


Liver Transplantation Reverses Hepatic Myelopathy in 2 Children With Hepatitis A Infection

Roshan Koul, MD, DM, FRCPCH, FAAN¹ , Bikrant Bihari Lal, MD, DM²,
 Viniyendra Pamecha, MS, FRCS³, Shiv Sarin, MD, DM²,
 and Seema Alam, MD²

Abstract

Objectives: To report 2 children with acute hepatic myelopathy after hepatitis A infection who recovered completely after living donor liver transplantation. **Methods:** All the children admitted into liver intensive care unit (LICU) from November 1st 2018 to 31st October 2019, were evaluated for the neurological features. The data was collected from the admission register of the LICU unit in children below 15 years age. Medical records of these children were reviewed and data collected. Established clinical criteria were used to categorize the various grades of hepatic encephalopathy/myelopathy. **Results:** 37 children were seen over 1-year period between 6 months to 15 years age. There were 24 male (64.9%) and 13 females. Acute liver failure was seen in 19 (51.3%) and acute on chronic liver failure in 18 (48.7%). There were 10 cases of hepatitis A in acute liver failure group, 10 of 19 cases (52.6%), while Wilson's disease and undetermined etiology group formed the chronic group. 2 cases of hepatic myelopathy were seen in acute liver failure following hepatitis A infection. Both these children underwent live liver donor transplantation and recovered completely. Further in hepatitis A group, 3 children had spontaneous recovery, 4 died and 1 child was discharged with end of life care. Overall out of all 37 children with liver failure, 20 (54%) were discharged, 6 (16.2%) were advised end of life care and 11 (29.8%) died. **Conclusion:** Two cases (10.5%) of reversible hepatic myelopathy were seen in acute liver failure group of 19 cases. 18 out of 37 (48.6%) children had residual neurological features at discharge time.

Keywords

hepatic encephalopathy, hepatitis A, neurological complications, myelopathy, liver transplantation

Received August 4, 2020. Received revised November 12, 2020. Accepted for publication December 6, 2020.

Introduction

Neurological complications are often seen with chronic liver disease.^{1,2} Extrapyramidal features and neuropsychiatric manifestations are common in chronic liver diseases.² Hepatic encephalopathy (HE), the most serious and life threatening condition is seen in acute liver failure and in acute on chronic liver disease.² Raised intracranial pressure, a life threatening condition seen in acute HE, is not a common feature in the chronic liver disease.³ Spinal cord involvement is an uncommon complication and is usually associated with extensive porto-systemic shunt of blood either surgically created or occurring spontaneously in chronic liver disease.^{2,4} Spinal cord involvement is labeled as hepatic myelopathy. Hepatic myelopathy is more often a feature of chronic liver disease but can be seen in acute hepatic encephalopathy.^{4,5} Hepatic myelopathy

following acute fulminant liver failure is rarely seen and reported. Two children in our series had hepatic myelopathy following HE after acute fulminant hepatitis A infection, which reversed after liver transplantation (LT).

¹ Pediatric Neurology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi, India

² Pediatric Hepatology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi, India

³ Hepatobiliary Surgery, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi, India

Corresponding Author:

Roshan Koul, Neurology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi, India.

Email: koulroshan@gmail.com



Methods

All the children admitted into liver intensive care unit (LICU) from November 1st 2018 to 31st October 2019, were evaluated for the neurological outcome. The data was collected from the admission register of the LICU unit in all children below 15 years age. All the medical records of these children were seen and data collected. The diagnosis of HE was based on well-established clinical criteria in children and was graded into 4 grades.⁶ The indication for admission to LICU was presence of grade 3 or 4 HE requiring ventilator support or plasma exchange. An initial neurological examination was made before admission to LICU. Neurological assessment was also done after transfer from LICU to the ward. Final neurological examination and outcome were assessed at the time of discharge. King's College Hospital criteria was used to list the children for liver transplantation [LT] and LT was done based on trend of rising international normalized ratio (INR) and increasing HE.⁷ The institute has a living donor LT program. Plasmapheresis was done as a bridge to LT whenever there was a delay.⁸ The children requiring liver transplant were assessed before, after liver transplantation and at discharge. The children undergoing plasmapheresis were assessed in the ward at the time of discharge from hospital. Baseline blood including complete blood count, liver biochemical tests, PT, APTT, serum copper, serum ceruloplasmin, autoimmune profile, ammonia, renal functions, hepatitis profile and day to day blood tests were done. Imaging of the abdomen was done in all. Brain imaging and EEG were done when the clinical condition required. The children with myelopathy were diagnosed after liver transplantation (LT) when there was complete reversal of encephalopathy but there was weakness of upper and lower limbs with sphincteric involvement. Myelopathy was diagnosed on the classic features of upper motor neuron signs in upper and lower limbs. MRI brain and spine were done in both children to rule out other causes in brain and spine. Nerve conduction study was also done in them.

