approval

This study has been approved by the Adıyaman University Non-Interventional Clinical Research Ethics Committee (approval date 24.05.2022, number 2022/5-16). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: HU, SY; Concept: HU, SY, SO; Design: HU, MT, SBO; Data Collection or Processing: HU, SO, NE; Analysis or Interpretation: HU, NE, MT; Literature Search: HU, SBO; Writing: HU, SY, NE. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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