

EVALUATION OF NEUROLOGICAL MANIFESTATIONS IN HUMAN IMMUNODEFICIENCY VIRUS-AIDS PATIENTS ADMITTED TO SOUTH INDIAN TERTIARY CARE HOSPITAL – A CROSS-SECTIONAL STUDY

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ABSTRACT

Objective: The objective of the study was to describe, evaluate, and analyze neurological manifestation in human immunodeficiency virus HIV positive patients admitted to a tertiary care center.

Methods: The study was a prospective cross-sectional study, in which 103 HIV patients were analyzed. All patients were interviewed face to face and evaluated by the investigator with particular reference to neurological manifestations. They were classified into various stages of HIV using the World Health Organization staging system.

Results: The mean age in males was 37 (standard deviation [SD] 8.0) years and in females 35 (SD 7.0) years. A greater proportion of females were diagnosed in the asymptomatic state during screening, either during pregnancy or when the spouse was found to be positive. Headache was the most common neurologic symptom and fundus abnormalities were the most common neurological sign documented in patients. The mean CD4 counts in males are 156.5/mm³ and in females are 229.57/mm³ whereas the mean absolute leukocyte count in males is 1088.30/mm³ and in females is 1473.52/mm³. The CD4 counts showed a better correlation with the occurrence of neurological manifestations than absolute leukocyte count.

Conclusion: Headache was a significant predictor of the occurrence of neurological complications (p=0.01). CD4 counts were significantly lower in patients with neurological complications and most of the neurological manifestations; on the contrary, all the opportunistic infections were documented in patients with CD4 counts below 200/mm³. Neurological complications did not show any correlation with the patient being on anti-retroviral therapy.

Keywords: Cryptococcal meningitis, Human immunodeficiency virus/AIDS, Neuro-infections, Toxoplasmosis, Tuberculosis.

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INTRODUCTION

India is mainland to the third population of people living with human immunodeficiency virus (HIV) and AIDS [1]. With the first case detected in 1986 among female sex workers, today India reports more than 5.134 million infections [2,3]. HIV belongs to the class of lentiviruses genus (Retroviridae family), characterized by immunodeficiency, neoplasia, and neurologic manifestations. HIV is a neurotrophic and neurovirulent syndrome which is classified under primary neurologic disease and secondary (opportunistic infection [OI]). The presumed mechanism of central nervous system (CNS) invasion states under the term "Trojan horse," in which monocytes are admitted into the blood-brain barrier followed by an aggressive immune response in the recrudescence of the disease [4]. Shorter survival of AIDS is strongly associated with late diagnosis and development of CNS-related OI [5].

With a multidisciplinary approach under the umbrella of the National AIDS Control Organization (NACO), India has made great progress to control the spread of the infection. Still due to socio-diverse culture with limited resource antiretroviral is unaffordable to a larger section of society [6]. This had resulted in the rise of neurological manifestation cases in HIV/AIDS. In spite of wide prevalence, there is a scare in neuroepidemiology studies on HIV patients from the southern part of the Indian sub-continent. The objectives of the study were to evaluate the prevalence of neurological manifestation in HIV positive patients admitted to a tertiary care center and also to find the possible predictors of neurological manifestations.

METHODS

Setting

This is a prospective observational study carried out between October 2017 and June 2019 on 103 consecutive HIV patients in different stages of disease seen as inpatients in NRI Medical College and General Hospital, Chinakakani, Guntur, Andhra Pradesh. All respondents were adults, aged >18years who gave informed consent were included in the study.

Patients

Patients were selected on an in-patient basis. The in-patients were those who were admitted to the medical wards of NRI Medical College and General Hospital, Chinakakani, during the aforementioned period with a diagnosis of HIV infection. The first consecutive 103 patients admitted and who were willing to participate in the study were included in the study.

All patients were interviewed and examined by the investigator. Emphasis was particularly laid on identifying the stage of the disease and also on recognizing neurological manifestations of HIV. Investigations were done based on the needs of the patients after a thorough clinical evaluation.

Tests

HIV was confirmed by the ELISA test. Total count and differential count were performed in the laboratory using automated counting

chambers and confirmed manually. CD4 counts were analyzed using the flow cytometry method. Other tests were done as per the needs of the patient.

Patients with a diagnosis of neuro-AIDS were treated according to the NACO guidelines using anti-retroviral treatment (ART), antitubercular, antifungal, decongestants, antibiotics, and anticonvulsants medications. Associated OI were treated with respective drugs.

Sample size

All 103 patients who presented to the hospital during the study period were chosen.