Case Summaries

Case 1. A 5 year 8 months boy presented in a critical condition to the hospital emergency of institute of liver and biliary sciences (ILBS). The boy had 3 days history of jaundice, 1 day history of deranged sensorium. He was intubated before transfer from a peripheral hospital. At admission he had bradycardia (heart rate of 45/minute) and pupils were reacting both sides. Laboratory work up revealed INR 3.17, serum bilirubin of 23.3mg/dl (15.6mg/dl direct), ASAT-1035 (5-40 IU/L), ALAT-1358 (10-40 IU/L), serum ammonia ranged between 290-434 (12-60 ug/L), normal ceruloplasmin 0.21 (0.2-0.6 g/L). HIV profile was negative. ANA, double stranded DNA were negative. Hepatitis B, C and E were negative. IgM Hepatitis A antibody was positive. Renal functions were normal. EEG revealed bi-hemispherical delta activity suggestive of encephalopathy with raised intracranial pressure. An urgent living donor LT was performed within 72 hours of hospitalization with father as donor. The surgery was uneventful without any complications. The child was extubated 24 hours after LT. After 48 hours of liver transplantation encephalopathy started improving but he was not able to move upper and lower limbs. Examination revealed normal cranial nerves. Both upper and lower limbs had grade 1/5 power. Deep tendon reflexes were exaggerated and plantars were upgoing. MRI brain and spinal cord were normal. Nerve conduction study was normal. Liver functions returned to normal in 2 months time. His power in limbs improved gradually. He was able to sit after 2 weeks, stand after 4 weeks and walking at the day of discharge (60 day of hospitalization).

Case 2. A 5 year girl presented to the emergency of ILBS hospital with hepatic encephalopathy and raised intracranial pressure. She had been intubated outside due to grade 4 HE. On examination the pupils were reacting both sides. Laboratory work up revealed INR 5.6, serum bilirubin of 23.6mg/dl (10mg/dl direct), ASAT-1174 (5-40 IU/L), ALAT-336 (10-40 IU/L), serum ammonia ranged between 334-443 (12-60 ug/L), normal ceruloplasmin 0.22 (0.2-0.6 g/L). HIV profile was negative. ANA, double stranded DNA were negative. Hepatitis B, C and E were negative. IgM anti HAV was reactive. Hepatitis A antigen was positive. Renal functions were normal. CT brain was normal. EEG revealed bilateral delta activity. She underwent living donor LT within 36 hours of admission with mother as donor. She required prolonged ventilation and underwent tracheostomy on post operative day 13. While recovering from encephalopathy weakness of upper and lower limbs was noted. She had features of upper motor neuron lesion in both upper and lower limbs. MRI brain and spinal cord was normal. Nerve conduction was normal. The girl recovered gradually and was able to walk after 2 months of liver transplantation.

Results

37 children were admitted in LICU over 1 year period. The age ranged between 6 months to 15 years of age with a mean of 8.9 years. There were 24 male (64.9%) and 13 females (35.1%). Acute liver failure (ALF) was seen in 19 (51.3%) and acute on chronic liver failure in 18 (48.7%). Hepatitis A was the main cause in ALF group 10 out of 19 (52.6%), Wilson disease and undetermined cause in chronic group. Associated multi-organ involvement was seen in 4, renal failure in 3 and pneumonia in 1. Table 1 shows types of liver disease and neurological work up. Neurological features and outcome are given in the Table 2. Two children with acute hepatic myelopathy were seen after recovering from hepatic encephalopathy. They recovered completely in about 8 and half weeks(60 days) after LT.

Discussion

Neurological complications are often seen with chronic liver disease.^{1,2} Extrapyramidal features and neuropsychiatric features are common in chronic liver diseases.² Hepatic encephalopathy is the most serious and life threatening condition seen in acute liver failure and in acute on chronic liver disease.² Raised intracranial pressure is the life threatening condition seen in acute hepatic encephalopathy,³ which is not a common feature in the chronic liver disease. Intracranial hemorrhages, focal deficit and seizures are uncommon but seen in these children.² Spinal cord involvement is uncommon and usually associated with extensive porto-systemic shunt of blood either surgically created or occurring spontaneously in chronic liver disease.^{4,5} Spinal cord involvement is labeled as Hepatic myelopathy (HM). It is most often seen in chronic liver disease.⁹⁻¹¹ Acute hepatic myelopathy gets obscured by dominant encephalopathy in acute liver failure, hence less often reported. The underlying mechanism for hepatic myelopathy on autopsy studies have shown selective demyelination of corticospinal tracts, possible due to the nitrogenous toxins like ammonia.¹⁰ There is symmetrical loss of myelin in the lateral pyramidal

Table 1. Shows Types of Liver Disease and Neurological Work up.

