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The Association of Hepatitis E Virus Infection with Guillain-Barré Syndrome: A Systematic Review of Case Studies

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Abstract Over 200 recent Guillain-Barré syndrome (GBS) cases in India have raised public health concerns. Infections, notably Campylobacter jejuni and some vaccines, are known risk factors, but causes are still not fully understood. Reports link GBS with Hepatitis E virus (HEV) infection, especially since HEV is common in developing countries like India. This systematic review examines comorbidities, clinical features, and outcomes in GBS patients with HEV infection. A systematic review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, focusing on published case reports of HEV infection in patients later diagnosed with GBS. Google Scholar was used to find relevant studies, including all available full-text reports of GBS after HEV infection. Data were organized in tables and analyzed, and the review protocol was registered with the International Prospective Register of Systematic Reviews (PROSERO: CRD420251102115). After applying selection criteria, 15 case reports from 13 different countries were analyzed. Of the 15 patients (average age 44.6 years), 11 were male (73%). The primary treatment was intravenous immunoglobulin (IVIG), which resulted in complete recovery for 13 cases (87%), while 2 patients (13%) achieved only partial recovery, experiencing residual limb weakness. There were no fatalities reported. This review shows that GBS is a notable extra-hepatic complication of HEV infection. Diagnosing GBS in HEV cases requires thorough cerebrospinal fluid (CSF) analysis and nerve conduction tests. Patients with HEV should be monitored for neurological symptoms, as early detection and intervention can improve outcomes and minimize lasting neurological issues.

Keywords: *Guillain-Barré syndrome (GBS), Hepatitis E virus (HEV), Infection, Neurological signs, Nerve conduction study, Cerebrospinal fluid (CSF)*

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1. Introduction

Hepatitis caused Hepatitis E virus (HEV) is a zoonotic disease which causes acute viral hepatitis. It is the leading cause of viral hepatitis in developing countries. HEV is a single- stranded RNA virus belonging to the *Orthohepevirus* genus of the *Hepeviridae* family and measures around 27 to 34 nm in diameter. HEV is primarily spread via contaminated water and undercooked meat. Its small size and non-enveloped structure facilitate feco-oral transmission, and aids in resistance to environmental stressors such as heat and acidic conditions, thereby contributing to its pathogenicity. People infected with HEV develop both hepatic and extra hepatic manifestations making the prognosis of patients extremely challenging. Most common extra hepatic manifestations include neurological complications such as Guillain Barré syndrome (GBS) and bilateral brachial neuritis [1,2]. Here, in this systematic review, we discuss the inter-relationship between HEV being the predisposing factor for GBS.

GBS, also known as acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is a rare autoimmune disorder affecting mainly peripheral nervous system and produces neurological manifestations. GBS is of public health concern right now in various countries [3]. The aetiology of GBS is multifactorial which includes infectious triggers like *Campylobacter jejuni*, *Mycoplasma pneumoniae*, Cytomegalovirus (CMV), Epstein Barr virus (EBV) etc., and other triggers include vaccinations, surgery and trauma [4]. GBS generally has a history of starting few days after viral infections [5].

Although it was rare in the past, GBS linked to HEV infection has been on the rise in recent decades. Initial symptoms include fatigue and jaundice with elevated liver enzymes- alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Additional hepatic

manifestations of HEV infection include hepatomegaly, pale stools, dark urine, etc. Few patients also reported respiratory failure [6], myocarditis [7] muscle pain [8], peripheral neuropathy [9], and impaired superficial and deep reflexes [10] after the acute phase of HEV infection. This systematic review is carried out to elucidate potential comorbidities, presentations and outcomes of patients with HEV infections developing GBS.

2. Methods

This systematic review is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The study period extends from March 2025 to February 2026 and to locate potential papers, we searched the PubMed and Google Scholar databases. Medical Subject Headings (MeSH) keywords including "Hepatitis E virus (HEV)" infection, "Guillain-Barré syndrome (GBS)", "HEV and GBS case reports", "HEV diagnosis", "GBS diagnosis", "Guillain-Barré syndrome pathophysiology", "GBS electromyography, and nerve conduction investigations" were used throughout the literature extraction procedure (PROSERO, the International Prospective Register of Systematic Reviews registration number: CRD420251102115).

2.1. Diagnostic Criteria for Guillain–Barré Syndrome

To ensure consistency and validity in case identification, we applied established diagnostic criteria for GBS. Specifically, the Brighton Collaboration case definition was used, which provides standardized levels of diagnostic certainty based on clinical features, cerebrospinal fluid (CSF) analysis, and electrophysiological findings.

The core clinical criteria included:

a. Acute onset of bilateral and relatively symmetric limb weakness.
b. Decreased or absent deep tendon reflexes in affected limbs.
c. Monophasic illness pattern with progression over ≤ 4 weeks.

Supportive criteria included:

d. CSF findings of albuminocytologic dissociation (elevated protein with normal cell count).
e. Electrophysiological evidence of demyelination or axonal neuropathy.

Cases were classified according to Brighton levels of diagnostic certainty (Level 1–4), with Level 1 representing the highest diagnostic confidence. Where studies did not explicitly reference Brighton criteria, we assessed whether reported diagnostic features aligned with these standards.

By clearly defining and applying standardized diagnostic criteria, this review minimizes heterogeneity in case ascertainment and strengthens the reliability of conclusions regarding the association between HEV and GBS [11,12].

2.2. Inclusion Criteria

This investigation includes English-language literature, case reports of patients of all ages, patients with a positive HEV infection, and patients with a GBS diagnosis.

2.3. Exclusion Criteria

The study excluded comprehensive reviews and meta-analyses, intervention studies such as randomized and clinical control trials, GBS cases resulting from other etiologies, duplicate case reports, and articles without full text access.

