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Mononeuritis multiplex associated with primary EBV infection

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SUMMARY

A 20 year old lady presented to the acute medical unit with new neurological deficits. She described gastrointestinal symptoms in the preceding 24 hours. Her case was discussed with infectious diseases and neurology overnight, both of whom were resident at a hospital on the other side of the city. The infectious diseases team were concerned enough to discuss the case with Public Health England for consideration of botulism antitoxin. When this diagnosis was discounted on the basis of asymmetric neurological deficits, the patient was admitted under the care of the neurologists. Mononeuritis multiplex of unclear aetiology was diagnosed. A subsequent infectious diseases review resulted in a diagnosis of primary EBV infection, the likely trigger of the symptoms. Whilst neurologic deficits resolved, neuropathic pain continues. Learning points include the importance of an early, accurate description of neurologic deficits and the need to consider EBV as an infectious trigger of mononeuritis multiplex. Collaboration between neurology and infectious disease physicians was key in managing this patient and disentangling the broad array of infectious and non-infectious differential diagnoses.

Background

Although primary EBV infection is common, neurological sequelae are seldom encountered. The presence of gastrointestinal symptoms in this case led away from the eventual diagnosis, and stimulated an overnight discussion with Public Health England about acquiring botulism antitoxin. Patients presenting with rapidly progressing neurological deficits present a diagnostic conundrum that must be disentangled quickly in case specific treatments are required to prevent progression. This case reinforces the value of an objective neurological examination undertaken by an experienced clinician, and the success of collaboration between infection and neurology physicians in reaching a diagnosis.

Case presentation

A 20 year old female student presented to the emergency department having found it difficult to walk, such that she had fallen and chipped her tooth. She described two episodes of loose stool and several vomits within the preceding 24 h. An erythematous rash had developed over the internal aspect of her left elbow, right anterior shin and left knee.

The patient had not travelled in the preceding twelve months and had spent some of her childhood in Australia, returning to the UK ten years previously. There was no history of tick bites or recent walking holidays. There was no history of consuming food past its expiration date, undercooked food or food that had been canned/pickled at home.

Examination findings were initially described as purely motor, affecting the left arm and right leg with a left ptosis. As the night progressed the receiving medical team discussed the case with the neurology/infectious disease registrars who were based at a different site within the same hospital trust. These discussions suggested progression of the deficits, prompting the infectious diseases registrar to telephone his consultant to discuss the faint, but not-to-be-missed, prospect of food borne botulism. There was sufficient concern to escalate the discussion to the on call Public Health England consultant, who in turn spoke with a colleague specialising in botulism. The case was de-escalated on the basis of asymmetric neurologic deficits, inconsistent the symmetric deficits associated with botulism. A single dose of intravenous ceftriaxone was given to cover for neuroborreliosis.

The patient was admitted to neurology, where examination revealed a left miosis and partial ptosis, attributed to damage to the parasympathetic outer fibres and the somatic inner fibres of the oculomotor nerve, respectively. Left ulnar distribution paraesthesia, and left ulnar myotome weakness were present, resulting in a positive Froment's sign.

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There was right common peroneal nerve distribution weakness resulting in right foot drop, with associated paraesthesia over the right lateral heel, posterior aspect of the lower leg and popliteal fossa. Erythema was noted over the medial aspect of the left elbow, right anterior shin and left anterior knee. A clinical diagnosis of mononeuritis multiplex was made. The infectious diseases team were asked to review the patient to investigate for an infectious trigger.

Investigations

A neutrophil leucocytosis of 17.06 $\times$ 10^9/L and monocytosis of 1.09 $\times$ 10^9/L were noted on admission bloods, alongside a transaminitis (ALT 108 IU/L, reference 0–33). C reactive protein was elevated at 61 mg/L (reference 0–5). A vasculitic screen and autoimmune panel were unremarkable. Cerebrospinal fluid (CSF) contained a low white cell count (2 $\times$ 10^6/L), normal protein (0.25 g/L) and yielded no organisms on culture. CSF PCR was negative for Herpes Simplex, Varicella Zoster and Enterovirus.

