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Neurological Manifestations in Patients with HIV Infection in the Era of Combined Antiretroviral Therapy

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***Abstract*—**Neurological disorders are the most debilitating of manifestations seen in patients infected with HIV. The clinical profile of neurological manifestations in HIV patients has undergone a shift in recent years with opportunistic infections being controlled with combination anti-retroviral therapy and the advent of drugs which have higher central nervous system penetrability. The aim of this paper is to study the clinical, investigation profile and various neurological disorders in HIV patients on anti-retroviral therapy. Fifty HIV patients with neurological manifestations were studied. A complete neurological examination including neurocognitive functioning using Montreal Cognitive Assessment and HIV Dementia scale were assessed. Apart from relevant investigations, CD4 count, cerebrovascular fluid analysis, computed tomography (CT) and magnetic resonance imaging (MRI) of brain were done whenever required. Neurocognitive disorders formed the largest group with 42% suffering from HIV associated Neurocognitive Disorders. Among them, asymptomatic neurocognitive impairment was seen in 28%; mild neurocognitive disorder in 12%, and 2% had HIV-associated dementia. Opportunistic infections of the nervous system accounted for 32%, with meningitis being the most common. Four patients had space occupying lesions of central nervous system; four tuberculomas, and one toxoplasmosis. With the advent of highly active retroviral therapy, HIV patients have longer life spans with suppression of viral load leading to decrease in opportunistic infections of the nervous system. Neurocognitive disorders are now the most common neurological dysfunction seen and thus neurocognitive assessment must be done in all patients with HIV.

***Keywords*—**Anti retroviral therapy, cognitive dysfunction, dementia, neurological manifestations, opportunistic infections.

I. Introduction

HUMAN immunodeficiency virus is one of the greatest challenges faced by the medical fraternity in the 21st century. The infection has become pandemic in many parts of the world and affected every corner of the globe. According to the data released by NACO Annual Report 2012-2013, the revised estimate of people with HIV as of 2011 is 2.08 million (equivalent to 0.27% of the adult population) [1]. Though these figures represent a positive trend of decreased incidence of new cases, the prevalence is not changed as HIV patients are now able to live for longer time because of the advent of Highly Active Antiretroviral Therapy (HAART).

The virus has the unique ability to mutate itself constantly and conveniently integrates itself into the genome of the cells of the immune system which ironically are supposed to protect us from infections. Although many drugs are active against the virus, it has so far eluded complete cure [2].

HIV is known to affect all organ systems in the body causing a wide variety of clinical manifestations. Neurological disorders among them are considered to be among the most debilitating of manifestations seen in HIV positive patients. Opportunistic infections of the CNS were the main cause of neurological deterioration for a vast majority of these patients in the earlier times when combination anti-retroviral treatment for HIV was not yet instituted [3]. The major neurological disorders in HIV patients are opportunistic infections, immune reconstitution, HIV associated neuro-cognitive disorders (HAND), sensory neuropathies among others. As the patients are now able to have longer life spans with good viral control the clinical profile of neurological manifestations and disorders has undergone a paradigmal shift with opportunistic infections being controlled with combination ART and the advent of drugs which have higher CNS penetrability. Neurocognitive and neuropsychiatric manifestations are the new area of focus with emphasis being made on diagnosing and treating their subclinical forms [4].

II. Material and Methods

The study was done on HIV patients getting admitted in a tertiary hospital and research center in Vijayapur. Fifty HIV positive patients with clinical neurological manifestations during this period have been included in the study.

A. Inclusion Criteria

HIV patients on combined anti-retroviral therapy having signs and symptoms caused by neurological dysfunction.

B. Exclusion Criteria

- Patients with pre-existing neurological conditions like epilepsy, mental retardation, cerebrovascular diseases, Parkinsonism, movement disorders not attributable to the HIV.
- Patients not on any therapy
- Patients who have discontinued their treatment for duration of more than a month.

