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ORIGINAL RESEARCH

Central Nervous System (CNS) Manifestations In Patients With Human Immunodeficiency Virus And Hepatitis C Virus Co-Infection: A Case Series with Review of Literature

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Abstract
Central Nervous System (CNS) is one of the major system involved in HIV and HCV infected individuals. There are various mechanisms through which virus enters into the brain tissue and activates immunological response to cause damage to brain tissue. Consequences can ranges from minor cognitive motor impairment to life threatening secondary opportunistic infections like progressive multifocal leukoencephalopathy, toxoplasmosis, cryptococcosis and mycobacterial infection e.g. tubercular meningitis and tuberculoma. Stroke is also one of the rare complication which can be seen as a sequelae of vasculitis. Previous studies have shown significant association between HIV and HCV pathogenesis to involve central nervous system. In this case series, ten cases are discussed in which CNS manifestations of individuals affected with co-infection with HIV and HCV. All these individuals presented at younger age showing its significant association to cause the CNS manifestations.
Key words: Hepatitis C Virus, Human Immunodeficiency Virus, Central Nervous System, Tuberculoma, Progressive Multifocal Leuckoencephalopathy, Seizures, Infarct

Introduction

Worldwide, there are an estimated 130 million chronic hepatitis C virus (HCV) infections, with an overall prevalence of 3%. Approximately 4 to 5 million persons are co-infected with HIV. In the US and Western Europe, among HIV-infected persons, HCV prevalence is 72% to 95% among injection drug users (IDU), 1% to 12% in men who have sex with men (MSM), and 9% to 27% in heterosexuals.[1]Co-infections of Human immunodeficiency virus (HIV) and hepatitis c virus (HCV) are on the rise owing to common and shared modes of transmission and risk factors. Patients with HIV and HCV co-infection have a rise in systemic manifestations including nervous system manifestation. Nervous system involvement occurs both in the form of central nervous system (CNS) and peripheral nervous system (PNS).[2] Central nervous system involvement can be seen in the form of cortical and subcortical

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involvement ranging from cognitive, neuropsychiatric, pyramidal, extrapyramidal and myelopathy to peripheral nervous system in the form of neuropathy and myopathy. Infection with HIV in HCV positive patients and vice versa augments and accelerates the underlying pathophysiology of disease leading to rapid deterioration and poor response to drug therapy.
In this case series and narrative review, we attempt to focus on the CNS manifestations of HIV-HCV coinfection.

Methodology

Study site and design: The current study was a retrospective case series study conducted in the Department of Medicine from a tertiary care teaching hospital of Punjab. **Study duration:**The study was conducted over a period of six months (01-Apr-2023 to 31-10-2023).**Inclusion criteria:** 1. All the cases of HCV and HIV co-infection with central nervous system manifestations were collected from the medical records retrospectively. 2. Cases with complete medical records were included in the study. **Exclusion criteria:** 1. Cases with HCV and HIV co-infection without central nervous system manifestations. 2. All the cases with isolated HIV or HCV infection were excluded from the study. 3. Cases with incomplete medical records wereexcluded from the study. The cases which fulfilled the inclusion criteria were randomly included in the study irrespective of gender and sex. We searched literature in PUBMED database with keywords “Central nervous system manifestations of HIV & HCV” OR “HIV-HCV co-infection and Central nervous system” OR “CNS and HIV-HCV” from 1993 to 2023 independentlyby 2 authors and studies were segregated. We found 31 studies which are shown in Table 1.Studies with manifestations other than CNS, unavailability of full text, language other than English were excluded from the study. Out of these 31 studies which were screened, 11 studies fulfilled the criteria for the review.

Table 1. Literature review

S. No.	Year	Authors	Study type	Sample size	Manifestations of HIV-HCV co-infectuion	Neuroimaging	Reference
1.	2011	Eva A. Operskalski and Andrea Kovacs	Review article	NA	Global cognitive impairment: Learning and memory	-NA-	[3]
2.	2005	Clifford, David B; Evans, Scott R; Yang, Yijun; Gulick, Roy M	Multicentric study under TRIAL A5095	264	Sleep disorders Neurocognitive impairment	-NA-	[4]
3.	2005	Cacoub, Patrice[a]; Saadoun, David[a]; Limal, Nicolas[a]; Léger, Jean Marc[b]; Maisonobe, Thierry[b].	Review article	NA	Clinically, stroke episodes, transient ischaemic attacks, progressive reversible ischaemic neurological deficits, lacunar infarctions, or encephalopathic	MRI findings of the brain have been consistent with ischaemia, showing either small lesions of the periventricular white matter and the cerebral trunk	[5]

