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Epstein-Barr Virus-associated Encephalitis and Lumbosacral Radiculitis, Evolved to Normal Pressure Hydrocephalus in an Immunocompetent Adult: A Case Report

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Case Report

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Abstract

Background

Epstein-Barr virus (EBV) rarely causes central nervous system (CNS) infection in immunocompetent adults. EBV encephalitis is typically monophasic, with viral clearance expected. Reports of multiphasic EBV-related CNS disease with persistent infection are exceptionally scarce.

Case Presentation:

A previously healthy adult presented with acute EBV meningoencephalitis confirmed by cerebrospinal fluid (CSF) analysis (EBV DNA positive) and MRI (left frontal FLAIR hyperintensity), manifesting as aphasia and fever. Initial treatment with antivirals, moderate-dose glucocorticoids, and intravenous immunoglobulin (IVIG) resolved encephalitis. However, the patient subsequently developed acute demyelinating lumbosacral radiculitis (back pain, lower limb paralysis, albumin-cytological dissociation in CSF, EMG-confirmed demyelination), despite negative autoantibody panels. Symptoms resolved after a second IVIG course. Long-term follow-up revealed persistent EBV DNA and elevated protein in CSF for over 3 months, prompting extended antiviral and low-dose glucocorticoid maintenance therapy. Although no encephalitis recurrence occurred, the patient later developed normal pressure hydrocephalus (NPH), receiving lumbo-peritoneal shunting. Residual functional impairment persisted.

Conclusions

This case illustrates a unique, multiphasic EBV CNS infection involving sequential meningoencephalitis and radiculitis, with persistent intrathecal EBV replication and chronic neuroinflammation culminating in NPH. It challenges the paradigm of EBV encephalitis as solely monophasic and highlights the potential role for sustained immunomodulation alongside antivirals. Persistent CSF EBV and inflammation warrant vigilant monitoring for late complications like NPH.

Introduction

Epstein-Barr Virus (human herpesvirus 4, EBV), a ubiquitous human DNA virus which infects over 95% of the human population, predominantly causes central nervous system infections in immunocompromised hosts and children, while remaining rare in immunocompetent adults[1]. Current evidence suggests EBV accounts for 15–23% of viral meningoencephalitis cases [2–4].

When CNS invasion occurs, EBV can manifest as encephalitis, meningitis, myelitis, or radiculitis, typically presenting as an acute, monophasic illness. The long-term consequences of CNS EBV infection remain poorly characterized and represent a significant knowledge gap.

This case report details an unprecedented presentation of multiphasic EBV-related CNS disease in an immunocompetent adult, featuring sequential meningoencephalitis and acute demyelinating radiculitis, persistent CSF EBV viremia and inflammation over months despite treatment, and eventual progression to NPH. It provides crucial clinical insights challenging the traditional view of EBV CNS infection as monophasic and self-contained, underscores the diagnostic and therapeutic complexities of persistent neurotropic EBV infection, and highlights the potential for severe late complications driven by chronic neuroinflammation.

Case presentation

A previously healthy 71-year-old male was admitted to the hospital with aphasia accompanied by low-grade fever and headache for 5 days. Neurological examination on admission revealed an alert patient with incomplete mixed transcortical aphasia (manifesting as word-finding difficulties and impaired auditory comprehension), neck stiffness (3 finger-breadths), a positive left palmomental reflex, muscle strength of grade 5/5 in all four limbs, normal deep tendon reflexes (grade ++), and positive Kernig's sign, Brudzinski's sign, and bilateral pathological reflexes. Laboratory investigations showed an elevated C-reactive protein (CRP) level (24.25 mg/L), leukocytosis (white blood cell count (WBC) 13.42 × 10^9/L) with a neutrophil predominance (71.5%), lymphocyte percentage (20.8%), and monocyte percentage (6.0%). Screening tests for serological tumor markers, hepatitis, syphilis, and HIV were negative. Electroencephalography (EEG) was unremarkable. Brain magnetic resonance imaging (MRI) T2 FLAIR sequence demonstrated abnormally hyperintense signal involving the gyri of the left frontal lobe (Fig. 1A). Lumbar puncture (LP) revealed an opening pressure of 200 mmH_2O, cerebrospinal fluid (CSF) pleocytosis (white blood cell count 149 × 10^6/L), and elevated CSF protein (0.979 g/L). Pathogen detection in the CSF by high-throughput metagenomic next-generation sequencing (mNGS) identified a single Epstein-Barr virus (EBV) genetic sequence (DNA sequence reads: 33; relative abundance: 100%). A diagnosis of EBV-associated encephalitis was established. Treatment was initiated with intravenous acyclovir (0.5 g IV q8h for 14 days), intravenous immunoglobulin (IVIG) pulse therapy (0.4 g/kg/day*62.5 kg*5 days), and moderate-dose corticosteroid therapy (methylprednisolone 120 mg IV qd for 3 days, subsequently tapered to 15 mg qd over 12 days and discontinued).