Statistical analysis

Data analysis was performed using SPSS for Windows version 13.0. Mean and median were used as measures of central tendency and standard deviation (SD) were used as a measure of dispersion for descriptive statistics. Chi-square and Pearson's test has been used to test the association between CD4 counts and absolute lymphocyte count (ALC) counts and their association with neurological manifestations and duration of HIV.

RESULTS

Demographic distribution and HIV classification

In Table 1, of 103 patients, 78.6% were male and 21.4% were female. The mean age in males was 37±8.0 and females was 35±7.0 consecutive years. Seventy-three patients were married whereas 41 (39.8%) of participants had 0–10 months duration of HIV history.

A greater proportion of females were in the asymptomatic state during screening, either during pregnancy or when their spouse found positive. Patients were classified under HIV using stage criteria. Nineteen (18.4%) were in Stage 1, 14 (13.6%) were in Stage 2, 23 (22.3%) were in Stage 3, and 47 (45.6%) were in Stage 4, respectively.

Neurological investigation

Cerebral spinal fluid (CSF) examination was diagnosed in 35 of the 40 (87.5%) of patients who underwent the study.

The computed tomography/magnetic resonance imaging findings were cerebral edema in 18%, cerebral atrophy in 10%, space-occupying lesions brain in 10%, periventricular infarcts in 10%, and other infarcts in 7%. In 45% the imaging studies were normal. The space-occupying lesions detected include toxoplasmosis (2), CNS Lymphoma (1), and tuberculoma in a patient with Disseminated tuberculosis (1) (Table 2).

Out of the six patients who had symptoms suggestive of peripheral neuropathy, three patients had an abnormality detected on the ENMG. Small fiber neuropathy may be associated with a normal electroencephalogram (EEG).

EEG was done in five patients and all of them were normal. Sural nerve biopsy was done in two patients showed sensory axonal neuropathy. Brain biopsy finding in one patient showed CNS lymphoma.

Neurological signs and symptoms

Headache was the most common symptom seen in 39 patients and was associated with vomiting in 31 patients. This was followed by seizures and altered sensorium. Gait abnormalities (12%) included spastic (4%), ataxic (4%), and paralytic (4%). These were the most common neurological signs at presentation. The etiological diagnoses in these patients included tuberculous meningitis (TBM) and Cryptococcal meningitis (3), TBM (3), and CNS Lymphoma (1). Monoplegia documented in three patients was due to TBM (Fig. 1).

Disease spectrum

In Table 3, of the 103 patients 41 had neurological complications subdivided into TBM (13.6%) was the most common neurological manifestation seen, followed by cryptococcal meningitis (10.7%),

Table 1: Demographic distribution of the study population (n=103)

Characteristics	n [□]	%
Sex		
Male	81	78.6
Female	22	21.4
Age		
20–30 years	22	21.4
31–40 years	54	52.4
41–50 years	19	18.4
>50 years	8	7.8
Marital status		
Single	14	13.6
Married	73	70.9
Widowed	16	15.5
Duration of HIV		
0–10 months	41	39.8
11–20 months	26	25.2
21–30 months	9	8.73
31–40 months	7	6.8
41–50 months	8	7.8
51–60 months	7	6.8
>61 months	5	4.5
Mode of diagnosis		
OI	62	60.2
Spouse positive	21	20.4
Routine	18	17.5
Intercurrent illness	2	1.9
Substance abuse		
Alcohol	62	60.2
Smoking	65	63.1
HIV staging		
1 stage	19	18.4
2 stage	14	13.6
3 stage	23	22.3
4 stage	47	45.6
Residential area		
Hyderabad	1	0.9
Bengaluru	32	31.2
Karnataka outside Bengaluru	36	5.0
Andhra Pradesh	20	19.5
Tamil Nadu	9	8.7
North East	1	0.9
Kerala	3	2.9

□Frequency of socio-demographic details. HIV: Human immunodeficiency virus

Table 2: CSF and neuroimaging findings in the study population

Investigation	Frequency	
CSF picture		
Not done	63	
TBM	22	
Cryptococcus meningitis	6	
Normal	5	
Others	4	
Viral meningitis	3	
Other CSF investigation	Positive	Negative
CSF India Ink	10	25
CSF crypto antigen	13	22
CSF VDRL	1	34
CSF Gram's stain	0	35
CT/MRI		
Not available	63	
Normal	18	
Cerebral edema	7	
Cerebral atrophy	4	
Brain SOL	4	
Periventricular infarct	4	
Other infarcts	3	