An informed consent was obtained from the patients prior

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to their inclusion in the study. A detailed history, general physical examination with thorough neurological examination was done. The patients were also assessed for their cognitive functions as a part of neurological examination using Montreal Cognitive Assessment (MoCA) [5], International HIV Dementia Scale (IHDS) [6]. If cognition was affected, it was quantified based on the effect it had on everyday activities using Lawton scale for Instrumental Activities of Daily Living [7]. The tests were performed on all patients in study. Patients were classified as HAND based on the scoring and clinical judgment of impaired performance in at least two domains of MoCA and IHDS tests.

MoCA was assessed on delayed recall, executive function, visuospatial function, attention, language function, abstract thought and orientation. The maximal score was 30 and patients with <26 score were interpreted to be having cognition deficit.

IHDS was scored on three variables motor speed, psychomotor speed and memory recall, the patients are scored on each of these. The maximum possible score was 12 points. A patient with a score of <10 were further evaluated for possible dementia.

The patients with HAND were further subdivided into Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND) or HIV-associated dementia (HAD) using revised research criteria for HIV associated neurocognitive disorders (HAND) [4]. The patients in study group not diagnosed with HAND were used as reference group for standardized neuropsychological tests and compared.

Demographic, relevant clinical data and laboratory data were collected. Data included age, sex, level of education, occupation, current CD4 cell count, and antiretroviral therapy. Laboratory work up include hemogram, CSF analysis and imaging like CT/MRI when needed.

C. Statistical Analysis

The data was entered in MS Excel Sheet and analyzed using SPSS 18 software. Appropriate statistical test like Chi square standard deviation mean and z test were used.

III. Results

The mean age of the patients was 32.3 years with all of them being between 20 to 45 years. There were 36 males and 14 females. The mean years of education of the group was 6.41 years with only 30% being employed in professional jobs and the rest either unemployed or intermittently worked as unskilled labor as shown in Table I.

The most common symptom in these patients was headache seen in 42% of cases followed by fever (30%) and altered sensorium (10%). Seizures were present in three of the five patients with space occupying lesions as depicted in Table II.

Neurocognitive dysfunction were the most common neurological disorders (42%) followed by opportunistic infections (32%). The MoCA and IHAD test results were used to diagnose the patients with HAND. These patient data were then compared with the other HIV patients who underwent these tests. ANI was present in 28%, 12% had MND and 2% were suffering from HAD. The patients with neurocognitive disorders were included in group A and the rest in group B as shown in Table III.

TABLE I
Demographic Data

Mean Variable	**Group A** Patients with other Neurological manifestations (29)	**Group B** Patients with HAND (21)	Total (50)	p Value
Age				
Mean (years)	33.27 SD = (5.64)	31.0 SD = (5.51)	32.3	<0.01
Gender				
Male	22 (79%)	14 (67%)	36 (72%)	
Female	7(21%)	7 (33%)	14 (28%)	
Education (years)	6.28 (SD= 4.15)	6.54 (SD = 4.06)	6.41	
Occupation	Unemployed	20 15	35 (70%)	
	Employed	9 6	15 (30%)	

TABLE II
Presentations of Symptoms

Main symptom	No of patients	%
Headache	21	42
Fever	15	30
Altered sensorium	5	10
Seizures	3	6
Tingling numbness	2	4
Memory loss	1	2
Others	3	6

TABLE III
Comparison of Scores on Cognitive Tests by Cognitive Status

Montreal Cognitive Assessment Domains	**Group A** Other Neurological disorders	**Group B** HAND
MoCA - Visuospatial/Executive	4.13 (SD = 0.63)	3.47 (SD = 0.67)
MoCA - Naming	2.89 (SD = 0.30)	2.71 (SD = 0.56)
MoCA - Attention	5.8 (SD=0.47)	5.28 (SD = 0.46)
MoCA - Language	2.82 (SD= 0.38)	2.57 (SD= 0.50)
MoCA - Abstraction	1.93 (SD = 0.37)	1.42 (SD=0.50)
MoCA – Recall	4.68 (SD = 0.47)	4.38 (SD=0.49)
MoCA - Orientation	5.55 (SD = 0.50)	4.90 (SD=0.62)
MoCA - Total	27.82 (SD=0.80)	24.66 (SD=0.73)
IHDS – Motor speed	3.79 (SD=0.41)	2.95 (SD=0.21)
IHDS – Psychomotor speed	3.68 (SD=0.47)	3.28 (SD=0.56)
IHDS - Memory	3.96 (SD=0.18)	3.19 (SD=0.60)
IHDS - Total	11.48 (SD=0.57)	9.33 (SD=0.85)