Following initial therapy, the patient's headache and aphasia resolved. However, he later developed urinary incontinence. On day 4 after completing the antiviral course, he experienced acute paraplegia of the lower limbs. Repeat neurological examination revealed cognitive impairment (Mini-Mental State Examination [MMSE] score 19/30), mild neck stiffness (1 finger-breadth), intact cranial nerves, right upper limb muscle strength of grade 4/5, left upper limb muscle strength of grade 5/5, bilateral lower limb muscle strength of grade 3/5, brisk deep tendon reflexes (+++) in all limbs, and absent pathological reflexes. Electromyography (EMG) and nerve conduction studies (NCS) showed absent motor responses and absent/prolonged F-wave and H-reflex latencies in the lower limbs, with normal sensory nerve conduction velocities, suggestive of demyelinating injury affecting the proximal motor nerves or nerve roots. Urodynamic studies confirmed a neurogenic bladder. Repeat brain MRI showed partial resolution of the left frontal lobe lesion (Fig. 1C). Spinal MRI revealed no evidence of spinal cord involvement.

Repeat LP demonstrated albumin-cytological dissociation (CSF protein 1.556 g/L, CSF WBC 18 × 10^6/L). Serial LP findings and CSF analysis during hospitalization and follow-up are summarized in Table 1.CSF testing for autoimmune encephalitis antibodies (20-item panel), oligoclonal bands, anti-neurofascin/contactin antibodies (node of Ranvier antibodies), central demyelinating disease antibodies, and paraneoplastic antibodies were all negative. A diagnosis of EBV-associated acute lumbosacral radiculoneuritis was considered. The patient received a second course of IVIG (0.4 g/kg/day*56 kg*5 days) and underwent rehabilitation training for one month, resulting in near-complete recovery of motor function. Repeat EMG/NCS showed significant normalization of F-wave and H-reflex latencies. On the planned day of discharge (day 55 after initial symptom onset), the patient experienced a sudden episode of impaired consciousness with tonic upward gaze deviation, lasting approximately one minute. Following this episode, he reported photophobia and metamorphopsia when viewing distant bright objects. Ambulatory EEG showed only non-specific slow-wave activity. A third LP revealed significantly elevated CSF protein (1.795 g/L) with a slightly increased CSF white blood cell count (13 × 10^6/L). Treatment was initiated with oral prednisone (30 mg qd) and sodium valproate (200 mg tid), leading to the resolution of these new symptoms. At discharge, the patient had mild residual cognitive impairment and partial urinary dysfunction.

Follow-up at 3 months post-onset, the patient developed gait instability. Neulogical examination revealed cognitive impairment (MMSE 21/30), supple neck, right lower limb muscle strength of grade V-, and grade V strength in all other limbs, brisk deep tendon reflexes (+++), with absent pathological reflexes. Repeat brain MRI FLAIR sequence showed minimal residual hyperintensity in the left frontal lobe, along with ventriculomegaly and cerebral atrophy (Fig. 1E, F). LP revealed an opening pressure of 100 mmH_2O, CSF protein 1.304 g/L, and CSF WBC count 11 × 10^6/L. CSF mNGS detected EBV nucleic acid (9054 sequence reads, relative abundance 99.8%). Treatment with oral acyclovir (0.4 g tid po) was initiated for 1 month. No recurrence of encephalitis or neuritis was observed, and symptoms such as metamorphopsia or loss of consciousness did not reappear. Prednisone and sodium valproate were gradually discontinued.

