

Prevalence of Toxoplasmosis among HIV/AIDS patients and Correlation of Radiological Investigations with Laboratory Findings

Abstract

Background: *Toxoplasma gondii* an intracellular protozoan causes toxoplasmosis a worldwide neglected tropical disease, which also causes severe disease in immunocompromised patients. The Toxoplasmosis was known for cerebral involvement more commonly among patients with HIV/AIDS and serious than extra-cerebral toxoplasmosis. For cerebral toxoplasmosis patients the definitive diagnosis is crucial by demonstrating the presence of the tachyzoite form of *Toxoplasma gondii* directly in the cerebral tissues. This study was undertaken to assess the prevalence of toxoplasmosis among HIV patients and role of radiological investigation in the diagnosis

Material and Methods: A prospective cross-sectional study was conducted at Department of Microbiology, Government Medical College and Hospital, Nagpur, Maharashtra, India. A total of 362 HIV positive patients attending ART clinic and provides informed consent were included in this study. The relevant investigations of each patient with clinical history was noted. ELISA test was carried out from blood samples to detect anti-toxoplasma IgM and IgG antibodies as per the manufacturer's instructions. Data was analyzed using SPSS version 21.

Results: Out of 362 HIV positive patients, Majority of the male patients were positive for HIV positive than females, 62.43% and 37.57% respectively. About 99.17% of patients were married and most of them were from urban area (86.46%), Majority of the patients were labourers (39.78%) followed by house wives (20.72%). A total of 23.48% HIV positive patients were co-infected with toxoplasmosis of which 21.55% patients were married and from urban area. Most of the HIV positive patients and co-infected with toxoplasmosis were between the age groups of 25-34 and 35-44 years. The overall correlation of serological and radiological features was seen in 68.23%. Although radiological investigations were helpful in providing better localization of toxoplasmosis but less confirmatory than ELISA. So combination of modalities should be used in diagnosis of toxoplasmosis for appropriate management. Both the ELISA and the CT-scan were simultaneously positive in 75 (20.72%) and negative in 172 (47.51%) cases. Among all HIV-toxoplasma co-infected patients, hyper

33 density was seen in 15.29% patients, hypo density was present in 43.52% patients. Ring
34 enhancement was observed among 29.41% cases.

35 **Conclusion:** We conclude from this study that the prevalence of toxoplasmosis in HIV
36 positive patients was high (23.48%) and more commonly found between the age groups of
37 25-34 and 35-44 years. Radiological investigations were helpful in providing better
38 localization of toxoplasmosis but less confirmatory than ELISA.

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40 **Key words:** Toxoplasmosis, Prevalence, Sero-positivity, HIV/AIDS, ART Centre

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66 INTRODUCTION

67 In immunocompromised patients *Toxoplasma gondii* causes severe disease¹⁻². Among the
68 immunocompromised patients who previously acquired latent infection can lead to develop
69 reactivated toxoplasmosis with encephalitis. The disseminated toxoplasmosis and
70 toxoplasmic encephalitis have been noted in patients with immunodeficiency because of
71 various underlying causes, such as Hodgkin's disease or immunosuppressive therapy.
72 Disseminated toxoplasmosis may also complicate the transplantation of organs resulting due
73 to either from transplantation of an organ from a *Toxoplasma gondii* infected donor to a
74 susceptible recipient or from reactivation of a latent *Toxoplasma gondii* infection in the
75 recipient due to immunosuppressive therapy.³⁻⁵

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77 The prevalence of toxoplasmosis infection varied dependent on the geographical regions and
78 socio-demographic characteristics. In European and other tropical regions, prevalence of
79 toxoplasmosis is over 50%⁶. In US, majority of HIV-infected patients had antibodies against
80 *T. gondii* and sero-prevalence data of HIV-infected patients was at the range of 3-22%^{7, 8}. It
81 was 9.8% in Hong Kong⁹, Nigeria 75.4%¹⁰, 58.4% in Tunisia¹¹, 28.5% in Benin¹², 40.2% in
82 Senegal¹³, 74.5% in South Brazil¹⁴, 63.7% in Paris¹⁵, Kodym et al., reported 30% in Chezech
83 republic¹⁶. A study from Telangana, India, reported the sero-prevalence of 34.78% among
84 HIV-positive patients¹⁷. Another study by Sucilathangam et al., observed 15% of Toxoplasma
85 sero-positivity in HIV-positive people¹⁸.