Patient demographics (age, sex, and country), the interval between the onset of HEV infection symptoms and GBS-like symptoms, neurological and non-neurological comorbidities, the methods used for GBS diagnosis, treatment, and management, and patient outcomes were all carefully recorded with reference to each case study that was part of the systematic review.

2.4. Assessment of Study Quality and Risk of Bias

To strengthen the validity of this review, we systematically assessed the methodological quality and risk of bias of all included studies. Two reviewers independently performed the assessments, with disagreements resolved by consensus. (Figure 1)

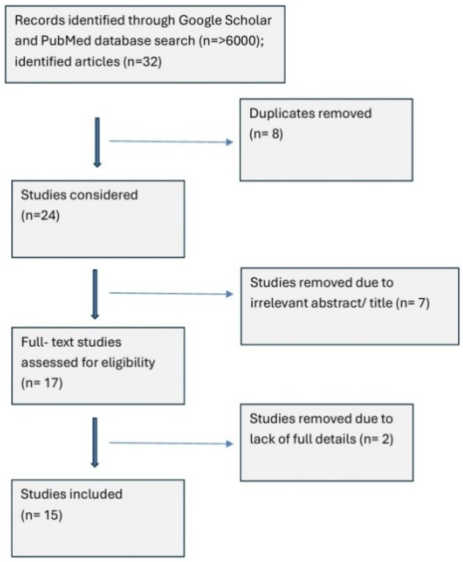


Figure 1. PRISMA Flow Diagram Illustrating the Study Selection Process

3. Results

HEV-related GBS was found in 32 research articles; 8 duplicates were removed, and 24 papers were reviewed, 17 of which were full-text articles. According to the exclusion criteria, two items were still deemed unsuitable. 15 case reports were therefore included in the study.

We included 15 reports from 13 different nations out of 32 articles. The patients' average age was 44.6 years. Of them, four (26.6%) were women and eleven (73.3%) were men. After receiving intravenous immunoglobulin (IVIG) treatment, 13 of them healed completely, while 2 only partially recovered with limb weakness. (Table 1)

Table 1. Overview of patient demographics, clinical presentation, laboratory findings, and outcomes

Country, year, Reference	Age/Sex	Time between HEV infection and development of neurological symptoms	Neurological presentation	Non-neurological Presentation	Biochemical findings	Diagnosis	Treatment	Patient outcome
China, 2024[13]	14, Female	Did not specify	Acute upper-limb weakness that quickly developed to tetraplegia, rendering her unable to stand without help. She was initially diagnosed with acute myelitis, with muscular strength rated as MRC 2 in both lower limbs and the left upper limb, and MRC 3 in the right upper limb. Deep tendon reflexes were diminished, plantar and lower limb reflexes were absent, and pain sensitivity was elevated to the groin on both sides.	Abdominal pain, stool and urinary retention	Elevated liver enzymes- ALT levels of 205 U/L and AST levels of 60 U/L. CSF examination revealed normal intracranial pressure, elevated WBC count (20*10^6/L), and an elevated protein level 780 mg/L. CSF analysis indicated a normal albumin level (536 mg/L), normal IgG level (75.2 mg/L), and a normal CSF-to-serum albumin ratio 12.3	Neurological conduction studies revealed peripheral neuropathy. CSF analysis showed protein cytological dissociation, with an increased protein level of 1317.5 mg/L and a normal cell count of 4 cells/mm3	IVIG administered at a dose of 0.4 g/kg/day and continued for 5 days. Rituximab infusion at a dose of 100 mg, with one-week intervals for two times.	Recovered; regained full strength (5/5) in all muscle groups in the upper extremities and had a strength of 3/5 in the lower extremities. As liver function continued to improve, her neurological condition is stable. She experienced progressive improvement in muscle strength in all limbs and was able to briefly stand with assistance.
Sudan, 2023[14]	33, Male	8 days	Patients had ascending paraesthesia that reached the elbows and knees, as well as gait problems. Lower limb weakness followed by numbness and tingling in both hands and feet, slight paralysis of the lower limbs The Medical Research Council (MRC) Scale for Muscle Strength 5/5 at upper limbs and 1/5 at lower limbs, reduced sensation, generalized reflex absence, and downward-directed plantar reflexes.	Cough, mild jaundice, and dark coloured urine	The liver function test (LFT) showed increased aspartate aminotransferase (AST) 290 U/L, alanine aminotransferase (ALT) 466 U/L, total bilirubin (TB) 3.3 mg/dL, and direct bilirubin (DB) 1.3 mg/dL.	1. Serology for HEV-IgM- positive, 2. Cerebrospinal fluid (CSF) analysis showed absence of monocytes, glucose was 4.6 mmol/L, and protein level was 275.3 mg/dL, which likely suggested albuminocytologic dissociation. 3. nerve conduction study (NCS) indicated demyelinating neuropathy affecting both motor and sensory fibers.	Patient was treated with intravenous immunoglobulin (IVIG) at a dose of 0.4 mg/kg per day for five days.	Recovered; patient's clinical condition and muscle power improved gradually, and the patient had no complaints of respiratory distress or malaise. Repeat CSF examination 2 weeks after admission revealed 10/μL monocyte and 85.7 mg/dL protein level.
Portugal, 2023[15]	72, Male	Did not specify	Symmetrical numbness and weakness in both lower extremities. Relatively symmetric paraparesis with grade 4/5 strength in the lower limbs and decreased sensation in the stocking-glove distribution. Quadriparesis, hyporeflexia, swallowing problems, and shortness of breath worsen.	The patient's past medical history was relevant for hypertension, type 2 diabetes mellitus.	Laboratory tests showed elevated liver enzymes, and positive serology for HEV with a high viral load	Abdominal ultrasound showed slightly increased echogenicity, suggestive of steatohepatitis 1. Positive serology for HEV with a high viral load 2. A lumbar puncture was performed, showing albuminocytologic dissociation with increased proteins and a	The patient received a five-day course of IVIG 0.4 g/kg per day	Partially recovered at the time of discharge; The patient-maintained areflexia with mild residual weakness in the proximal muscles of the lower and upper limbs. He was referred to a rehabilitation clinic for further recovery.

