

Original Research Article

PREVALENCE OF INTESTINAL PARASITOSIS AMONG MENTALLY ILL PERSONS IN NEUROPSYCHIATRIC HOSPITAL, CALABAR, NIGERIA

ABSTRACT

Aim: The prevalence of intestinal parasitosis in relation to mental illness among inpatients of Federal Neuropsychiatric Hospital, Calabar was investigated with a view to improving the quality of their **medical care**.

Study design: This was cross sectional study. Ethical approval and patients' informed consent were sought and obtained before collection and processing of samples.

Place and Duration of Study: Federal Neuropsychiatric Hospital, Calabar, between February and August, 2016.

Methodology: We included 246 (126 **patients**, 120 apparently **healthy**) subjects. Intestinal parasites were detected by direct stool microscopy and formol ether concentration technique and the cellophane anal swab method for *Enterobius vermicularis*. Chi square analysis was used to compare percentages.

Results: The prevalence of intestinal parasitosis among the 126 studied **patients** was 49.2% compared to 11.7% recorded among the 120 apparently healthy (control) subjects examined ($P < 0.0001$). There was no significant association between intestinal parasites prevalence and gender in **test** as well as **control** subjects (60.0% v. 45.1%, respectively, $p = 0.2022$) and (14.3% v. 8.8%, respectively, $P = 0.3113$). Subjects with chronic mental cases insignificantly harbored more intestinal parasites than those with acute cases (53.8% v. 47.1%, respectively; $P = 0.5699$). Parasites detected in the study were Hookworm 34.6%, *Entamoeba histolytica/dispar* 25%, *Ascaris lumbricoides* 17.3%, *Trichuris trichiura* 9.6%, *Enterobius vermicularis* 5.8%, *Giardia intestinalis* 3.8%, *Taenia* species and *Schistosoma mansoni* 1.9% each. Hookworm ranked highest 34.6% among the parasites encountered in the test subjects while *Ascaris lumbricoides* 33.3% took the lead in the control group. People diagnosed with Variance Psychosis disorder recorded highest infection rate (68.4%) while those with substance abuse had the least (28.0%).

Conclusion: Intestinal parasitosis may possibly play aetiologic or enhancement role in mental ill health. For effective management of the mental challenge, periodic parasitic investigations and appropriate therapy before and after admittance should be effected in all psychiatric institutions.

Keywords: Mental Illness, Psychiatric disorder, Intestinal parasitosis, Prevalence, Calabar.

1. INTRODUCTION

Intestinal parasites are associated with significant morbidity and mortality worldwide, particularly in developing countries [1] where an estimated 3.5 billion people are affected, the majority being children [2], the aged, people with low nutritional and immune status, and institutionalized persons [3]. Socioeconomic and environmental factors including poor personal and food hygiene, sanitation, poverty, and overcrowding have been documented to promote intestinal parasitic infections [4]. **Transmission of**

16 intestinal infection occurs through ingestion of mature cyst of protozoa, egg or larva of
17 helminthes or larval skin penetration of certain helminthes. Common symptoms of intestinal
18 parasitic infections include diarrhoea, nausea or vomiting, gas or bloating, dysentery, rash or
19 itching around the anus or vulva, abdominal discomfort, fatigue, weight loss and passing a worm
20 in stool [5]. These infections may lead to low nutritional and immune status, impaired growth, and poor
21 cognitive performance which complicate and contribute to other illnesses [6, 7, 8, 9].

22 Mental illness refers collectively to all of the diagnosable mental and emotional conditions and are
23 characterized by abnormalities in cognition, emotion or mood, or the highest integrative aspects of
24 behavior, such as social interactions or planning of future activities [10, 11]. When the mental illness
25 significantly interferes with the performance of major life activities such as learning, working and
26 communicating, among others, the term “psychiatric disability” is applied [11]. It is a core tenet of modern
27 science that behavior and our subjective mental lives reflect the overall workings of the brain as the
28 mental functions are all mediated by the brain [10].