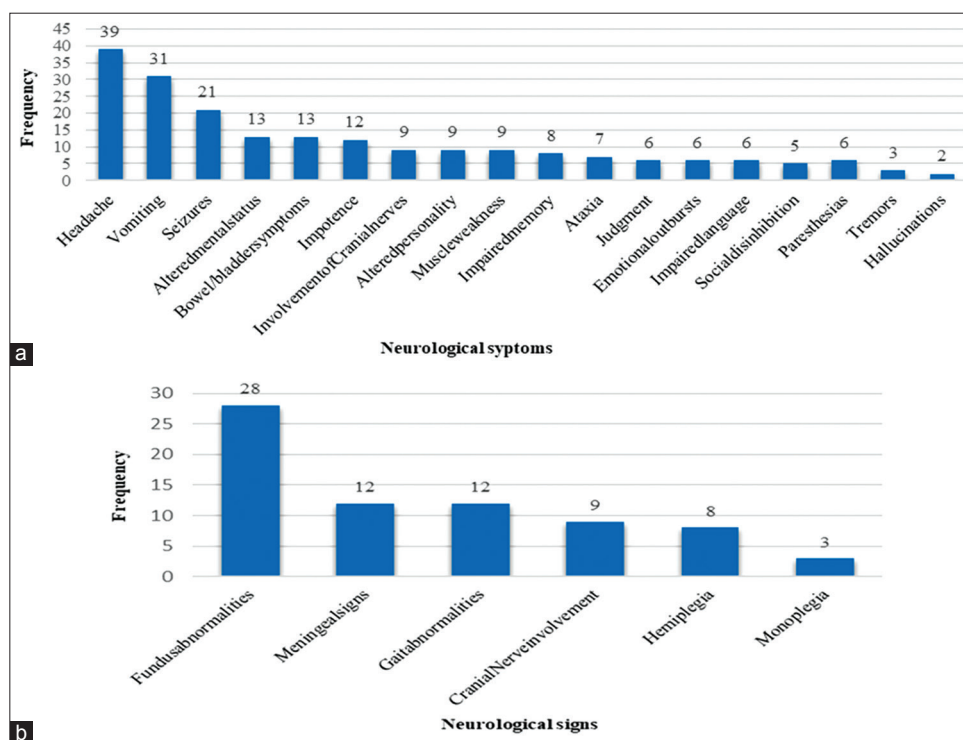


Fig. 1: (a and b) Clinical neurological manifestations in human immunodeficiency virus patients

three additional patients had coexistent tuberculous and cryptococcal meningitis. Thus, infections are the most common neurological manifestations in patients with HIV. Among the three patients with neuropathy, one patient was on Stavudine (STV) and the neuropathy was related to the drug and the other two patients probably had HIV induced neuropathy.

Association of CD4 and absolute lymphocyte count with neurological manifestation

The mean CD4 with neurological manifestations was 107.34 and without neurological manifestations was 213.93. This was statistically significant (p=0.00). The mean ALC in patients with neurological manifestations was 1009.22 and in those without neurological manifestations was 1280.37. This was not statistically significant (p=0.06). Thus, CD4 counts showed a better correlation with the occurrence of neurological manifestations than ALC (Table 4).

Correlation of ART and the neurological manifestation

The duration of ART did not show a correlation with the occurrence of neurological complications (Table 5).

DISCUSSION

Neurological manifestations in HIV patients are influenced by host genetic factors, environmental factors unique to developing countries, and patient’s accessibility to treatment. Hence, a comparative analysis of the neurological manifestations from different regions of the world is necessary. This study is aimed at studying the neurological manifestations in a South Indian population.

As this, an inpatient based study; patients with more advanced disease are likely to be included in the study. Due to the dynamics of the disease spread in our population as discussed below, males are more likely to be in an advanced disease state as compared to females, which reflects in the greater percentage of widowhood in females. Females have generally been diagnosed as HIV-positive during either routine Ante Natal checkups or when their husbands came with OI [7-9].

Table 3: Relation of mean CD4 count and neurological diagnosis in the study population

Neurological diagnosis	Frequency	M [†] CD4
None	63	216.78
TBM	19	134.54
Crypto meningitis	3	63.55
Toxoplasmosis	2	66.00
CNS lymphoma	2	133.00
Distal symmetrical sensory neuropathy	2	118.00
AIDS dementia complex	2	143.50
Small vessel vasculitis	2	178.00
Viral meningitis	3	154.00
TBM+Crypto meningitis	3	63.25
Neurosyphilis	2	91.00

[†]Results are expressed in Mean; calculation of mean CD4 is based on a neurological diagnosis.

