

Original Research Article

A study of neurological problems in HIV infection

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Received: 07 March 2020

Accepted: 07 April 2020

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ABSTRACT

Background: Knowledge of central nervous system manifestation (CS) is crucial for clinical practitioners, which is why this study was conducted to identify the neurological manifestations in HIV patient is crucial problems with HIV and the difficulties in managing these patients.

Methods: The present study was conducted on patients of HIV infection who were either admitted or being treated in OPD during study period. The cases were selected based seropositivity for HIV on two consecutive occasions by ELISA and presence of WHO surveillance definition criteria. Based on a detailed history account including high risk behaviour to HIV infection was obtained from patients or relatives. Then each patient was subjected to thorough physical examination with specific attention to any clinical evidence of immunosuppression viz oral thrush. Thorough neurological examination was done to localize the part of central nervous system affected. Patients were then categorized into various clinical neurological syndromes.

Results: Commonest finding was single or multiple ring enhancing lesions seen in 21(35%) patients followed by basal exudates (21.6%). Hydrocephalus was seen in 5 patients (8.3%) and infarct due to vascular lesion in 4(7%) patients. Oral thrush was more commonly seen in patients with *cryptococcal meningitis*. CSF analysis was useful and revealed abnormalities in most of the patients with infective disorders.

Conclusions: In conclusion, variety of neurologic manifestations occur and any part of nervous system can be affected in HIV infection and high index of suspicion is required to pick up the cases early in the course which may help to improve the quality and life span of these suspicion patients.

Keywords: *Cryptococcal meningitis*, CSF, HIV infection, Neurological problems

INTRODUCTION

In the developing countries like India where malnutrition and infectious disease are stayed on, the impact of HIV enormous. Under reporting of infective disease coupled with ignorance, poor hygiene and low socioeconomic status have compounded the issue.

Because neuro invasive, infection enter the central nervous system (CNS).^{1,2}

It is proven that, HIV has become chronic but treatable instead of incurable.³ The presence of HIV-2 in India was

first reported by Mumbai in 1991.⁴ Following the introduction of highly active antiretroviral therapy (HAART) in 1996, the incidence of HIV related CNS infection decreased in high incomes countries, although mortality was still high.⁵⁻⁹

Knowledge of central nervous system manifestation (CS) is crucial for clinical practitioners, which is why this study was conducted to identify the neurological problems with HIV and the difficulties in managing these patients.

Objective of the study is to determine the neurological problems in HIV seropositive patients and to assess the

course of illness in these patients and find out the difficulties faced in managing these patients.

METHODS

The present study was conducted on patients of HIV infection who were either admitted or being treated in OPD during study period. The cases were selected based seropositivity for HIV on two consecutive occasions by ELISA and presence of WHO surveillance definition criteria.

A detailed history account including high risk behavior to HIV infection was obtained from patients or relatives. Then each patient was subjected to thorough physical examination with specific attention to any evidence of immunosuppression viz oral thrush. Thorough neurological examination was done to localize the part of nervous system affected. Patients were then categorized into various clinical neurological syndromes.

Routine investigations were done in all patients such as Hb%, ESR, CBC, Urinalysis, Chest X-ray, Serum electrolytes, BUN, Creatinine; Liver function tests. Blood and CSF VDRL tests were done as and when felt necessary.

CSF analysis included cell count, sugar and protein estimations, India ink preparation, bacterial and fungal cultures. Smear for bacteria, AFB. Antitoxoplasma titers, cryptococcal antigen titers were done whenever (indicated) possible. CT and / or MRI imaging of appropriate regions were done and repeated whenever needed. EEG was done whenever indicated. EMG/NCV studies were done whenever indicated.

Management

Patients were hospitalized as far as possible and started on appropriate therapy. Response to specific treatment for certain conditions whenever possible and course of illness was closely monitored. Antioedema measures were instituted whenever felt essential and antiepileptic drugs were used when indicated. In patients after discharge were called for regular follow ups. Patients were assessed for progression/ regression of illness and appearance of new lesions if any on follow-up visits. In event of death, autopsy was performed whenever possible and every attempt was made to obtain neuropathologic diagnosis.

