Oculomotor Nerve Palsy as a Presenting Symptom of Epstein-Barr Virus-Associated Infectious Mononucleosis: Case Report and Review of the Literature

Leon Amadeus Steiner\textsuperscript{a} Aslihan Erbay\textsuperscript{a} Florence Pache\textsuperscript{a}
Moritz Niederschweiberer\textsuperscript{a} Eberhard Siebert\textsuperscript{b} Karen Gertz\textsuperscript{a}
Klemens Ruprecht\textsuperscript{a}

\textsuperscript{a}Department of Neurology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; \textsuperscript{b}Institute of Neuroradiology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität, Berlin, Germany

Keywords
Oculomotor nerve palsy · Epstein-Barr virus · Infectious mononucleosis · Magnetic resonance imaging · PCR

Abstract
Primary Epstein-Barr virus (EBV) infection is the main cause of infectious mononucleosis (IM), which typically presents with a triad of fever, lymphadenopathy, and tonsillar pharyngitis in young adults. In contrast, neurological manifestations of IM are rare. We report on a 23-year-old man with subacute oculomotor nerve palsy followed by symptoms of IM 6 days later. Primary EBV infection was confirmed by PCR detection of EBV DNA in blood as well as by subsequent serology. High-resolution magnetic resonance imaging revealed an edematous change at the root exit zone and gadolinium enhancement of the right oculomotor nerve as well as pial enhancement adjacent to the right ventral mesencephalon. A review of the literature identified 5 further patients with isolated oculomotor nerve palsy as the presenting symptom of unfolding primary EBV infection. MRIs performed in 3 of those 5 patients

Leon Amadeus Steiner and Aslihan Erbay contributed equally to this work.
revealed a pattern of contrast enhancement similar to that of the present case. This case report and literature review highlight that, although rare, IM should be considered in the differential diagnosis of oculomotor nerve palsy in young adults.

© 2021 The Author(s). Published by S. Karger AG, Basel

Introduction

Over 90% of human beings become infected with Epstein-Barr virus (EBV) during the course of their lives [1]. Primary EBV infection usually occurs in early childhood, where it is asymptomatic. However, primary EBV infection in young adulthood frequently manifests as infectious mononucleosis (IM), which typically presents with a triad of fever, lymphadenopathy, and tonsillar pharyngitis [1]. The average incubation period of EBV-associated IM is 6 weeks. While serologic testing for EBV antibodies may be negative during the first weeks of the disease, EBV DNA can be detectable in peripheral blood as early as 3 weeks prior to symptom onset [1]. Neurological involvement in IM is rare, occurring in only 1–7% of patients [2, 3]. Previously recognized neurological manifestations of IM include encephalomyelitis, meningoencephalitis, aseptic meningitis, transverse myelitis, optic neuritis, peripheral neuritis, and Guillain-Barré syndrome as well as facial and other cranial nerve palsies [4–8]. Here, we report on a patient with isolated oculomotor nerve palsy as the presenting symptom of IM. Additionally, we review previously reported patients with oculomotor nerve palsies associated with IM.

Case Report

A 23-year-old man presented in the emergency department of our hospital with subacute binocular diplopia. Diplopia had first appeared 1 day before admission, after the patient had developed fever and night sweats the night before. Another 3 days earlier, he had noted holo-cranial headaches of medium intensity and pain on eye movements. Except for migraine, the patient’s past medical history was unremarkable. Neurological examination showed incomplete right oculomotor nerve palsy with pareses of the right inferior rectus and inferior oblique muscles. Pupils were equal in size and reactive to light, and no ptosis was detectable on either side. The Bielschowsky head tilt test was negative. A cranial CT scan was normal.

Initial laboratory tests showed an increased C-reactive protein of 45 mg/L (reference range: <5 mg/L) and leukopenia of 3.4/nL (reference range: 3.9–10.5/nL). Neither immunoglobulin (Ig)G antibodies to Epstein-Barr nuclear antigen-1 (EBNA-1) nor IgM or IgG antibodies to the EBV viral capsid antigen (VCA) were detectable in serum. Soluble interleukin-2 receptor was elevated in serum with 2284 IU/mL (reference range: <710 IU/mL), while levels of angiotensin-converting enzyme and calcium were normal. Microscopic examination of a blood smear revealed reactive lymphocytes.