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87 The initial presentation of toxoplasmic encephalitis among patients with HIV/AIDS may be
88 subacute. The patients present with various clinical symptoms such as headaches, fever and
89 altered mental status, associated with focal neurologic deficits. The progression of the
90 infection could lead to further symptoms like confusion, drowsiness, seizures, hemiparesis,
91 hemianopsia, aphasia, ataxia, and cranial nerve palsies. As disease prolongs the motor
92 weakness and speech disturbance are seen. If the patients are not treated promptly, they may
93 progress to coma within few days to weeks. Toxoplasmosis rarely present as a rapidly fatal
94 form of diffuse or global encephalitis with profound changes in mental status, nausea and
95 vomiting usually with elevated intracranial pressure.¹⁹⁻²³

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97 The cerebral involvement is common among HIV/AIDS patients and more serious than extra-
98 cerebral toxoplasmosis. For cerebral toxoplasmosis patients the definitive diagnosis is crucial

99 by demonstrating the presence of the tachyzoite form of *Toxoplasma gondii* directly in the
100 cerebral tissues. For cerebral toxoplasmosis the presumptive diagnosis including the clinical
101 symptoms, In clinical practice the radiological findings, serological and molecular diagnosis
102 for *Toxoplasma* infection and good response to anti-toxoplasma therapy are widely accepted..
103 The favorable outcome of cerebral toxoplasmosis is the improvement of clinical and
104 radiological features after 2 to 3 weeks of therapy. The clinical diagnosis is a dilemma
105 because of the cerebral toxoplasmosis mimics with other brain diseases. Which makes it
106 difficult to diagnose. Differential diagnosis of HIV/AIDS-associated cerebral toxoplasmosis
107 is extremely important. The local neuro-epidemiology and the degree of immunosuppression
108 in the host are two key factors involved.²⁴⁻²⁶

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110 The radiological observations, either by computed tomography (CT) or magnetic resonance
111 imaging (MRI) are useful modalities in the presumptive or empirical diagnosis of cerebral
112 toxoplasmosis. These findings are however not pathognomonic of cerebral toxoplasmosis.
113 Radiological diagnosis can be classified as typical findings of hypodense lesions with ring
114 enhancing and perilesional edema are observed in nearly 80% of cerebral toxoplasmosis
115 cases.²⁷

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117 Cerebral toxoplasmosis poses a diagnostic problem that relies on classical serological
118 methods to detect anti-toxoplasma immunoglobulins because clinical blood samples from
119 patients with immunodeficiency can fail to produce sufficient titers of specific antibodies.
120 Sero-evidence of toxoplasma infection, independent of antibody levels is generally seen in all
121 patients before developing cerebral toxoplasmosis. Most cerebral toxoplasmosis patients have
122 high titers of anti-toxoplasma IgG antibodies with high IgG avidity that provides serological
123 evidence of infection and this also supports a conclusion that this is the result of a secondary
124 reactivation of latent or chronic toxoplasma infection. Therefore, it is important to determine
125 the toxoplasma sero-status in all HIV-infected patients in order to define the population at
126 risk for cerebral toxoplasmosis. At the onset of cerebral toxoplasmosis, significant rises in
127 anti-toxoplasma antibody titers are found in only a marginal number of these patients. The
128 level of rising titers may occur before the onset of cerebral toxoplasmosis and it does not
129 seem to predict the occurrence of cerebral toxoplasmosis. Anti-Toxoplasma IgM antibody, as
130 measured by the indirect fluorescent or ELISA tests, is rarely found in cerebral toxoplasmosis
131 patients. In cases of cerebral toxoplasmosis, a negative or low titer of serological results or

132 even the absence of anti-toxoplasma antibodies does not exclude positive diagnosis and the
133 anti-toxoplasma therapy should be started without delay if clinical and radiological
134 presentations are consistent with cerebral toxoplasmosis. A positive serology result seems to
135 be even less useful in areas where there is a high prevalence of toxoplasmosis in the general
136 population, while a negative result does have a high negative predictive value.²⁸⁻²⁹ However,
137 there is paucity of adequate information on the prevalence of *Toxoplasma gondii* infection
138 among HIV/AIDS patients in India. Therefore, the present study was undertaken to assess the
139 prevalence of toxoplasmosis among HIV patients and role of radiological investigation in the
140 diagnosis.