Follow-up at 5 months post-onset, the patient exhibited fluctuating gait instability with festination, severely impairing independent ambulation even with a cane. Evaluation at an external hospital revealed worsening hydrocephalus on repeat brain MRI (Fig. 1H). LP findings supported a diagnosis of normal pressure hydrocephalus (NPH).

After 9 months, he underwent lumboperitoneal shunt placement under general anesthesia at an external hospital. Preoperative examination documented bilateral upper limb strength of grade III and bilateral lower limb strength of grade II. CSF opening pressure was normal, with protein 0.637 g/L and white blood cell count 2 × 10^6/L. At 4-month follow-up after lumboperitoneal shunt placement, the patient demonstrated mild psychomotor slowing and improved gait stability. Muscle strength assessment showed bilateral upper limbs at grade III and bilateral lower limbs at grade IV.

A chronological overview of the patient's symptoms, diagnostic workup, therapeutic interventions, and follow-up is presented in Fig. 2.

Table 1
Serial lumbar puncture findings and CSF analysis including EBV test.

Examination	Normal range	D10	D30	D60	M3	M5	M14
Opening pressure(mmH_2O)	80–100	200	120	60	100	/	/
CSF analysis							
WBC count(10^6/L)	0–8	149	18	13	11	/	2
Neutrophils (%)	0–6	6	3	3	25	/	/
Lymphocytes (%)	15–80	94	97	97	75	/	/
Protein(mg/L)	0.15–0.45	0.979	1.556	1.795	1.304	0.539	0.63
EBV DNA sequence reads by mNGS	negative	33	/	/	9054	/	/
EBV relative abundance (%) by mNGS	/	100	/	/	99.8	/	/

Discussion

Epstein-Barr virus (EBV), a member of the gamma herpes virus subfamily within the Herpesviridae family (HHV-4), exhibits a seroprevalence exceeding 90% in the human population often staying latent in B-lymphocytes and epithelial cells of the body[1]. EBV is recognized as an opportunistic pathogen, which can reactivate and drive life-threatening disorders in immunocompromised individuals. While acute EBV infection is commonly observed in pediatric or immunocompromised patients, its involvement in causing central nervous system (CNS) injury in immunocompetent adults is relatively rare. When EBV invades the CNS, it can affect various anatomical sites, leading to a spectrum of neurological disorders, including acute encephalitis, meningitis, myelitis, polyradiculitis, and peripheral neuropathy [5]. However, the simultaneous or sequential involvement of multiple neurological sites within a single patient due to EBV infection is exceedingly uncommon. This case report describes a patient who sequentially developed meningoencephalitis followed by radiculitis, both attributed to EBV infection of the CNS. Notably, serial cerebrospinal fluid (CSF) analyses demonstrated persistent EBV presence within the CNS, a finding distinct from the typical resolution observed in classic EBV encephalitis. The initial presentation was acute encephalitis, characterized clinically by aphasia, fever, inflammatory CSF alterations, and magnetic resonance imaging (MRI) revealing hyperintensity in the left frontal lobe on fluid-attenuated inversion recovery (FLAIR) sequences. Following a full course of antiviral therapy, the patient subsequently developed acute lumbosacral radiculitis, manifesting as low back pain and acute lower limb paralysis.

CSF analysis at this stage showed albumin-cytological dissociation, and electromyography (EMG) indicated demyelinating changes in the nerve roots. During the convalescent phase, transient loss of consciousness and visual metamorphopsia occurred. Repeat CSF examination revealed persistent inflammatory activity. Furthermore, extended follow-up of this patient revealed detectable EBV in the CSF even 3 months post-onset. The patient later progressed to normal pressure hydrocephalus. This case illustrates the complete clinical course of an EBV-associated CNS disorder with unique features.