RESULTS

There were 88 males and 12 females. Their ages ranged from 20 yrs. to 55 yrs with mean of 31.23 yrs. It was observed that, majority i.e. 89% patients were between 20-40 yrs of age.

As is evident from the Table 1 CSF analysis was useful and revealed abnormalities in most of the patients with infective disorders. Non-specific abnormalities were also

seen in other conditions like encephalopathies and some patients of peripheral neuropathies (55.5%) particularly AIDP.

Table 1: Distribution of patients with CSF abnormalities in various diseases.

Neurological lesions	No. of patients		Abnormalities seen (%)
	Total	CSF Done	
Tubercular Meningitis	21	21	21 (100)
Cryptococcal Meningitis	21	21	17 (80.9)
Tuberculomas	8	6	6 (100)
Toxoplasmosis	11	11	8 (72.7)
Other mass lesion	2	2	1 (50)
Peripheral Neuropathy	10	9	5 (55.5)
Myelopathy	3	3	2 (66.7%)
Encephalopathy	13	13	5 (38.5)
Radiculopathy	2	1	1 (100)
Myopathy	1	1	0
Other	9	7	0
	100	94	61 (64.9)

Table 2: CT/ MRI abnormalities.

Abnormalities	No. Of pts.	Percentage
Ring enhancing lesions	21	35%
Basal exudates	13	21.6%
Cortical atrophy	2	3.3%
Hydrocephalus	5	8.3%
Infarcts and haemorrhage	4	7%

CT scan and or MR imaging was done whenever necessary and abnormalities were seen in 70% of patients thus studied. Commonest finding was single or multiple ring enhancing lesions were seen in 21(35%) patients followed by basal exudates (21.6%). Hydrocephalus was seen in 5 patients (8.3%) and infarct due to vascular lesion in 4(7%) patients (Table 2).

Oral thrush was more commonly seen in patients with *cryptococcal meningitis*. Meningeal signs and CSF abnormalities in the form raised proteins and pleocytosis were seen in almost all patients of TBM whereas meningeal signs and CSF abnormalities were less common in patients with *cryptococcal meningitis*. CSF proteins and cells were normal in 3/20 pts with *cryptococcal meningitis* while all patients with TBM had CSF abnormalities (pr. 20/21 cells 21/21) (Table 3).

Fever and headaches were slightly more common in patients with toxoplasma, so were seizures and oral thrush. 4 out of 12 patients of toxoplasma had extra pyramidal

signs like mask like face, hypophonic speech, tremors or cog wheel rigidity CSF abnormalities were more commonly seen in patients with tuberculomas (6 out of 8 pts.) and 4 out of 8 patients also had associated TBM.

Multiple ring enhancing lesions were seen in 8/11 pts. With toxoplasma mainly in basal ganglia region and in 5/8 patients with tuberculomas (Table 4).

Table 3: Clinical features and CSF abnormalities in patients with meningitis.

Category	HA.	Fever	Seizure	Oral Thr	Menin-signs	CSF	
						Pr	Cells
TBM (n-21)	18	18	6	9	21	28	21
<i>Crypto. Meningitis</i> (n-20)	16	17	11	17	17	10	15

Table 4: Clinical features and laboratory abnormalities in patients with intracranial mass lesions.

Category	H.A.	Fever	Seizure	Oral. Thr	Focal pyra.	Signs extra pyra	CSF		Ct/or mr rel	
							Pr	Cells	Soli	Mult
Toxo - plasma n - 11	7	8	7	6	5	4	7	2	3	8
Tuber - culoma n - 8	4	4	3	2	5	--	6	6	3	5
Unknown n - 2	1	1	---	---	2	--	1	1	--	2

HIV encephalopathy

Table 5: Features of HIV encephalopathy.

Category	No. Of patients	%
Cognitive impairment	12	12
Behavioral disturbance	10	10
Motor abnormalities	11	11

Table 6: Seizure analysis.