Cerebrospinal fluid (CSF) examination was normal with 2 cells/µL (reference: <5 cells/µL), total CSF protein of 363.5 mg/L (reference: ≤450 mg/L), and CSF glucose of 50 mg/dL (reference: 40–70 mg/dL). There were no CSF-specific oligoclonal bands. A multiplex PCR of the CSF for herpes simplex virus type 1 and 2, cytomegalovirus, human herpes virus type 6, EBV, parechovirus, varicella zoster virus, enterovirus, West Nile virus, Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, and cryptococcus was negative, as was CSF serology for Treponema pallidum and Borrelia burgdorferi.
A cerebral MRI performed 3 days after admission showed a focal hyperintense edematous change at the root exit zone of the right oculomotor nerve on fluid attenuated inversion recovery sequences (Fig. 1a). T1-weighted sequences with gadolinium demonstrated contrast enhancement of the right oculomotor nerve at its exit from the mesencephalon and a pial enhancement adjacent to the right ventral mesencephalon (Fig. 1b). On high-resolution 3D contrast-enhanced gradient echo (MPRAGE) sequences, the right oculomotor nerve appeared mildly thickened and abnormally enhancing along its cisternal course (arrows). Higher magnification of (b) showing a pattern of contrast enhancement resembling a “shooting star” (f), with the focal hyperintense edematous change at the oculomotor nerve exit zone corresponding to the meteor and adjacent leptomeningeal enhancement corresponding to the visible streak of light of a shooting star (g, h). Higher magnifications of MR images from previous case reports by Malclés et al. [9] and Erben et al. [10] showing a similar radiologic pattern with focal hyperintense edematous changes and leptomeningeal enhancement lining the adjacent part of the mesencephalon.

However, 6 days after admission and 2 days after remission of diplopia, the patient developed a sore throat with enlarged tonsils with whitish spots as well as cervical lymphadenopathy. This elicited determination of EBV DNA by PCR in ethylenediaminetetraacetic
acid (EDTA) blood, demonstrating 13,300 copies/mL EBV DNA (reference: <1,000 copies/mL). Based on the typical clinical presentation, detection of EBV DNA, and presence of reactive lymphocytes in blood, a final diagnosis of EBV-associated IM with right oculomotor nerve palsy as the presenting symptom was made.

On a follow-up examination 3 months later, the patient was asymptomatic, and neurological examination was normal. While EBV DNA in EDTA blood and VCA IgM in serum were undetectable, EBNA-1 IgG and VCA IgG were now detected in serum, confirming past EBV infection. A brain MRI with gadolinium enhancement showed complete resolution of the former findings.

**Review of the Literature**

The PubMed database was searched from inception to June 2021 for articles containing the terms “oculomotor” and “infectious mononucleosis.” This identified 5 case reports of 5 patients with oculomotor nerve palsies associated with IM, whose demographic, clinical, radiological, and laboratory findings are summarized in Table 1.

Cerebral MRIs were performed in 3 out of those 5 patients and, similar to the findings in our patient, showed a focal hyperintense edematous change at the root exit zone of the affected oculomotor nerve in all these 3 patients. Furthermore, pial enhancement adjacent to the ventral mesencephalon was likewise identified in 2 previous patients (Fig. 1g, h). The distinct pattern of gadolinium enhancement in the present and previous patients resembled a shooting star, with the focal hyperintense edematous change corresponding to the meteor and the adjacent leptomeningeal enhancement resembling the visible streak of light of the shooting star (Fig. 1e–h).

**Discussion**

This case report and review of the literature highlight oculomotor nerve palsy as the presenting symptom of unfolding primary EBV infection. While the patient’s initial accompanying symptoms, that is, fever, night sweats, and headaches, were unspecific, development of tonsillar pharyngitis and cervical lymphadenopathy during the further disease course of this young adult raised the suspicion of IM, which could be confirmed by detection of EBV DNA in blood and subsequent EBV serology.

