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Neurological Manifestations of HIV Infection

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Abstract

Aim and Objectives: The present study was undertaken to evaluate various neurological manifestations of HIV infection, their relation with CD4+ T Lymphocyte count, prophylaxis against opportunistic infections (OIs) and cART status, to evaluate the utility of various investigations in resource limited setting and to study the outcome of those manifestations.

Methods: Total 60 HIV positive patients of either six, age >18 years, who presented with signs and symptoms of neurological involvement were enrolled during a period from Jan 2005- Dec 2013. A detail history was taken; thorough clinical examination and appropriate investigations were done. Final diagnosis, appropriateness of management and outcome of the patient was noted.

Results: Altered sensorium was the most common neurological symptom (60%) while gait abnormality was the most common finding on CNS examination (46.66%). The correlation of neurological manifestations with CD4+ T lymphocyte count <200 cells/µl and with Known HIV's not on cART' as well as correlation between 'Neurological manifestations of HIV (prophylaxis available)' and 'Known HIV's not on prophylaxis' were statistically significant. The imaging (MRI) (46; 76.66%) was most useful investigation followed by CSF analysis (24; 40%). Toxoplasma encephalitis was the most common manifestation (23.33%) followed by TBM (16.66%). 100% of our cases received appropriate treatment according to their complications and it is observed that 76.66% (46) of case improved while 23.33% (14) of cases died even after receiving appropriate treatment as per their diagnosis.

Conclusion: OIs of HIV are more common than non-opportunistic complications of HIV in this part of the India. Most of the CNS OIs of HIV occurred when CD4+ count was <200 cells/µl while cART significantly reduces the risk of many neurological OIs in HIV patients. In this resource limited setting one could fairly rely upon the imaging and CSF analysis for the diagnosis of many neurological manifestations of HIV infection.

Keywords: HIV infection, Neurological manifestations, Lymphocyte, Altered sensorium, Prophylaxis, Toxoplasma encephalitis

Introduction

Among infectious disease causing agents, HIV is now the number one killer and presently infects approximately 33.3 million adults worldwide. India ranks third in AIDS related deaths. The total number of people living with HIV in India is estimated to be 2.4 million. Approximately 1.8 million died due to AIDS related causes throughout the world and approximately 172,000 people died in India as per report of NACO on 1st Dec 2012 [1]. While symptomatic neurologic dysfunction develops in more than 50% of patients infected with HIV, who are not receiving antiretroviral therapy, and neuropathologic lesions are detected at autopsy in approximately 90% of such cases and it causes considerable morbidity and is often associated with high mortality [2].

A wide variety of neurologic complications associated with HIV infection result from the infection itself or secondary to immunosuppression, or as a result of medication effects. These include CNS infections, vascular complications, peripheral neuropathies, myelopathies, myopathies, neurocognitive disorders, neoplasms etc. Although evidence of CNS infection can be observed in the early stages, evidence of central and peripheral nervous system dysfunction is usually seen in the later stages. Meningitis and focal lesions had emerged as the most common neurologic complications of HIV infection and the recent studies from the western literatures are showing increasing trend of HIV associated neurocognitve disorders [3].

Although HIV infection has been on a continuous and alarming rise in India, there are not many large clinical studies conducted on the neurologic manifestations of HIV infection. The insufficient number of cases and the inclusion in the analysis of outpatients limit the existing data from other studies. Hence, at Vivekanand Medical Foundation and Research Centre, Latur, we are aware of the condition ever since beginning, and therefore coming across a large number of patients suffering from neurological complications in HIV positive status. The manifestations being varied, diagnosis is difficult, therefore it was prudent to make a systematic ongoing prospective and retrospective study of this subject.

Materials and Methods

After obtaining Institutional Ethical Committee approval and written informed consent from all the patients, this observational, combined retrospective and prospective study was carried out in Department of General Medicine at Vivekanand Hospital, Latur, Maharashtra during a period from Jan 2005- July 2011 (retrospective analysis) and Aug 2011 to Dec 2013 (prospective study). Total 60 HIV positive patients (known case at the time of admission or later tested to be positive) presented with symptoms and signs of neurological involvement, more than 18 years of age, irrespective of sex from the urban as well as rural area, who were admitted in IPD or attended OPD of Department of General Medicine were enrolled in the study. Patients with <18 years of age, pre-existing neurological disease and patient who refused to give consent or consent from the accompanying relative (in critically ill patients) were excluded from the study.

