

# Hepatitis B-Related Mononeuritis Multiplex

<sup>1</sup>Budha Charan Singh, <sup>2</sup>Vinay N Gowda and <sup>3</sup>Prasan Kumar Panda

<sup>1</sup>Department of Internal Medicine, All India Institute of Medical Sciences (AIIMS), India

<sup>2</sup>Department of Pathology and Lab Medicine, All India Institute of Medical Sciences (AIIMS), India

<sup>3</sup>Department of Medicine (Division of Infectious Disease), All India Institute of Medical Sciences (AIIMS), India

## Article history

Received: 29-08-2022

Revised: 25-10-2022

Accepted: 31-10-2022

## Corresponding Author:

Prasan Kumar Panda  
Department of Medicine  
(Division of Infectious  
Disease), All India Institute of  
Medical Sciences (AIIMS),  
India  
Email: motherprasanna@rediffmail.com

**Abstract:** Hepatitis B Virus (HBV) infection can present with varied multisystem manifestations involving the skin, kidneys, blood, and nervous system. We report a 57-year-old man with HBV-related mononeuritis multiplex who had symptoms of multiple sensory-motor axonal polyneuropathies. He was evaluated for his neuropathy with nerve conduction studies and a sural nerve biopsy that revealed necrotizing small-vessel vasculitis. He also had an acute liver injury. He was started on direct-acting oral antiviral therapy followed by steroid therapy and this treatment led to the resolution of his symptoms and normalization of transaminases without significant changes in nerve conduction studies at a one-year follow-up.

**Keywords:** Antiviral Therapy, Hepatitis B Virus, Peripheral Neuropathy, Small-Vessel Vasculitis, Steroid

## Introduction

Vasculitis due to infection has been established only in few situations through a wide range of infections that can be attributed as its cause. Of these, hepatitis B has been reported in few instances to cause mononeuritis multiplex and the mechanism with which it causes such a condition is believed to be immune-mediated or vascular (Mehndiratta *et al.*, 2013; Wada *et al.*, 2008; Tabor, 1987). Depending on the vascular bed involved it can result in immune-mediated demyelinating neuropathies. Similar pathology has been incriminated in the development of chronic inflammatory demyelinating polyneuropathy and Guillain-Barre syndrome with acute hepatitis a (Tabor, 1987). However, classical stocking-glove neuropathy may not be encountered. In such cases, a sural nerve biopsy is an important diagnostic procedure for the evaluation of such vasculitis and to prove its association (Prada *et al.*, 2019).

Hence, we describe a case of hepatitis B infection who presented with mononeuritis multiplex.

## Case Report

A 57-year-old man, reformed chronic smoker, presented in the month of February 2020 with complaints of fever for around 3-weeks. There was myalgia in all limbs and low backache and subsequently, he developed edema of both hands and feet along with facial puffiness. Following 2 to 3 days, he developed tingling sensation and numbness in both hands and feet. These sensory symptoms started in the

radial aspect of the left hand, then the ulnar aspect then involving the right hand and lower limbs. In the next few days, he felt weakness in his feet and his hands which gradually progressed into difficulty in walking with buckling of his knees. He also noticed difficulty in gripping objects by his hands, and buttoning his shirt. There was no history of double vision, and other visual disturbances, abnormal sensations in other body parts, and weakness on the face or the bulbar muscles. The patient subjectively does not report any shortness of breath.

On examination, he was found to have normal vitals with bilateral pedal and hand edema. Systemic examination of the respiratory, cardiovascular, and abdominal systems revealed no abnormalities. Nerve thickening was noticed in his bilateral common peroneal nerves. Handgrip strength was reduced in his right hand; the power of the right ankle at both extension and flexion was noted to be 4-/5. Deep tendon reflexes (knee and ankle) were decreased in his right lower limb. There was no evident wasting or fasciculation in any of the muscle groups.

Routine investigations were normal except for hemoglobin 10.75 g/dL (13.5-17.5 g/dL), alanine aminotransferase 86 U/L (5-45 U/L), aspartate aminotransferase 76 U/L (5-40 U/L), alkaline phosphatase 562 U/L (<240 U/L), GGT 95 U/L (<41 U/L) and ESR 46 mm/hr (0-22 mm/hr). Keeping the possibility of acute inflammatory demyelinating polyneuropathy, CSF analysis was sent and it reported no albumin-cytological dissociation and a sterile culture. Other investigations for endemic infections (Dengue, Scrub typhus, Malaria) were all

negative. The possibility of Zika was not considered based on the absence of risk factors in the index case and the lack of presenting clinical features. Chikungunya may be a far-fetched diagnosis as he doesn't present with any prodromal symptoms and hence active search to rule out the inciting agent for this uncommon presentation was not considered. Syphilis particularly secondary and tertiary syphilis may give rise to such a condition. However, the absence of high-risk behaviors and non-revealing history outweighed a mandatory diagnostic evaluation. Blood and urine cultures were sterile. He was incidentally found to be HBsAg positive (done using Chemiluminescent Immunoassay) with very high HBV DNA levels (quantitative PCR - 7,86,00,000 IU/mL (1 IU corresponds to approximately 7.5 copies/ml; a cut-off value of 3.8 IU/mL was used)).

