İstanbul Med J 2021; 22(3): 213-7
DOI: 10.4274/imj.galenos.2021.01058

First Case-Control Study of Intestinal Parasites in Follow-up Schizophrenia Patients: Are We Overlooking the Role of These Agents?

Takip Edilen Şizofreni Hastalarında Barsak Parazitleri Araştırılmasındaki İlk Olgu Kontrol Çalışması: Bu Ajanların Rolünü İnceliyor muyuz?

Zeynep Yalnız[1], Ersel Bulu[2], Yasin Kavla[2], Burcu Sapmaz[1], Reyhan Çalışkan[1], Cana Aksoy Poyraz[2], Yaşar Ali Öner[1], Ömer Faruk Demirel[2], Özer Akgül[1]

[1]İstanbul Aydın University Faculty of Medicine, Department of Medical Microbiology, İstanbul, Turkey
[2]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Psychiatry, İstanbul, Turkey

ABSTRACT

Introduction: Disability and decrease in the quality of life owing to the nature of schizophrenia are considered factors that predispose patients to parasitic infections. This study aimed to investigate intestinal parasites in schizophrenia and healthy volunteers with similar age-gender data and to contribute to the literature and/or clinical practice by determining the underlying cause of gastrointestinal complaints (such as side effects of psychiatric drugs or overlooked parasitic infection) in patients with schizophrenia.

Methods: This case-control study included 30 patients with schizophrenia and 30 healthy volunteers. Their stool samples were examined for the presence of intestinal parasites primarily microscopically or serologically in cases requiring differential diagnosis.

Results: The overall positivity rate of intestinal parasites was 25% (15/60). The difference between the intestinal parasite detection rates, which was 36.7% (11/30) in the schizophrenia group and 13.3% (4/30) in the healthy control group, was significant (odds ratio: 3.76; 95% confidence interval: 1.04-13.65; $p<0.05$). The distribution of parasite species varied: 6 (20%) patients had *Blastocystis* spp., 3 (10%) had *Giardia intestinalis (G. intestinalis*), and 2 (6.7%) had *Entamoeba histolytica* in the schizophrenia group, whereas 3 (10%) had *Blastocystis* spp. and 1 (3.3%) had *G. intestinalis* in the healthy control group.

Conclusion: To increase the quality of life of patients with a chronic psychiatric disease such as schizophrenia and to prevent possible transmission, periodic examination of parasitic agents is necessary in addition to psychiatric treatment and further studies are needed.

Keywords: Intestinal parasites, schizophrenia, healthy control

ÖZ

Amaç: Şizofreninin doğası gereği gözlenen yetiyitimi ve yaşam kalitesindeki azalma, sekonder olarak paraziter enfeksiyonlara zemin hazırlayan bir faktör olarak değerlendirilmektedir. Bu olgu-kontrol çalışmasına, şizofreni tanısı ile takip edilen hastalar ve yaş-cinsiyet verileri benzer sağlıklı gönüllüler dahil edilerek bu olgu grubundaki barsak parazitlerinin araştırılması amaçlanmıştır. Ayrıca, şizofreni hastalarındaki gastrointestinal şikayetlerin altta yatan nedeni (psikiyatrik ilaç yan etkisi veya gözden kaçırılan paraziter enfeksiyon varlığı) konusunda bilgi sahibi olunarak literatüre ve/veya klinik pratiğe katkı sağlanması amaçlanmıştır.

Yöntemler: Çalışmaya 30 şizofreni tanılı hasta ve 30 sağlıklı gönüllü dahil edilmiş, toplamda 60 olgudan dışkı örnekleri alınmış ve bu örneklerdeki bağırsak parazitleri öncelikli olarak mikroskobik ayrıcı tanı gereken durumlarda ise serolojik olarak araştırılmıştır.

Bulgular: Çalışmada, barsak parazitlerinin genel pozitiflik oranı %25 (15/60) olarak belirlenmiştir. Şizofreni grubundaki hastalarda %36,7 (11/30), sağlıklı kontrol grubunda %13,3 (4/30) olarak dağılım gösteren barsak paraziti saptanma oranları arasındaki farkın ise istatistiksel olarak anlamlı olduğu belirlenmiştir (olasılık oranı: 3,76; %95 güven aralığı: 1,04-13,65; $p<0,05$). Şizofreni grubunda 6 olguda (%20) *Blastocystis* spp., 3 olguda (%10) *Giardia intestinalis* (*G. intestinalis*) ve 2 olguda (%6,7) ise *Entamoeba histolytica* saptanmış; sağlıklı kontrol grubunda ise 3 olguda (%10) *Blastocystis* spp. ve 1 olguda (%3,3) ise *G. intestinalis* saptanmıştır.