A detail history was taken; thorough clinical examination and appropriate investigations were done. The final diagnosis, appropriateness of management and outcome of the patient was noted. HIV status was confirmed by using TRIDOT kit and ELISA / Western blot technique. CD4+T lymphocyte count was done by using flow cyotmetry. CSF analysis (routine,

microscopy and India ink), Serological examination and histopathological examination of biopsy sample were done when needed. SIEMENS MAGNETOM CONCERTO 0.2 Tesla MRI machine was used for imaging.

Statistical analysis

Percentage, Mean, Ratio, Standard deviation, Chi square test were used where ever applicable. WHO EPI Info version 3.5.1 software was used for data analysis.

Observations and Results

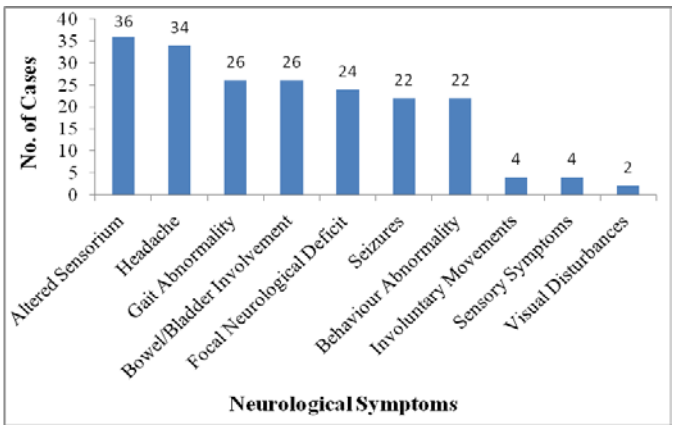
Total 60 out of 525 HIV positive patients had neurological manifestations, prevalence of 11.42% was observed. 34 (56.66%) were already known case of HIV at the time of presentation, while 26 (43.33%) of cases subsequently tested to be HIV positive. Among 60 patients, 42 (70%) were male and 18 (30%) were female. Male to female ratio was 2.3: 1. The majority of the patients (52; 86.66%) were in age group of 31-50 years, ranged from 23-60 years, (Table 1). Mean age in males was 39 years 6 months (ranged- 30-60years) and in females it was 38 years 2 months (Ranged-23-60years).

Table 1: Age and Sex wise distribution of patients

Age group (Years)	No. of cases (%)	
	Male	Female
<21	0 (0%)	0 (0%)
21-30	2 (4.76%)	2 (11.11%)
31-40	24 (57.14%)	10 (55.55%)
41-50	14 (33.33%)	4 (22.22%)
>50	2 (4.76%)	2 (11.11%)
Total	42 (100%)	18 (100%)

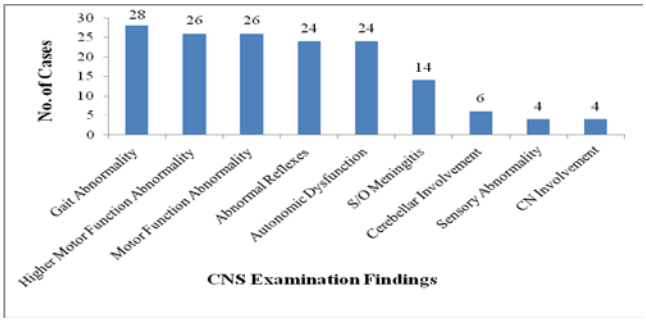
Altered sensorium was the most common symptom found in 60% of patients, followed by headache (56.66%), gait abnormality (43.33%) and bladder/ bowel abnormality (43.33%) and other symptoms are shown in figure 1.

Figure 1: Distribution of patients based on neurological symptoms



Gait abnormality was the most common finding on CNS examination (46.66%) followed by higher motor function abnormality and motor function abnormality in 43.33% of patients each as depicted in figure 2.

Figure 2: Distribution of patients based on CNS examination findings



CD4+ T Lymphocyte count of <200 cell/µl was found in 63.33% (38) of cases and 46.66% (22) cases had count >200 cells/µl. Correlation between 'Neurological manifestations of HIV due to OIs' and 'CD4+ T lymphocyte count <200 cells/µl' was found to be statistically significant, (p=0.03), (Table 2).