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					syndrome may occur. Stroke episodes and encephalopathic syndromes have been attributed to ischaemia or rarely to hemorrhage	or extensive supra and infratentorial white matter lesions, suggesting cerebral vasculitiS	
4.	2009	Clifford DB, Smurzynski M, Park LS, et al.	AIDS Clinical Trials Group Longitudinal Linked Randomized Trials	172	Neurocognitive decline	-NA-	[6]
5.	2013	Bladowska J, Zimny A, Kołtowska A, et al.	Cross sectional study	65	Neurologically asymptomatic	Significantly lower NAA/Cr ratios in the Anterior Cingulate Gyrus area on MRS	[7]
6.	2004	Ramos-Casals M, Cervera R, Lagrutta M, et al.	Review article	82	Optic neuropathy Stroke Migraine Epilepsy Multiple TIA	-NA-	[8]
7.	2022	FadelallahEljack MM, Nassir Mohammedali NF, Hussien Mohamed Ahmed KA, et al.	Case report	1	Stroke	Left parietal infarct	[9]
8.	2008	Aronow HA, Weston AJ, Pezeshki BB, Lazarus TS.	Cohort study	159	Cognitive-motor impairment	-NA-	[10]
9.	2015	Clifford DB et al.	Cross sectional study	1,582	No significant difference in HIV HCV coinfection in comparison with absence of coinfection	-NA-	[11]
10.	2010	Thiyagarajan A et al.	Cross sectional	27	Neurocognitive decline	-NA-	[12]
11.	2005	Clifford DB	Review	-NA-	Neurocognitive	-NA-	[13]

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			article		and motor testing deficits		

Cases

CASE 1. 32-YEAR MALE WITH HIV-HCV CO-INFECTION WITH PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

This Patient with HCV-HIV co-infection presented to Medicine Emergency Department with history of fever since 1 month, right sided weakness, abnormal body movements in the form of generalised tonic clonicsiezuressince 2 days and altered sensorium since 1 day. His neurological examination revealed deviation of angle of mouth towards left side, tone was decreased and leg holding was absent (drift) on right side. Plantar response was extensor bilaterally. Magnetic Resonance Imaging (MRI) brain (Figure 1.)was done which was suggestive of a large heterogenous T2/FLAIR hyperintense area in the subcortical deep white matter and periventricular region of left fronto-parietal region, posterior ganglio-capsular and ipsilateral cerebral peduncle, it was also seen crossing the splenium towards the opposite side to involve the parietal white matter likely progressive multifocal leukoencephalopathy. Patient started on IV antibiotics, anticonvulsants, osmotic diuretics and ART was started simultaneously. Patient improved gradually with and review examination revealed MMSE of 16 suggestive of cognitive decline. Complex motor, memory and executive functions were impaired on testing. Patient had history of anger outbursts, emotional liability and decreased appetite. Patient is currently on regular follow up. Follow up detailed examination showed progressive neurocognitive impairment.

CASE 2. 23-YEAR MALE WITH HIV-HCV CO-INFECTION WITH TUBERCULAR MENINGITIS

This patient was multi substance abuser presented to Medicine Emergency Department in altered sensorium. There was history of low-grade fever and cough with sputum since 15 days. Although patient did not have any history of tubercular contact. On respiratory examination coarse crepitations were heard over right side. On neurological examination, meningeal signs were seen in the form of positive Kernig sign, neck rigidity and Brudzinski leg and neck sign. Deep tendon reflexes were exaggerated and bilateral planters were extensor.CEMRI Brain (Figure 1.) done was suggestive of small acute infarcts are seen in left thalamus, right para hippocampal, left half of mid brain, left cerebellar peduncle and bilateral vermis region possibility of vasculitic infarcts. There was subtle meningeal enhancement seen in basal cistern and along left inferior cerebellar peduncle suggestive of basal meningitis likely tubercular. CSF analysis done was suggestive of higher values of ADA (79.8 IU/L). Patient was started on Antitubercular drugs, intravenous antibiotics, corticosteroids and supportive treatment. Patient dramatically improved within 2 days. Later ATT was continued and ART was started after 2 weeks on follow up. Patient is now on regular follow up.