Category	No. Of patients
HIV encephalopathy (n -12)	1
Meningitis (n-42)	
A. Tubercular (n - 21)	6
B. Cryptococcal (n - 21)	12
Intracranial (n - 21) Mass lesion	
A. Toxoplasma (n - 11)	7
B. Tuberculoma (n - 8)	3
C. Other (n - 2)	3
Idiopathic (?HIV related)	32

Table 5 shows that out of 100 patients studied 12 patients had history of cognitive impairment like forgetfulness and slowed response, behavioral disturbance in the form of lack of interest, apathy and social withdrawal and motor abnormalities like gait ataxia and lower limb weakness with occasional incontinence. Of 12 patients 8 had oral thrush. There was no clinical evidence of meningitis or focal neurologic deficit. 3 patients had evidence of peripheral neuropathy and one had both myelopathy and peripheral neuropathy in addition to mild cognitive slowing. In all the patients' laboratory investigations did not show evidence of or metabolic abnormalities and CSF ruled out any infective aetiology. CT scan did not show any structural abnormality or mass lesion. On clinical

features and normal investigations, these patients were labelled as HIV encephalopathy.

Out of 100 patients studied 32 patients had focal or generalized seizures. Of these 32 patients 12 had *Cryptococcal meningitis*, while 7 had toxoplasma, 6 had tubercular meningitis and 3 patients had tuberculomas. 1 patient of HIV encephalopathy had seizures. 3 patients had no apparent cause of seizure though one of them had geniculate zoster causing lower motor facial palsy (Table 6).

Neuropathies

Table 7: Cranial nerve involvement in patients

Category	Cranial nerve involvement					
	II	III	IV	VI	VII	
					Unilat LMN	Bilat
TBM			4		----	14
<i>Cryptococcal</i>	1		1		----	2
<i>Toxoplasma</i>	1		1		----	----
AIDP	---		---		----	3
<i>Geniculate zoster</i>	---		---		2	----
Others			1		----	5

Bilateral facial weakness was commonest and seen in 14 pts. all of whom had underlying disease like Tubercular or *Cryptococcal meningitis* etc. of all patients with cranial nerve involvement only two patients presented with isolated involvement of unilateral lower motor facial palsy. Both of them had geniculate zoster as underlying disorder. In other patients cranial nerve involvement was part of underlying processes like meningitis or raised intra cranial pressure (Table 7).

DISCUSSION

Age group

In present study, age ranged from 20 yrs. to 55 yrs. with a mean of 31.23 yrs. Majority i.e. 89% of patients were between 20-40 yrs.

Mc Arther from their study of 186 patients reported the age range from 18 to 72 yrs. with a mean of 36 yrs while Snider studied 50 patients who were 16 to 69 yrs old.^{10,11}

Cryptococcal meningitis

It was seen in 21% of patients. Headache and fever were less common and less severe as compared to tubercular meningitis. Oral thrush was present in majority (17/21) and meningeal signs were subtle but could be elicited in 18 out of 21 patients. 12 patients had seizures either before admission or during hospital stay. CSF analysis showed mild protein rise ranging from 50-240 mg/l and cells from 20-360 cells. cmm in 17 patients. In remaining 3 patients CSF was normal. Levy R M reported incidence of cryptococcal meningitis to be 12.5%.¹² Mc Arther studied 186 patients of HIV infection with neurologic complications and found that 6% of patients had cryptococcal meningitis, while it was 4% in the series reported by Snider et al, and Sharma et al, reported incidence of cryptococcal meningitis to be 14.2%.^{10,11,13}

Toxoplasmosis

Cerebral toxoplasmosis was encountered in 11 patients. Fever and headache were symptoms in 70-80% of patients. Focal seizures were seen in 7 patients. Oral thrush was present in 54% of patients and focal weakness in 45%. 4 patients demonstrated unilateral or bilateral cogwheel rigidity and parkinsonian features. CSF abnormalities were observed in 7 patients and were mostly limited to rise in proteins. CT scan showed multiple ring enhancing lesions mostly in and near basal ganglia region in 8 patients while 3 patients had solitary ring enhancing lesion with perilesional oedema. In two patients double dose contrast delayed films were taken to demonstrate contrast enhancement. Serum Toxoplasma titers (IgG) were done in three patients which were raised 2-3 folds.