29 Mental illnesses are disabling and common globally but underestimated and under-treated in many
30 developed and developing countries with estimated global burden between 21.2% - 32.4% of years lived
31 with disability (YLDs) [12] and around 450 million people currently suffering from such conditions
32 worldwide [13].

33 An estimated 20%–30% of the Nigerian population are believed to suffer from mental disorders [14];
34 unfortunately, inadequate attention is given to this health problem as only about three percent of the
35 government's budget on health, according to the World Health Organization estimates, goes to mental
36 health [15]. This, coupled with misconceptions and poor level of awareness of the Nigerian public on
37 mental health issues [16], has compounded this problem. Despite several previous reports of high
38 prevalence of intestinal parasitosis in many mental facilities elsewhere, very limited studies have been
39 documented in Nigeria.

40 The cause of mental illness and psychiatric disorders is controversial but a combination of factors,
41 including biological, psychological, environmental, social and spiritual factors have been incriminated [17,
42 18]. Genetic and biological factors have been associated with schizophrenia, depression, and alcoholism
43 [17]. There are records of accumulated evidence showing Schizophrenia and Bipolar Disorder as complex
44 diseases in which many predisposing genes interact with one or more environmental agents to cause
45 symptoms, *Toxoplasma gondii* being an example of infectious agent that has been linked to
46 schizophrenia and in which genes and an infectious agent interact. Such infections may occur early in life and
47 are thus consistent with neurodevelopmental as well as genetic theories of psychosis [19].
48

49 Risk factors of mental disorders include traumatic brain injury [20], substance abuse, viral
50 infections [21], and general physical health. Researches show that a number of mental disorders occur in
51 people suffering from other diseases more often than would be expected by chance as in infection,
52 Coeliac disease, etc and this is often never investigated. Currently, science believes that mental illness is
53 linked to genetic flaws. However, recent medical research also points to immune system dysregulation,
54 most likely originating from gastrointestinal dysfunction as another factor. Psychiatrist Dr C.M. Reading,
55 after over 30 years of practice believed that a significant percentage of those with mental illness suffer due
56 to gastrointestinal & physical problems manifesting as Coeliac or latent Coeliac disease, food allergies,
57 infections, auto-immune disease and malabsorption [22]. The role of the gastrointestinal system in the
58 development of many illnesses, especially mental illness and neurological disorders has often been
59 overlooked. Recent research findings have linked mental disorders to microbiota – brain- gut interaction
60 (Brain-Gut Axis) through adjustment in the gut microbiota and activation of certain immune system cells in
61 response to an infection, or on an ongoing basis (chronic inflammation) and studies are under way to
62 evaluate the use of anti-inflammatories in treating depression and schizophrenia [23].

63 Repeated immune response due to infection or allergy may result in inflammation, particularly in
64 the area of the small bowel and over time this may lead to damage of the mucosal villi and in turn increase
65 mucosal permeability. Recurrent gastrointestinal infection, gastritis, post antibiotic infection (colonization

66 of bad bacteria), tropical sprue and inherited gastro-immunological disorders such as coeliac sprue, non-
67 coeliac sprue and food intolerances may lead to the development of mental illness and disease [22].
68 Inflammation plays a key role in mood disorders and mental illness. When inflammatory antibodies cross
69 the blood-brain barrier, it interferes with the brain's ability to function. The immune system secretes
70 antibodies that are distributed in the blood to help fight the infection or repair the problem. The blood-brain
71 barrier is supposed to protect the brain from those antibodies. But for yet unknown reasons, when
72 inflammation reaches the brain, the cytokines wreak havoc on the neurotransmitters, interfering with the
73 brain function [24]. Auto-immune response can lead to symptoms like anxiety, depression, and
74 hallucinations [25] and some studies have even found higher levels of inflammation in patients with
75 depression and suicidal thoughts, PTSD, and chronic fatigue [26, 27].

76 The relationship between mental and medical illnesses further emphasizes the need for continued
77 mental health research for proper diagnosis of psychiatric illness [28].