Table 2: Distribution as per CD4 Count of Individual Diagnosis (<200 / >200 cells/µl)

Diagnosis		CD4+ T Lymphocyte Count (cells/µl)	
		>200 [No. (%)]	<200 [No. (%)]
Neurological manifestations of HIV due to OIs	Toxoplasma Encephalitis (TE)	4 (28.57%)	10 (71%)
	TBM	4 (40%)	6 (60%)
	Cryptococcal	0 (0%)	8 (100%)

	Meningitis (CM)		
	CNS Tuberculoma (T'OMA)	0 (0%)	6 (100%)
	HSV Encephalitis (HE)	2 (50%)	2 (50%)
	PML	2 (50%)	2 (50%)
Non opportunistic neurological manifestations of HIV	Stroke	4 (50%)	4 (50%)
	Myelitis	2 (100%)	0 (0%)
	CSVT	0 (0%)	2 (100%)
	Neurofibroma	1 (100%)	0 (0%)

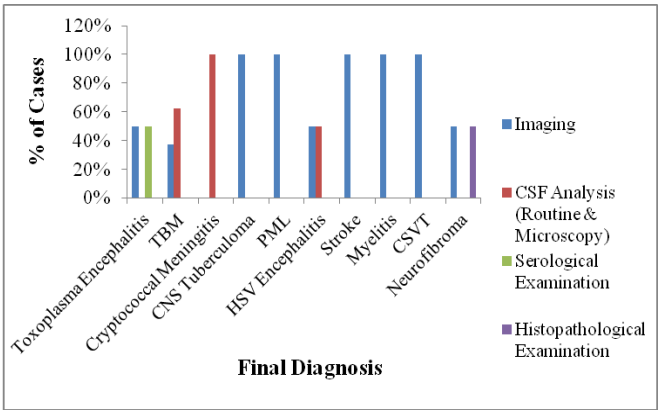
Out of 34 (56.66%) already known case of HIV, 22 (64.7%) were not on cART and prophylaxis against OIs. Statistically significant correlations between 'Neurological manifestations of HIV due to OIs' and 'Known HIV's not on cART' and between 'Neurological manifestations of HIV (prophylaxis available)' and 'Known HIV's not on prophylaxis' were observed (P- 0.0004), (Table 3).

Table 3: Distribution as per Prophylaxis Status and ART Status of Old Cases (Individual Diagnosis)

Diagnosis		Prophylaxis Status	
		Yes	No
Neurological manifestations of HIV (prophylaxis available)	Toxoplasma Encephalitis (TE)	0 (0%)	6 (100%)
	TBM	2 (33%)	4 (67%)
	Cryptococcal Meningitis (CM)	0 (0%)	2 (100%)
	CNS Tuberculoma (T'OMA)	2 (50%)	2 (50%)
	HSV Encephalitis (HE)	0 (0%)	2 (100%)
Neurological manifestations of HIV (prophylaxis not available)	PML	0 (0%)	2 (100%)
	Stroke	6 (75%)	2 (25%)
	Myelitis	2 (100%)	0 (0%)
	CSVT	0 (0%)	0(0%)
	Neurofibroma	0 (0%)	2 (100%)
Diagnosis		ART Status	
		Yes	No
Neurological manifestations of HIV due to OIs	Toxoplasma Encephalitis (TE)	2 (33.33%)	4 (66.66%)
	TBM	0 (0%)	6 (100%)
	Cryptococcal Meningitis (CM)	0 (0%)	2 (100%)
	CNS Tuberculoma (T'OMA)	2 (50%)	2 (50%)
	HSV Encephalitis (HE)	0(0%)	2 (100%)
	PML	0 (0%)	2 (100%)
Non opportunistic neurological manifestations of HIV	Stroke	6 (75%)	2 (25%)
	Myelitis	2 (100%)	0 (0%)
	CSVT	0 (0%)	0 (0%)
	Neurofibroma	0 (0%)	2 (100%)

In this resource limited setting imaging (MRI), in 46; 76.66% of cases, proved to be the most useful investigation followed by CSF analysis in 24; 40% of cases. While histopathological examination (2; 3.33%) was done only for neurofibroma and serological examination (14; 23.33%) was advised only for toxoplasma encephalitis, (Figure 3).

Figure 3: Contribution of Each Investigation to the Final Diagnosis of Individual Manifestation



Toxoplasma encephalitis was the most common manifestation found in 23.33% (14) of cases followed by TBM 16.66% (10) and cryptococcal meningitis & stroke in 13.33% (8) of cases. While myelitis, CSVT & neurofibroma 3.33% (2) were amongst the rarer manifestations. Tuberculoma was found in 10% (6) and HSV encephalitis & PML were found in 6.66% (4) of cases.