Levy et al, found 18 patients with focal deficits or seizure and altered mentation. They concluded from their study that serum Toxoplasma IgG titers are neither specific nor sensitive for the diagnosis. They got a dramatic response to therapy but recurrence rate was as high as 30%.¹²

Lanjewar et al, from India reported 10 patients of toxoplasma from their autopsy series.¹⁴ While Gupte et al, and NIMHANS series had only one case each.¹⁵

Mc Arthur reported 15 patients while Snider et al, had 5 patients of CNS toxoplasmosis. They found MRI to be more sensitive than CT for picking up multiple lesions and

felt that therapy should be started as early as possible even empirically in suspected cases since response is quite dramatic and encouraging.¹⁰

Tuberculomas

Out of 100 patients 8 had intracranial tuberculomas. 4 of them had associated TBM. Presenting features were headaches and fever seen in 4 patients each, while seizures occurred in 3 patients. Focal signs were seen in 5 patients, oral thrush was seen in only 2 patients. CSF was done in 6 patients and was abnormal in all, consisting raised proteins ranging from 50-300 mg and pleocytosis of 25-300 cells/cmm.

Other intracranial mass lesions

Two patients had intracranial mass lesions in which aetiology could not be ascertained. One female had headache and fever of 3 months duration and was on antitubercular drugs for 2 months without significant benefit. She was brought in an altered sensorium and examination revealed meningeal signs, bilat. V1 and Rt. III parasis with hemiplegia. Another patient presented with subacute onset of right upper limb weakness and dysarthria and examination showed right homonymous visual field defect and pyramidal weakness in right upper limb.

HIV encephalopathy

Of 100 patients 12 had HIV encephalopathy. Clinical presentation was subacute onset of cognitive slowing with lack of interest and social withdrawal and gait disturbance. 8 patients had oral thrush, 3 patients had associated peripheral neuropathy and one had myeloneuropathy with mild cognitive slowing. Opportunistic infections were ruled out by CSF analysis and CT head scans revealed cortical atrophy in 2 patients, in others it was normal. Metabolic parameters were normal. Levy et al, reported it to be about 27% Snider et al, in their study of 50 patients noted it in 18 patients.^{11,12} Mc Arthur reported 38 out of 186 patients having cognitive - motor abnormalities.¹⁰

Seizures

In 29 patients having seizures, 12 patients had cryptococcal meningitis. 7 had toxoplasma, 6 had TBM and 3 had tuberculomas. In remaining 4 patients 1 patient had HIV encephalopathy. In 3 patients no obvious aetiology could be determined and hence were labeled as idiopathic even though one patient had genulate zoster, it appeared to be unrelated.

Wong et al reported incidence of seizures to be 11%.¹⁶ Several earlier reports have noted seizures in patients with neurological manifestations of HIV infection or AIDs and figures range from 12-18%. Holtzman et al, while studying 100 patients found that 18% of patients had seizures as a presenting symptom of HIV infection.¹⁷

Increasing number of patients develop seizures as HIV disease advances. It was also noted that only 30-50% of patients with seizure had demonstrable focal lesion on CT or MRI and among remaining about half had cortical atrophy and half with normal brain imaging which suggest that HIV infection of brain itself may be the responsible factor for seizures in these patients. Seizures were noted in 25% of the patients.¹³

Myelopathy

In present study 4 patients had myelopathy. One patient presented with subacute onset of spastic paraparesis with bladder involvement and a sensory level over trunk. Another patient had subacute onset of spastic ataxic paraparesis, clinically he had pyramidal and post column signs in lower limb only. MRI showed extrinsic mass compressing mid dorsal cord. Third patient had nutritional myeloneuropathy and fourth one had evidence of peripheral neuropathy and mild cognitive impairment suggesting early dementia. Mc Arthur described 9 patients of myelopathy. Half of them had accompanying dementia. Autopsies in these patients showed vacuolation in white matter of lateral and posterior columns.¹⁰

Peripheral neuropathies

10 patients had various types of neuropathies, of these 10 patients only 2 patients had cranial neuropathy. Other patients who had cranial nerve involvement like bilateral facial or 3rd 4th 5th or bilateral 6 had other underlying primary lesions like meningitis or intracranial mass lesions, so these case are not included in cranial neuropathy category.