Imaging consisted of a plain chest radiograph, an abdominal ultrasound, and MRI brain/whole spine with contrast. These studies were unremarkable.

Nerve conduction studies performed 6 days after presentation demonstrated proximal pathology of the left ulnar nerve consistent with early mononeuritis multiplex. No clear abnormalities in nerve conduction were seen within the symptomatic right leg, with a comment made that pathology in the early stages of evolution might not yet be apparent.

SARS CoV-2 PCR and a multiplex PCR panel for seasonal respiratory viruses were negative. There was no serological evidence of past or present infection with viral hepatitides (including hepatitis A and E), Human Immunodeficiency Virus, Borrelia, syphilis or Cytomegalovirus. Anti-streptolysin O titre was not elevated.

EBV IgM antiviral capsid antigen (VCA) antibodies were detected, alongside weakly positive EBV VCA IgG antibodies. Ebstein Barr nuclear antigen (EBNA) IgG antibody was not detected. EBV DNA was detected in blood at 2.85 log copies/ml (707 copies/ml). The serology and PCR results are suggestive of recent acute primary EBV infection.

Serology was repeated eight weeks later: although VCA IgM was still present, this was at a lower index. The VCA IgG was detected at a higher index. EBNA IgG was not detected. Although reactivated EBV infection could have caused a low level viraemia, our clinical judgement is that the sero-evolution is in support of a diagnosis of recent acute primary EBV. EBNA IgG positivity may develop in time (Table 1.)

Differential diagnosis

Acute onset neurologic deficits in a young patient carry a wide differential diagnosis. Given the gastrointestinal symptoms foodborne botulism was considered early on. This condition requires rapid treatment with botulism antitoxin, which is only available from the Colindale Public Health England site. As the story unfolded, it transpired that the deficits were both motor and sensory and asymmetric, making this diagnosis unlikely. This enabled de-escalation following expert discussion.

Vasculitic neuropathies causing this presentation without an established diagnosis of a systemic vasculitis were dismissed after vasculitic screen and autoimmune panel came back unremarkable.

Neuroborreliosis can present with cranial nerve deficits and motor/sensory radiculopathies (Schwenkenbecher et al., 2017). This diagnosis was considered, but lack of epidemiologic exposure made it unlikely. This was later confirmed by negative Borrelia serology. The Miller Fisher variant of Guillan-Barré was also considered, but the neurologic deficits fortunately did not progress and only one eye was implicated, making this less likely.

Other infectious precipitants of mononeuritis include hepatitis A, B, C and E, parvovirus B-19, Herpes simplex virus, HIV, Cytomegalovirus and leprosy (Lenglet et al., 2011; SathiSh Pai and Pai, 2013; Palma et al., 2018).

Table 1
Anticipated serologic and virologic findings in primary, established, and reactivated EBV infection. VCA = Viral Capsid Antigen; EBNA = Epstein Barr Virus Nuclear Antigen.

	Primary Infection	Past infection	Reactivated infection
VCA IgM	Present	Absent	Present or absent
VCA IgG	Present or absent	Present	Present
EBNA IgG	Absent	Present in most cases	Present or absent
EBV viraemia	Present	Absent	Present

Treatment

Intravenous ceftriaxone was administered to cover neuroborreliosis, but later discontinued on the basis of lack of epidemiologic exposure. Otherwise treatments were supportive, consisting of paracetamol and codeine for neuralgic pains.

Outcome and follow-up

After two months motor and sensory deficits have almost entirely resolved. The patient still has neuropathic pain in the ulnar sensory distribution of her hand and the sole of her right foot. She also reports uneven pupils occasionally and a droopy left eyelid.

Discussion

Epstein-Barr Virus (EBV) is a human herpes virus spread predominantly through shared saliva (Fafi-Kremer et al., 2005). In a seroprevalence study in England, more than half of 11 year olds showed evidence of past infection, rising to 93% of 22–24 year olds (Winter et al., 2019). Often asymptomatic in children, primary EBV infection in adolescents and adults may give rise to 'infectious mononucleosis', characterised by fever, lymphadenopathy and pharyngitis (Cohen, 2000). Complications including airway obstruction, meningoencephalitis, haemolytic anaemia, thrombocytopaenia and rash (particularly in association with penicillin administration) occur with a frequency greater than one percent. An array of rarer complications occur with a frequency less than one percent, and include pneumonitis, myocarditis, pancreatitis, and parotitis (Odumade et al., 2011).