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142 **MATERIAL AND METHODS**

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144 **Study design**

145 The present prospective hospital based study was conducted in the Department of
146 Microbiology, Government Medical College and Hospital, Nagpur, Maharashtra, India. A
147 total of 362 HIV positive patients included through following criteria attending ART clinic
148 during this study period. The convenient sampling method was adopted and the demographic
149 data were recorded on data collection sheet such as age, sex, marital status, occupation and
150 residency, risk factors for HIV transmission, clinical and laboratory data on toxoplasmosis.

151

152 **Inclusion criteria**

153 All volunteered confirmed HIV/AIDS positive patients with CNS signs and symptoms
154 suggestive of toxoplasmosis such as headache, fever, increased intracranial tension, seizure,
155 altered sensorium, papilloedema, cerebellar signs were included in this study.

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157 **Exclusion criteria**

158 Patients with immunocompromised status due to other than HIV infection were excluded
159 from this study.

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161 To maintain the strict confidentiality and to conceal the identity of the patient, coding system
162 for sample was followed which was known only to investigator and password protected data
163 was stored electronically. After taking written informed consent, detailed clinical history and
164 all relevant investigations (including radiological for the diagnosis of toxoplasmosis) of each

165 patient was done and findings were noted as per standard predesigned and pretested clinical
166 proforma.

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168 Blood samples to provide the sera for ELISA test were taken by venipuncture. At least 5 ml
169 of blood was obtained to ensure that there will be enough serum for the test. Immediately
170 blood was transferred from the syringe into dry stoppered sterile tube and allowed to clot.
171 When the serum has separated, it was pipetted off into a sterile tube.³⁰ Serum samples were
172 then subjected to ELISA test for detecting anti-toxoplasma IgM and IgG antibodies as per the
173 manufacturer's instructions. Process was performed as per standard protocol.³¹

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175 Data was compiled in MS Excel and checked for its completeness and correctness. Then it
176 was analysed using SPSS version 21, quantitative tests were applied with p value of < 0.05
177 was considered statistically significant for interpretation of the findings. Final diagnosis
178 (based on ELISA) was compared with the radiological findings to assess the accuracy of
179 radiological investigations. The prior ethical approval was sought for this study by the
180 institutional ethics committee.

181

182 **RESULTS**

183 Out of these 362 HIV positive patients, 226 (62.43%) were males and 136 (37.57%) were
184 females. Most of the HIV positive patients, 359 (99.17%) were married and only 3 (0.83%)
185 were unmarried and 313(86.46%) were from urban area whereas 49 (13.54%) were from
186 rural area. Majority of the patients were laborers 144 (39.78%) followed by house wives,
187 skilled employee, drivers, farmers and others were 75 (20.72%), 64 (17.68%), 52 (14.91%),
188 12 (3.31%) and 15 (4.14%) respectively. Total 85 (23.48%) HIV positive patients were co-
189 infected with toxoplasmosis. 65 (17.96%) were males and 20 (5.52%) were females. All of
190 the co-infected patients were married and 78 (21.55%) from urban area. Whereas, 7 (1.93%)
191 were from rural area. Majority of the co-infected patients were laborers 35 (9.67 %) followed
192 by drivers, skilled employee, house wives, farmers and others were 17 (4.70%), 13 (3.60%),
193 12 (3.31%), 3 (0.82%) and 5 (1.38%) respectively (Table 1).

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195 **Table 1: Prevalence of Toxoplasmosis co-infection among HIV positive patients**
196 **according to socio-demography.**