IHDS, International HIV Dementia Scale; MoCA, Montreal Cognitive Assessment.

Cryptococcal meningitis was the most common infection accounting for 14% followed by tubercular meningitis with 12% of the cases. Co infection was seen in six cases. There was one case each of myelitis and toxoplasma. Space occupying lesions were found in five cases, four of which were tuberculomas and one lymphoma as depicted in Table IV.

TABLE IV
NEUROLOGICAL MANIFESTATIONS AND DIAGNOSIS

Neurological Diagnosis		No. of patients	%	Total%
Group A i) Infections	Cryptococcal meningitis	7	14	32
	Tubercular meningitis	6	12	
	Other meningitis	1	2	
	Toxoplasmosis	1	2	
	Myelitis		2	
ii) Others		8	16	Others
iii) Intracranial masses	Tuberculoma	4	8	10
	Lymphoma	1	2	
Group B HIV associated neurocognitive disorders (HAND)	Asymptomatic Neurocognitive Impairment (ANI)	14	28	42
	Mild Neurocognitive Disorder (MND)	6	12	
	HIV Associated Dementia (HAD)	1	2	

According to WHO immunological classification for established HIV infection based on CD4 counts [8]; 52% had severe disease, 24% had advanced disease, 4% had mild disease and remaining 4% did not have significant disease. Fifty six percent of patients in group A had CD4 count less than 200 cells/mm^3 [severe disease] and of the 21 patients in group B, 71.5% had severe disease as shown in Table V.

TABLE V
CD4 COUNT IN DIFFERENT NEUROLOGICAL DISORDERS

Diagnosis	No of patients with CD4 count >500 cells/mm^3	CD4 count between 499-350 cells/mm^3	CD4 count between 349-200 cells/mm^3	CD4 count <200 cells/mm^3
Group A				
Cryptococcal meningitis			1	6
Tubercular meningitis		1	2	3
Other meningitis	1			
Toxoplasmosis			1	
Myelitis			1	
Tuberculoma			3	1
Lymphoma				1
Group B				
HAND	1	1	4	15
Total	2 (4%)	2 (4%)	12 (24%)	26 (52%)

Nineteen patients underwent CT scan and/or MRI of which 13 had normal scan results, five patients were diagnosed to be having intracranial masses, four tuberculomas and one lymphoma. Toxoplasma was suspected in one patient, which was later confirmed with finding Toxoplasma- IgM antibodies in blood. One patient had features on CT suggestive of encephalomyelitis.

CSF analysis was done in 17 patients of whom seven were diagnosed with cryptococcal meningitis by India ink preparations. Six patients had findings suggestive of tubercular meningitis.

IV. DISCUSSION

Neurologic abnormalities are common in late stages of HIV infection and are an AIDS defining condition. Central nervous system disease occurs in 40-90% of HIV positive patients. The predominant cell types that are infected are monocytes and macrophages. Virus may enter the brain through infected monocytes and release cytokines that are toxic to neurons as well as chemotactic factors that lead to infiltration of the brain with inflammatory cells [9].

Our study showed a male preponderance towards neurological manifestations in HIV with 72% of the patients being male similar results was seen in other studies. Deshpande et al reported 87.5% male patients [10] and Chan LG et al had 93.3% male subjects [11]. This could be attributed to higher incidence of multiple sexual partners in males compared to females, except for high risk groups like commercial sex workers.