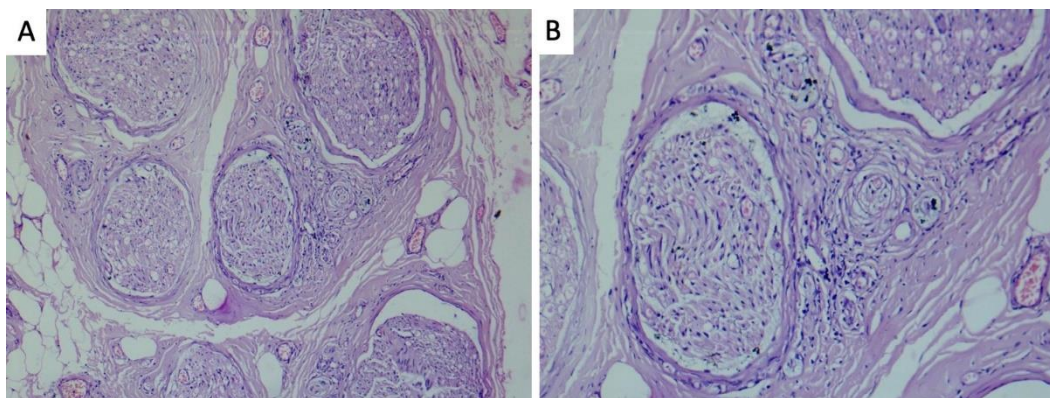
His initial liver enzymes were elevated around twice the upper limit of normal and the possibility of hepatitis was supplemented by ultrasonography of the abdomen that revealed borderline hepatomegaly with periportal cupping showing features of hepatitis. These findings along with an HBsAg positive state with high HBV DNA with a prior history of fever in the preceding 3 weeks led to a presumptive diagnosis of acute/sub-acute Hepatitis B infection. Although HBeAg and anti-HBc IgM were sought it couldn't be done due to technical constraints and a similar obstacle was encountered. Meanwhile, the Fibroscan of the liver showed F2 fibrosis. Hence, an upper GI endoscopy was performed that revealed a normal study. With symptoms of peripheral neuropathy, a nerve conduction study was done and it was suggestive of sensory > motor axonal neuropathy in all four limbs. A left sural nerve open excision biopsy (4 cm segment) was done that revealed necrotizing small-vessel vasculitis (Fig. 1).

Demonstration of deposition of hepatitis B core antigen through immunostaining and C4d complement immunostaining to demonstrate that the lesions in vascular endothelial cells as well as around the vessels are associated with HBV leading to neuritis couldn't be done due to technical constraints. There were negative slit skin

smears from the ear lobule. There were no other mucocutaneous manifestations or involvement of other organs that might give strong clues to suspect systemic vasculitides such as polyarteritis nodosa and Wegner's granulomatosis. Common infections that are associated with the development of neuropathy such as Hepatitis C and HIV were ruled out. He also had no skin manifestations to suspect of herpes zoster with postherpetic neuralgia and neuropathy. As this index case was a farmer, a rare possibility of insecticides or toxins causing his neuropathic symptoms can be considered. However, there was no history of such exposure and hence was not investigated further. His blood sugar levels were normal and hence a probable cause of diabetic neuropathy was dismissed. The patient's dietary pattern consists of both vegetarian and non-vegetarian meals and other sensory symptoms of Vitamin B12 deficiency. Hence, weightage was not given to investigate further in that line. Finally, HBV infection as the cause of his neuropathy was considered after an exhaustive differentials.

He was started on tenofovir 300 mg once daily orally. Gabapentin was also started for the neuropathic pain. However, there was worsening of his neuropathic pain such that he has to be started on duloxetine 30 mg twice daily. Oxcarbazepine was also started and its doses were escalated to 300 mg twice daily over a period of a few days after assessing the pain scale. A fentanyl patch of strength 25 micrograms was also tried and increased to a 50-microgram patch gradually. With all these measures, pain control was poorly achieved. Daily physiotherapy was performed for the weakness and although there was no progression of weakness, no improvement in the muscle power was also noted during the initial treatment period.