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Variables	HIV Positive (%) N=362	IgG positive (%), N=71	P value	IgM positive (%), N=14	P value	IgG + IgM (%)
Age in Years						
15-24	23 (6.32)	3 (0.82)	0.488	0 (0)	0.734	3 (0.82)
25-34	171(47.23)	32 (8.84)		6 (1.66)		38 (10.50)
35-44	133(36.74)	31 (8.56)		5 (1.38)		36 (9.94)
45-54	29(8.01)	5 (1.38)		2 (0.55)		7 (1.93)
55 and above	6 (1.66)	0 (0)		1 (0.28)		1 (0.28)
Total	362 (100)	71(19.61)		14 (3.86)		85 (23.48)
Sex						
Male	226 (62.43)	53 (14.72)	0.018*	12 (3.31)	0.093	65 (17.96)
Female	136 (37.57)	18 (4.97)		2 (0.55)		20 (5.52)
Marital Status						
Married	359 (99.17)	71 (19.61)	0.390	14 (3.86)	0.737	85 (23.48)
Unmarried	3 (0.83)	0 (0)		0 (0)		0 (0)
Residence						
Rural	49 (13.54)	6 (1.66)	0.162	1 (0.28)	0.531	7 (1.93)
Urban	313 (86.46)	65 (17.96)		13 (3.60)		78 (21.55)
Occupation						
Driver	52 (14.91)	15 (4.14)	0.488	2 (0.55)	0.749	17 (4.70)
Farmer	12 (3.31)	3 (0.82)		0 (0)		3 (0.82)
Laborer	144 (39.78)	28 (7.73)		7 (1.93)		35 (9.67)
Housewife	75 (20.72)	11 (3.03)		1 (0.28)		12 (3.31)
Skilled Employee	64 (17.68)	11 (3.03)		2 (0.55)		13 (3.60)
Others	15 (4.14)	3 (0.82)		2 (0.55)		5 (1.38)

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205 **Table 2: Prevalence of Toxoplasmosis co-infection among HIV positive patients**
 206 **according to signs, symptoms and other risk factors.**

Variables	IgG positive (%)	P value	IgM positive (%)	P value	IgG + IgM
Signs and symptoms					

Headache	68 (18.78)	0.000*	12 (3.31)	0.019*	80 (22.10)
Fever	57 (15.75)	0.000*	12 (3.31)	0.013*	69 (19.06)
Increased intracranial tension	21 (5.80)	0.555	8 (2.20)	0.004*	29 (8.01)
Seizure	6 (1.66)	0.898	5 (1.38)	0.000*	11(3.04)
Altered sensorium	4 (1.10)	0.573	3 (0.82)	0.024*	7 (1.93)
Papilloedema	6 (1.66)	0.095	3 (0.82)	0.001*	9 (2.49)
Cerebellar sign	2 (0.55)	0.547	0 (0)	-	2 (0.56)
History of pet contact					
Yes	37 (10.22)	0.000*	6 (1.66)	0.002*	43 (11.88)
No	34 (9.40)		8 (2.20)		42 (11.60)
History of meat ingestion					
Yes	54 (14.91)	0.000*	13 (3.600)	0.000*	67 (18.50)
No	17 (4.70)		1 (0.28)		18 (4.98)
Past history of Toxoplasmosis					
Yes	5 (1.38)	0.000*	0 (0)	-	5 (1.38)
No	66 (18.23)		14 (3.87)		80 (22.10)
Mode of Transmission					
STD	64 (17.68)	0.487	12 (3.31)	0.516	76 (20.10)
Blood transfusion	0 (0)		0 (0)		0 (0)
Unknown	7 (1.93)		2 (0.55)		9 (2.49)
CD4 cell count					
<100	20 (5.52)	0.227	2 (0.55)	0.292	22 (6.08)
101-200	10 (2.76)		3 (0.82)		13 (3.60)
201-500	28 (7.73)		9 (2.49)		37 (10.22)
>501	13 (3.59)		0 (0)		13 (3.60)
Response to treatment					
Yes	51 (14.10)	0.000*	12 (3.31)	0.000*	63 (17.40)
No	20 (5.52)		2 (0.55)		22 (6.08)

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208 As shown in **table 2**, the toxoplasmosis co-infection among HIV positive patients according
209 to signs, symptoms and other risk factors was assessed. The signs and symptoms associated
210 with co-infection showed that majority of the patients had headache (22.10%) and fever
211 (19.06%). Whereas, 8.01%, 3.04%, 2.49%, 1.93%, and 0.56% co-infected patients had
212 symptoms of increased intracranial tension, seizure, papillo-edema, altered sensorium and
213 cerebellar signs respectively. Almost half of the patients (43 (11.88%) had history of pet

214 contact, 67 (18.50%) history of meat ingestion and 5 (1.38%) had past history of
 215 toxoplasmosis, which were statistically significant. Mode of transmission was through sexual
 216 contact among 76 (20.10%), whereas, among 9 (2.49%) patients the transmission was
 217 unknown. Decreased CD4 cell count was observed <100 among 22 (6.08%), 101-200, 201-
 218 500 and >501 CD4 cells among 13 (3.60%), 37 (10.22%) and 13 (3.60%) respectively.
 219 However, majority of the patients, 63 (17.40%) responded to treatment.