Features	Conditions	Number	
Types of liver disease	Hepatitis A	10	27.0 %
	Hepatitis E	1	2.7 %
	Autoimmune hepatitis	3	8.1 %
	Biliary atresia (BA)	8	21.6 %
	Wilson	7	18.9 %
	Undetermined	7	18.9 %
	Drug induced	1	2.7 %
HE grades clinical	1	5	13.5 %
	2	9	24.3 %
	3	8	21.6 %
	4	15	40.5 %
Procedures	Liver transplant	11 (Hepatitis A-2, Biliary atresia-5, Unknown-4)	
	Plasma exchange	13	
EEG (6)	Grade 4	5	
	Normal	1	
Brain imaging (7)	MRI-	Basal ganglia changes	1
		Hemorrhage	1
		Normal	2
	CT-	Edema	1
		Normal	2

Percentage of 4, 5, 6 rows not done as the number is small.

tracts, with demyelination beginning in the cervical spine, becoming more intense at lower levels, and occasionally being associated with axonal loss.^{5,10} In the early stages, demyelination seems to predominate, but as the disease progresses, axonal loss occurs, and this is likely to be irreversible.¹⁰ MRI studies have shown abnormalities in the corticospinal tracts but often there are no abnormalities seen in the spinal cord.⁵ In a detailed review from 1966 to 2013, 90 cases of HM were diagnosed. The first description of the case of the HM goes to 1949.^{5,10}

Hepatic myelopathy is difficult to diagnose in acute liver failure encephalopathy as acute encephalopathy obscures the signs of myelopathy and particularly when the patient is in higher grades of encephalopathy or intubated. After the liver transplant these patients recover rapidly in higher functions but they are unable to move upper and lower limbs. Examination reveals typical upper motor neuron features in the limbs characteristic of myelopathy. A pathology anywhere in the corticospinal tracts could manifest as weakness of upper and lower limbs. Normal higher mental functions, language and cranial nerves after extubation suggest pathology in the spinal cord most likely when there is acute weakness of upper and lower limbs. This pattern was seen in our 2 cases. A normal MRI has been reported in patients with myelopathy due to cirrhosis.⁵ One has to differentiate hepatic myelopathy from compressive and non-compressive myelopathy, transverse myelitis,¹² acute myo-neuropathy associated with hepatitis A infection¹³ and critical care / intensive care associated neuropathy in these patients. In this latter condition, the weakness is of lower motor neuron type with areflexia. Nerve conduction study further helps

Table 2. Shows Neurological Features and Outcome.

Neurological features		Number	Percent
At admission to ICU (37)	HE	37	100.0
	Raised intracranial pressure	13	35.1
At discharge (20)	Focal deficit (hemiparesis)	1	2.7
	Seizures	3	8.1
	Extrapyramidal features	8	21.6
	Neuropsychiatry features	4	10.8
	Myelopathy (recovered)	2	5.4
	No deficit	2	5.4
	Discharge	20	54.0
Outcome (37)	End of Life Care (ELC)	6	16.2 (Hepatitis E-1, Hepatitis A-1, Wilson-3, undetermined-1)-
	Death	11	29.7 (Hepatitis A-4, Wilson- 1, Biliary atresia-3, autoimmune- 1, metabolic/ mitochondrial-1/1)

in differentiating this from myelopathy. MRI is often normal in hepatic myelopathy, as it was in both of our children.⁵ Medical treatment and shunt surgeries have made some improvement in myelopathy but liver transplantation may reverse the neurological deficit.^{10,14} The grade of improvement is related to the time interval between onset of the first symptoms of hepatic myelopathy and liver transplantation.^{5,10} If the liver transplant is done early there is complete reversal of the myelopathy. Recovery of myelopathy after liver transplantation is slow and may be incomplete in chronic liver disease as these patients have undergone axonal loss due to the chronicity of the disease. However in acute liver failure associated myelopathy, the recovery is fast and complete as these patients have only demyelinating changes and not the axonal loss.^{5,14} Furthermore these patients receive steroids and tacrolimus after liver transplantation which may also be helpful in recovery. After liver transplantation our 2 children had a rapid recovery on follow up.

Conclusions

Acute reversible hepatic myelopathy is uncommon and rarely reported. It becomes obvious after recovery from hepatic encephalopathy when the person is not able to move the limbs. Rapid recovery suggests demyelinating mechanism involved in the spinal cord. This weakness has to be differentiated from other causes in brain, spine, nerves and muscles.


Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Roshan Koul  <https://orcid.org/0000-0002-5048-1223>

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