100% of our cases received appropriate treatment according to their complications and it is observed that

76.66% (46) of case improved while 23.33% (14) of cases died even after receiving appropriate treatment as per their diagnosis. 100% mortality rate was observed for PML while 50% cases of HSV encephalitis, 42.85% cases of toxoplasma encephalitis and 33.33% cases of tuberculoma died. On the other hand 100% cases of TBM, cryptococcal meningitis, stroke, myelitis, CSVT & neurofibroma improved after receiving appropriate treatment, (Table 4).

Table 4: Distribution as Per Outcome of Individual Manifestation on Standard Management

Final Diagnosis	Improved	Died	Total
Toxoplasma Encephalitis	8 (57.14%)	6 (42.85%)	14 (23.33%)
TBM	10 (100%)	0 (0%)	10 (16.66%)
Cryptococcal Meningitis	8 (100%)	0 (0%)	8 (13.33%)
Stroke	8 (100%)	0 (0%)	8 (13.33%)
CNS Tuberculoma	4 (66.66%)	2 (33.33%)	6 (10%)
HSV Encephalitis	2 (50%)	2 (50%)	4 (6.66%)
PML	0 (0%)	4 (100%)	4 (6.66%)
Myelitis	2 (100%)	0 (0%)	2 (3.33%)
CSVT	2 (100%)	0 (0%)	2 (3.33%)
Neurofibroma	2 (100%)	0 (0%)	2 (3.33%)
Total	46 (76.66%)	14 (23.33%)	60 (100%)

Discussion

In the present study prevalence of neurological manifestations in HIV infection was found to be less i.e. 11.42% as compared to the studies done in western countries [4, 5] and in bigger cities of India because of ignorance of the condition in HIV prevalent society and poor economic condition of the patient coming to our hospital resulting in their untimely death due to other opportunistic infection occurring early in the course of the disease. Education and appropriate interventions about this unfortunate scenario is the need of this time. Majority of our patients (86.66%) were in economically and sexually active age group (31-50 years). Because of the previously mentioned causes of ignorance and poverty many HIV patients died before the age of 50 years as a result of the other opportunistic infections. Presentation of females (30%) were less as compared to the males (70%) mostly due to the social pattern of our society where female health is ignored and females are decreased to the household works and socializes less. We need strict measures to increase an awareness of the condition especially among the young adults, housewives and CSWs.

The various transmission routes were blood transfusion (before 1987), surgery, IV drug abuse and multiple sexual partners. In present study, combination of multiple sexual partners + blood transfusion was thought in 3 (5%) patients of 'multiple routes' while multiple sexual partners + contacts with CSWs were thought to be the cause of heterosexual transmission in 93.33% cases. In 1 patient the exact mode of transmission of HIV could not be ascertained. As per the department of AIDS Control Ministry of Health & Family Welfare, Annual Report 2011-12 [1] heterosexual mode of HIV transmission accounts for 88.2% of HIV positive cases detected, mother to child transmission accounts for 5.0%, Infected Syringe and Needle 1.7%, Homosexual 1.5% and contaminated blood and blood products account for 1.0% of HIV infections. In India, males are the bread earners and most of them harbor the disease from commercial sex workers, when they go far away from their family to earn their livelihood. Most of them are laborers and belong to low socioeconomic status. Females mostly contract this disease from their husbands. In this study 83.33% (50) of patients were married at the time of presentation, 15% (9) were single / divorced and 1 (1.66%) was unmarried. Because of the culture of our country majority of people have sexual intercourse after their marriage but because of the growing influence of

western country this pattern is rapidly changing and more and more people are engaging in premarital sex. As per the department of AIDS Control Ministry of Health & Family Welfare, Annual Report 2011-12 [1] long-distance Truckers (1.62%) and Single Male Migrants (2.35%) constitute a significant proportion of clients of sex workers (4.94%). As in this part of India people mainly depend on farming for their livelihood, majority of our patients were farmer (43.33%) and their wives contracting this disease from their husbands (21.66%) followed closely by long distance drivers (10%) coming from different states for the transport of goods. Teachers / clerks (5; 8.33%), laborers (4; 6.66%) and the least affected group were students (1; 1.66%).

Because of the ignorance of the conditions in our society most of our patient ignored the early signs and symptoms of the disease and presented late in the course of disease when more sinister symptoms and signs in the form of altered sensorium (60%), altered HMF (43.33%) and seizures (36.66%) which is correlated with the previous studies [6, 7]. As there are no specific symptoms and signs of the most of complications, presentation may range from headache to the altered sensorium and signs may range from subtle sensory changes to the disturbance of higher mental functions hence high degree of suspicion is needed to diagnose the condition on behalf of the treating physician.

