Clinical Profile of Neurological Manifestations in HIV-Reactive Patients and Their Relation with CD4 Count.

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ABSTRACT

Background: Neurologic abnormalities have been noted in one-third of patients with AIDS, but at autopsy the nervous system is affected in all of them. Aim: To study the clinical profile of neurological manifestations in HIV reactive patients and their correlation with CD4 counts. **Methods:** A randomized case study was conducted at Department of Medicine, Government Medical College, Patiala over a period of 2 years. 200 HIV-infected adult and adolescent patients (>15 years of age) were studied. The diagnosis of HIV was confirmed by 3 HIV ELISA& RAPID positive reports in symptomatic patients. **Results:** In the present study, 37% of the patients were in the age group of 26-35 years. Males are affected more frequently than females, with a male to female sex ratio of 2.56: 1. Meningitis, HIV associated dementia, Progressive multifocal leukoencephalopathy& peripheral neuropathy are the commonest neurological disorders observed in HIV-infected patients. Tuberculosis is the commonest opportunistic infection in retroviral positive patients. **Conclusion:** Central nervous system infections, intracranial mass lesions, stroke, and HIV-associated dementia are more common in patients with a CD4+ count less than 200.

Keywords: AIDS, Human Immunodeficiency Virus, CD4 Count.

INTRODUCTION

HIV infected individuals can experience a variety of neurologic abnormalities due either to opportunistic infections and neoplasms or to direct effects of HIV. It has been demonstrated in the brain and CSF of infected individuals with and without neuropsychiatric abnormalities. The main cell types that are infected in the brain in vivo are the perivascular macrophages and the microglial cells; monocytes have already been infected in the blood can migrate into the brain, where they then reside as macrophages, or macrophages can be directly infected within the brain.^[1] Neoplasms directly attributable to HIV occur throughout the course of the infection and may be inflammatory, demyelinating, or degenerative in nature.^[1]

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The diseases which are produced due primarily to pathogenic process of HIV infection include aseptic meningitis, HIV encephalopathy (AIDS dementia complex), various myelopathies, neuropathies and myopathy.^[2] Common opportunistic diseases involving the CNS are toxoplasmosis, cryptococcosis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma^[2] This study thus evaluates the neurological complications in HIV-reactive patients.

MATERIALS AND METHODS

Study Design A randomized case study was conducted at Department of Medicine ,Government Medical College, Patiala, over a period of 2 years; December 2012 to October 2014. 200 HIV-infected adult and adolescent patients (>15 years of age) where including in the study. The demographical data like name, age, sex, address, occupation, marital status, socioeconomic status, was collected in all patients. History of high risk behavior, major surgery, and blood transfusion was asked in all patients. The diagnosis of HIV was confirmed by 3 HIV ELISA & RAPID positive reports in symptomatic patients. All patients were subjected to detailed general examination and systemic examination with special attention to the central nervous system. All patients were subjected to routine investigations like haemogram, blood biochemistry, and chest X-ray. Other special investigations like CSF analysis, serology, nerve

conduction velocity (NCV) studies and neuroimaging were undertaken as appropriate to individual patient only when mandatory for research project. Absolute CD4+ T-cell count was done in all patients. Lumbar puncture was done for CSF analysis. The CSF sample was analyzed in the Department of Biochemistry, Pathology and Microbiology at Government Medical College, Patiala Punjab India for sugar and protein, cytology, staining including grams staining, acidfast bacillus and India ink preparation. The following reference values were considered abnormal.^[3].

 \Box CSF sugar <40 mg/dL

 \Box CSF protein >50 mg/dL

□ CSF Leucocyte count >5/mm³ (Neutrophils \ge 1/mm³, Lymphocytes \ge 5/mm³)

NCV-EMG studies were carried out in patients presenting with lower motor neuron type of weakness to diagnose and classify type of neuropathy/radiculoneuropathy/myopathy. CT scan of head (with or without contrast injection), was performed in patients, as indicated.