Sonuç: Şizofreni gibi kronik bir psikiyatrik hastalığı olan hastaların yaşam kalitesinin artırılması ve olası bulaşın engellenmesinde psikiyatrik tedavinin yanı sıra paraziter ajanların da periyodik olarak araştırılması ve bu konuda daha ileri araştırmalara ihtiyaç olduğu düşünülmüştür.

Anahtar Kelimeler: Barsak parazitleri, şizofreni, sağlıklı kontrol

Address for Correspondence/Yazışma Adresi: Özer Akgül PhD, İstanbul Aydın University Faculty of Medicine, Department of Medical Microbiology, İstanbul, Turkey
Phone: +90 532 565 99 44 **E-mail:** akgulozer@hotmail.com, akgulozer@aydin.edu.tr
ORCID ID: orcid.org/0000-0002-3802-3270

Received/Geliş Tarihi: 28.04.2021
Accepted/Kabul Tarihi: 01.06.2021

Cite this article as/Atıf: Yalnız Z, Bulu E, Kavla Y, Sapmaz B, Çalışkan R, Aksoy Poyraz C, Öner YA, Demirel ÖF, Akgül Ö. First Case-Control Study of Intestinal Parasites in Follow-up Schizophrenia Patients: Are We Overlooking the Role of These Agents?. İstanbul Med J 2021; 22(3): 213-7.

Introduction

Schizophrenia is a chronic psychiatric disease with an early onset and variable clinical and related disability. The general prevalence of schizophrenia varies between 1% and 1.5%, without significant difference between genders in terms of its incidence, but the age of onset is earlier in men than in women (1). In the etiology of schizophrenia, theories related to genetic factors, obstetric anomalies, intrauterine infections, neurodevelopmental, and neurotransmitters are emphasized (2). Pathogens that can manipulate neurotransmitter levels and are therefore defined as neurotrophic microorganisms have been frequently investigated recently to elucidate the etiology of various psychiatric diseases, especially schizophrenia (3,4).

Slow proliferation, ability to escape from the immune system, potential for latent infection, and affinity to the central nervous system are listed as basic characteristics of neurotrophic microorganisms. Among the neurotrophic microorganisms, viruses in the Herpesviridae family (Herpes Simplex virus 1/2, Epstein-Barr virus, and cytomegalovirus), influenza virus, and *Toxoplasma gondii*, a parasite, are shown as the strongest candidates (5). However, studies investigating the relationship between other medically important parasites and psychiatric diseases have remained quite limited, and the implications of the possible presence of parasitic infection in this patient group have not yet been elucidated.

Parasitic intestinal infections remain an important public health problem in our Turkey, similar to global data. Factors determining the social frequency of parasitic intestinal infections include age, gender, socioeconomic level, education, nutrition, traditions, climatic factors, presence in public areas, and hygienic habits (6). In groups with underlying diseases or need of special care, diagnosis of intestinal parasitic infections gains importance to reduce social transmission and to develop more effective strategies in combating parasitosis (7).

In addition to strengthening this hypothetical approach by investigating the correlation between the pathophysiology of psychiatric disease and microorganisms (8), the investigation of intestinal parasites as comorbid infection agents in patients with psychiatric disorders and disability is underestimated. Increasing the quality of life, preventing possible contamination in hospitalization, which is frequently applied for therapeutic purposes, and providing in-home care in patients who are diagnosed with a chronic psychiatric disease such as schizophrenia due to loss of function (3) are important for both psychiatric clinic and public health.

This study was designed to bridge the research gap in this topic. Patients diagnosed with schizophrenia and healthy volunteers with similar age and gender data were included in this case control study. The presence of intestinal parasites was examined microscopically. ELISA was used in cases where the differential diagnosis was required, and the results obtained were compared with sociodemographic characteristics and disease status.