Neurologic complications of primary EBV infection have been described including brachial plexopathy (Dodig, 2010) facial palsy (Diedler et al., 2006) sensory neuropathy (Rubin and Daube, 1999) and optic neuritis (Corssmit et al., 1997). Mononeuritis multiplex has been described in a small number of case reports, the first of which reported possible recrudescence of a past infection (Corssmit et al., 1997) one in association with cryoglobulinaemia (Villeneuve et al., 2016) and once case from 1974 associated with a positive Paul-Bunnel test (Liveson and Goodgold, 1974). Nerve damage due to viral infection is thought to be mediated by one of two mechanisms: direct damage by the virus, or secondary immune mediated para infectious damage (Pezzini and Padovani, 2020). In Guillan Barré syndrome, which may be triggered by another human herpes virus (Cytomegalovirus), a phenomenon of molecular mimicry occurs, whereby the immune response to the virus cross reacts with epitopes on peripheral nerves (Yuki and Hartung, 2012). It is feasible that a similar mechanism may underlie nerve damage associated with EBV, although we are not aware of any experimental evidence to support this. Therapies such as intravenous immunoglobulins or steroids might play a role in modifying this pathophysiology, but this is purely speculative.

EBV serology is notoriously difficult to interpret. During acute infection the virus is in a lytic phase and this is associated with expression of viral capsid antigens (VCA). Usually IgM VCA antibodies

develop in early infection, followed by IgG VCA antibodies. Over coming weeks IgM VCA antibody titres wane, but can be detectable for several months (De Paschale, 2012). Once acute infection has resolved the virus establishes latency. This is associated with the expression of EBV nuclear antigens (EBNA), resulting in detectable EBNA IgG. Approximately 5% of patients do not develop EBNA antibodies (De Paschale et al., 2009). Reactivated infection can be associated with the presence of VCA IgM and IgG alongside EBNA IgG (Table 1).

In this case the detection of VCA IgM and IgG, alongside a low level viraemia, was indicative of recent past infection. Sero-evolution helped to confirm the diagnosis, with titres of IgM VCA falling after eight weeks. The titres of VCA IgG increased after 8 weeks. EBNA IgG was not detected. This could be because it was too early after the acute infection; it is also possible that EBNA IgG will never develop in this patient. CSF PCR for EBV was not undertaken in this case. Although the rarity of this presentation means that it is uncertain whether EBV might be detected in CSF with mononeuritis, the test would have been of interest, whether positive or negative.

Learning points

- *Neurologic complications can follow primary EBV infection, although these are rare. EBV should be considered as a precipitant of unexplained mononeuritis multiplex.*
- *EBV serology requires careful interpretation, and it is often necessary to repeat serology at a later date to demonstrate evolution of antibody responses and confirm the diagnosis.*
- *Neurologic deficits can be triggered by a wide range of infections. An assiduous neurological examination, repeated over time, is necessary to inform the differential diagnosis.*
- *Neurologists and infection doctors have complementary skill sets, which work well in the investigation and management of such patients*

Patient's perspective

" My right pupil was much larger than the left
I had a dreadful headache behind my right eye.
I had nausea and vomiting, difficulty keeping food down.
I was unable to see clearly to read, and subsequently require spectacles.
It was all very frightening, especially as nobody knew why it was happening, but all of the staff were so lovely and reassuring.
I still have unequal pupils occasionally, and the drooping of my left eye.
I get occasional numbness in my right foot and left hand; I have fallen down the stairs twice.
I get occasional nausea and diarrhoea, although the headaches seem to have disappeared.
I have stopped amitriptyline, and just get occasional pain in my foot.
Will this happen to me again? "

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CRediT authorship contribution statement

Peter Johnston: Conceptualization, Writing – original draft. **Suha Akili:** Conceptualization, Project administration. **Aijaz Khan:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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