Inclusion criteria

- 1. Age more than 15 years
- 2. Previously or newly diagnosed HIV positive patients (ART and Pre ART)

Exclusion criteria

- 1. HIV patients with past history of neurological diseases like cerebrovascular accidents, epilepsy, parkinsonism.
- 2. Comorbid conditions like diabetes mellitus.

3. Addiction of alcohol and other drug abuses like narcotics, sedatives, and hypnotics.

Ethical issues: The study adhered to standards ethics of research involving humans. Ethical clearance was obtained from the Ethical Committee of the institution and written consent of the patient or patient's relatives was also obtained.

Statistical analysis: Data were analysed by chisquare test and Z-test for difference between proportions of two populations were used.

RESULTS

In our study, Out of 200 seropositive HIV patients admitted in various medical wards of Rajindra Hospital Patiala from December 2012 to October 2014, a total of 57 (28.5 %) cases of HIV-reactive patients with neurological manifestations were studied [Table 1,2,3]. In our study 27 out of 57 (47.40%) had Tubercular Meningitis, 8 out of 57 (14%) had crypotococcal meningitis, 4 out of 57 (7%) had bacterial meningitis among the patients with neurological manifestation. 5 patient out of 57 (8.80%) had HAD (HIV Associated Dementia) / HIV Encephalopathy, 3 out of 57 (5.30%) had PMLE (Progressive multifocal leukoencephalopathy, another 3 out of 57 (5.30 %) had peripheral neuropathy among the patients with neurological manifestations. 2 out of 57 (3.50%) patients with were of each intracranial tuberculoma, toxoplasmosis and CVA(stroke), 1 out of 57 (1.80%) patient had acute inflammatory demyelinating polyneuropathy (AIDP) among the patients with neurological manifestations [Table 4,5].

Table 1: Neurological Manifestations in Study Subjects.								
Sr. No. Neurological Manifestations Frequency Percentage								
1	Absent	143	71.50%					
2	2 Present 57 28.50%							
	Total	200	100%					

Table 2: Sex-wi	Table 2: Sex-wise distribution of various neurological complications in HIV-reactive patients.							
Sr. No.	Sr. No. Sex Frequency Percentage							
1	Female	64	32%					
2	Male	135	67.50%					
3	Transgender	1	0.50%					
	Total	200	100%					

Cable 3: Age-wise distribution of various neurological complications in HIV-reactive patients.						
Sr. No.	Age Group	Frequency	Percentage			
1	16-25	30	15%			
2	26-35	74	37%			
3	36-45	67	33.50%			
4	46-55	17	8.50%			
5	56-65	12	6%			
	Total	200	100%			

Table 4: Distribution of various neurological complications in HIV-reactive patients.							
Neurological Complication Number of Patients Percentage							
Tuberculous Meningitis	27	47.40%					
Bacterial Meningitis(Non-Tubercular)	4	7%					
Cryptococcal Meningitis	8	14%					
Toxoplasmosis	2	3.50%					
CVA	2	3.50%					
Peripheral Neuropathy	3	5.30%					
Tuberculoma	2	3.50%					
HIV-Associated Dementia	5	8.80%					
AIDP	1	1.8%					
PMLE	3	5.30%					

Table 5: Neurological illness and CD4 Count.			
Neurologic illness (No. of cases)	CD4 count (mean +sd)	X ²	P value
Tuberculous Meningitis (27)	181 <u>.4</u> 00 + 83.52	0.926	1.000
Cryptococcal Meningitis (8)	<u>97</u> .25 + 71.27	0.750	0.993
Bacterial Meningitis(Non-Tubercular) (4)	_110 + 57.63	0.000	1.000
AIDP (1)	65	00	00
CVA (2)	_184 + 96.17	0.000	1.000
Peripheral Neuropathy(3)	15 <u>9</u> .33 + 40.22	0.000	1.000
Toxoplasmosis(2)	_ 70 + 22.63	0.000	1.000
PMLE (3)	6 <u>3</u> .67 + 13.05	0.000	1.000
HAD (5)	9 <u>2</u> .40 + 31.63	0.000	1.000