Methods

A total of 60 patients (30 patients with schizophrenia and 30 healthy volunteers) between January 2020 and September 2020 were included in this case-control study. The study was approved by the İstanbul Aydın University Non-invasive Clinical Research Ethics Committee (approval number: 2019/128). Written and/or oral informed consent was obtained from all patients.

Thirty patients with schizophrenia living in Istanbul who were followed up in the Department of Psychiatry at İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, were included as the first group. The diagnosis of schizophrenia was made according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria. The healthy control group consisted of 30 participants without any psychiatric disease or family history according to semi-structured interviews with the Structured Clinical Interview for DSM-5 and having similar age and gender data with the schizophrenia group. Sociodemographic data of all participants were recorded, and participants using antiparasitic drugs were excluded from the study.

Stool samples were taken from the 60 study participants. Stool samples collected were first examined macroscopically and then microscopically. For microscopic examination, Native-Lugol and formol-ethyl acetate concentration methods were used, and the presence of intestinal parasites in the preparations was evaluated microscopically at 10x and 40x magnifications. If parasite identification was unclear in the microscopic examination, these samples were examined by ELISA (Seramun Diagnostica GmbH, Wolzig, Germany), and the parasitological diagnosis was confirmed.

Statistical Analysis

The number of cases to be included in the study groups was calculated with the G*Power 3.1.9.6 program by taking α=0.5 and β=0.20 so that the power of the test would not be less than 80%. Statistical analysis of the study results was carried out using the IBM SPSS program 26.0 version (IBM Corp., Armonk, NY, USA). Descriptive statistics including tables were used to describe the data. Categorical variables are represented as counts, and frequency distributions were compared with Pearson's chi-square tests. Continuous variables are expressed as median and interquartile range (IQR). Mann-Whitney U test was used to identify differences between groups. To control for confounders that were significant in the univariate analysis, a multiple logistic regression model was employed to investigate the independent association of schizophrenia with intestinal parasites. Odds ratio (OR) along with its 95% confidence interval (CI) was used to assess the relationship between dependent and independent variables. The significance limit was accepted as two-tailed at $p<0.05$.

Results

A total of 60 patients (schizophrenia group, n=30; healthy group, n=30) were included in this case-control study, and stool samples were examined by microscopic and/or serological methods to detect intestinal parasites.

The median patient age in the schizophrenia group was 37 years (IQR: 47-31) and that in the healthy control group was 40 years (IQR: 46-32), and the two data were comparable (OR: 0.03; 95%; CI: -0.10 to 0.13; p=0.859). There were 10 (33.3%) female and 20 (66.7%) male patients

in the schizophrenia group and 11 (36.7%) female and 19 (63.3%) male volunteers in the healthy control group, and gender data were evaluated as statistically similar (OR: 1.16; 95% CI: 0.40-3.35; p=0.787). In the schizophrenia group, 24 (80%) patients were single and 6 (20%) were married; in the healthy control group, 16 (53.3%) were single and 14 (46.7%) were married, and the difference in the marital status was different (OR: 0.28; 95% CI: 0.09-0.90; p=0.018). Similarly, the median total duration of education was 8.5 years (IQR: 14-5) in the schizophrenia group and 12 years (IQR: 16-8) in the healthy control group, and the difference was significant (OR: -0.29; 95% CI: -0.58 to 0.00; p=0.043). As regards sociodemographic features, the groups demonstrated significant difference in working status. The number of working/non-working patients in the schizophrenia group was 11 (36.7%)/19 (63.3%) and that in the healthy control was 25 (83.3%)/5 (16.7%), respectively, and the difference was highly significant (OR: 8.64; 95% CI: 2.56-29.07; p<0.001). Comparative sociodemographic data of all cases included in the study are shown in Table 1.

The presence of intestinal parasites in stool samples was examined microscopically and/or serologically. Intestinal parasites were detected in 11 (36.7%) patients in the schizophrenia group, while no parasites were found in 19 (63.3%) patients. Intestinal parasite was detected in 4 (13.3%) of the volunteers in the healthy control group, while no parasites were detected in 26 (86.7%). Higher rates of intestinal parasites were detected in the schizophrenia group than in the healthy control group, and the difference was significant (OR: 3.76; 95% CI: 1.04-13.66; p=0.021). In the multivariate logistic regression analysis, only having a schizophrenia diagnosis had a significant influence on the presence of intestinal parasites (OR: 5.16; 95% CI: 1.11-23.97; p=0.036), and all results are summarized in Table 2.