78 The impact of mental illness is grave on the victims, their family members and the communities
79 [29-31]. In addition to the health and social costs, those suffering from mental illnesses are also victims of
80 human rights violations, stigmatization and discrimination, both inside and outside psychiatric institutions.
81 Many psychiatric institutions have inadequate, degrading and even harmful care and treatment practices,
82 as well as unhygienic and inhuman living conditions [32]. With memory loss, poor reasoning, low
83 education, poverty, and low hygiene level, mentally ill persons are likely to acquire and spread infectious
84 agents which in turn promotes the already underlying health problem.

85 Although a relationship between infectious diseases and psychiatric disorders has been
86 suggested, this relationship is yet to be well demonstrated and be considered important by many health
87 care providers [8, 17]. A better understanding of the role of infection may speed treatment and prevention
88 efforts and reduce the degree of disability and stigma associated with mental illness. This study therefore,
89 aimed to investigate the prevalence of intestinal parasites among hospitalized psychiatric patients in the
90 Federal Neuropsychiatric Hospital, Calabar and its relationship with demographic variables of interest.

91 Related risk factors and consequences of intestinal parasitic infections among the study subjects were
92 also assessed and action initiated for treatment of the infected persons.

93

94 **2. MATERIALS AND METHODS**

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97 This study was carried out at the Federal Neuropsychiatric Hospital, Calabar situated in the tropical
98 rain forest of Southern Nigeria between February and August, 2016. It is the only psychiatric institution in
99 the state and serves as a home as well as hospital for people with mental illnesses from across the state
100 and neighboring states. At the time of the study, the institution had a 235 bed capacity with 181
101 inmates/inpatients, mostly adults. With ethical approval from the hospital research ethics
102 committee and informed consent of participants, a total of 126 (91 males/35 females) patients of the
103 hospital who complied and 120 (57 males/64 females) apparently healthy subjects from
104 the general population without any history of anti-parasitic medication in last preceding month were
105 recruited for the study. Demographic data and health status of each studied subjects were obtained
106 through the instrument of interviewer- administered questionnaire, with the help of the hospital/faculty
107 workers, based on medical records. Subjects were also questioned for recent abdominal discomforts,
108 diarrhoea, anal itching or emergence of nematodes from the anus, and anti-parasitic medication.

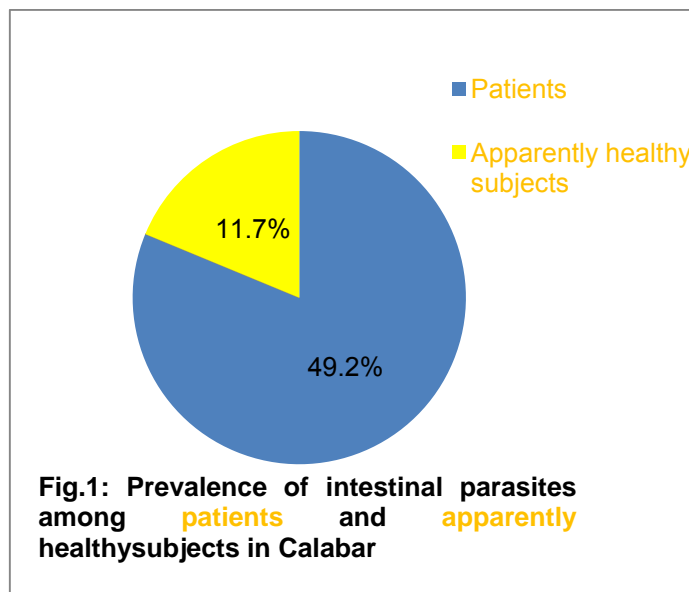
109 All studied subjects were screened for intestinal parasites based on stool and anal swab
110 examination. The subjects or their informants were each given a sterile screw-capped wide mouth
111 universal container for collection of stool sample and cellophane anal swab for collection of anal swab.
112 Anal swabs of the subjects were obtained early in the morning (before defecating/bathing) using the
113 cellophane anal swab (8 by 2- cm of transparent adhesive tape), held sticky side out, over the end of a
114 glass microscope slide [33]. Samples were processed and examined in the University of Calabar
115 Teaching Hospital laboratory. The stool samples were macroscopically examined for appearance,
116 consistency, presence of blood, mucus, worm segments and worms. Stool samples were further
117 processed by direct smear microscopy and formol ether concentration technique. The
118 preparations and the anal swabs were examined microscopically using the 10x and 40x
objectives for the presence of larva, cysts, and eggs of parasites [6]. Percentages were compared using

119 Chi square analysis. All parasites infected subjects were recommended to their health care providers for
120 appropriate antiparasitic treatment.