						normal cell count. 3. Electromyography showed decreased conduction velocities suggestive of generalized demyelinating polyneuropathy		
India, 2019[16]	30, Male	15 days	Bilateral lower-limb weakness. Neurological examination revealed that there was generalized areflexia and diminished power (MRC 3/5) in both lower limbs.	High grade intermittent fever (102°F) for 15 days was followed by jaundice, shortness of breath, icterus, and pedal oedema.	All serological markers were negative except HEV IgM antibody,	1. NCS revealed changes in nerve conduction velocity associated with pure motor axonal neuropathy of the lower limbs. 2. CSF examination revealed increased proteins (243 mg/dL (normal range: 15-45 mg/dL)) and normal cell count (total leukocyte count, < 5 cells/mL), indicating albuminocytologic dissociation.	1. Sofosbuvir 400 mg orally once-a-day for one month, and Ribavirin 200 mg orally twice-a-day for one month 2. Supportive measures, such as administration of intravenous fluids and nutritional therapy, were used for management of GBS.	Recovered: Four weeks following treatment, neurological power was completely restored. The patient's blood samples also tested negative for HEV IgM antibody and HEV RNA.
Iran, 2019[17]	30, Male	12 days	Muscle paralysis ascending from the legs to hands.	Ten days before to the commencement of icterus, the patient had lethargy, weakness, dark urine, nausea, fever, chills, and flu-like symptoms. The initial blood test revealed elevated C-reactive protein (CRP), hyperbilirubinemia, and liver function enzyme values.	Acute elevation of liver function tests AST 1062 UI/L, ALT 1813 UI/L, γ-GT 90 UI/L. ALP and serum bilirubin and were normal	Acute motor axonal neuropathy (AMAN) subtype of GBS was confirmed based on NCV findings	Five sessions of plasmapheresis sessions	Recovered; A complete recovery of neurological function and muscle strength. At a two-month follow-up, laboratory investigations demonstrated normal values for INR, aPTT, PT, ALP, ALT, AST, as well as TB and DB
China; 2018[18]	58, Male	11 days	Progressive weakening in the lower limbs, followed by numbness and altered pinprick sensation on the plantar surfaces, resulted in the inability to walk. This was followed by quickly deteriorating, symmetrical weakness in both the lower and upper limbs. He also described paraesthesia and	General fatigue, anorexia, cough, mild jaundice, and tea-coloured urine. Drooping of left eyelid, flat nasolabial fold, and incomplete eyelid closure on the right side was seen on physical	Elevated liver enzyme levels of AST 273 U/L, ALT 664 U/L, total bilirubin 51.8 μmol/L, and conjugated bilirubin 20.5 μmol/L.	1. Serological study was positive for IgM and IgG antibodies for HEV, 2. CSF examination showed absence of monocytes, 4.6 mmol/L glucose level, and 275.3 mg/dL protein level, which suggested albuminocytologic dissociation. 3. NCV studies showed evidence	He was treated with IVIG at a dose of 0.4 mg/kg per day for five days. methylprednisolone was used to suppress inflammatory responses. Glycyrrhizin, glutathione, and ademetionine were	Recovered; The patient's clinical status and muscle power improved steadily, and no complaints of respiratory distress or malaise. A month later, his liver function significantly improved. Six months later, serological study showed that IgM anti-HEV

			widespread asthenia. A cranial nerve evaluation revealed unilateral facial nerve palsy. Romberg's sign was affirmative, and so was the straight-leg raising test. Motor examination revealed weakness in all four limbs, with MRC 4/5 in the upper and 2/5 in the lower limbs. Muscle weakness persisted, with power in the upper extremities assessed at 2/5 in proximal muscles and 4/5 in distal muscles.	examination.		of demyelinating neuropathy with dysfunction of motor and sensory nerve fibres.	simultaneously administered for liver therapy.	antibodies were negative, which suggested full recovery from the acute hepatitis E. The patient continued to experience weakness in his right arm.
Iraq, 2018[19]	19, Female	3-4 days	Bilateral lower limb weakness in the absence of sensory engagement. Her legs were progressively weaker, followed by the start of minor upper-limb weakness.	Fever associated with nausea, decreased appetite, diarrhoea, and conjunctival icterus. Tender hepatomegaly was noted during abdominal examination.	LFT showed elevated TB level 2.8 mg/dL, ALT 829 U/L, AST 471 U/L. normal serum ceruloplasmin level. PT = 16 s, aPTT = 41 s. Reduced serum albumin level of 2.2 g/dL	1. Elevated levels of both anti-HEV IgM and anti-HEV IgG, 2. Initial NCS showed evidence of axonal motor neuropathy of symmetrical distribution affecting the lower limbs more than the upper limbs with normal sensory NCS parameters	The patient has been given no specific treatment except for close observation and supportive measures.	Recovered; Full recovery of motor neurophysiological parameters after 35 days
United Kingdom, 2017[20]	59, Male	3 days	Blurred vision in the left eye, slight distal weakness in the left leg, and mild disorientation. A neurological examination indicated a Glasgow Coma Scale of 15, impaired visual acuity in the left eye to finger counting, and partial left ptosis. Mild left-side hemiparesis (MRC 4), neck pain, developing occipital headache, slurred speech, and decreased vision in the left eye. The pupillary light reflex on the left was reduced. The power in the left lower limb was reduced to 3/5. Reflexes were brisk on the left, with flexor plantars bilaterally, a left relative afferent pupillary deficiency, nystagmus in all directions of gaze, left sixth	Fever (39°C) associated with blurring of vision in left eye, subtle distal weakness in left leg and mild confusion	Raised ALT (132 U/L)	NCS revealed severe peripheral nerve involvement with profound axonal loss in both motor and sensory nerves, which is consistent with acute motor and sensory axonal neuropathy. CSF examination revealed raised red blood cells (18X106/L). TLC (20X106/L), protein (1.6 g/L), and glucose (8.9 mmol/L)	IVIG in a dose of 0.4 g/kg/day for 5 days	Recovered; Three months later, the patient was spotted walking with a frame, and his overall condition had improved significantly.