The distribution of intestinal parasite species that were microscopically detected and serologically confirmed [for *Entamoeba histolytica (E. histolytica)/dispar* distinction] between groups was determined. No more than one intestinal parasite was detected in the same stool sample in any study participant. In the schizophrenia group, 6 (20%) participants had *Blastocystis* spp., 3 (10%) had *Giardia intestinalis (G. intestinalis)*, and 2 (6.7%) had *E. histolytica*. In the healthy control group, *Blastocystis* spp. was detected in 3 (10%) participants and *G. intestinalis* in 1 (3.3%) participant. The distribution of parasite species detected in schizophrenia and healthy control groups is summarized in Table 3.

Discussion

This case-control study investigated intestinal parasites in patients with schizophrenia undergoing follow-up and compared the results with healthy volunteers. Following literature review, to our knowledge, this is the first study that compared the distribution of intestinal parasites between the schizophrenia group and healthy control group. Primarily, this study found that intestinal parasites were detected more frequently in patients with schizophrenia (36.7%) than in healthy volunteers (13.3%), and the difference was significant (p<0.05).

Table 1. Sociodemographic characteristics of the participants

		Schizophrenia	Healthy control	Univariate OR (95% CI)	p-value
Age, median, years (IQR)		37 (47-31)	40 (46-32)	0.03 (-0.10 to 0.13)	0.859
Gender, n (%)	Female	10 (33.3%)	11 (36.7%)	1.16 (0.40-3.35)	0.787
	Male	20 (66.7%)	19 (63.3%)		
Marital status, n (%)	Single	24 (80%)	16 (53.3%)	0.28 (0.09-0.90)	**0.018**
	Married	6 (20%)	14 (46.7%)		
Education median years (IQR)		8.5 (14-5)	12 (16-8)	-0.29 (-0.58 to 0.00)	**0.043**
Employment, n (%)	Unemployed	11 (36.7%)	25 (83.3%)	8.64 (2.56-29.07)	**<0.001**
	Employed	19 (63.3%)	5 (16.7%)		

IQR: Interquartile range, OR: odds ratio, CI: confidence interval

Table 2. Distribution of intestinal parasite presence

		Schizophrenia	Healthy control	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Intestinal parasite, n (%)	Negative	19 (63.3%)	26 (86.7%)	3.76 (1.04-13.66)	<0.05	5.16 (1.11-23.97)	0.036
	Positive	11 (36.7%)	4 (13.3%)				

OR: Odds ratio, CI: confidence interval

Table 3. Distribution of intestinal parasite species

Intestinal parasite species	Schizophrenia, n (%)	Healthy control, n (%)
Blastocystis spp.	6 (20%)	3 (10%)
Giardia intestinalis	3 (10%)	1 (3.3%)
Entamoeba histolytica	2 (6.7%)	-
Total	11 (36.7%)	4 (13.3%)

In the study, the most common intestinal parasites in both schizophrenia and healthy control groups were *Blastocystis* spp. (9). The global prevalence of *Blastocystis* spp. varies between 1.5% and 50%, and this proportional difference may be related to bad hygienic habits and development level of patient's geographic location (10). Although its taxonomy, life cycle, and epidemiology are not yet clear, data on the pathogenicity of this parasite, which is widely detected worldwide, are inconsistent. According to current knowledge, if parasite is seen >5 times in a microscope field at 40x magnification and no other parasitic/viral/bacterial agent is detected, it is considered a pathogen, and if the patient experiences clinical signs, parasitism should be treated. Parasitism is still frequently associated with gastrointestinal complaints such as fatigue, anorexia, flatulence, abdominal pain, and diarrhea, which cannot be explained by any other reason (11). *Blastocystis* spp. was found in 6 (20%) of 30 patients with schizophrenia and in 3 (10%) of 30 healthy volunteers. Among the possible reasons for the more frequent detection of the parasites known to be transmitted by the fecal-oral route in the schizophrenia group is poor hygienic habits, which resulted from a lack of self-care.