121 3. RESULTS

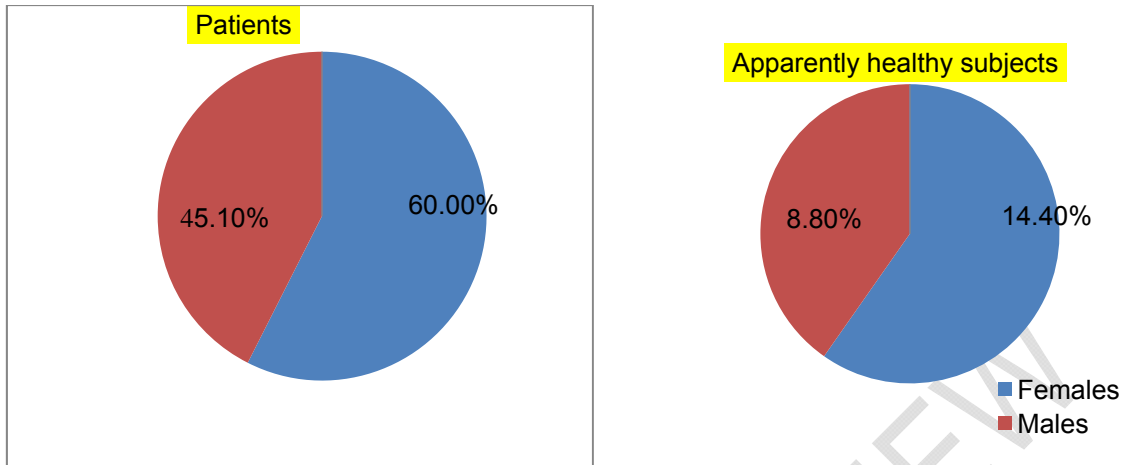
122 The results of this study are as shown in Figures 1-4 and Tables 1-2.

123 Fig. 1 displays the prevalence of intestinal parasites among patients and apparently healthy subjects in
124 Calabar. Sixty two (49.2%) of the 126 test versus 14 (11.7%) of 120 control subjects examined significantly
125 tested positive for parasites ($P < 0.0001$).



126

127 Patients as well as apparently healthy female subjects were insignificantly more infected than their
128 male counterpart (21/35) 60.0% v. (41/91) 45.1%, respectively, $p = 0.2022$ and (9/64) 14.4% v. (5/57)
129 8.8%,



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131

132 respectively, $p = 0.3113$ (Fig. 2).

133 **Fig. 2: Prevalence of intestinal parasites among mental and healthy subjects in Calabar by gender**

134 Persons with chronic cases of mental problem were insignificantly more infected with intestinal
 135 parasites than those having acute cases 53.8% v. 47.1%, respectively, $P = 0.5699$) (Table1).

136 **Table 1: Distribution of Intestinal Parasites among Patients by Duration of Case**

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| Case | No. Examined | No. (%) Positive for Parasites |
|---------|--------------|--------------------------------|
| Acute | 87 | 41 (47.1) |
| Chronic | 39 | 21 (53.8) |
| Total | 126 | 62 (49.2) |

