Hepatitis E Virus-Associated Acute Encephalitic Parkinsonism

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Abstract

Hepatitis E virus (HEV) is a common infection worldwide and is an emerging infectious disease in the developed countries. The unique characteristics of HEV is that it displays different epidemiological and clinical characteristics between developing and developed countries. Neurological disorders are emerging extra hepatic manifestations of both acute and chronic Hepatitis E virus infection. We report a 17 year old sportsman presenting with acute encephalitic Parkinsonism concurrent with acute hepatitis. Serology was positive for Hepatitis E virus (HEV) and HEV RNA was confirmed. Patient improved completely with symptomatic treatment. We suggest offering diagnostic testing for Hepatitis E virus in patients of neurological disorders with concurrent liver impairment.

Introduction

Neurological manifestations of Hepatitis E virus (HEV) infection are rare and underrecognized. Usually HEV infection manifests as a self-limiting acute hepatitis. A literature review found 25 reports of neurological manifestations in both acute and chronic infections of HEV.[1,2] Most common are Guillain Barre syndrome,[1] brachial neuritis,[1] seizures, Bell`s palsy, cranial nerve palsies, meningitis, encephalitis,[2] transverse myelitis,[3] pseudotumour cerebri, ataxia,[1] proximal myopathy and painful sensory peripheral neuropathy.[2] We report an unusual presentation of acute encephalitic Parkinsonism associated with Hepatitis E virus infection.

Case Report

A 17 year old boy, with a history of recent travel, came with complaints of high grade fever, diffuse dull aching headache and flu like symptoms for10 days. He had dysphagia and drooling of saliva on third day followed by jaundice. On Day 6 patient developed severe tightness of the limbs, paucity of limb movements with reduced blink rate and facial expression. No history of psychosis, seizures, or use of psychotropic drugs or alcohol abuse. On examination he was mentally slow at obeying commands and had icteric eyes with severe asymmetrical akinetic rigid parkinsonism characterized by axial neck dystonia, amimea, anarthria, limb rigidity more on the left side, with generalised hyporeflexia and striatal toes. He did not have any tremor. Clinical differential diagnoses of meningo-encephalitis of viral and malarial etiology were considered.

Laboratory evaluation (at the time of admission) was suggestive of acute viral hepatitis with significant transaminitis ,>25 times the normal level ie; AST -933 IU/L(N=15-37 IU/L) and ALT - 1951 IU/L (N=30-65 IU/L), bilirubin of 3.2 mg(N=0-0.3 mg/dl), and Alkaline phosphatase- 250 U/L (N=50-136 U/L), and plasma ammonia 78 (N= 20-70 micrograms/dl). Serology was positive for anti-HEV immunoglobulin IgM (Index 5.59 against a threshold value of 1- ELISA test) in serum which was confirmed with detection of HEV RNA in Serum. Other Hepatitis viruses like A, B, C and Delta and HIV were negative. Peripheral smear for Malaria parasite was negative.

MRI Brain (Figure 1a - 1d) revealed T2 and FLAIR hyper intensities noted in bilateral basal ganglia (right more than left), temporal and fronto-parietal region with thickened gyri, and

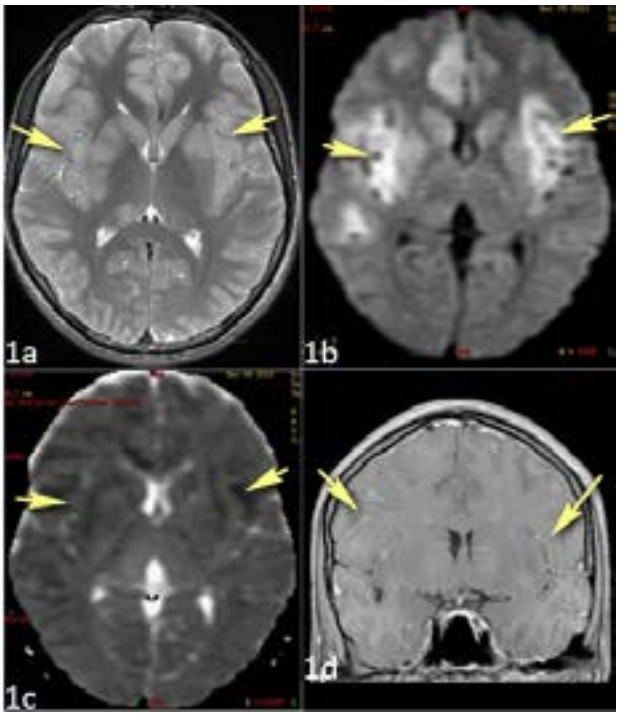

Fig. 1: (a) T2 Axial MRI Brain showing hyperintensities in bilateral basal ganglia, thalamus, insular, frontal, temporal and parietal regions (Arrow) (b-c) DWI MRI brain (b) showing the hyperintensities of bilateral frontotemporal regions with hypointensity on ADC MRI Brain (c) (Arrow) (d) T1 coronal Post contrast MRI showing enhancement of the leptomeninges