			nerve palsy progressing to muscle weakness and antigravity in the left leg, and MRC 4 in all other limbs. There was a left upper limb intention tremor associated with a left extensor plantar.					
Korea, 2016[21]	58, Male	79 days	Weakness of the lower limb he was bedridden, unable to move against gravity	The symptoms included jaundice, pruritus, and anorexia. His physical examination revealed jaundice, pain in the right upper quadrant, and an enlarged liver. A liver biopsy using aspartate aminotransferase revealed that the periportal region was home to an accumulation of lymphocyte-dominant inflammatory cells. No fatty alteration was present. Hepatocyte swelling and localized apoptosis were observed. There was periportal fibrosis and bridge necrosis.	TB >35.0 mg/dL, AST level of 292 IU/L, and ALT level of 525 IU/L.	Immunoassay for IgM anti-HEV and IgG anti-HEV were both positive NCS showed findings compatible with GBS	IVIG 30 g/day was administered for 5 days	Recovered; Significantly improved neurologic symptoms were seen during the follow-up period and IgM anti-HEV converted negative on 12 months after admission.
India, 2015[22]	43, Female	14 days	Acute ascending weakness that first affects the lower limbs and then progresses to the upper. This was followed by trouble swallowing solids and drinks. Progressive hoarseness of voice, trouble breathing, and inability to close the eyes. A neurological examination revealed lower motor neuron palsy in the bilateral seventh, ninth, and tenth cranial	Fever, yellowish discoloration of urine, loss of appetite, nausea and icterus. Her single breath counts progressively declined, abdominal examination revealed soft and tender hepatomegaly.	LFT revealed AST 1080 U/L, ALT 1950 U/L, Alkaline phosphatase (ALP) 350 U/L, TB 5 mg/dL, conjugated bilirubin 3 mg/dL, normal hemogram, Serology for Campylobacter, varicella-zoster virus, and Cytomegalo virus (CMV) was negative. Normal prothrombin time (PT) and activated partial thrombin (aPTT). Anti-ganglioside antibody (GM1) returned positive	1. Anti-HEV IgM-positive, anti-HEV IgG-negative 2. CSF study showed albuminocytological dissociation with albumin being 350 mg/dL and total protein 450 mg/dL. Total Leukocyte count of 12/mm^3, glucose level of 65 mg/dL, and Adenosine Deaminase (ADA) of 1.2 U/L. 3. NCS testing	IVIG was administered at a rate of 0.4 gm/kg/day for five days. Rehabilitation programme-initiated side by side	Recovered; Patient showed gradual signs of improvement with supportive therapy and patient was taken off the ventilator after seven days. patient managed to stand independently and walk with support.

			nerves, as well as quadriparesis. All four limbs were flaccid and areflexic, with MRC 4/5 in the upper and 2/5 in the lower limbs. There were no superficial reflexes on either side, including plantar responses.			revealed features of both demyelination and axonal neuropathy.		
Japan, 2015[23]	49, Male	14 days	Bilateral numbness in the upper and lower extremities, followed by quickly worsening leg weakness, trouble walking, and dysgeusia (loss of taste perception) There was distal predominance of motor weakness in both the upper and lower extremities. Hypoesthesia with a glove-and-stocking distribution was revealed by sensory testing. All limbs lacked the deep tendon reflexes.	Low back pain, abdominal discomfort and general fatigue	Elevated levels of TB (0.9 mg/dL); AST (275 U/L); ALT (1,246 U/L); alkaline phosphatase (ALP) (472 U/L); and gamma-glutamyl transpeptidase (γ-GTP) (744 U/L)	A Temporal dispersion was observed in the peroneal nerve. The F-wave latency was prolonged in the median nerve, while F-waves were absent in both the ulnar and peroneal nerves. No sensory nerve action potentials were evoked in the median nerve.	IVIG treatment 0.4g/kg per day was administered for five days	Recovered; After two weeks, the patient could walk, and two months later, their taste and muscle strength had improved. Three months later, the blood test revealed negative serology and normal ALT and AST.
Portugal, 2012[24]	58, Male	17 days	The patient experienced rapid ascending muscle weakness and sensitivity loss, as well as hypoventilation, decreased reflex cough and hoarseness, tetra paresis, and areflexia. He also showed autonomic instability, including bradycardia and hypertension.	Symptoms included nausea, vomiting, stomach discomfort in the right upper quadrant, jaundice, tenderness in the right upper quadrant, and an enlarged.	Serological screening to detect hepatitis viruses was negative for all except HEV, which was positive for anti-HEV IgM but negative for anti-HEV IgG, indicating an acute infection with HEV.	Electromyography nerve conduction investigations in the upper and lower limbs revealed a severe acquired demyelinating sensory and motor polyneuropathy.	The patient received IVIG (0.4g per kg body weight per day for five days) and ceftriaxone (4g/day for ten days), along with breathing support and sedation. Tracheostomy was performed.	Recovered; After two months of rehabilitation, he was able to walk with help.
France, 2011[25]	60, Female	Did not specify	Lower limb weakness and complete loss of deep-tendon reflexes but no paraesthesia.	Severe generalized physical weakness, Jaundice.	Liver function tests showed elevated serum TB 35 µmol/L and elevated ALT 384 IU/L. glucose 6.2 mmol/L	1. Anti-HEV IgM and IgG were detected in the serum. HEV RNA was also detected in serum and fecal samples, confirming a diagnosis of acute HEV 2. CSF protein was 2g/L, leukocyte count 14 × 109 cells/L The patient's clinical and laboratory findings are best explained by acute inflammatory demyelinating polyneuropathy (Guillain-	She was given IVIG at 0.4 g/kg per day for five days	Partially recovered; Neurological condition improved with persistence of residual weakness in lower limbs and liver enzyme levels progressively returned to reference limits within 4 weeks. HEV RNA became undetecTable 1 month after initial examination.