CASE 3. 38-YEAR MALE WITH HIV-HCV CO-INFECTION WITH PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Patient was known PLHA on ART with HCV infection presented to Medicine Emergency Department history of fever since 1-month, abnormal body movements in the form of generalised tonic clonic seizures, right sided weakness with slurring of speech for 2 days and altered sensorium for 1 day. On neurological examination deviation of angle of mouth towards left side was noted, tone decreased on right side, bilateral planter extensor response with no signs of meningeal irritation. MRI brain (Figure 1.)was suggestive of multiple pleomorphic asymmetrical geographical areas of altered signal intensity in periventricular and subcortical white matter, bilateral frontal, parietal, temporal, occipital and both cerebellar hemispheres. Lesions were hypointense on T1 and hyperintense on T2 & FLAIR with further high T2 signal intensity surrounding the primary area suggestive of the milky way sign with

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no diffusion restriction. These findings were indicative of progressive multifocal leukoencephalopathy. Patient was managed conservatively with intravenous antibiotics, anticonvulsants and ART was started. Patient gradually improved over 1 week of intensive care but had residual neurocognitive decline. MMSE was 17.

CASE 4. 23-YEAR MALE WITH HIV-HCV CO-INFECTION WITH TUBERLOMA WITH TUBERCULAR MENINGITIS

Patient was multisubstance abuser with PLHA on ART with hepatitis c reactive. Patient presented to Medicine Emergency Department with history of fever for 2 months, abnormal body movements and altered sensorium for 1 day. There was history of pulmonary tuberculosis 2 years back for which he took complete treatment for 6 months and got recovered. On neurological examination, tone decreased on right side with no leg holding, right planter was mute while left was extensor. MRI Brain (Figure 1.) with contrast done was suggestive of multiple conglomerated ring enhancing lesions with associated diffuse perilesional edema is seen in the left frontal and left temporal region and appearing hyperintense on T2W and FLAIR images and isodense on T1W images with T2W hypointense rim and few of them showing patchy diffusion restriction. There is associated nodular enhancement is seen in left temporal region with larger conglomerated lesion measuring approximately 21 x 14 mm in size. There was heterogenous patchy and nodular enhancement is seen along the basal cistern with associated mild dilatation of the bilateral lateral 3rd and 4th ventricle. Tiny foci of diffusion restriction was seen in right thalamic region. All findings were in favour of tuberculoma with basal meningitis with smallvasculitic infarcts and hydrocephalus. Patient was managed conservatively, was started on ATT along with other symptomatic measures. Patient responded to ATT and is clinically improving past with no residual weakness.

CASE 5. 19-YEAR MALE WITH HIV-HCVCO-INFECTION WITH POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Patient was multisubstance abuser presented to us in Medicine Emergency Department in unconscious state. After successful resuscitation detailed history was taken from attendants. There was history of headache, blurring of vision and abnormal body movements for 1 week. On neurological examination, Pupils were bilateral normal size reacting to light, tone was normal bilaterally, DTR's were 2+ with bilateral plantersflexors. There were no signs of meningeal irritation. MRI Brain (Figure 1.) was suggestive of altered intensity in bilateral Parietal-occipital cortex (right>left) hyperintensities on T2/FLAIR suggestive of posterior reversible encephalopathy syndrome.

CASE 6. 45-YEAR HIV-HCV CO-INFECTION WITH MILIARY TUBERCULOSIS WITH TUBERCULAR MENINGITIS

Patient was IVDU with PLHA who was ART but non-compliant with treatment presented to Medicine Emergency Department with history of fever and cough for 2 months, headache and vomiting for 5 days, altered sensorium for 1 day. On neurological examination, pupils bilateral mid dilated, tone increased, planters were bilateral extensor with neck rigidity present.X -ray chest was done suggestive of miliary picture. CEMRI BRAIN (Figure 1.) wassuggestive of leptomeningeal enhancement along the basal cisterns and sulcal space suggestive of meningitis and multiple areas of diffusion restriction noted in bilateral gangliocapsular region, bilateral temporal lobe, brainstem and middle cerebellar peduncle on right side along with cerebellum on right side showing no blooming on SWI suggestive of acute infarcts. CSF analysis revealedlymphocytic pleocytosis.CSF ADA was raised (63.8 IU/L). Patient was immediately started on antitubercular treatment, IV antibiotics, antiepileptics,corticosteroids and other supportive measures. Patient improved over a period of 3 days. After 2 weeks, ART was started and now patient on follow up in OPD. His follow up MMSE is 20 and residual motor weakness and spasticity on right side.