HBV DNA levels were repeated after 2 weeks of antiviral that declined to 46500 IU/mL. A trial of short-course high-dose steroids was given with an injection of triamcinolone 80 mg IM that was later followed with tab prednisolone 30 mg for a period of 10 days. There was an objective improvement in his pain scale following it.



**Fig. 1:** Biopsy of left sural nerve with low power (A, 100 x) and high power (B, 200 x) showing nerve bundles with features of vasculitic infarct

At the time of discharge, he was advised to continue physiotherapy of the affected limbs. Tenofovir at 300mg once daily was continued with tapering steroids that were stopped after a duration of 10 days. He was lost to follow-up due to the ongoing COVID pandemic. However, after one year, the patient was contacted and he was told there was a gradual improvement in the functional status and power of the limbs as he continued antiviral therapy with self-medication for a year and stopped since maximum recovery was obtained with no disability status. On this visit, a repeat HBV DNA level was done that showed no detectable viral levels. However, a repeat nerve conduction study showed the same features as at the time of diagnosis.

## Discussion

The case had a rapid clinical progression over a few weeks of fever followed by the development of sensory and motor symptoms involving the extremities of hands and feet. It is one of those rare events where a patient presented with only signs and symptoms of mononeuritis multiplex with an association with HBV infection and recovered with antiviral and steroid therapy (Pelletier *et al.*, 1985).

Vasculitic neuropathy can present in the following three patterns: Multiple mononeuropathy or multifocal neuropathy, confluent multiple mononeuropathies, and distal symmetric polyneuropathy (Collins *et al.*, 2003). The pathophysiology of HBV leading to these neuropathies is poorly understood. Various studies have shown the deposition of immune complexes composed of HBV in the vasa nervosum leading to endoneurial and epineurial vascular lesions which ultimately produce direct nerve injury. The same is illustrated in this case by the development of necrotizing small-vessel vasculitis in the sural nerve biopsy. Although, the duration of HBV infection couldn't be related in this case with certainty as he denies any risk factor of acquisition of the infection, ultrasonography findings of the liver were suggestive of chronic pathology. This is supplemented by high viremia. The chronic nature of the disease and its effects on the liver parenchyma may also suggest the failure to significantly raise the liver enzymes which was recorded weeks after the initial onset of the clinical disease. Hence,

the possibility of a flare can be kept resulting in the current neural pathology.

With the neurological manifestations, this may pose a question in such patients on the choice of antivirals and duration of treatment. The available literature also didn't mention specifications on chronic HBV infection resulting in flares and with such presentations. The duration of treatment with antivirals whether to continue lifelong and if not whether it carries an inherent risk of relapse neuropathy when rebound viremia occurs after HBV reactivation is an area that requires further studies. Also, the basis for monitoring both clinical and biochemical improvement in such conditions and future preventive measures or identification of factors that might pose a risk for this condition demands follow-ups in this small group of cohorts. The possibility of another infection causing this immune-mediated phenomenon can also be considered but the majority of this has been ruled out based on the epidemiology and prevalence of such conditions in the region.

This case provided a basis for a holistic approach toward the management of HBV infection and mononeuritis multiplex. The patient had severe neuropathic pain which was not readily controlled despite the use of opioids and anticonvulsive agents for neuropathic pain. There was also weakness and wasting of the muscles involved as a spectrum under peripheral neuropathy that leaves scopes for further studies as it was not amenable to routine physiotherapy and improvement of nutrition. However, this case showed marked clinical improvement after the initiation of high-dose steroids and this led to further perplexity whether steroids should be a routine recommendation in such scenarios. Hence, there is a need for a broader approach involving multidisciplinary disciplines toward the management of such rarely reported cases. Following is a review of the literature regarding Hepatitis B related neuropathy and vasculitis (Table 1) (Mehndiratta *et al.*, 2013; Wada *et al.*, 2008; Tsukada *et al.*, 1987; 1983). In one refractory case of Hepatitis B related Myasthenia gravis, Rituximab has survival benefits; even therapeutic plasma exchange can act as a bridge to recovery, especially in self-limiting illnesses such as viral hepatitis (Singh *et al.*, 2020a; 2020b).