Fable 6: Distribution of study subjects based on imaging (CT /MRI).							
Sr.No.	CT / MRI	Frequency	Percentage	X ²			
1	Normal	28	49.10%	62.491			
2	Infective Etiology	3	5.30%				
3	Hypodense Lesion	5	8.80%	(p value 0.000)			
4	Cerebral Edema	9	15.80%				
5	Multiple Enhancing Lesion	3	5.30%				
6	Single Enhancing Lesion	1	1.80%				
7	Not Done	8	14%				
	Total	57	100%				

Neuro-imaging (CT / MRI) done in total 49 (86%) patients out of them 28 (49.10%) were normal. Abnormal neuro-imaging is observed in 21 (36.84%) patients. The most common abnormality was cerebral oedema in 9 (15.80%) patients, followed by hypodense lesion in 5 (8.80%) patients then inflammatory exudates in 3 (5.30%), single enhancing lesion in 1 (1.80%), multiple lesions in 3 (5.30%), our results are statistically significant with p value 0.000 [Table 6].

DISCUSSION

A detailed normal study of coronary arteries would This study included 200 HIV positive patients registered in ART centre Rajindra Hospital Patiala during the study period from December 2012 to October 2014. Only symptomatic patients between the age group of 15 to 65 years were enrolled. The data was collected, formulated and analyzed for its statistical significance.

Age Group: In the present study, the age ranged from 21 to 51 yrs. Mean age was 36.28+10.20 year. Mean age of males was 34.30 + 7.29 year and mean age of females was 29.27 + 6.47 year.

Majority of the patients were in the economically productive age group of 20-45 yrs. The difference in the mean age was statically not significant. Our results are comparable to Sinder et al^[4], Dhadje et al^[7], Patel et al^[6] millogo et al^[5] and patill et al^[8]. snider et al in their study of 50 cases found that the age range was 25 to 56 years in HIV reactive patients with neurological manifestations.^[4]

General Symptoms:-Amongst the general symptoms fever was present in 41 (71.93%) out of 57 patients with neurological manifestations, and significant weight loss in approximately 40.35% (23 out of 57) patients which is comparable to a study done by Patel et al who observed that the commonest presenting symptom was fever (72.38%), followed by loss of weight (56.19%).^[6]

Neurological symptoms:- Altered sensorium was the commonest symptom seen in 36 patients out of 57 patients with neurological manifestation (63.16%), followed by head ache in 30 patients (52.63%), focal neurological deficit (FND) in 15 patients (26.32%) and convulsion in 15 patients (26.32%) of the patients.

Table 7: Comparisons of various Neurologic Symptoms.								
Symptom	Present Study	Satyendra et al	Sharma et al	Patel et al ^[6]	Atill et al ^[9]	Sircar at al ^[22]		
Headache	52.63%	67.4%	62.5%	27.62%	70.17%	65%		
Altered Sensorium	63.16%	58.1%	55%	18.1%	31.57%	36%		
Convulsion	26.32%	14.0%	25%	-	-	28%		
FND	26.32%	-	27.5%	6.7%	31%	33%		
Weight loss	40.35%	-	-	56.19%	-	-		

Neurological Signs

Fundus abnormality was present in 12 (21%) out of 57 patients with neurological manifestations. Among the fundus abnormality 15.79% (9 out of 57) patients had bilateral papilledema and 5.26% (3 out of 57) patients had other abnormalities in the form of HIV retinopathy, choroid tubercle and cotton wool spot.

Atill at al found papilledema in 35.08% ^[9] sharma et al observed papilledema 3 out of 40 patients (7.5%).^[10]

Meningeal signs were documented only in 25 out of 57 patients with neurological manifestation (43.86%). Only 62.96% (17 put of 27) of TBM and 62.50% (5 out of 8) of Cryptococcal meningitis had neck rigidity. Therefore it is obvious that signs of meningeal irritation are not reliable for diagnosing meningitis.