						Barré syndrome)		
Belgium, 2009[26]	66, Male	Few days; Did not specify	Weakness in both legs, associated with paraesthesia of the lower limbs, mainly in the evenings. He developed ataxia and neuropathic pain few days later. Neurological assessment revealed gait and stance ataxia with a positive Romberg's sign and distal hypoallaesthesia. Symmetrical diminished reflexes in the upper limbs and areflexia in the lower limbs with severe proximal weakness.	Patient was completely asymptomatic at presentation.	LFT revealed elevation of AST 1062 UI/L, ALT 1813 UI/L, and γ-GT 90 UI/L.	Serum antiganglioside antibodies GM2 IgM and IgG were positive, with negative IgM, for EBV, adenovirus and herpesvirus. 1. Positive serology for IgM antibodies against HEV 2. CSF examination showed markedly increased protein levels of 1722 mg/L, with increased IgG and without an increased number of leucocytes. 3. Electrophysiological examinations of the lower limbs were consistent with acute demyelinating polyradiculoneuropathy	IVIG were given at a dose of 0.4 g/kg per day for five days.	Recovered; Patient's overall condition improved markedly, with progressive neurological recovery characterized by increased walking ability and reduction in neuropathic pain. Liver enzyme levels returned to normal, and at four months of follow-up, he demonstrated near-complete neurological recovery.
Bangladesh, 2006[27]	20, Male	10 days	Weakness in the lower limbs, which spread to the upper limbs over the next two days, was coupled with difficulty swallowing foods and drinks, as well as respiratory discomfort. The neurological examination revealed bilateral lower motor neuron facial palsy and dysphagia. Muscle strength was reduced to 2/5 in all four limbs, along with decreased tone. Deep tendon and superficial reflexes were absent, and plantar responses were inconclusive.	Low grade fever, anorexia, nausea, vomiting, dyspnoea and Jaundice-yellowish discoloration of skin, sclera and urine. Systemic examination revealed mild tenderness in right hypochondrium and soft enlarged tender liver about 2 cm from the right costal margin.	Laboratory evaluation revealed leucocytosis with a total WBC count of 18,700/mm3, comprising 12% lymphocytes, 2% monocytes, and 1% eosinophils. Liver function tests showed elevated bilirubin (3.6 mg/dL), ALT (2509 U/L), AST (290 U/L), and ALP (580 U/L). Renal function, electrolytes, and coagulation profile were within normal limits.	1. Anti HEV IgM was positive 2. Ultrasonography revealed hepatomegaly suggestive of acute hepatitis 3. NCS studies revealed both demyelinating and neuropathic sensory motor polyneuropathy. 4. CSF analysis revealed an albumin level of 190 mg/dL with no detectable cells, findings consistent with albuminocytologic dissociation	Patient was advised for immunomodulation by either IVIG or plasmapheresis but did not receive either due to financial constraints.	Recovered; his muscle power showed significant improvement within one week of admission and reached 4/5 at lower limbs and 3/5 at upper limbs by two weeks of admission. Patient was successfully extubated seven days after admission.

HEV-Hepatitis E Virus, GBS-Guillain-Barré Syndrome, MRC-Medical Research Council, ALT – Alanine Aminotransferase, AST-Aspartate Aminotransferase, CSF-Cerebrospinal Fluid, IgG-Immunoglobulin G, IgM-Immunoglobulin M, IVIG-Intravenous Immunoglobulin, TB-Total Bilirubin, DB-Direct Bilirubin, LFT-Liver Function Test, NCS-Nerve Conduction Study, NCV-Nerve Conduction Velocity, AMAN-Acute Motor Axonal Neuropathy, γ-GT-Gamma-Glutamyl Transferase, ALP-Alkaline Phosphatase, INR-International Normalized Ratio, PT-Prothrombin Time, aPTT-Activated Partial Thromboplastin Time, TLC-Total Leukocyte Count, ADA-Adenosine Deaminase, GM1-Monosialotetrahexosylganglioside, GM2-Disialotetrahexosylganglioside, GD1a-Disialotetrahexosylganglioside (variant), GQ1b-Tetrasialotetrahexosylganglioside

4. Discussion

4.1. Patient Demographics and Recovery Outcomes

This descriptive systematic review identified 15 cases of GBS associated with HEV infection, reported from 13 diverse countries, underscoring the global nature of this clinical phenomenon[1–3]. The mean age of the cohort was 44.6 years, with a predominance of male patients (11 males, 73.3%; 4 females, 26.6%), reflecting trends observed in previous epidemiological studies of HEV-associated neurological complications. Recovery outcomes were generally favourable: 13 patients (86.6%) achieved full recovery after treatment, while 2 patients (13.3%) experienced partial recovery and continued to suffer from residual muscle weakness, consistent with the variable prognosis seen in GBS irrespective of the underlying trigger. HEV was implicated as a precipitating factor for GBS, with the interval between HEV infection and onset of neurological symptoms ranging from as short as 2 days to as long as 79 days (mean 17±20 days), highlighting the unpredictable latency period and suggesting the need for vigilance in patients with recent viral hepatitis[1]. Diagnostic confirmation relied heavily on CSF analysis, which typically demonstrated albuminocytologic dissociation, and nerve conduction studies (NCS), both of which are regarded as critical investigations for accurate diagnosis of GBS in the context of HEV infection. Therapeutically, IVIG was the principal intervention and remains the cornerstone of GBS management, with high rates of success documented in HEV-associated cases. Nevertheless, a minority of patients may experience incomplete recovery, with persistent weakness or neurological deficits, which mirrors findings in other aetiologies of GBS. Importantly, the association between HEV and GBS has been described across multiple HEV genotypes and geographic regions, further emphasising its significance in global clinical practice and the necessity for multidisciplinary approaches to both diagnosis and management [28,29,30,31].

