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

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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

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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.

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 holocranial 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 pneumonia,* and cryptococcus was negative, as was CSF serology for *Treponema pallidum* and *Borrelia burgdorferi*.

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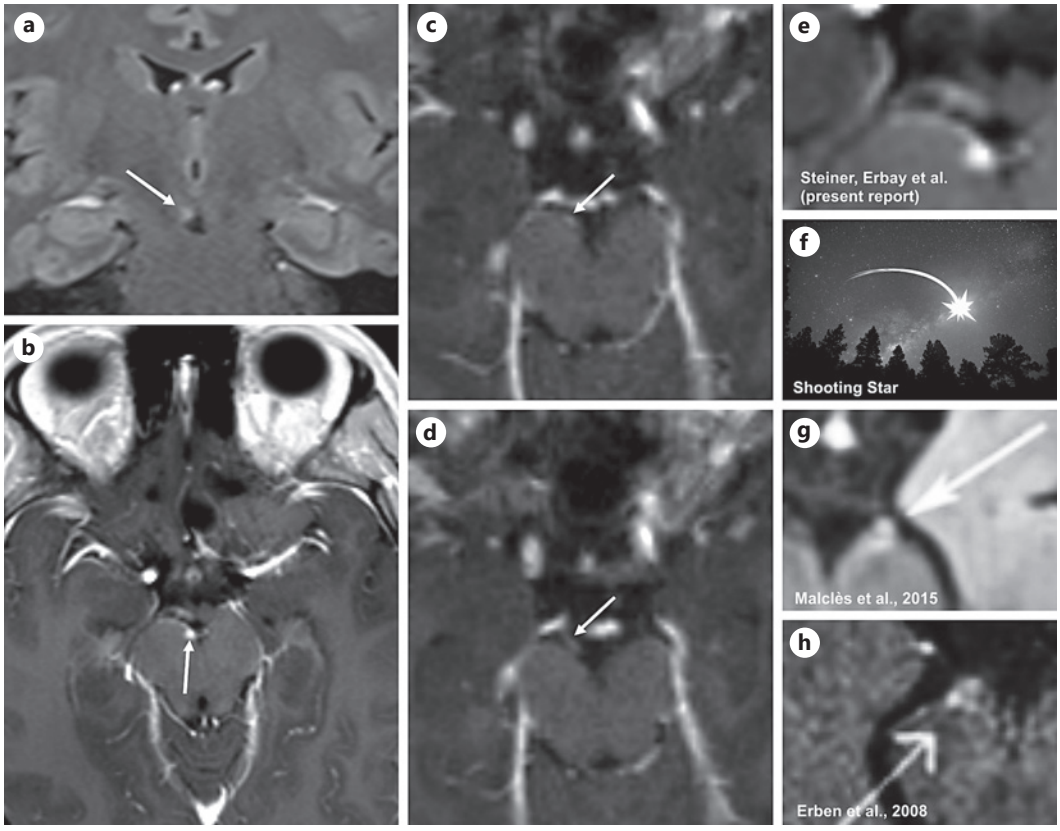

Fig. 1. Magnetic resonance imaging of the present and previous cases of oculomotor nerve palsies in EBV-associated infectious mononucleosis. **a** Coronal fluid attenuated inversion recovery sequence showing a focal hyperintense edematous change at the root exit zone of the right oculomotor nerve (arrow) in the interpeduncular fossa. **b** Contrast-enhanced axial T1-weighted sequence reveals a mildly swollen and pathologically enhancing oculomotor nerve root exit zone (arrow). **c**, **d** On consecutive high-resolution 3D contrast-enhanced gradient echo (MPRAGE) sequences, the right oculomotor nerve is mildly thickened and abnormally enhancing along its cisternal course (arrows). **e** 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.

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 sequences (MPRAGE), the right oculomotor nerve appeared mildly thickened with subtle abnormal enhancement along its cisternal course (Fig. 1c, d). A presumptive diagnosis of parainfectious oculomotor nerve palsy was made and the patient treated with a total of 145 g intravenous immunoglobulins over 4 days, which was associated with disappearance of diplopia 2 days after treatment initiation.

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*

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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

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Table 1. Systematic review of the literature on oculomotor nerve palsies in primary EBV infection

References	Nellhaus [11]	Watters [12]	Ishibashi et al. [13]	Erben et al. [10]	Malclès et al. [9]	Steiner et al. (present report)
Sex/age, years	Male, 10	Male, 24	Male, 20	Male, 19	Female, 18	Male, 23
Clinical findings	Oculomotor nerve palsy/diplopia, fatigue, vomiting, swollen lymph nodes, splenomegaly	Oculomotor nerve palsy/diplopia	Oculomotor nerve palsy/diplopia, fever, swollen bilateral cervical and inguinal lymph nodes, splenomegaly	Incomplete oculomotor nerve palsy/diplopia, unilateral headache	Oculomotor nerve palsy/diplopia	Incomplete oculomotor nerve palsy/diplopia, holocranial headaches, fever
EBV serology on admission	"Negative antibody titer," no further specification	"Negative antibody titer," no further specification	Negative VCA IgM and IgG and EBNA-1 IgG	Positive VCA IgM and IgG, negative EBNA-1 IgG	Positive VCA IgM and IgG, negative EBNA-1 IgG, EBV PCR 65,000 copies/mL (blood)	Negative VCA IgM and IgG and EBNA-1 IgG, EBV PCR 13,300 copies/mL (blood)
EBV serology on follow-up	Positive heterophile antibodies (*4 weeks after onset of symptoms*)	Positive heterophile antibodies (*3 weeks after onset of symptoms*)	Positive VCA IgM and IgG and EBNA-1 IgG (*few days after onset of symptoms*)	Positive VCA IgM and IgG (*6 weeks after onset of symptoms*)	na	Positive VCA IgG and EBNA-1 IgG, negative EBV PCR and VCA IgM (*3 months after onset of symptoms*)
CSF findings on admission	Unremarkable	Unremarkable	Mild pleocytosis (8 cells/μL)	Mild pleocytosis (13 cells/μL)	Unremarkable	Unremarkable
MR findings on admission	na	na	No abnormal findings	Gadolinium enhancement, hyperintense T2-signal in the right oculomotor nerve, leptomeningeal enhancement of right ventral mesencephalon	Gadolinium enhancement, hyperintense T2-signal in the left oculomotor nerve, leptomeningeal enhancement of left ventral mesencephalon	Gadolinium enhancement of the right oculomotor nerve at its exit from the mesencephalon, leptomeningeal enhancement of right ventral mesencephalon
MR findings on follow-up	na	na	Gadolinium enhancement at the base of the right oculomotor nerve (*2 weeks after onset of symptoms*)	Significant reduction of hyperintense T2-signal and gadolinium enhancement (*6 weeks after onset of symptoms*)	Decrease of hyperintense T2-signal, mild residual gadolinium enhancement (*8 weeks after onset of symptoms*)	Complete remission of gadolinium enhancement (*3 months after onset of symptoms*)
Therapy and outcome	Spontaneous remission	Spontaneous remission	Remission of symptoms under therapy with steroids	Spontaneous remission	Spontaneous remission	Remission of symptoms under therapy with intravenous immunoglobulins

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.

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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.

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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.

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