The precise mechanisms how EBV infection induces neurological damage remain incompletely elucidated. Potential mechanisms include direct EBV invasion of the CNS and antibody-mediated post-infection inflammatory response [6]. Evidences have shown that cytotoxic CD8 + T lymphocytes caused by EBV infection infiltrate into the perivascular area of the leptomeninges and neural tissue can cause direct immune damage[7]. Furthermore, non-specifically proliferating B cells and dysfunctional regulatory T cells (Tregs) secondary to EBV infection, coupled with the high degree of structural similarity between EBV nuclear antigens (EBNAs) and molecules expressed on the surface of glial cells, elevate the risk of autoimmunity. This dysregulated immune system may subsequently mount an attack on the nervous system, leading to further neurological damage. Cases have been reported that various antibodies including anti-ganglioside antibody, anti-oligodendrocyte-glycoprotein antibody, anti-triosephosphate isomerase antibody in acute cerebellar ataxia have been detected positive in EBV infection patients [8–10].

No consensus guidelines about how to treat EBV infection has been established Based on the pathogenic mechanisms of CNS complications caused by EBV, current treatment strategies for EBV-associated encephalitis have been supported by previous reports suggesting that early combination therapy with antiviral agents (e.g., acyclovir) and early intervention with immunotherapy such as glucocorticoids and IVIG may improve clinical symptoms and prognosis [5, 11, 12]. In this case, the patient's encephalitis symptoms significantly improved following initial combination therapy with antivirals, moderate-dose glucocorticoids, and intravenous immunoglobulin (IVIG). However, the patient subsequently developed acute demyelinating lumbosacral radiculitis. Although screening for peripheral nerve antibodies, autoimmune encephalitis antibodies, and paraneoplastic syndrome antibodies yielded negative results, the concurrent cerebrospinal fluid (CSF) findings suggested possible immune-mediated pathogenesis during the course of this EBV infection. A second course of IVIG was administered, resulting in effective resolution of the radiculitis symptoms, which indirectly supports the involvement of immune mechanisms. Following effective treatment for the acute-phase EBV encephalitis and lumbosacral radiculitis, long-term follow-up of this patient revealed persistent EBV detection in the CSF and sustained elevation of CSF protein levels, indicating ongoing viral activation and neuroinflammation. Consequently, extended-duration antiviral therapy and maintenance immunomodulatory therapy (low-dose glucocorticoids) were initiated. No recurrence of encephalitis was observed under this regimen. Nevertheless, the patient later developed normal pressure hydrocephalus (NPH), which was considered likely related to chronic neuroinflammation-driven impairment of CSF circulation. The patient subsequently underwent lumboperitoneal shunt surgery. Although the surgical outcome was acceptable, the patient remained limited in activities of daily living.

This case underscores several lessons. Compared to central nervous system (CNS) infections caused by other viruses, EBV infection of the CNS manifests with complex and diverse clinical symptoms, exhibits a propensity for relapse, poses challenges for effective viral clearance, and frequently leads to chronic neuroinflammation following the acute phase. While EBV-associated encephalitis has traditionally been considered a monophasic illness, this case suggests that EBV neurological infection can present with a multiphasic course. This necessitates enhanced clinical vigilance and long-term follow-up. A few patients may exhibit persistent EBV activation following initial infection as evidenced by ongoing positive EBV-DNA tests, which raises a potential risk of chronic lymphoproliferation and chronic neuroinflammation in EBV-associated CNS disorders. Maintenance immunomodulatory therapy may be warranted under this circumstance. In this case, we utilized low-dose glucocorticoids empirically and achieved good outcome. If conventional immunomodulatory agents prove insufficient, rituximab treatment may be a safe and efficient method for eliminating EBV-infected B cells and achieving rapid clearance of EBV-DNA according to a single-center study[13]. Meanwhile, we learned from this case that NPH can be a long-term complication of EBV-associated meningoencephalitis. Since effective pharmacological agents to halt the progression of normal pressure hydrocephalus (NPH) are lacking currently, enhanced screening for hydrocephalus is required for these patients. Timely surgical intervention may improve outcomes for some patients.