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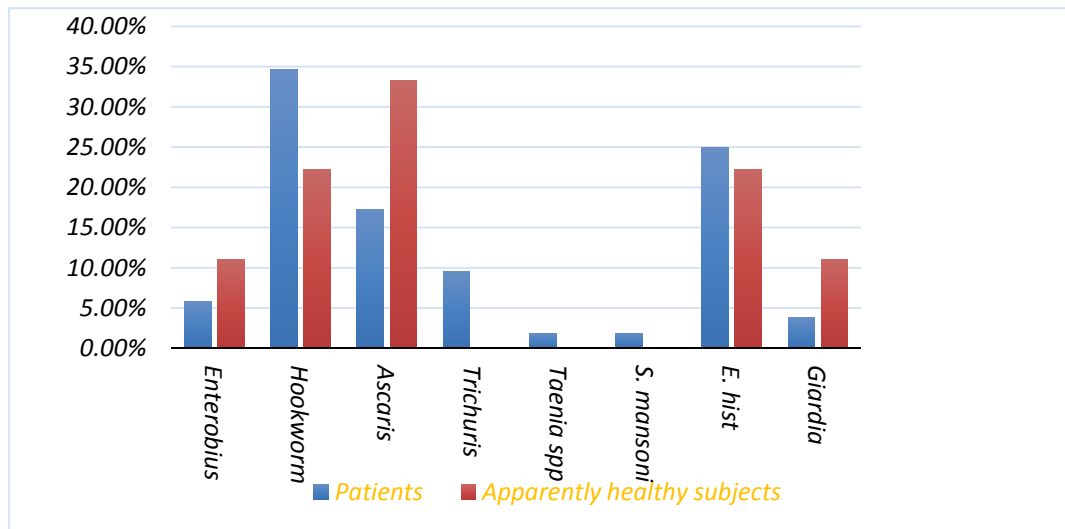
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Key: Acute - Newly admitted patients with sudden onset, high degree but short-term condition (who spent less than 4 weeks at the care center).

Chronic - Patients with long-lasting condition (who spent more than 4 weeks at the care center), who sometimes acted normally, but at other times suffered from periods of rage, hallucination, delusions and the like.

150 The most frequently detected parasite among the patients was hookworm 34.6% followed by
 151 *Entamoeba histolytica/dispar* 25.0%. Other parasites detected in descending order of frequency were
 152 *Ascaris lumbricoides* 17.3%, *Trichuris trichiura* 9.6%, *Enterobius vermicularis* 5.8% (in one sampling),
 153 *Giardia intestinalis* 3.8%, *Taenia species* and *Schistosoma mansoni* 1.9% each, whereas among the
 controls, *Ascaris* ranked highest 33.3% followed by hookworm and *E. histolytica/dispar* 22.2% each,

154 *Enterobius* and *Giardia* 11.1% each (Fig. 3).



155

156 **Fig. 3: Frequency of intestinal parasites among patients and healthy subjects**

157 Table 2 shows occurrence of mixed parasitic infections among patients. The rate of single infection
 158 was higher than that of mixed infection 68.1% and 31.9%, respectively. Mixed infections with 2 parasites
 159 were more often encountered 86.4% than those with 3 parasites 13.6%.

160 **Table 2: Occurrence of Mixed parasitic infections among patients**

161

| Parasites grouping/No. | Occurrence | Frequency (%) |
|-------------------------|------------|---------------|
| Mixed Infections | | |
| 2 Parasites | 19 | (27.5) |
| 3 Parasites | 3 | (4.3) |
| Subtotal | 22 | (31.9) |
| Single Infection | | |
| 1 Parasite | 47 | (68.1) |
| Total | 69 | (100.0) |