4.2. Neurological and Systemic Presentations

The neurological manifestations of HEV-associated GBS are diverse, with ascending symmetrical weakness being the most prominent clinical feature. Patients frequently reported paraesthesia affecting the distal extremities, which typically progressed proximally, often accompanied by generalised areflexia. Cranial nerve involvement was not uncommon, with bilateral lower motor neuron facial palsy and dysphagia being observed in several cases. Quadriparesis, ranging from mild to profound muscle weakness, was a hallmark of more severe presentations. Respiratory compromise, attributed to diaphragmatic or intercostal muscle involvement, occasionally necessitated mechanical ventilation, particularly in cases with bulbar symptoms or rapid disease progression.

Neurophysiological investigations, especially NCS, revealed a spectrum of findings. The most common pattern was demyelinating polyneuropathy, consistent with the acute inflammatory demyelinating polyneuropathy (AIDP) subtype of GBS. However, some individuals exhibited axonal motor neuropathy or mixed central and peripheral demyelination, highlighting the heterogeneity of the neurological involvement in HEV-associated GBS. Systemic symptoms often paralleled the neurological decline. Commonly reported features included low-grade fever, anorexia, nausea, vomiting, pruritus, and abdominal discomfort. In rare instances, patients developed severe complications such as myocarditis or acute respiratory failure, underscoring the potential for multi-organ involvement in HEV infection. Hepatic manifestations were also prominent and included clinical features such as jaundice, hepatomegaly, dark-coloured urine, and biochemical evidence of hepatic dysfunction, with elevated liver enzymes (ALT, AST, and bilirubin) documented in most cases. These findings reinforce the importance of a multidisciplinary approach to diagnosis and management, as both neurological and hepatic systems may be simultaneously affected in HEV-associated GBS [32].

4.3. Diagnostic Methods

The diagnosis of HEV-associated GBS relies on a combination of serological, CSF, and neurophysiological investigations to confirm both the infectious and neurological components of the disease. Serological testing typically involves enzyme immunoassays for the detection of anti-HEV IgM and IgG antibodies, which serve as markers for acute and past infection, respectively. In cases where additional confirmation is required, molecular techniques such as polymerase chain reaction (PCR) are employed to identify HEV RNA in serum or stool samples, thereby establishing an active viral infection and increasing diagnostic specificity.

CSF analysis is a cornerstone in the diagnosis of GBS, with the most consistent finding being albuminocytologic dissociation, characterised by elevated protein concentrations in the absence of significant pleocytosis (increased cell count). This hallmark pattern supports the diagnosis of GBS in the appropriate clinical context. Neurophysiological studies, particularly NCS, are indispensable for further characterising the subtype of GBS. The majority of HEV-associated GBS cases

demonstrate evidence of demyelinating polyneuropathy, though axonal neuropathy or mixed demyelinating and axonal features may also be observed. Collectively, these diagnostic modalities enable clinicians to differentiate HEV-associated GBS from other causes of acute flaccid paralysis and guide appropriate management strategies [28,33,34].

4.4. Treatment and Management Strategies

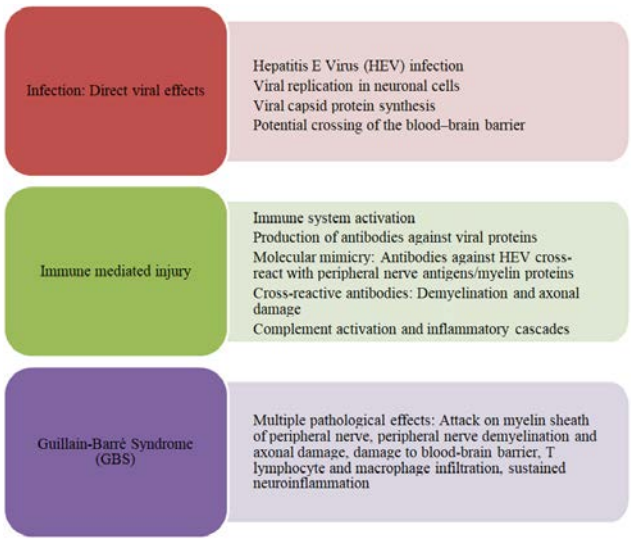
The management of patients with HEV-associated GBS was multidisciplinary, focusing on both neurological and hepatic aspects of the disease. IVIG therapy represented the cornerstone of neurological intervention, with the standard regimen consisting of an infusion at a dose of 0.4 g/kg/day over five consecutive days. This approach was associated with favourable outcomes, including significant improvement in muscle strength and functional recovery in most cases. In instances where IVIG was not feasible due to financial or logistical constraints, plasmapheresis was considered as an alternative immunomodulatory therapy, although its use was less common in the reviewed cohort. Supportive care played a crucial role in the overall management strategy. Mechanical ventilation was initiated for patients experiencing respiratory compromise, often necessitated by bulbar involvement or ascending paralysis. In addition, comprehensive rehabilitation programmes, including physiotherapy, occupational therapy, and nutritional support, were implemented to facilitate neuromuscular recovery and prevent complications such as contractures or malnutrition. Hepatic management was tailored to the severity of liver involvement. Patients presenting with acute hepatitis manifestations, such as jaundice and hepatomegaly, were closely monitored and managed with hepatoprotective agents. In select cases, corticosteroids and antiviral medications were administered to mitigate hepatic inflammation and reduce viral replication, respectively. The integration of hepatic and neurological interventions, combined with vigilant supportive care, was instrumental in achieving optimal recovery and minimising the risk of long-term sequelae [34].