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CASE 7. 39-YEAR MALE WITH HIV-HCV CO-INFECTION WITH TUBERCULOMA WITH STATUS EPILEPTICUS

Patient was PLHA on ART presented to Medicine Emergency Department in altered sensorium with history of abnormal body movements in the form of generalised tonic clonic seizures, 10 – 12 episodes for 1 day without regain of consciousness. On neurological examination, pupils bilateral normal size reacting to light, tone decreased, planters bilateral mute with no signs of meningeal irritation. MRI Brain (Figure 1.) was done suggestive multiple sub centimetric well defined T2/FLAIR hyperintense areas with some of them showing diffusion restriction on DWI and some of them showing enhancement pattern on post gad images are noted in the bilateral cerebral and cerebellar hemisphere, involving bilateral basal ganglia and brainstem suggestive of tubercular granuloma. CSF ADA values were higher than cut off value (49.3 IU/L). Patient started on ATT along with IV antiepileptics and other symptomatic management. Patient gradually improved and discharged on oral medication. On follow up, his MMSE was 26 with no residual weakness or breakthrough seizures.

CASE 8. 24-YEARMALEHIV-HCV CO-INFECTION WITH STROKE WITH HEMORRHAGIC TRANSFORMATION AND MICROANGIOPATHY WITH INFECTIVE ENDOCARDITIS

Patient was multisubstance abuser with known case of hepatitis C presented to Medicine Emergency Department with history of high-grade fever, cough with expectoration and palpitation since 15 days and altered sensorium with weakness of left side since 1 day. On neurological examination, pupils were mid dilated sluggishly reacting to light bilaterally, angle of mouth deviated to right side, tone decreased on left side, DTR's were 2+ on right side and absent on left, left planter showed extensor response. X ray chest was done suggestive of consolidation of right middle zone. MRI Brain (Figure 1.) was done suggestive of large right MCA territory infarct with hemorrhagic transformation with multiple SWI hypointense lesions seen in bilateral cerebral hemispheres, left thalamus and bilateral cerebellar hemispheres suggestive of microhemorrhages possibility includes multiple cavernoma or microangiopathy. 2D Echocardiography was done suggestive of vegetations on tricuspid leaflets. Patient was managed by giving IV antibiotics, IV fluids and other supportive management. Then patient was referred to higher centre for CVTS opinion in view of large vegetation on tricuspid valve and was lost to follow up.

CASE 9. 26-YEAR MALE WITH HIV-HCV CO-INFECTION WITH PULMONARY TUBERCULOSIS WITH TUBERCULAR MENINGITIS

Patient was PLHA with hepatitis C with known case of pulmonary tuberculosis on ATT presented to Medicine Emergency Department with abnormal body movements and altered sensorium since 1 day. On neurological examination, pupils bilateral normal size reacting to light, tone was increased, bilateral planters extensors with neck rigidity was present. X Ray Chest was suggestive of right upper zone opacity. MRI brain (Figure 1.) was done suggestive of acute infarct with hemorrhagictransformation, hydrocephalus and ill-defined leptomeningeal enhancement seen in the region of the brainstem and along the bilateral sylvian fissures suggestive of meningitis likely tubercular. Patient was started on ATT and gradual improvement was seen over a period of 2 weeks.

CASE 10. 32-YEAR MALE WITH HIV-HCV CO-INFECTIONWITH TUBERCULAR MENINGITIS WITH HYDROCEPHALUS

Patient was hepatitis C reactive presented to Medicine Emergency Department with history of fever x 2 months, cough since 1 month and altered sensorium since 2 day. On neurological examination, pupils bilaterally mid dilated, sluggishly reacting to light, tone was increased, bilateral planters extensors with neck rigidity was present. MRI brain (Figure 1.) was done

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suggestive of bilateral lateral ventriculomegaly with leptomeningeal enhancement seen in the region of brainstem suggestive of meningitis likely tubercular.
The investigations of all the cases are summarised in the Table 2. and the MRI Brain findings are shown in Figure 1. and 2.