162

163 The highest prevalence of infection was recorded among persons diagnosed with Variance Psychosis
 164 68.4%, closely followed by those with Mania Disorder 63.6%, Acute Schizophrenia 56.2%, Chronic
 165 Schizophrenia 48.2%, Depression 46.7%, Organic Source 45.4%, while those with Substance Abuse
 166 recorded the least prevalence 28.0% (Fig. 4).
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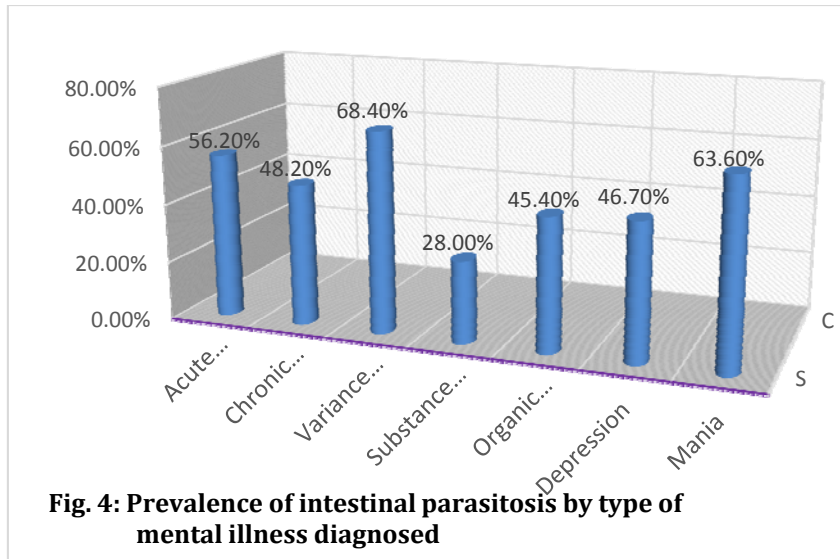


Fig. 4: Prevalence of intestinal parasitosis by type of mental illness diagnosed

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177 4. DISCUSSION

178 The prevalence of intestinal parasitosis among **mentally ill** subjects in this study was 49.4% as
179 against 11.4% recorded among the controls ($P < 0.0001$). These findings are similar to those of
180 Sirivichayakul *et al.* [34] in Thailand where a higher prevalence was also observed among
181 institutionalized mentally handicapped than non-institutionalized **healthy** individuals (57.6% v. 7.5 %,
182 respectively, $p < 0.05$). The 49.4% prevalence recorded in this study is high compared to 8.4% recorded
183 in mental hospitals in North Taiwan [35], 7.3% in New York [36], 20.5% in Urmia, Iran [37], 35.7% in
184 Korea [38] but is related to 52.3% reported in Puerto Rico [39], 53.8% in Italy [8], and 76.7% in Egypt
185 [40]. The higher prevalence observed among our studied subjects compared to controls may be
186 attributed to the poor state of hygiene usually observed among this (institutionalized) group of persons,
187 coupled with their abnormal behavior, limited access to anti-parasitic therapy poor environmental
188 conditions and poor sanitary practices within the facility.

189 The prevalence rate observed in the study area, being hospital environment, may not necessarily
190 reflect the endemicity level of intestinal parasitoses in the general population of Calabar as Calabar wide
191 prevalence data on intestinal parasitoses is lacking and most of the mentally ill persons are victims of
192 displaced homes (may not be Calabar residents), **poverty**, low levels of education, poor hygiene and

193 feeding problems which are known risk factors of parasitoses. It is believed that those persons might
194 have been harboring these infectious agents before admittance into the hospital, since no routine
195 medical examination was done on their admission. However, the possibilities of hospital-acquired
196 infection and inter-hospital transfer are inevitable.

197 The higher prevalence of parasites (49.4%) noted among the test subjects in this study may not
198 necessarily attribute their mental illnesses to intestinal parasitoses but our results being consistent with
199 those reported elsewhere, Puerto Rico 52.3% [39], Italy 53.7% [8], and Egypt 76.7% [40] is suggestive that
200 intestinal parasitosis may possibly play etiologic or enhancement role in mental disorders.

201 **Test** as well as the control females were insignificantly more infected with intestinal parasites than
202 their males counterpart (60.0% v. 45.1%, respectively, $P = 0.2021$) and (14.4% v. 8.8%, respectively, $P =$
203 0.3113). This differs from the findings in Iran [36] where infection rates among males and females were
204 similar (20.3% v. 20.5%, respectively).

205 The prevalence of intestinal parasites among the patients insignificantly increased with duration of
206 cases as subjects with chronic (long-lasting) condition showed a higher parasites prevalence (53.8%) than
207 those with acute (short-term) mental problems (47.4%) ($P = 0.5699$). This may be attributed to difference in
208 the degrees of chronic stresses and immune system deficiency (which might be higher in the chronic cases)
209 usually associated with mental disorders which are also known risk factors of parasitosis [41].