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221 **Table 3: Correlation between radiological features in CT-scan head and ELISA for**
 222 **anti-toxoplasma antibodies**

Radiology	ELISA		Total (%)
	Positive (%)	Negative (%)	
Positive	75 (20.72)	105 (29.00)	180 (49.72)
Negative	10 (2.76)	172 (47.51)	182 (50.28)
Total (%)	85 (23.48)	277 (76.52)	362 (100)

223 McNemars χ^2 test=78.48 (Software used: Stata ver.10.0), Odd's Ratio =12.29, 95%
 224 Confidence Interval = (5.84-26.53); p value <0.0001 considered significant.

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226 The correlation between the ELISA sero-positivity and radiological feature is shown in **Table**
 227 **3 and 4**, both the ELISA and the CT-scan were simultaneously positive in 75 (20.72%) and
 228 negative in 172(47.51%) cases, the overall correlation seen in 247(68.23%). Strong
 229 association between ELISA and CT-scan by McNemars χ^2 test was found. 10 (2.76%) cases
 230 were positive by ELISA and negative by radiological examination for toxoplasma. The Odds
 231 ratio was found to be 12.29 with 95% CI = (5.84-26.53) which was found to be statistically
 232 significant.

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237 **Table 4: Comparative evaluation of Radiological test with ELISA**

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Statistic	Formula	Value	95% CI
Sensitivity	$\frac{a}{a + b}$	88.24%	79.43% to 94.21%

Specificity	$\frac{d}{c + d}$	62.09 %	56.10% to 67.83%
Positive Likelihood Ratio	$\frac{\text{Sensitivity}}{100 - \text{Specificity}}$	02.33	1.96 to 2.76
Negative Likelihood Ratio	$\frac{100 - \text{Sensitivity}}{\text{Specificity}}$	00.19	0.11 to 0.34
Positive Predictive Value	$\frac{a}{a + c}$	41.67% (*)	34.38% to 49.23%
Negative Predictive Value	$\frac{d}{b + d}$	94.51 % (*)	90.13% to 97.33%

239 Note: a-true positive, b-false positive c-false negative, d-true negative³²

240

241 **Table 5: Radiological features in HIV-toxoplasmosis co-infected patients (N=85).**

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Radiological features	No. of cases (%)	p-value
Only Hyperdensity	13(15.29)	0.408
Only Hypodensity	37(43.52)	0.026*
Only Ring-enhancement	25(29.41)	0.000 *
Hyperdensity + Ring-enhancement	04(4.70)	0.384
Hypodensity + Ring-enhancement	06(7.05)	0.280
Total (%)	85(100)	-

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244 As shown in table 5 the radiological features suggestive of toxoplasmosis in HIV-
 245 toxoplasmosis co-infected patients in the CT-scan head (n=85). Out of these hyper density
 246 and hypo-density was present in 13 (15.29%) and 37 (43.52%) patients respectively.
 247 Whereas, 25 (29.41%) cases showed only ring enhancement as the radiological feature. Only
 248 4 (4.70%) patients had hyper density and ring-enhancement features. Whereas, 6(7.05%)
 249 cases showed hypo density and ring-enhancement. Only hypo density and only ring-
 250 enhancement were the radiological features which were found to be statistically significant
 251 (p<0.05).

252 DISCUSSION

253 Toxoplasmosis is the most common opportunistic infection in HIV-infected patients. A high
 254 seroprevalence of anti-*Toxoplasma gondii* IgG antibody has been reported in HIV-infected
 255 subjects³²⁻³⁵. This study showed that the seroprevalence of *Toxoplasma gondii* was 23.48%.