Table 4: Association of ALC and CD4 count with neurological complications

	s		p*
	Yes (M±SD)*	No (M±SD)*	
CD4	107.3±16.4	213.9±16.4	0.001
ALC	1009.2±82.6	1280±105.1	0.06

*Result are expressed in mean and standard deviation. *p<0.05 statistically significant

Table 5: Association of ART and neurological complications

		Neurological complications		p*
		No	Yes	
ART	No	35	24	0.072
	Yes	24	17	

*p<0.05 statistically significant

The most common symptom in our study was a headache with vomiting. Seizures and altered sensorium were the other common symptoms. This is comparable with the study done by Wadia *et al.* [10], who documented neurological symptoms in 30% of their patients.

Incidence of fundus abnormalities was low in our study as compared to the other Indian studies [11]. The high incidence of fundal abnormalities, some of which are pathognomonic underscores the importance of fundus examination in these patients.

CSF examination is an invaluable investigation in HIV-positive patients with neurological symptoms as they are simple to perform in limited-resource settings whereas it is cost-effective and fairly accurate [12,13]. A study by Satishchandra *et al.* [14] revealed features of cerebral atrophy in 19% and hydrocephalus in 10% of cases from NIMHANS, Bengaluru, India. Hydrocephalus was not found in any of our patients. Neuroimaging is useful for the diagnosis of many problems but is crucial for ruling out space occupying lesion and hydrocephalus, where the performance of a linear optimization may be detrimental to the patient.

Out of the 100 patients, 41 had neurological complications. This is comparable with the study done by Wadia *et al.* [10] where neurological complications of HIV disease were seen in 20% of outpatients in HIV clinics and almost half of HIV patients being treated as inpatients. Another study by Levy *et al.* [15] showed that at least one-third of patients with advanced HIV infection will develop neurological complications during the course of their illness.

The CD4 count and neurological manifestation were in concordance with previous studies [9,10]. The neurological manifestations that were seen in patients with CD4 counts greater than 200/mm³ were viral meningitis in two patients and sensory axonal neuropathy, probably Stavudine induced in 1 patient. This is an expected finding as most OIs and most HIV related neurological complications occur at low CD4 counts.

The mean duration of ART in patients with neurological manifestations was 9.63 months and the mean duration of ART in patients without neurological manifestation was 10.24 months (difference not significant). Most of the manifestations have occurred within the 1st year of ART.

OIs occurring in the early part of the ART could represent an incomplete immune reconstitution or an immune reconstitution syndrome. Many of our patients probably represent the former group because the CD4 counts were below 200/mm³. The lack of correlation between the duration of ART and the occurrence of neurological manifestations is reflected in the lack of correlation between the duration of ART and the CD4 counts. One reason for this could be different baseline CD4 counts. A subset of patients could be having treatment failure.

Our study was not designed to address this issue, but it was heartening to note that those patients whose CD4 counts were above 200/mm³ were protected from most of the neurological complications.

Few limitations of the study were first, the cross-sectional design which affects the serial monitoring of patients. Second, the sample size of the study and selection bias due to a greater proportion of patients being in the World Health Organization Stages 3 and 4 is another limitation, as the study was done in a tertiary care center.

CONCLUSION

Headache was a significant predictor of the occurrence of neurological complications ($p=0.01$). CSF examination revealed a positive diagnosis in the majority of the patients who underwent the test. A neurological problem was detected in 41 out of the 103 patients studied. OI remained the most common problems detected, including TBM, Cryptococcal meningitis, a combination of both and viral meningitis. HIV-related neurological problems documented (six out of 41) included AIDS Dementia Complex, neuropathy, and CNS lymphoma.

CD4 counts were significantly lower in patients with neurological complications and most of the neurological manifestations and all the OIs were documented in patients with CD4 counts below 200/mm³. Neurological complications did not show any correlation with the patient being on ART or otherwise or with the duration of ART. The possible reasons for this include differing baseline CD4 count at the start of ART and treatment failure in a subset of patients.

FUTURE SCOPE

Evaluation of neurological manifestations in HIV-AIDS patient in WHO Stages 1 and 2 to understand the primary stage of clinical findings.

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CONFLICTS OF INTEREST

No conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

Dr. Arun Singh Tejavath and Dr. Amit Mathur conceptualized and gathered the data in regard to this work. Dr. Pratima Singh, Dr. Supriya Suman, and Dr. Preeti Raj analyzed these data and necessary inputs were given toward the designing of the manuscript. All authors discussed the methodology and results and contributed to the final manuscript. Dr. Arun Singh Tejavath and Dr. T. Murali Venkateswara Raosupervised the whole work until the completion of the whole manuscript.

ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT

The study was approved by the institutional ethics committee of NRI Medical College and General Hospital, Chinakakani, Guntur, Andhra Pradesh.

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