210 Hookworm ranked highest among the parasites encountered in the test subjects 34.6% followed by
211 *Entamoeba histolytica/dispar* 25%, *Ascaris lumbricoides* 17.3%, *Trichuris trichiura* 9.6%, *Enterobius*
212 *vermicularis* 5.8% (in one sampling), and *Giardia intestinalis* 3.8%, *Taenia* species and *Schistosoma*
213 *mansoni* 1.9% each whereas, among the controls, *Ascaris* ranked highest 33.3% followed by hookworm
214 and *E. histolytica/dispar* 22.2% each, *Enterobius* and *Giardia* 11.1% each. **It is possible that infection with**
215 **these parasites may have come from institutional food or water in the psychiatric hospital and/or may be the**
216 **result of poverty, a condition intimately linked with mental illness.** The high prevalence of hookworm here
217 may be attributed to the habit of walking bare foot, observed among some of the test subjects, and poor
218 hygiene related to faeces. *Taenia* species and *Schistosoma mansoni* encountered here probably represent
219 imported infection and have been related to organic sources of mental disorder and their associated

220 symptoms [8, 9]. According to various authorities, taeniasis is thought to be the cause of psychiatric
221 symptoms due to its neural and psychological effects. These claims have been confirmed in a taeniasis
222 case study of a 36 year-old woman whose psychiatric symptoms (obsessive and compulsive neurosis and
223 depression) decreased after the taeniasis treatment [11].

224 *Entamoeba histolytica/dispar* was the leading protozoan infection (25%) in this study. Although this
225 study was limited to stool examination, this organism has been previously reported to be capable of causing
226 extra intestinal infection in other parts of the body including the brain [42]. Amoebic brain abscesses which
227 have been rarely reported [43], result when trophozoites invade the central nervous system [44] leading to
228 headache, altered mental confusion, focal neurologic signs and seizures.

229 Extra intestinal migration of *Enterobius vermicularis* has been documented to result in severe health
230 disorders, including nervousness or even death, especially in population dense areas and institutionalized
231 persons [45, 46]. Among the parasite positive persons, single infections recorded 65.9%, mixed infections
232 34.1% (31.7% double and 2.4% triple) prevalence.

233 The highest prevalence of parasites was noted among subjects diagnosed of Variance Psychosis
234 68.4% closely followed by those having Mania 63.6%, Acute Schizophrenia 56.2% while those with
235 Substance Abuse had the least prevalence 28.0%. Poor mental health in association with parasitic
236 infections may produce extreme anxiety with recurrent attacks of Mania and Depression [10]. The least
237 parasites prevalence, 28.0% observed among Substance Abuse subjects suggests the need to investigate
238 hard substances (cocaine, cannabis, etc.) and their lethal effect on intestinal parasites.

239 A number of mental disorders have often been tentatively linked with microbial pathogens [47],
240 particularly viruses and parasites [48]. *Taenia solium*, *Naegleria fowleri*, and *Toxoplasma gondii* are all
241 parasites that have been documented to infect the human brain resulting in symptoms such as headaches,
242 fever, confusion, nausea, seizures, loss of balance, and hallucinations with *Toxoplasma* being the cause of
243 most cases of schizophrenia and bipolar disorder [21]. Acute infection with *Toxoplasma gondii* has been
244 shown to produce personality changes and psychosis; incidence of infection in schizophrenic patients being
245 twice that of control subjects (42 % versus 11 %, respectively). *T. gondii* is usually spread to humans
246 through cat's faeces contact; exposure to cats in childhood revealed in two studies as a risk factor for the

247 **development of schizophrenia [8]**. The parasite has been documented might play a role in the development
248 of these disorders by affecting the production of dopamine -- the chemical that relays messages in the brain
249 controlling aspects of movement, cognition and behavior [49]. *The Toxoplasma gondii parasite has been*
250 *linked, in another study, to the brain cells damage leading to suicide attempts [50]* while meningitis or
251 encephalitis was found in 24 % of 1300 cases of trichinosis reported from Germany [8].