Table 2. Investigations of the cases

Investigations	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8	CASE 9	CASE 10
ECG	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
X Ray Chest	Normal	Normal	Normal	Normal	Normal	Miliary Mottling	Normal	Right middle zone showing opacity	Right upper zone opacity seen	Normal
CBC (Hb/TLC/Plt)	10.1 / 12.88 / 155	10.9 / 6.58 / 256	11.4 / 4.53 / 147	12.4 / 3.41 / 170	9.4 / 8.56 / 211	8.8 / 3.21/ 122	9.8 / 11.2 / 134	11.1 / 30.93 / 63	9.7 / 4.44 / 176	11.4 / 8.9 / 134
RFT (Urea/creat)	24 / 0.8	49 / 1.2	34 / 0.9	20 / 0.7	57 / 1.3	65 / 1.5	34 / 1.0	51 / 0.7	34 / 0.9	42 / 0.9
LFT (Total/ Direct/ SGOT/SGPT/ ALP)	0.5 / 0.2 / 67 / 77 / 391	0.6 / 0.1 / 76 / 78 / 51	0.8 / 0.2 / 48 / 78 / 126	0.5 / 0.1 / 54 / 67 / 64	0.8 / 0.2 / 45 / 56 / 134	0.9 / 0.2 / 56 / 57 / 103	0.9 / 0.4 / 44 /56 / 144	0.9 / 0.3 / 76 / 78 / 171	0.8 / 0.2 / 69 / 77 / 143	0.9 / 0.3 / 68 / 67 / 132
Serum Na+ / K+/Cl-	145 / 4.8 / 110	123 / 4.4	132 / 4.3 / 101	139 / 4.4	132 / 4.3 / 104	123 / 3.4 / 101	132 / 4.3 / 112	132 / 4.4	131 / 3.6 / 112	121 / 4.4 / 109
CSF Biochemistry - Glucose/ Proteins/ Chlorides	66 / 50 / 116	50 / 61.2 / 107	66 / 21 / 109	45 / 66 / 101	56 / 24 / 111	33 / 78 / 104	45 / 68 / 104	54 / 25 / 120	67 / 78 / 108	56 / 78 / 106
CSF Cytology	Acellular smear	TLC- 4 cells/mm3, Lymphocytes- 4 cells	Acellular smear	4 cells/mm3, lymphocytes- 4 cells	Acellular smear	5-6 cells / mm3, lymphocytes – 100%	5 cells / mm3, lymphocytes – 5 cells	TLC- 245 / mm3,	8 cells / mm3, lym	6 cells / mm3, lymphocytes – 100%

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								Neutrophils 80 %, Lymphocytes 20 %	phocytes – 100 %	
CEMRI BRAIN	Large heterogenous T2/FLAIR hyperintense area in the subcortical deep white matter and periventricular region of left fronto-parietal region, posterior ganglio-capsular and ipsilateral cerebral peduncle, it was also seen crossing the spleniu	Small acute infarcts are seen in left thalamus, right para hippocampal, left half of mid brain, left cerebellar peduncle and bilateral vermis region possibility of vasculitic infarcts. There was subtle meningeal enhancement seen in basal cistern and	Multiple pleomorphic asymmetrical geographical areas of altered signal intensity in periventricular and subcortical white matter, bilateral frontal, parietal, temporal, occipital and both cerebellar hemispheres. Lesions were hypointense on T1 and	Multiple conglomerated ring enhancing lesions with associated diffuse perilesional edema is seen in the left frontal and left temporal region and appearing hyperintense on T2W and FLAIR images and isodense on T1W images with	Bilateral Parietal-occipital cortex (right>left) hyperintensities on T2/FLAIR suggestive of posterior reversible encephalopathy syndrome.	Leptomeningeal enhancement along the basal cisterns and sulcal space suggestive of meningitis and multiple areas of diffusion restriction noted in bilateral ganglio capsular region, bilateral temporal lobe, brainstem and middle cerebell	Multiple sub centimetric well defined T2/FLAIR hyperintense areas with some of them showing diffusion restriction on DWI and some of them showing enhancement pattern on post gad images are noted in the bilateral cerebral and	Large right MCA territory infarct with hemorrhagic transformation with multiple SWI hypointense lesions seen in bilateral cerebral	Acute infarct with hemorrhagic transformation, hydrocephalus and ill-defined leptomeningeal enhancement seen in the region of the brainstem and	Bilateral lateral ventriculomegaly with leptomeningeal enhancement seen in the region of brainstem suggestive of meningitis likely tubercular.