Our results are comparable to RANA et al who observed neck rigidity in 76% of TBM and 57% cryptococcal meningitis^[11] and Sharma et al who observed that signs of meningeal irritation were present in 50% of the cases.^[10]

Gait abnormalities were found in 9 (17.54%) out of 57 patients of neurological manifestation, which included spastic 5.26% (3 out if 57) and hemiplegic 10.53% (6 out of 57) gaits. Sharma at al observed gait abnormalities in 10% patients 4 had ataxia of which 2 patients had cerebellar ataxia and the other 2 had sensory ataxia.^[10]

Cranial nerve abnormalities were present in 4 (7.02%) out of 57 of the patients with neurological manifestations; of these 2 had upper motor neuron type of VIIth cranial nerve palsy which was associated with hemiplegia and in 22 other patient; 3,4,6 cranial nerves were involved secondary to TBM. Sharma et al observed that cranial nerve involvement was seen in 17.5% patients and among them 7th cranial nerve was the most commonly involved [10] Hemiplegia was documented in 6 patients (10.52%) out of 57 with neurological manifestations. The causes included TBM and Cryptococcal Meningitis, PMLE and CVA. Sharma et al observed 11 patients (27.5%) have motor weakness in the form of hemiparesis.^[10] Satyendra et al observed that 6 patient out of 43 (13.95) presented with motor weakness.^[12][Table 7]

CD4 Count

Our study is comparable to a study done by Dhadke et al which showed that 76% patient had CD4

count <200/mm3 whereas only 24% patient had CD4 count >200/mm3,^[7] Hemant et al studied HIV patients with neurological complication had other opportunistic infections and most of these patients had CD4 count less than 200, Only 10 (20%) of patients had CD4 counts more than 200.^[13] Satyendra et al in a study of 38 HIV-infected patients with neurological manifestations observed that the mean CD4 count was 177.9 +105.0, of which 24 (63.2%) patients had CD4 count less than 200,^[12] Sharma et al who did a study in 37 patients reported that in 13 (35.14%) patients CD4 count was between 200-500mm3. In 24 (64.86%) patients ^[10]

CSF analysis :

CSF analysis was helpful in differentiating types of meningitis. It was done in 49 out of 57 (85.96%) patients with neurological manifestations patients. It was not done in 8 out of 57 (8.77%) patients with neurological manifestations as it was contraindicated or not indicated. Among the patients who underwent a CSF analysis, 27 showed features suggestive of TBM, 8 had Cryptococcal meningitis and 4 had bacterial meningitis. 2 patients had intracranial tuberculoma. Cell counts ranged from 02 to 1352 with mean of 191/mm3. Most cases had predominant lymphocytes. CSF Cells > 50/mm3 were seen in 36 cases (73.47%) Protein level ranged from 32 mg/dl to 450 mg/dl. 89.80% ^[14] cases had CSF protein > 50 mg/dl. Sugar level ranged from 20-80 mg/dl.

Virtually all patients with HIV infection had some degree of nervous system involvement with the virus. This is substantiated by the fact that CSF findings are abnormal in 90% of patients, even during the asymptomatic phase of HIV infection. CSF abnormalities included pleocytosis (50-65% of patients), detection of viral RNA (75%), elevated CSF proteins (35%) and evidence of intrathecal synthesis of anti-HIV antibodies (90%).^[1]

Thus, CSF examination is an invaluable investigation in HIV positive patients with neurological symptoms of headache and vomiting even though they do not have clinical signs of meningitis. It is simple to perform even in limited resource settings, it is cost effective and fairly accurate.

Neurological manifestation

Prevalence of neurological manifestation [Table 8,9,10] :

In the present study, 57 patients out of 200 patients (28.5%) were diagnosed to have neurological manifestations of HIV. This shows a high prevalence of neurological manifestation in HIV patients.