Conclusion

This case highlights an unusual multiphasic course of EBV-associated central nervous system infection, characterized by sequential meningoencephalitis and radiculitis, persistent intrathecal EBV replication, and chronic neuroinflammation that ultimately progressed to normal pressure hydrocephalus. These findings suggest that EBV-related encephalitis may not always follow a monophasic pattern and that some patients may require prolonged clinical surveillance after the acute phase. In cases with persistent CSF EBV positivity and ongoing inflammatory activity, combined antiviral treatment and sustained immunomodulatory therapy may be considered. Careful long-term follow-up is also warranted to detect delayed complications, including normal pressure hydrocephalus, at a stage when timely intervention may improve neurological outcomes.

Declarations

Author Contributions

Conceptualization, Q.L.; methodology, G.L. and M.J.; validation, S.C. and M.J.; formal analysis, H.Z. and Y.S.; investigation, G.L. and S.C.; data curation, H.Z. and Q.L.; writing-original draft preparation, Y.S.; writing-review and editing, H.Z. and Q.L.; visualization, Y.S.; supervision, Q.L. All authors have read and agreed to the published version of the manuscript. H.Z. and Y.S. contributed equally to this work.

Informed Consent Statement

Written informed consent was obtained from the patients' legal guardians for publication of the cases and any accompanying data. This report does not contain any personal information that could lead to the identification of the patient.

Data Availability Statement

All data related to this study are present in the article. Other data associated with this work are available from the corresponding authors upon request.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Figures