**Table 1:** Conclusions of various case studies of Hepatitis B-related neuropathy

Sr No	Citation	Conclusion
	Mehndiratta <i>et al.</i> (2013)	Neurological manifestations in hepatitis B may take the form of Guillain-Barré syndrome and vasculitis-related mononeuritis multiplex
2.	Wada <i>et al.</i> (2008)	Vaccination might induce an aberrant hypersensitivity state and cause HBV-associated vasculitis
3.	Tsukada <i>et al.</i> (1987)	Electron-dense deposits, suggestive of immune complexes composed of hepatitis B virus, is demonstrated in the endoneurium of the patient with chronic relapsing polyneuropathy
4.	Tsukada <i>et al.</i> (1983)	Immune complexes composed of the hepatitis B virus might play a significant role in the pathogenesis of endoneurial and epineurial vascular lesions
5.	Singh <i>et al.</i> (2020a) (Present case)	HBV infection can lead to mononeuritis multiplex due to secondary vasculitis that can be treated with antiviral therapy (like tenofovir) and a short course of steroid

In conclusion, mononeuritis multiplex due to secondary vasculitis can be a rare manifestation of HBV infection. Antiviral therapy (e.g., tenofovir) and steroids may be the treatment of choice in this case. Nerve conduction studies may lag behind clinical recovery.

### Declarations

No funding was received to assist with the preparation of this manuscript. The authors have no conflicts of interest to declare that are relevant to the content of this article. This case report is written under ethical guidelines with obtained patient consent.

### Funding Information

The authors have not received any financial support or funding to report.

### Authors Contributions

**Budha Charan Singh and Vinay N Gowda:** Data collection, analysis, drafting, approval.

**Prasan Kumar Panda:** Concept, analysis, critical review, approval.

### Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

### References

Collins, M. P., Periquet, M. I., Mendell, J. R., Sahenk, Z., Nagaraja, H. N., & Kissel, J. T. (2003). Nonsystemic vasculitic neuropathy: Insights from a clinical cohort. *Neurology*, 61(5), 623-630.  
<https://doi.org/10.1212/01.WNL.0000082715.48844.3E>

Mehndiratta, M., Pandey, S., Nayak, R., & Saran, R. K. (2013). Acute onset distal symmetrical vasculitic polyneuropathy associated with acute hepatitis B. *Journal of Clinical Neuroscience*, 20(2), 331-332.  
<https://doi.org/10.1016/j.jocn.2012.03.029>

Pelletier, G., Elghozi, D., Trépo, C., Laverdant, C., & Benhamou, J. P. (1985). Mononeuritis in acute viral hepatitis. *Digestion*, 32(1), 53-56.  
<https://doi.org/10.1159/000199217>

Prada, V., Massucco, S., Venturi, C., Geroldi, A., Bellone, E., Mandich, P., ... & Schenone, A. (2019). Diagnostic value of sural nerve biopsy: Retrospective analysis of clinical cases from 1981 to 2017. *Frontiers in Neurology*, 10, 1218.  
<https://doi.org/10.3389/fneur.2019.01218>

Singh, D. P., Agarwal, S., Singh, R., Nandan, D., & Gupta, A. (2020a). Therapeutic Plasma Exchange in Parvovirus B19-induced Acute Hepatic Failure. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine*, 24(5), 361.  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7358866/>

Singh, R. K., Joshi, D., & Rath, S. (2020b). Successfully Treated Hepatitis B Positive Refractory Myasthenic Crisis with Rituximab. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine*, 24(1), 71.  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7050184/>

Tabor, E. (1987). Guillain-barré syndrome and other neurologic syndromes in hepatitis A, B and non-A, non-B. *Journal of Medical Virology*, 21(3), 207-216.  
<https://doi.org/10.1002/jmv.1890210303>

Tsukada, N., Koh, C. S., Inoue, A., & Yanagisawa, N. (1987). Demyelinating neuropathy associated with hepatitis B virus infection: Detection of immune complexes composed of hepatitis B virus surface antigen. *Journal of the Neurological Sciences*, 77(2-3), 203-216.  
[https://doi.org/10.1016/0022-510X\(87\)90123-7](https://doi.org/10.1016/0022-510X(87)90123-7)

Tsukada, N., Koh, C. S., Owa, M., & Yanagisawa, N. (1983). Chronic neuropathy associated with immune complexes of hepatitis B virus. *Journal of the Neurological Sciences*, 61(2), 193-210.  
[https://doi.org/10.1016/0022-510X\(83\)90005-9](https://doi.org/10.1016/0022-510X(83)90005-9)

Wada, Y., Yanagihara, C., Nishimura, Y., & Oka, N. (2008). Hepatitis B virus-related vasculitis manifests as severe peripheral neuropathy following influenza vaccination. *Clinical Neurology and Neurosurgery*, 110(7), 750-752.  
<https://doi.org/10.1016/j.clineuro.2008.05.006>