This result was in agreement with Wadia et al and Teja et al. Neurological complications were observed in 20.24% of patients attending the outpatient clinic and in 44.57% of in-patients in a study by Wadia et al in Pune.^[15] in a study by Teja et al, an overall prevalence of 25.6% was obtained, which ranged from 15.8% in 1993 to 26.6% in 2003.^[16]

Table 8: Neurologic	Table 8: Neurological Diagnosis, Comparison of neurological illness								
Diagnosis	Present study	Dhadke et al ^[7]	Rana et al ^[11]	Patel et al	Satyendra et al ^[12]	Sharma et al ^[10]	Levy et al	Wadia et al ^[15]	
Tubercular meningitis	47.40%	34%	34%	34%	48.83%	37.5%	<1%	18.6%	
Cryptococcal meningitis	14%	4%	14%	14%	16.27%	10%	13%	67.44%	
Bacterial meningitis	7%	14%	-	-	16.27%	5%	-		
HIV Encephalopathy	8.80%	6%	4%	4%	9.30%	-	0%		
PMLE	5.30%	-	8%	12%	2.33%	-	2%		
Peripheral neuropathy	5.30%	8%	22%	22%	-	20%	6%		
Toxoplasmosis	3.50%	2%	10%	10%	2.33%		32%	66.13%	
CVA	3.50%	16%			6.98%	7.5%	1.5%		
AIDP	1.80%	-	4%	4%	2.33%				
CNS tuberculoma	3.50%	14%	-	-	4.66%	2.5%	-	16%	

Table 9: TBM Comparison				
	Present study n=27	Hemant et al ^[13]	Dhadke et al ^[7]	Atili et al ^[9]
Fever	26 (96.30%)	100%	76.47%	92%
Headache	13(48.10%)	94.73%	58.82%	80%
Altere sensorium	21 (77.80%)	78.95	52.94%	36%
FND	5(18.50%)	10.52%	17.64%	24%
Convulsion	8(29.60%)	68.42%	23.52%	28%
Weight loss	7(25.90%)			
Lymphadenopathy	5(18.50%)			
Mean CSF Protein	139.90 + 80.52			186 + 67
Mean CSF Sugar	48.37 + 13.63			30 + 8
Mean CSF Cell Count	184.70 + 125.69			97.4 + 49.4
Neck rigidity	9 (40.91%)		70.58%	
Tuberculoma	2 (3.50%)		14%	4%
Infarct (Vasculitis)	3(5.26%)			
Mean CD4 Count	184.70 + 125.69	100 -250		190 + 170

Cryptococcal Meningitis

In this study 8 (14%) out of 57 patients with neurological manifestations were diagnosed to have

Cryptococcal meningitis based on CSF India ink preparation.

Table 10: Cryptococcal Meningitis comparison (Symptom Profile)								
	Present study	Sharma et al ^[10]	Amit et al ^[23]	Atili et al ^[9]	Rana et al	Dhadke et al	Hemant et al	
Fever	75% (6)	75%	63%	75%	51%	50%	100%	
Headache	87.50% (7)	100%	70%	87.5%	71%	100%	88.9%	
Alt. Sensorium	4 (50%)	75%%	24%	37.5%	71%	0%	11.11%	
Convulsions	2(25%)	0%	-	50%	43%	0%	33.3%	
FND	0(0%)	0%	16%%	12.5%	0%	0%	33.3%	

Bacterial meningitis :

In our study 4 (7%) out of 57 patients with neurological manifestations had bacterial meningitis. This study was in accordance with Dhadke SV et al who observed 14^{% [7]} Satyendra et al 16.27%,^[12] Sharma et al 5%,^[10] Bolokadze et al 4% cases of bacterial meningitis.^[17]

Toxoplasmosis

Our study, showed a 3.50% prevalence of CNS toxoplasmosis.

The incidence of CNS toxoplasmosis varies between 10 and 30% in western countries such as USA and Western Europe. The incidence of CNS toxoplasmosis is much lesser in India and was reported to be about 3% in the study by Kumaraswamy et al^[18]Dhadke et al obtained 1 case (2%),^[7] Patil et al reported 1 case (1.234%),^[8] Atili et al found 5 cases (8.77%) of toxoplasmosis.^[9]