4.5. Geographical and Genotype Variations

Analysis of patient outcomes in HEV-associated GBS reveals notable geographical and genotype-specific variations. In Asian regions such as India, China, Korea, Japan, Iraq, Iran, and Bangladesh, genotype 1 HEV appears to predominate, frequently presenting with severe hepatic manifestations alongside neurological symptoms. These patients typically exhibited pronounced jaundice, hepatomegaly, and elevated liver enzyme levels, with recovery outcomes often dependent on the prompt initiation of IVIG therapy. Notably, full recovery was observed in several cases, although the presence of severe hepatic involvement occasionally contributed to residual neurological deficits or prolonged convalescence [35]. In African cohorts, exemplified by cases reported in Sudan, patients with HEV infection predominantly developed acute demyelinating neuropathy. The administration of IVIG was associated with favourable clinical outcomes, leading to complete neurological recovery in most instances. This suggests that regional differences in HEV genotype and healthcare access may influence both the severity of GBS presentations and the likelihood of optimal recovery.

In contrast, European cases, particularly those from France, Belgium, Portugal, and the United Kingdom, were often linked to genotype 3 HEV infection. These patients tended to be older and frequently presented with a broader spectrum of recovery outcomes, ranging from full resolution of symptoms to persistent weakness or partial recovery. The variability in prognosis may reflect differences in host factors, underlying comorbidities, and genotype-specific pathogenic mechanisms. Furthermore, genotype 3 has been associated with less severe hepatic involvement but a higher propensity for neurological sequelae in elderly populations [36]. Collectively, these findings underscore the importance of considering both geographical origin and HEV genotype when assessing clinical presentation, management strategies, and recovery outcomes in HEV-associated GBS. Further multicentre studies are warranted to clarify the mechanisms underlying these regional and genotype-related disparities and to inform tailored therapeutic approaches.

4.6. Pathophysiological Mechanisms



HEV: Hepatitis E virus; GBS: Guillain barre syndrome; BBB: Blood brain barrier; CNS: Central nervous system

Figure 2. Proposed pathway by which HEV may precipitate GBS

The interplay between HEV infection and GBS illustrates a complex pathogenic mechanism that warrants deeper clinical attention. Evidence suggests HEV may exert direct neurotropic effects, replicating within neuronal cells and potentially breaching the blood–brain barrier. More prominently, immune-mediated pathways drive neurological injury: molecular mimicry between HEV antigens and host neural structures induces cross-reactive antibodies, leading to demyelination and axonal damage characteristic of GBS. Complement activation and inflammatory cascades amplify this process, while T lymphocytes and macrophages contribute to sustained neuroinflammation. These findings highlight that HEV-associated GBS is not a singular phenomenon but rather the result of converging viral replication, antibody cross-reactivity, and immune dysregulation. Recognizing this

multifactorial pathogenesis is essential for refining diagnostic strategies, guiding therapeutic interventions, and prioritizing genotype-specific research. Ultimately, integrating HEV into broader discussions of post-infectious neuropathies underscores the importance of vigilance in identifying emerging viral triggers of GBS within global neurology and infectious disease frameworks [31,37,38,39,40]. (Figure 2)

5. Diverse Microbial Etiologies Potentially Causing GBS

GBS is the most common cause of acute neuromuscular paralysis worldwide and is frequently postinfectious in origin. Approximately two-thirds of patients report a preceding respiratory or gastrointestinal illness. *Campylobacter jejuni* is the most strongly associated pathogen, with an estimated incidence of one GBS case per 1000 infections. The mechanism involves molecular mimicry, whereby bacterial lipo-oligosaccharides resemble host gangliosides including monosialotetrahexosylganglioside (GM1), disialotetrahexosylganglioside (GD1a), tetrasialotetrahexosylganglioside (GQ1b), leading to cross-reactive antibodies that damage peripheral nerves. Other infectious agents implicated include CMV, EBV, HEV, Influenza A virus (IAV), *Mycoplasma pneumoniae*, *Haemophilus influenzae*, and Zika virus. In particular, *Mycoplasma pneumoniae* infection has been linked to anti-galactocerebroside IgG antibodies, especially in pediatric cases. Viral outbreaks, such as Zika epidemics, have been associated with sharp increases in GBS incidence, underscoring the role of emerging pathogens. The clinical presentation typically involves rapidly progressive symmetrical weakness, areflexia, and potential respiratory compromise. These findings highlight the importance of infection-related immune responses in the pathogenesis of GBS and the need for vigilance during outbreaks of implicated pathogens. Understanding the etiological spectrum of infection-related GBS is critical for timely diagnosis, appropriate management, and the development of preventive strategies [41,42,43,44,45,46,47,48]. (Table 2)

Table 2. Infection-related GBS causing pathogens, mechanisms, neurological associations, biomarkers, treatment strategies, and prognosis