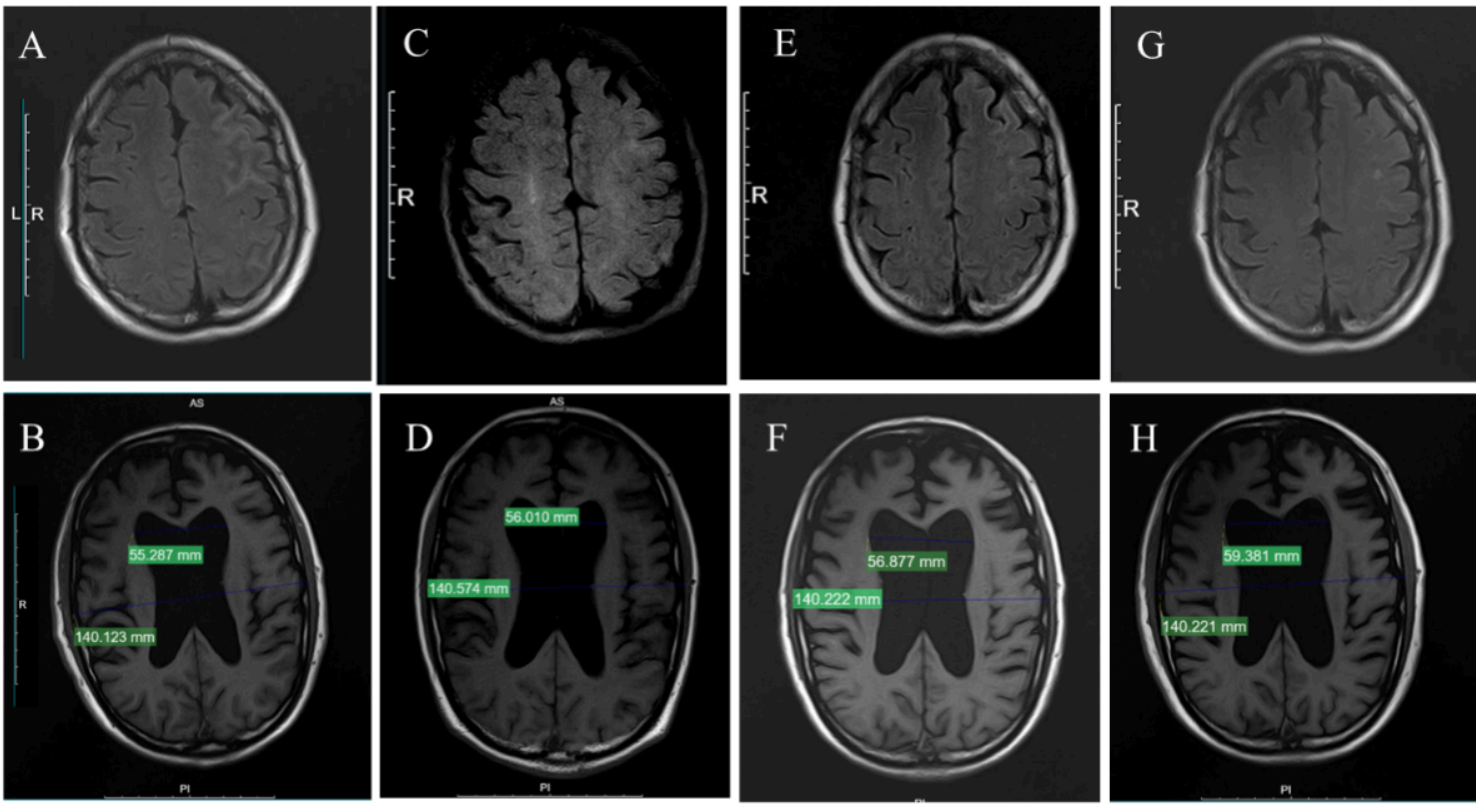


Figure 1

Brain MRI images at presentation and follow-up.

MRI findings in day 8 (A, B), day 30 (C, D), day 60(E, F) and M3(G, H) from symptoms onset. A, C, E and G showed the changes of lesions of the left frontal lobe; B, D, F and H showed the enlargement of lateral ventricles.

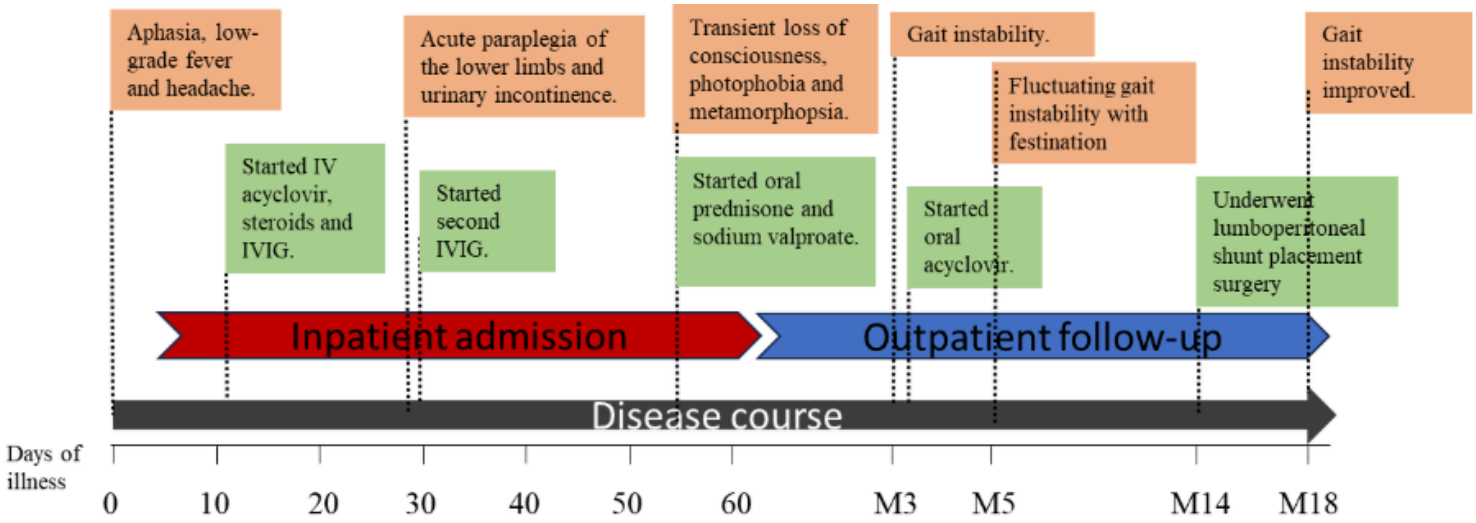


Figure 2

Timeline of the patient's clinical course, including symptom onset, diagnostic evaluation, treatment, and follow-up.