252 Psychiatric Disorders are illnesses of the brain and parasitic infections have been documented,
253 could alter normal functions by depleting the host's essential nutrients, interfering with enzyme and
254 neuroimmune functions, and releasing massive amounts of waste products, enteric poisons, and toxins
255 which may disable brain metabolism [8]. Previous reports show that tape worms have been associated with
256 direct brain invasion (as in neurocysticercosis) leading to depression and psychosis [8]. These tapeworms
257 could produce cysts, swelling, and encephalitis in brains of patients. Pittella [51] linked neurocysticercosis
258 with seizures, increased intracranial pressure, ischemic cerebrovascular disease, dementia, and signs of
259 compression of the spinal roots/cord. Tapeworm eggs are **spread** through food, water, or surfaces
260 contaminated with feces. **Humans get the tapeworm infection after eating raw or undercooked pork**
261 **contaminated with cysts of *T. solium* [51] while *Naegleria fowleri* is acquired when water containing**
262 ***Naegleria fowleri* enters the nose and the ameba migrates to the brain along the olfactory nerve.[52]**

263 There are several reports [51, 53, 54] on neuroschistosomiasis caused by *Schistosoma mansoni*
264 infection. These worms can evoke granulomatous inflammatory reaction when eggs are being transmitted
265 to the spinal cord or brain via the vascular system, or by inadvertent adult worms' migration to these organs
266 resulting in psychiatric symptoms, including seizures and increased intracranial pressure [51].

267 Other parasitic infections (giardiasis, ascariasis, etc.) may produce mental symptoms indirectly through
268 brain – gut - axis (BGA) which may clear after effective therapy [8].

269 The relationship between mental health problems and parasitic infections, although yet to be well
270 demonstrated, is real and needs to be given concrete consideration by health care providers. The results
271 obtained here further stresses the need for continued investigation on intestinal parasitosis and mental
272 health.

273 **5. CONCLUSION**

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276 This study has revealed a high prevalence of intestinal parasitic infections among institutionalized
277 mentally ill patients in the Federal Neuropsychiatric Hospital compared to apparently healthy persons in the
278 general population in Calabar, Nigeria. There is no prevalence data on intestinal parasitoses among
279 mentally ill people in Calabar and in Nigeria, such information is sparsely documented. The study strongly
280 suggests that intestinal parasites may play aetiologic or enhancement role in mental health problems.
281 Periodic parasitic investigations and appropriate therapy before and after admittance should be effected in
282 all psychiatric institutions.

282 **6. SIGNIFICANCE OF THE STUDY**

283 The findings of this study will improve the quality of **medical care** of patients treated at Federal
284 Neuro-Psychiatric Hospital, Calabar as intestinal parasitosis would be considered during clinical and
285 laboratory diagnosis.

286

287 **CONSENT**

288 All authors declare that written informed consent was obtained from the patients/guardians after
289 details of the study was explained to them, before recruitment into the study.

290 **INCLUSION AND EXCLUSION CRITERIA**

291 Participation in the study was strictly voluntary. Only those subjects who gave their consent with
292 compliance and were not on any antiparasitic medication were included in the study. On the other hand,
293 those who refused to give their consent and those on antiparasitic medication were left out of the study.

294 **ETHICAL ISSUE**

295

296

Ethical approval for the study was obtained from Committee on Research Ethics, Federal Neuro-
Psychiatric Hospital, Calabar.

297 **CONFLICT OF INTERESTS:** None declare

298

299 **AUTHORS' CONTRIBUTIONS**

300 Author IBOB designed the study and wrote the protocol. Author DII wrote the first draft of the
301 manuscript. Authors IBOB and OMO managed the analyses of the study. Author IBOB performed the
302 statistical analysis. Authors DII and OMO managed the literature searches. Author MFU critically revised
303 the manuscript for intellectual content. All authors read and approved the final manuscript.

304 **ACKNOWLEDGEMENTS**

305 The authors are grateful to management and staff of the Federal Neuro-Psychiatric Hospital, Calabar
306 for their co-operation and to Mr. Obong Lawrence Udobong for his assistance towards collection of the
307 samples used for this study.

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