In this case-control study, the second most common parasite was *G. intestinalis*. *G. intestinalis* is one of the most common anterior intestinal parasites among humans worldwide and is transmitted by contaminated water or food (12). Poor living conditions, living in a crowded house or a dirty environment, and having a low socioeconomic status are among other risk factors associated with transmission (13). *G. intestinalis* infections, which are often asymptomatic in healthy individuals, may lead to varying clinical pictures, ranging from mild diarrhea to severe malabsorption (14). In a study conducted after the water-borne *G. intestinalis* epidemic in Norway in 2004 (15), cases were examined 5 years after the epidemic, and 54.7% (29/53) of the cases were reported to have chronic fatigue syndrome due to giardiasis. In addition, the authors emphasized that pathogens such as *G. intestinalis* should be considered in the differential diagnosis of diseases that may have a psychiatric basis such as chronic fatigue syndrome (15). In our study, *G. intestinalis* was found in 3 (10%) patients in the schizophrenia group and only 1 (3.3%) in the healthy control group.

In our study, *E. histolytica/dispar* was detected microscopically in only two patients in the schizophrenia group, and the species distinction in these cases was made by ELISA. Amebiasis is a common parasitic disease caused by *E. histolytica* (16). Two clinical forms, namely, intestinal and extraintestinal, of clinical amebiasis are caused by *E. histolytica* present in contaminated water and food (17). *E. histolytica* amebiasis has varied prevalence worldwide, which varies between 0.4% and 18.4% in Turkey (18). Serological and molecular-based diagnostic methods should be applied routinely due to the insufficiency of microscopic methods in the differentiation of pathogenic amoeba species (19). Therefore, in our study, the differential diagnosis of two patients with *E. histolytica/dispar* was made by ELISA. In this study, *E. histolytica* was detected in only 2 (6.7%) patients in the schizophrenia group, and this parasite was not found in any participants in the healthy control group. To our knowledge, our study was the first study that comparatively identified intestinal parasites in patients with schizophrenia and healthy volunteers on a case-control basis. Only one study (20) conducted in Ghana in 2015 partially parallels the general concept of our study. That cross-sectional study included 111 patients in a psychiatric hospital, independent of psychiatric diagnosis, and did not include a healthy control group. Intestinal parasites in the included patients were examined only by microscopic methods. The authors reported that intestinal parasites were detected in 13.5% (15/111) of the patients, and the most common parasite was *E. histolytica/dispar* (20). The intestinal parasite detection rate of 13.5% reported in a previous study (20) was lower than that in our study (36.7%), and this difference was thought to be due to the study design and limitations reported by the authors.

Study Limitation

Besides the contribution of our study with preliminary results on the presence of intestinal parasites in patients with schizophrenia, this study has two major limitations that could be addressed in future research. First, this study enrolled a relatively small sample size due to the low compliance of patients with schizophrenia to the nature of this study, which would bias the results toward the null hypothesis. Second, we were unable to evaluate the serological methods for the detection of all intestinal parasites for economic reasons.

Conclusion

In addition to the pathophysiological/etiological basic enlightenment studies in chronic psychiatric diseases such as schizophrenia, further studies are needed to increase public health and the quality of life of the patient. For further research, it will be possible to reduce confusion for the gastrointestinal symptoms associated with parasitic infections or the side effects of antipsychotic drugs used in the treatment. Thus, this study may have clinical contributions to psychiatric treatment compliance.

Ethics Committee Approval: The study was approved by the İstanbul Aydın University Non-Invasive Clinical Research Ethics Committee (approval number: 2019/128).

Informed Consent: Written and/or oral informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Z.Y., E.B., Y.K., B.S., Y.A.Ö., Ö.F.D., Ö.A.; Concept - Ö.F.D., Ö.A.; Design - Y.A.Ö., Ö.F.D., Ö.A.; Data Collection or Processing - Z.Y., E.B., Y.K., B.S., R.Ç., C.A.P., Ö.F.D., Ö.A.; Analysis or Interpretation - Z.Y., E.B., B.S., R.Ç., Y.A.Ö., Ö.F.D., Ö.A.; Literature Search - Z.Y., E.B., Y.K., B.S., R.Ç., C.A.P.; Writing - Z.Y., E.B., Y.A.Ö., Ö.F.D., Ö.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This work was supported by the Istanbul Aydin University Scientific Research Projects Unit (2020/13).

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