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) was found in 7 patients. Distal symmetric peripheral neuropathy (DSP) was seen in 8 patients as evidenced by feet dysesthesiae, and distal sensory loss in lower limbs and absent ankle jerks.

Levy et al, found them in 25.78% of patients, while Snider et al, have reported lower figures of 16%.^{11,12} Mc Arthur reported 47/186 patients with peripheral neuropathies and 11 of them were inflammatory demyelinating type while. 26 patients had sensory neuropathy.¹⁰

Mc Arthur reported guarded prognosis in the patients with distal symmetric predominantly sensory neuropathy, which usually occurs in late stages of immunosuppression and responds poorly. However categories particularly nutritional or drug induced need to be borne in mind as seen in one of this patients, who responded to pyridoxine supplementation.¹⁰

Pathogenesis of AIDP is thought to be immune based. As against previous belief recent evidence suggested that AIDP does not seem to be more common during seroconversion than seen in any other viral infection.¹⁸

Cerebrovascular strokes

Total 6 patients in this study had sudden onset of focal neurologic deficit and deficit was attributable to carotid territory stroke. One patient had zoster related ICA antitis causing subcortical MCA territory ischemic stroke confirmed by MR angiography. Another patient had large vessel of left common carotid which was tender and non-palpable. He had subcortical MCA territory ischemic stroke. Third patient was hypertensive and had left putaminal haemorrhage with moderate oedema which was responsible for dense right hemiplegia and global aphasia. Three other patients had sudden onset of upper and lower limb weakness on one side with upper motor facial weakness. Two patients were being treated for meningitis (1 TBM and other cryptococcal) and one patient had a history of transient right-hand weakness and dysarthria 3 months prior. He presented with cryptococcal meningitis and CT showed lacunar infarcts due to small vessel vasculitis. Other two patients possibly had stroke due to vasculopathy.

Levy et al, found seven patients (5.40%) of AIDS with cerebrovascular complications. 4 had infarct and three had intracerebral bleed. They proposed that infarction could be secondary to nonbacterial thrombotic endocarditis in 4 cases and possible herpes zoster arteritis in one.¹²

Mc Arthur reported 9 cases (7%) of cerebrovascular strokes which included both infarcts and haemorrhages snider et al, could get six cases (12%) of cerebrovascular strokes and postulated that granulomatous angitis could be one of the aetiologies of cerebral infarction.¹⁰

Miscellaneous group

One patient presented with fever, headache and vomiting of 8-10 days duration. Second patient had subacute onset of it sided weakness and left gaze paresis. Other two patients tested Elisa positive for HIV 2-4 months prior and presented with acute behavioral change and irrelevant talk and with hallucinations. One patient was given antipsychotic drugs before he was seen by us. In another study, Headache was the most common neurological symptom seen in 25% of the patients.¹³

It is quite clear from the study that the main bulk is formed by opportunistic infections notably tuberculosis, cryptococcal and toxoplasma. Excepting *cryptococcal meningitis* other two are potentially treatable and results of treatment are encouraging hence it is very much necessary to be aware of these infections and with a slightest doubt be investigated as effective treatment is available and early institution of therapy is rewarding.

It was observed in present study that, HIV infection can affect directly or indirectly almost every part of neuraxis and present with myriads of clinical manifestations hence it is prudent to keep high index of suspicion in any unusual case coming with a neurologic problem and to make a

Careful search for subtle signs to detect the presence of disease early and institute measures against them.

CONCLUSION

In conclusion, variety of neurologic manifestations occur and any part of nervous system can be affected in HIV infection and high index of suspicion is required to pick up the cases early in the course which may help to improve the quality and life span of these patients.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Shivpuje A, Singhal P. A study of neurological problems in HIV infection. *Int J Adv Med* 2020;7:829-34.