Although HIV infection can remain asymptomatic for many years most of the patient presents to the hospital for the first time when they suffer from some form of opportunistic infection or when they develop late complications of HIV infection itself. Education about the condition and encouraging high risk group for the early screening of HIV infection is very effective way of preventing many complications. As most of the opportunistic neurological complications occur when CD4+ count falls <200 cells/µl, frequent measurement of CD4+ count should be the key for management of any HIV positive patients. In present study, the correlation between 'Neurological manifestations of HIV due to OIs' and 'CD4+ T lymphocyte count <200 cells/µl' was found to be statistically significant (P-0.03). These results are comparable with the study done by Bolokadze et al [6] and Satyendra et al [7]. Out of 34 (56.66%) already known case of HIV, 12 (35.29%) were on cART and on prophylaxis against OIs while 22 (64.7%) were not on cART and any prophylaxis, (P-0.0004). As most of the OIs occurs in HIV positive patient without prophylaxis against them when CD4+ count falls <200 cells/µl, starting prophylaxis at appropriate time (before CD4+ count falls below 200 cells/µl) is a wise move from treating physician. However, ART significantly reduces the risk of many neurological OIs in HIV patients, initiating cART from start and keeping an eye for an early signs of ART failure should be the key for management of any HIV positive patients. These results are accordance with the other studies [8-15].

The final diagnosis was made with the help of one or more available investigations and patient starts improving on therapy. As per individual manifestations, In toxoplasma encephalitis serological examination and imaging (MRI brain- multiple ring enhancing lesions) contributed equally to the final diagnosis, in TBM contribution of CSF analysis (high protein, normal/low sugar, mononuclear cell predominance) was 62.5% and of MRI brain (altered signal intensity at bases) was 37.5%, in cryptococcal meningitis 100% cases were diagnosed on India ink exam of CSF (positive for fungal capsule), in HSV encephalitis CSF analysis (proteins elevated, mononuclear cell predominance,

RBC's present) and MRI brain (altered signal intensity of bilateral or unilateral temporal lobes) and in neurofibroma histopathological examination and MRI spine (ill circumscribed intradural mass lesion) had its equal contribution, while imaging (MRI brain) had its 100% contribution in diagnosis of stroke (altered signal intensity of the brain hypo intense on T1, hyper intense on T2 & flair and bright on DWB images), tuberculoma (single or multiple ring/ disc enhancing lesions) , PML (focal or diffuse demyelinating lesions), myelitis (altered singnal intensity in cord) and CSVT (loss of flow void in cerebral sinuses with altered signal intensity at cerebral cortex). These findings are correlated well with the earlier studies [16-19]. From the findings of these studies [16-19] we can conclude that in resource limited setting one could fairly rely upon the imaging and CSF analysis for the diagnosis of many neurological manifestations of HIV infection but universal availability of newer and higher investigations (electrophysiological studies, biopsy, serological examination, PCR, etc.) for making concrete diagnosis is the need of this era.

Opportunistic infections (OIs) of CNS were more common in present study than the non-opportunistic complications of HIV infection. Frequently observed non OIs of CNS in other studies like primary CNS lymphomas or HAND were probably missed in this study may be due to the invasive and risky procedure like brain biopsy or simpler or non-invasive method like MMSE (due to underestimated diagnostic strength of comparative analysis) was not used for the diagnosis. So it is recommended that in this ever advancing world treating physician should regularly update his/her knowledge about the newer and rare conditions and their comparatively simpler way of diagnosis like keeping and analyzing the frequent records of MMSE for the diagnosis of HAND the most prevalent neurological manifestation of HIV infection.

Conclusion

OIs of HIV are more common than non-opportunistic complications of HIV in this part of the India. Most of the CNS OIs of HIV occurred when CD4+ count was < 200 cells/µl. Known HIV patients who were not on any prophylaxis against opportunistic CNS infections consequently developed those complications when CD4+ count was <200 cells/µl and cART significantly reduces the risk of many neurological OIs in HIV patients. In this resource limited setting one could fairly rely upon imaging and CSF analysis for the diagnosis of many neurological manifestations of HIV infection. Observed mortality rate was lower as compared to the other studies and most of the patient who died was either due to the late presentation to the hospital or non-availability of the specific treatment like for PML.

Here once again we wants to emphasis that the great suspicion about complications, early diagnosis with the sensitive and specific investigation and keeping an eye for the advances in the field of management and investigations is the need of this era.

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