Of note, initial EBV serologies in the present and previous patients with oculomotor palsy during IM showed either no EBV antibodies or VCA IgM and VCA IgG in the absence of EBNA-1 IgG, consistent with a very early stage of primary EBV infection [1]. Importantly, as EBV viremia generally precedes seroconversion, detection of EBV DNA by PCR is therefore essential for diagnosing EBV-associated IM in the acute phase.

The precise pathophysiology of oculomotor nerve palsy but also of other neurologic manifestations of primary EBV infection is not completely understood. However, lack of PCR detection of EBV DNA in CSF and normal CSF findings in our case together with normal CSF findings or just mildly elevated CSF cell counts in the previous cases (Table 1) rather argue against a direct CNS infection by EBV. Instead, a parainfectious mechanism could be at play. Given the therapeutic efficacy of intravenous immunoglobulins in other neurological diseases deemed parainfectious, for example, the Guillain-Barré or Miller-Fisher syndrome [14, 15], the improvement of symptoms under intravenous immunoglobulin therapy seen in our patient appears compatible with such a mechanism. Nevertheless, clinical improvement under intravenous immunoglobulin does by no means prove a parainfectious mechanism, as remission could also have
**Table 1. Systematic review of the literature on oculomotor nerve palsies in primary EBV infection**

| References | Sex/age, years | Clinical findings | EBV serology on admission | EBV serology on follow-up | CSF findings on admission | MR findings on admission | Therapy and outcome |
|------------|----------------|-------------------|---------------------------|---------------------------|---------------------------|--------------------------|---------------------|
| Nellhaus [11] | Male, 10 | Oculomotor nerve palsy/diplopia | “Negative antibody titer,” no further specification | Positive VCA IgG and IgM (6 weeks after onset of symptoms) | No abnormal findings | Unremarkable | Spontaneous remission |
| Watters [12] | Male, 24 | Oculomotor nerve palsy/diplopia | “Negative antibody titer,” no further specification | Positive VCA IgG and IgM (6 weeks after onset of symptoms) | No abnormal findings | Unremarkable | Spontaneous remission |
| Ishibashi et al. [13] | Male, 20 | Oculomotor nerve palsy | Negative VCA IgM and IgG and EBNA-1 IgG (8 weeks after onset of symptoms) | No abnormal findings | Mild pleocytosis (8 cells/µL) | Unremarkable | Spontaneous remission |
| Erben et al. [10] | Male, 19 | Oculomotor nerve palsy/diplopia | Positive VCA IgG and IgM and EBNA-1 IgG (few days after onset of symptoms) | No abnormal findings | Mild pleocytosis (13 cells/µL) | Unremarkable | Spontaneous remission |
| Malclès et al. [9] | Female, 18 | Oculomotor nerve palsy/diplopia | Positive VCA IgG and IgM (6 weeks after onset of symptoms) | Positive VCA IgG (6 months after onset of symptoms) | No abnormal findings | Unremarkable | Spontaneous remission |
| Steiner et al. (present report) | Male, 23 | Oculomotor nerve palsy, headache | Positive VCA IgG and IgM and EBNA-1 IgG (8 weeks after onset of symptoms) | No abnormal findings | Mild pleocytosis (4 cells/µL) | Unremarkable | Spontaneous remission |

**EBV**, Epstein-Barr virus; VCA, virus capsid antigen; EBNA-1, Epstein-Barr nuclear antigen-1; PCR, polymerase chain reaction; CSF, cerebrospinal fluid; na, not available.
occurred spontaneously, as suggested by the frequent spontaneous remission in the previously reported cases. Remarkably, MRI findings in the present and previous cases of oculomotor nerve palsy associated with primary EBV infection showed a rather similar pattern of gadolinium enhancement, compatible with inflammation of the oculomotor nerve and pointing toward a common pathophysiological mechanism in these patients.

**Conclusions**

Altogether, this case report and review of the literature emphasize that, although rare, EBV-associated IM should be considered in the differential diagnosis of oculomotor nerve palsy in young adults. Still, a high degree of suspicion is required, as early diagnosis may be obscured by the initial absence of classical IM symptoms and a negative EBV serology. Detection of EBV DNA by PCR is key for diagnosing primary EBV infection in this situation.

**Acknowledgment**

The authors would like to thank the patient for approval to publish anonymized data related to this case report.