Pathogen / trigger microbe	Mechanism	Relative risk	Associated neurological disorders	Key biomarkers	Treatment and management strategies	Prognosis and recovery outcomes
Bacteria-*Campylobacter jejuni*	Molecular mimicry with gangliosides (GM1, GD1a, GQ1b) → cross-reactive antibodies	~1 in 1000 infections lead to GBS	GBS (AMAN, AIDP variants)	Anti-GM1, Anti-GD1a antibodies	IVIG, plasma exchange, supportive care	Mortality ~5%; 20–30% long-term disability
Virus-Cytomegalovirus (CMV)	Induction of anti-ganglioside antibodies; immune-mediated nerve damage	10–15% of GBS cases in some cohorts	GBS, Miller Fisher Syndrome (MFS)	Anti-GM2 antibodies	IVIG, plasma exchange, antivirals (rare)	Mortality ~3–5%; residual weakness common
Virus-Epstein–Barr virus (EBV)	Immune activation, cross-reactivity with peripheral nerve antigens	Less frequent, but documented	GBS, Bickerstaff brainstem encephalitis (BBE)	Anti-GQ1b antibodies	IVIG, plasma exchange, supportive care	Mortality ~3–4%; recovery usually good
Virus-Hepatitis E virus (HEV)	Postinfectious immune response	Sporadic outbreaks linked to GBS	GBS	No specific biomarker identified	IVIG, plasma exchange, liver support if needed	Mortality ~4–5%; recovery variable
Virus-Influenza A virus	Immune dysregulation post-infection or vaccination	Rare, but observed during epidemics	GBS, post-vaccination neuropathies	Elevated neurofilament light chain (NfL)	IVIG, plasma exchange, respiratory support	Mortality ~5%; 15–20% residual deficits
Bacteria-*Mycoplasma pneumoniae*	Anti-galactocerebroside IgG antibodies, esp. in children	Pediatric cases more common	GBS, acute neuropathies	Anti-Gal-C antibodies	IVIG, plasma exchange, antibiotics for infection	Mortality <5%; recovery generally favorable
Bacteria-*Haemophilus influenzae*	Possible mimicry with nerve glycolipids	Rare trigger	GBS	No specific biomarker identified	IVIG, plasma exchange	Mortality ~3–4%; most recover fully
Virus-Zika virus	Strong outbreak association; immune cross-reactivity with neural antigens	Significant rise in GBS incidence during epidemics	GBS, MFS, overlap syndromes	Anti-GQ1b antibodies	IVIG, plasma exchange, outbreak surveillance	Mortality ~5–6%; higher disability rates
Virus-SARS-CoV-2 (COVID-19) vaccines	Rare post-vaccination immune response	~5–6 excess cases per million doses	GBS, rare neuropathies	Elevated NfL, peripherin	IVIG, plasma exchange, supportive care	Mortality ~2–3%; recovery usually good

GBS-Guillain-Barré Syndrome, AMAN-Acute Motor Axonal Neuropathy, AIDP-Acute Inflammatory Demyelinating Polyradiculoneuropathy, CMV-Cytomegalovirus, MFS-Miller Fisher Syndrome, GM1-Monosialotetrahexosylganglioside, GM2-Disialotetrahexosylganglioside, GD1a-Disialotetrahexosylganglioside, GQ1b-Tetrasialotetrahexosylganglioside, EBV-Epstein–Barr Virus, BBE-Bickerstaff Brainstem Encephalitis, HEV-Hepatitis E Virus, IAV-Influenza A Virus, NfL-Neurofilament Light Chain, IgG – Immunoglobulin G, IgM-Immunoglobulin M, Gal-C-Galactocerebroside, IVIG-Intravenous Immunoglobulin, SARS-CoV-2-Severe Acute Respiratory Syndrome Coronavirus 2, CNS-Central Nervous System, BBB-Blood–Brain Barrier

Study Limitations

This review has several limitations that should be acknowledged. First, the search strategy may not have been exhaustive, as it relied on a limited number of databases and may have missed relevant studies published elsewhere. Second, the inclusion and exclusion criteria were not always applied with the rigor expected in systematic reviews, which raises the possibility of selection bias. Third, the heterogeneity of the included studies, spanning different populations, diagnostic methods, and reporting standards, limits the ability to synthesize findings into a unified conclusion. Fourth, quality assessment of the included studies was not consistently performed using validated tools, making it difficult to evaluate the strength of the evidence. Fifth, the review is descriptive rather than quantitative; no meta-analysis was conducted, which restricts the ability to estimate pooled effect sizes or assess statistical significance. Finally, the review is context-specific and may not reflect broader epidemiological patterns across different regions or healthcare systems. These limitations mean that the findings should be interpreted cautiously and viewed as preliminary rather than definitive.

Future Recommendations

Future studies should adopt more rigorous and standardized methodologies to strengthen the evidence base on the association between HEV infection and GBS. Large, multicenter, prospective studies are needed to establish causality and to better define the epidemiological burden across different regions. Researchers should employ comprehensive diagnostic protocols, including molecular assays and serological confirmation, to ensure accurate case identification. Comparative studies examining HEV-associated GBS versus GBS triggered by other viral infections would help clarify unique clinical features and outcomes. In addition, systematic reviews in this area should follow exhaustive database searches, and formal risk-of-bias assessments. Finally, future work should explore therapeutic responses and long-term neurological outcomes in HEV-associated GBS patients, which could inform clinical management and public health strategies.

6. Conclusion

In summary, the evidence presented substantiates HEV as a significant infectious trigger for GBS, with clinical onset typically occurring within days to weeks of acute infection. The syndrome most frequently manifests as ascending weakness, areflexia, and cranial nerve involvement, often accompanied by hepatic dysfunction such as jaundice and raised liver enzymes. Diagnosis is supported by HEV serology and RNA detection, with CSF analysis demonstrating albuminocytologic dissociation and nerve conduction studies confirming demyelinating or axonal neuropathy. IVIG remains the principal therapeutic approach, with adjunctive use of plasmapheresis, corticosteroids, or antivirals guided by the extent of hepatic involvement. Prognosis is generally favourable, though a subset of patients may experience persistent deficits. Notably, genotypic variation appears to influence geographic distribution and possibly neurotropism, underscoring the importance of genotype-specific research. The underlying pathogenesis is likely driven by molecular mimicry, mirroring mechanisms seen in GBS triggered by other pathogens. These findings highlight the necessity for clinicians to include HEV in the differential diagnosis of GBS, particularly in endemic areas or when hepatic symptoms are present. Further prospective studies are warranted to elucidate incidence rates, genotype correlations, and long-term outcomes in this context.

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Conflict of interest

None

Ethical considerations

Approval of the research protocol

No human participant was involved in this study

Informed Consent

Not applicable

Registry and the Registration No. of the study/trial

Not applicable

Animal Studies

Not applicable

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