In our study, the most common manifestation of HIV patients with neurological disorder was headache, seen in 42% patients which corroborated with other studies. Sharma SK et al. also reported headache as the commonest neurological manifestation seen in 62.5% cases [12]. The neurological symptoms associated with HAND like forgetfulness, mental slowness, poor concentration, clumsiness, tremors, apathy were seen in less than six percent of people although HAND accounted for 42% cases. This data suggests the huge propensity to miss the diagnosis of cognitive dysfunction as the disease usually exists in its subclinical form with little or no symptoms. The few patients who did have these symptoms did not associate them to their disease.

The approach towards neurological diseases in HIV has always been directed towards opportunistic infections. Most studies on neurological complications did not assess for neurocognitive disorders although some studies have reported on dementia. In our study the prevalence of neuro-cognitive disorders surpassed opportunistic infections of CNS in HIV patients. HAND was seen in 42% of the cases similar to study done by Chan LG et al. in Singapore where the prevalence was 22.7% [11]. They also used the revised 2007 updated research nosology for HAND [4]. Singh R. et al. reported a 33.65% incidence of HIV associated Dementia. This study showed similar result to our study but the assessment was done using MMSE [11].

Deshpande AK et al reported only 6% patients with dementia [10]. Sharma et al. did not report on neurocognitive disorders [12]. Satishchandra et al. reported dementia in only four patients out of 100 patients [14]. All these studies did not employ an objective methodology for assessing the cognitive function and based their results on clinical and neurological examination findings. It is very common to assess cognitive impairment based on clinical judgement and brief bedside neurological examination, this methodology though novel severely limits the providers' ability to diagnose subclinical forms of cognitive dysfunction and being subjective their results cannot be used to compare with studies were standardized tests were employed.

TABLE VI
REVISED RESEARCH CRITERIA FOR HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND)

(Modified from HIV Neurobehavioral Research Center Criteria) [4]

HIV-associated asymptomatic neurocognitive impairment (ANI)

- Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
- The cognitive impairment does not interfere with everyday functioning.
- The cognitive impairment does not meet criteria for delirium or dementia.
- There is no evidence of another preexisting cause for the ANI.

HIV-1-associated mild neurocognitive disorder (MND)

- Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.
- The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):

a) Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning

b) Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning.

- The cognitive impairment does not meet criteria for delirium or dementia.
- There is no evidence of another preexisting cause for the MND.

HIV-1-associated dementia (HAD)

- Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically, the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means.
- The cognitive impairment produces marked interference with day-to-day functioning.
- The pattern of cognitive impairment does not meet criteria for delirium; or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present.
- There is no evidence of another, preexisting cause for the dementia.

The CD4 counts in patients with HAND are below 200 cells/mm^3 in 71.4% of cases. Thus, we concluded that HAND is usually seen with lower CD4 counts associated with severe form of disease. Chan L. G. et al. reported similar findings were HAND was seen in patients with CD4 counts less than 200 cells/mm^3 in 63.3% [11], Singh R. et al. reported similar findings in 83.52% patients [13].

Our study did have its shortcomings, our sample size was smaller and strict compartmentalization of neurological disorders into opportunistic infections and neurocognitive dysfunction may have given a lower incidence of opportunistic infections. Thus further studies need to be taken up with larger sample sizes using standardized cognitive assessment tests.

V. CONCLUSION

With the widespread use of HAART, the incidence and mortality associated with HIV is decreasing throughout the world. By keeping of the viral loads suppressed and prolonging the lifespan of HIV individuals a new profile of neurological disorders is emerging which warrants a change in approach to the management. Along with opportunistic infections emphasis must be made towards diseases caused by direct effect of the virus on the nervous system. Neurocognitive and neuropsychiatric illnesses should be thoroughly investigated using standardized mental status examination, those acceptable in updated research nosology for HAND considering resource limited contexts as depicted in Table VI; as they can be subclinically present severely affecting the patient's daily activities and add to the overall burden of the disease.

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