**Statement of Ethics**

According to the Ethics Committee of Charité – Universitätsmedizin Berlin, no specific ethical approval is required for publication of a case report and literature review. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**Conflict of Interest Statement**

K.R. received research support from Novartis Pharma, Merck Serono, German Ministry of Education and Research, European Union (821283-2), Stiftung Charité, and Arthur Arnstein Foundation; speaker honoraria from Bayer; and travel grants from the Guthy Jackson Charitable Foundation. All other authors declare that they have no conflicts of interest.

**Funding Sources**

This research received no specific funding from any agency in the public, commercial, or not-for-profit sector. L.A.S. and F.P. are participants of the BHI-Charité (Junior) Clinician Scientist Program funded by Charité – Universitätsmedizin Berlin and the Berlin Institute of Health.

**Author Contributions**

L.A.S., A.E., F.P., M.N., K.G., and K.R. were involved in clinical care of the patient. E.S. reviewed the radiological findings. L.A.S., A.E., E.S., and K.R. wrote the manuscript. All authors reviewed and approved the manuscript.
Data Availability Statement

Original data are available from the corresponding author upon reasonable request.

References

1. Dunmire SK, Hogquist KA, Balfour HH. Infectious mononucleosis. *Curr Top Microbiol Immunol*. 2015;390(Pt 1):211–40.
2. Epstein SH, Dameshek W. Involvement of the central nervous system in a case of glandular fever. *N Engl J Med*. 1931;205(26):1238–41.
3. Silverstein A, Steinberg G, Nathanson M. Nervous system involvement in infectious mononucleosis. The heralding and-or major manifestation. *Arch Neurol*. 1972;26(4):353–8.
4. Long CM, Kerschner JE. Parotid mass: Epstein-Barr virus and facial paralysis. *Int J Pediatr Otorhinolaryngol*. 2001;59(2):143–6.
5. Joki-Erkkilä VP, Hietaharju A, Numminen J, Dastidar P, Puhakka H. Multiple cranial nerve palsies as a complication of infectious mononucleosis due to inflammatory lesion in jugular foramen. *Ann Otol Rhinol Laryngol*. 2000;109(3):340–2.
6. Johns MM, Hogikyan ND. Simultaneous vocal fold and tongue paresis secondary to Epstein-Barr virus infection. *Arch Otolaryngol Head Neck Surg*. 2000;126(12):1491–4.
7. Schellingear PD, Sommer C, Leithäuser F, Schwab S, Storch-Hagenlocher B, Hacke W, et al. Epstein-Barr virus meningoencephalitis with a lymphoma-like response in an immunocompetent host. *Ann Neurol*. 1999;45(5):659–62.
8. Tselis A, Duman R, Storch GA, Lisak RP. Epstein-Barr virus encephalomyelitis diagnosed by polymerase chain reaction: detection of the genome in the CSF. *Neurology*. 1997;48(5):1351–5.
9. Malclès A, Ronsin S, Agard E, Abouaf L, Tili kete C, Vighetto A, et al. Isolated oculomotor nerve palsy revealing infectious mononucleosis. *Acta Ophthalmol*. 2015;93(6):e518–9.
10. Erben Y, Gonzalez Hofmann C, Steinmetz H, Ziemann U. Isolated neuritis of the oculomotor nerve in infectious mononucleosis. *Nervenarzt*. 2008;79(4):462–4.
11. Nellhaus G. Isolated oculomotor nerve palsy in infectious mononucleosis. A report of an unusual case and review of the literature. *Neurology*. 1966;16(2):221–4.
12. Watters MR. Oculomotor palsy in infectious mononucleosis: case report. *Mil Med*. 1984;149(1):33–4.
13. Ishibashi A, Sueyoshi K, You M, Yolokura Y. MR findings in isolated oculomotor nerve palsy associated with infectious mononucleosis caused by Epstein-Barr virus infection. *J Comput Assist Tomogr*. 1998;22(6):995–7.
14. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med*. 2001;345(10):747–55.
15. Arakawa Y, Yoshimura M, Kobayashi S, Ichihashi K, Miyao M, Momoi MY, et al. The use of intravenous immunoglobulin in Miller Fisher syndrome. *Brain Dev*. 1993;15(3):231–3.