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	m towards the opposite side to involve the parietal white matter likely progressive multifocal leukoencephalopathy	along left inferior cerebellar peduncle suggestive of basal meningitis likely tubercular	hyperintense on T2 & FLAIR with further high T2 signal intensity surrounding the primary area suggestive of the milky way sign with no diffusion restriction. These findings were indicative of progressive multifocal leukoencephalopathy.	T2W hypointense rim and few of them showing patchy diffusion restriction. There is associated nodular enhancement is seen in left temporal region with larger conglomerated lesion measuring approximately 21 x 14 mm in size. There was heterogenous patchy and nodular enhancement is seen along the basal		ar peduncle on right side along with cerebellum on right side showing no blooming on SWI suggestive of acute infarcts	cerebellar hemisphere, involving bilateral basal ganglia and brainstem suggestive of tubercular granuloma	hemispheres, left thalamus and bilateral cerebellar hemispheres suggestive of microhemorrhages possibility includes multiple cavernoma or microangiopathy	along the bilateral sylvian fissures suggestive of meningitis likely tubercular	

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				cistern with associated mild dilatation of the bilateral lateral 3rd and 4th ventricle. Tiny foci of diffusion restriction was seen in right thalamic region. These findings were suggestive of tuberculoma with basal meningitis with smallvasculitic infarcts and hydrocephalus						

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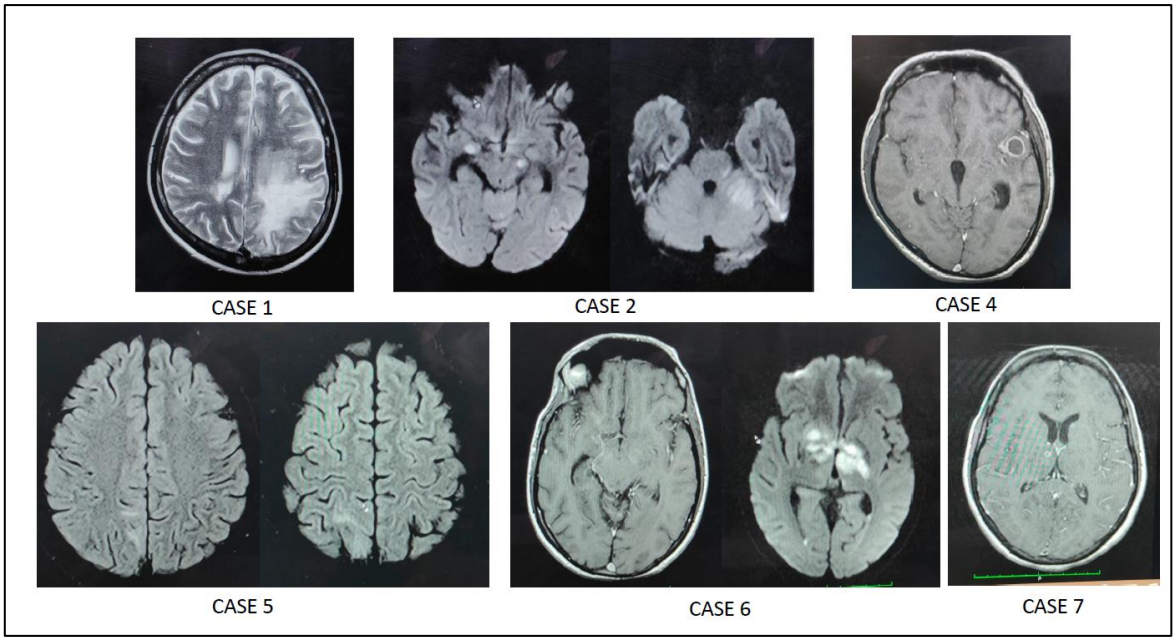