HIV associated Dementia

In our study 5 (8.80%) out of 57 patients with neurological manifestations had HIV associated dementia. HIV associated dementia was diagnosed based on neuropsychiatric symptoms and low MMSE score in the absence of any organic cause. Mean MMSE score among the patients with HAD was 21.40 + 1.52 MMSE score less than 23 was taken as the cut off for the diagnosis of dementia. All patients of HAD had mean CD4 count significantly less than the mean CD4 count of those with neurological manifestations. Our study was in concordance with the study by Dhadke et al who reported an incidence of 6% of HAD, Rana et al (4%),^[11] Patel et al (3.8%),^[6] Satyendra et al (9.30%),^[12]Patil et al (4.93%).^[8]

Cerebrovascular Accident/ Stroke

In the study 2 (3.5%) out of 57 cases of neurological manifestations presented with stroke, 1 had right sided hemiparesis and the other had left sided hemiparesis. This was in concordance with Mc. Arthur et al who reported 9 (7%) cases of Cerebrovascular accident,^[19] Levy et al who reported 7 (5.46%) cases of AIDS with Cerebrovascular complications out of 4 cases with infarct,^[20] Patil et al with 8 cases (9.87%),^[8] Sharma et al with 3 cases (7.5%),^[10] Satyendra et al with 8 cases (16%),^[7]

Peripheral neuropathy

Out study showed 5.30% (3 out of 57 patients with neurological manifestations) cases of peripheral neuropathy. Out of three 2 had distal symmetrical peripheral sensory neuropathy whereas 1 had sensory motor (mixed) type of neuropathy. Diagnosis was based on clinical findings as well as NCV testing. Out study was comparable to Dhadke et al who observed that 8% patients had peripheral neuropathy,^[7] Levy et al found that 6% patients had peripheral neuropathy in 5% patients.^[19]

Progressive Multifocal Leukoencephalopathy

Diagnosis of PMLE was based on findings of clinical examination and neuroimaging, JC virus testing was not done. Present study obtained 3 (5.30%) cases of PMLE out of 57 in Patients with neurological manifestations in HIV reactive patients. Our study was in concordance with Rana et al who observed 8% prevalence of PMLE,^[11]Atili et al who reported 5.30% prevalence of PMLD,^[9]Alka et al who observed 6.67% prevalence of PMLE.^[21]

Acute Inflammatory Demyelinating Polyradiculopathy:

Present study observed a single case (1.80%) of AIDP out of 57 patients with neurological manifestations which is comparable to observations by Patil et al with 3.70%,^[8] Satyendra et al with 2.33%,^[12] Patel et al with 3.8%.^[6] and Rana et al with 4% incidence.^[11]

CONCLUSION

Among the 57 patients with neurological manifestations 49.12% were in the age group of 26-35 years. This indicates the High Prevalence of HIV in Economically productive age group, and burden to the economy. Males were affected more frequency than females, with a male to female sex ratio of 2.56:1. The prevalence of neurological manifestations was 28.5% among HIV reactive patients. Main CD4 count of HIV reactive patients with neurological manifestations was 140.60 + 83.70 whereas among the patients of noneurological illnesses, it was 303.13 + 137.59. The most common primary illness was HIV associated dementia (8.80%) followed by distal symmetric polyneuropathy (5.30%), cerebrovascular accident Acute inflammatory (3.50%),demyelinating neuropathy (1.80%). Most common secondary CNS infection was tubercular meningitis (TBM; 47.37%), followed by cryptococcal meningitis (14%), bacterial meningitis (7%), progressive multifocal leukoencephalopathy (PML; 5.30%), cerebral toxoplasmosis (3.50%) and cranial tuberculoma (3.50%). Meningitis was the commonest Neurological presentation in HIV infection in this study (68.42%). CSF analysis was helpful in diagnosing and differentiating various types of meningitis. Imaging was useful in detecting lesions. Cranial CTs were abnormal in more than 50% of the cases. Central nervous system infections, intracranial mass lesions, stroke and HIV-associated dementia were more common in patients with a CD4 count less than 200/mm3, but may occur in CD4 count between 200-500/mm3. High index of clinical suspicion of nervous system involvement in HIV patients at all stages help in early diagnosis and institution of specific therapeutic measures which in turn will decrease mortality and morbidity.

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