256 The co-infection occurred most among married male from urban population with the history
257 of pet contact, meat ingestion and unsafe sexual activity. This rate is almost comparable
258 with the other studies reported elsewhere such as study by Holliman³⁶, in which the
259 seropositivity of toxoplasmosis found to be 26.06%, Sykora et al., found seropositivity of
260 toxoplasmosis 29.8% in HIV positive patients³⁷. Brindle et al., found seropositivity of
261 toxoplasmosis to be 22%³⁸. Oksenhendler et al., 1994 found that 25.4% was seropositivity
262 rate³⁹. Similarly, Minkoff et al 1997 found that 20.2% was the seroprevalence of
263 toxoplasmosis⁴⁰. Millogo et al 2000 found seropositivity in 25.4%⁴¹. The seropositivity was
264 found as 67.8%, 23.2%, 22.4%, & 21% by studies conducted by different authors like
265 Sukthana et al 2000, Nissapatorn et al 2001 and Nissapatorn et al 2002, respectively⁴²⁻⁴⁴.
266 Also, Hari et al 2007, Akanmu et al 2010 and Oshinaike et al 2010, carried out study to find
267 out seroprevalence of toxoplasmosis and found out to be 8%, 54% and 85.5% respectively⁴⁵⁻
268 ⁴⁷. This study revealed that there is high prevalence of *Toxoplasma gondii* co-infection among
269 HIV/ AIDS patients suggesting that HIV-infected populations should be protected from
270 *Toxoplasma gondii* infection to reduce the morbidity and burden of the disease.

271

272 In our study, both the ELISA and the CT-scan were simultaneously positive in 75 (20.72%)
273 and negative in 172 (47.51%) cases, the overall correlation seen in 247 (68.23%). In fact we
274 found a strong association between ELISA and CT-scan by McNemars χ^2 test. Also,
275 statistically was found to be highly significant (p=0.000). A retrospective study was done by
276 Venugopal A et al 2012, among AIDS patients in a tertiary care hospital. The diagnosis was
277 based on clinical features, demonstration of elevated IgG by ELISA and associated CT-scan
278 findings. 2826 HIV positives attended Infections Disease Cell from 2000 –2010, of which 33
279 (1.12%) had CNS toxoplasmosis. Mean level of IgG was 255.69. CT / MRI finding of ring
280 enhancing lesion or cerebritis was seen in 79 % of the cases with 18% of lesions in both basal
281 ganglia and parietal lobes. Cerebritis was most common lesion in CT/MRI, seen in 16 cases
282 while ring enhancing lesions were seen in 10 cases. 82% improved with treatment and 18%
283 died of complications. The possibility of cerebral toxoplasmosis should be considered in
284 every HIV-positive patient with neurological symptoms parietal lobe lesions were common in
285 their study, contrary to other existing data which say toxoplasma lesions are usually midline
286 lesions ⁴⁸.

287

288 In the present study, out of these 85 HIV-toxoplasma co-infected patients, only hyperdensity
289 was seen in 13(15.29%) patients, only hypodensity was present in 37 (43.52%) patients
290 whereas 25 (29.41%) cases showed only ring enhancement as the radiological feature. The
291 patients had both hyperdensity & ring-enhancement features were 4 (4.70%). Whereas, 6
292 (7.05%) cases showed hypodensity and ring-enhancement simultaneously. Similar
293 radiological features were reported in a study by Vidal et al., showed that typical findings of
294 hypodense lesions with ring enhancing and perilesional edema were present in nearly 80% of
295 cerebral toxoplasma patients²³. An another study reported that in patients with toxoplasma
296 encephalitis various lesions found were hypodense lesion with ring-enhancement and
297 perilesional edema, nodular enhancement and perilesional edema with small, enhancing
298 asymmetric nodule along wall of the lesions ²⁸.

299

300 **CONCLUSION**

301 This study concludes that the majority of the HIV positive patients were males (62.43%) than
302 females (37.57%. majority of them were married (99.17%) and from urban area (86.46%),
303 Majority of the patients were labourers (39.78%) followed by house wives (20.72%). A total
304 of 23.48% HIV positive patients were co-infected with toxoplasmosis of which 21.55%
305 patients were married and from urban area. Most of the HIV positive patients and co-infected
306 with toxoplasmosis were between the age groups of 25-34 and 35-44 years. The overall
307 correlation of serological and radiological features was seen in 68.23%. Although
308 radiological investigations were helpful in providing better localization of toxoplasmosis but
309 less confirmatory than ELISA. So combination of modalities should be used in diagnosis of
310 toxoplasmosis for appropriate management.

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