Figure 1. (Case 1-7): CEMRI findings in patients with HIV-HCV co-infection

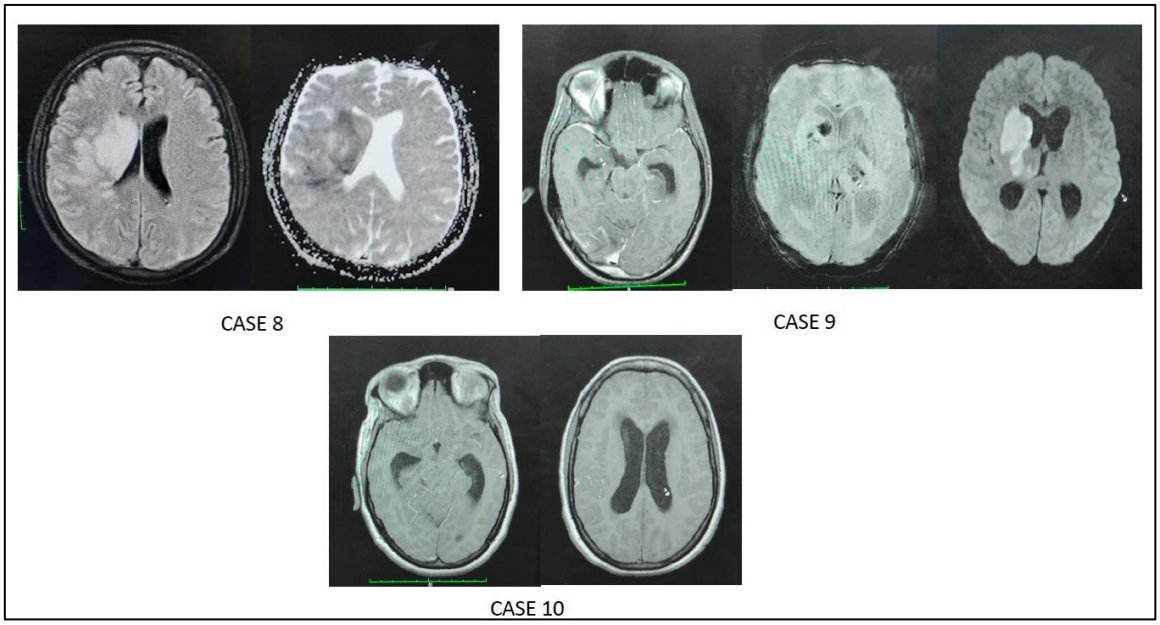

Figure 2. (Case8-10): CEMRI findings in patients with HIV-HCV co-infection

Table 3 summarize the various spectra of CNS manifestations that were found in the present case series

Table 3. CNS involvement in HIV-HCV Co-infection the present case series	
1.	Progressive multifocal leukoencephalopathy
2.	Tubercular meningitis, Tuberculoma
3.	Acute ischemic stroke with/without hemorrhagic transformation
4.	Seizures (Most commonly: Generalised tonic clonic semiology)
5.	Posterior Reversible Encephalopathy Syndrome
6.	Major cognitive decline/Dementia
7.	Dysxecutive syndrome
8.	Microangiopathic changes in brain parenchyma

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Discussion

Globally, an estimated 58 million people have chronic hepatitis C virus infection, with about 1.5 million new infections occurring per year. There are an estimated 3.2 million adolescents and children with chronic hepatitis C infection.[14]

39.0 million [33.1–45.7 million] people were living with HIV at the end of 2022. An estimated 0.7% [0.6-0.8%] of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions.[15]

HCV is a positive-strand RNA virus in the hepacivirus genus of the Flaviviridae family and a blood-borne pathogen. HCV replicates via an error-prone RNA-dependent RNA polymerase and persists as a diverse quasi species (QS) within infected individuals.[16]

The most frequently encountered neurological problems are an HIV-associated distal predominantly sensory peripheral polyneuropathy (DSPN) and a progressive central cognitive-motor impairment called HIV-associated cognitive-motor complex (HIV-CMC). Other diagnostic terms for this condition include HIV-associated dementia and, when the deficits are less marked, minor cognitive-motor disorder, AIDS dementia complex, and HIV/AIDS encephalopathy. Unlike HIV, the clinical sequelae of chronic hepatitis C are hepatic cirrhosis and hepatocellular carcinoma. However, HCV has also been implicated as a cause of autoimmune syndromes, cryoglobulinemia, and vasculitis, which, in turn, have been related to an increased incidence of stroke and peripheral neuropathy in HIV/HCV-coinfected persons.[17-20]