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Table 1: Association of virus and parkinsonism[5]

Viral genome	Virus family	Virus
DNA	Herpes viridae	Herpes simplex virus (HSV)
		Varicella zoster virus (VZV)
		Epstein barr virus (EBV)
		Cytomegalovirus (CMV)
RNA	Orthomyxoviridae	Influenza type A
	Paramyxoviridae	Measles
	Picornaviridae	Coxsackie
		Echo
		Polio
	Retroviridae	Human immunodeficiency virus (HIV)
	Flaviviridae	West Nile virus
		Japanese B encephalitis

diffusion restriction (DWI). Contrast enhanced MRI Brain confirmed gyriform enhancement of cortical regions suggestive of encephalitis. Possibility of viral encephalitis of herpes origin was considered however HSV DNA PCR (both 1 and 2) was negative in CSF. EEG showed diffuse slowing of the background activity and no evidence of epileptiform discharges.

Possibility of other viral encephalitides like Japanese encephalitis, West Nile virus was considered, which were however negative. CSF analysis was normal and HEV detection in CSF was not done due to logistic reasons. Cultures of blood, urine and CSF were sterile until 3 weeks.

Ultrasonography of the liver was normal. In view of predominant extra pyramidal symptoms associated with hepatitis, remote possibility of Wilson`s disease was considered. Work up (serum copper, Serum ceruloplasmin, 24 Hr urinary copper, and KF ring by slit lamp bio microscopy) was done and was found to be negative.

Severity of parkinsonism was assessed using Part 3 MDS-UPDRS scale[4] (MDS- Movement Disorder Society-Unified Parkinson disease rating scale) at admission which was 64. On Levodopa challenge test there was significant improvement of scores of Part 3 MDS-UPDRS[4] from 64 to 33 suggestive of 'levodopa responsive reversible parkinsonism'. Patient was treated with anti parkinsonian medication and low dose steroids. Patient significantly improved with resolving icterus with normalisation of transaminases and bilirubin in 2 weeks and Parkinsonism in 3 weeks duration. Follow up MRI Brain done 12 weeks later showed complete resolution of signal changes as well. Medication for Parkinsonism was tapered over 6 weeks and now at 2 years of follow-up he is doing well.

Discussion

Neurological presentations of HEV are extremely rare and acute encephalitic Parkinsonism has not been reported so far. In view of its temporal relationship between development of transaminitis and the neurological features (encephalitis with evidence of HEV infection, and exclusion of other potential hepatotropic and neurotropic causes suggests this association as causal. Kamar N et al had found a prevalence of 5.5% (7 out of 126 over 5 years) of neurological complications of autochthonous HEV infection in UK and France.[2]

Acute Parkinsonism is usually a secondary Parkinsonism resulting out of identifiable non degenerative disorders. The common etiologies include drugs (D2 receptor blockers), toxins (CO), infectious agents, post infectious, vascular insults, trauma, tumor, hydrocephalus and psychiatric disorders. Table 1 reviews the possible viral association for secondary Parkinsonism as a complication of encephalitis.[5]

Viral Parkinsonism usually has two types of clinical course like 'acute transient reversible' and 'chronic persistent permanent Parkinsonism'. Prototype of acute Parkinsonian syndrome was von Economos disease (ED) which has distinct criteria different from PEP (Post Encephalitic Parkinsonism). Our case had acute viral hepatitis E with cerebral involvement in the form of diffuse encephalitis involving cortical regions of frontal, temporal as well as sub-cortical basal ganglia manifesting as acute Parkinsonism. Similarities in this case and ED are the evidence of encephalitis and Parkinsonism while contrasting features are no evidence of hyper somnolence and Obsessive compulsive behavior, gaze palsies, oculogyric crises, and pyramidal signs.

Although phenomenology of viral Parkinsonism and idiopathic Parkinson disease are similar, it is unlikely that the pathophysiology is due to abnormal Lewy body and neurofibrillary tangle deposition in the brain tissue.[6] The pathophysiological mechanisms of how HEV gains access to CNS is uncertain; however neurotropic quasi-species may be directly neuropathogenic.

Literature review on neuroimaging of HEV encephalitis had shown only few single case reports where in the imaging findings ranged from normal[7] to diffuse white matter signal changes in both supratentorial and infratentorial brain parenchyma,[2] bilateral symmetrical basal ganglionic and substantia nigral hyperintensities[8-10] and hippocampal signal changes.[11]

Conclusion

The diagnosis of hepatitis E virus infection should be considered in any patient with transaminitis, concomitant with neurological symptoms and signs, regardless of age or travel history. The diagnosis may be suggested by HEV serology, however confirmation should be done by molecular documentation of HEV RNA in the serum, or CSF, or both.

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