HIV penetrates the CNS early in the course of infection. The same may be true for HCV. In 1999, Fujita and colleagues reported a case of acute viral encephalitis with subsequent discovery of acute HCV infection.[21]

Two other investigative teams have reported the presence of HCV by quantitative polymerase chain reaction (PCR) analysis in the cerebrospinal fluid (CSF) of HCV-infected patients. It was postulated that the virus was of plasma origin because, in most of the cases, the HCV genotype was the same in both the patient's plasma and CSF. The mechanism of transport of HCV from the systemic circulation into the CNS is likely to be similar to that of HIV because both viruses have been shown to infect monocytes, which cross the blood-brain barrier.[22-23]

Chronic active hepatitis is frequently associated with mixed cryoglobulinemia and has been shown to cause numerous CNS diseases, even in the absence of hepatic damage. The presumed mechanism is a vasculitis associated with cryoglobulinemia and multiple ischemic infarcts. Encephalopathy ranging from minor confusion to severe cognitive motor dysfunction has been described. [24-29]

Co-infection of HIV and HCV has a different course as compared to either of the infection alone. The course is more aggressive and the clinical presentationsmay vary depending upon the opportunistic infections. The viral load of HIV and course of CNS manifestations becomes more aggressive in the presence of HCV co-infection.[4]

The studies on HIV-HCV co-infections focus on CNS involvement in the form of decreased global neuropsychiatric performance which was quantified. In the present study, the detailed examination of cases at presentation could not be assessed as all of them presented in emergency department in altered mental state. Previous studies focused on neurocognitive decline and motor manifestations using assessment scale. The current study is in contrast focused on the CNS manifestations of this viral duo but involving the clinical, imaging findings and opportunistic infections. Most common infection was tuberculosis which was found to be associated with HIV-HCV co-infection. Patients infected with both human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are at a higher risk of developing TBM.[30]

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Second most common manifestation in current study was found to be Progressive multifocal leukoencephalopathy. It has been seen that in HIV patients, HCV co-infection has been associated with an increased risk of progressive multifocal leukoencephalopathy (PML).[31]
Although these conditions may be found to be associated with HIV alone, their occurrence with HCV co-infection tends to make these aggressive in course and clinical presentations may vary. In current study, patients with HIV-HCV co-infection presented with stroke. Also, provoked seizures secondary to infection, viral encephalitis as well as systemic and metabolic sequalae of infection can occur. In the present case series, seizures were secondary to either infection space occupying lesion like tuberculoma, meningoencephalitis, cortical infarct etc. Patients in whom MMSE scale could be applied on follow up shown that the average score was below cut-off scores indicative of cognitive decline in individuals, being mild or major neurocognitive decline.
Being a single-centred study of shorter duration is a limitation of the current study. A larger sample size and duration of study might have unfolded many other manifestations of this infectious duo. However, due to the scarcity of cases of co-infection with CNS involvement, these cases can add to the existing literature and carry this research question forward for future studies exploring the CNS manifestations of HIV-HCV co-infection. This study is one of its kind from the region which are the strengths of the study. Memory and executive dysfunction were the most common domains of neurocognition which were found to be affected amongst these individuals. Focal or lateralising findings were also found to be seen in HIV-HCV co-infection especially in setting of stroke.
All the patients were young with such a manifestation spectrum of this co-infection including young stroke, early onset dementia etc. depicts the ominous nature of HIV-HCV co-infection. The manifestations are not only limited to CNS but to other systems also from which it can be predicted that how the course and disease phenotype varies and manifest with a wide range and severity of systematic signs.
This case series along with review of existing literature is one of it's kind from the region. Cases of central nervous system manifestations in patients with co-infection of HIV and HCV have not been studied before. This adds to strengths of the study. Small sample size contributes to the limitation of the study. A larger sample will be required to know the spectrum of manifestations of HIV-HCV co-infection.

Conclusion

HIV-HCV co-infection presents with wider range of CNS manifestations including primary manifestations because of the infection and secondary manifestations due to opportunistic infections.

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Source of Funding: None
Acknowledgments: None

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