Title:
Homonymous hemianopia following yellow fever vaccination: a case of acute disseminated encephalomyelitis

Short running title:
ADEM following YF Vaccination

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Highlight:

A 42-year-old Caucasian man developed left homonymous hemianopia sixteen days after receipt of a live-attenuated 17D-204 yellow fever virus vaccine. MRI imaging of the brain revealed right occipital and left parieto-occipital lesions with marked hyperintensity consistent with demyelination, and a diagnosis of yellow fever vaccine-associated acute disseminated encephalomyelitis was made.
In June 2023, a 42-year-old Caucasian man received the live-attenuated 17D-204 yellow fever virus vaccine STAMARIL® (Sanofi, France). He planned to travel from Australia to Trinidad and Tobago, a World Health Organisation listed yellow fever endemic country, and required an International Certificate of Vaccination or Prophylaxis on return. His past medical history was notable for gastric sleeve surgery, gastro-oesophageal reflux disease, and keratoconus with no contraindications to receipt of a live vaccination. He took no regular medications. Along with other travel advice, he was counselled about the very rare possibility of serious systemic or neurological events. Sixteen days after receipt of the vaccine he complained of ‘shadows’ in his vision and would bump into doorframes on the left. He had no fever or headache and was systemically well and did not associate his symptoms with the recent vaccination. Overseas travel delayed an ophthalmological assessment for eight weeks, at which point a left homonymous hemianopia was documented.

On examination, sensorium was normal and, apart from the visual field defect, there were no focal neurological signs. Blood tests, including a full blood count, C-reactive protein and liver function, were all within normal limits. A CT brain was followed with an MRI brain. This revealed two discrete areas of abnormality in the right occipital and left parieto-occipital regions, with evidence of mild mass effect (figure 1). The lesions demonstrated marked hyperintensity with increased enhancement especially at the leading edge of the margins. Features favouring demyelination included the multifocality, degree of hyperintensity, subcortical location and diffusion restriction, making other differentials, such as lymphoma, glioblastoma multiforme and abscess, less likely.
CSF sampling revealed an absence of red and white cells, normal glucose of 3.3 mmol/L (ref 2.0 – 3.9) and a mildly elevated protein of 0.53 g/L (ref 0.15 – 0.45). Cryptococcal antigen and a herpes multiples PCR were negative. Neuromyelitis optica and anti-myelin oligodendrocyte glycoprotein antibodies were negative.

Based on symptom onset within 30 days of vaccination, neuroimaging consistent with multifocal demyelination and absence of an alternate cause, a diagnosis of suspect yellow fever vaccine-associated autoimmune disease with central nervous system (CNS) involvement was made according to the CDC’s Yellow Fever Vaccine Safety Working Group case definition. The patient was treated with three days of methylprednisolone 1g daily followed by oral prednisolone 80mg daily and tapering fortnightly. There was rapid restoration of vision within days of commencing glucocorticoid therapy. A repeat MRI-Brain (figure 2) was performed six weeks later demonstrating significant reduction in the size and intensity of the occipital and parieto-occipital region lesions. The homonymous hemianopia had largely resolved at 3 months follow up.

Yellow fever remains a cause of significant morbidity and mortality in Africa and South America where an estimated 12% of infections result in severe disease with a case fatality rate of 20-50%. The introduction of the highly effective 17D vaccine in 1938 has significantly curtailed the devastating effects of this mosquito borne haemorrhagic fever. Serious adverse events related to vaccination are rare but include yellow-fever vaccine-associated neurotropic disease (YEL-AND) and viscerotropic disease (YEL-AVD). Viscerotropic disease results from dissemination of the vaccine strain of YF virus and results in multiple organ failure. YEL-AND may also result from direct CNS invasion of the vaccine
virus strain resulting in meningitis or encephalitis, or may be mediated through an autoimmune reaction, as in our case¹.

In Australia, yellow-fever vaccination is administered only by authorised yellow fever vaccination providers. Approximately 24,000 vaccinations are administered annually in Australia³. Spontaneous reporting of adverse events is via the Australian government Database of Adverse Event Notifications (https://daen.tga.gov.au/medicines-search/). From 1998 through to January 2024 and not including our case, there have been three reports of encephalitis in a 40, 59 and 69-year-old, two reports of YL-AND in a 48 and 79-year-old and two reports of aseptic meningitis in a 22 and 31-year-old. This is a passive reporting system with limited clinical details and inherent limitations for causality assessment. Assuming 600,000 vaccine recipients and including our cause, this data suggests reporting rates for YL-AND of 1.3 cases per 100,000 vaccine recipients. This rate is remarkably similar to surveillance data from the United States of America (USA) where surveillance data of 627,079 vaccine recipients also documented 7 cases of YL-AND leading to a reporting rate of 1.1 per 100,000 of STAMARIL vaccine recipients⁴. In both sets of surveillance data, no other cases were identified as having acute disseminated encephalomyelitis. McMahon et al. reported 15 cases of YL-AND from the Vaccine Adverse Events Reporting System used in USA, three of which were diagnosed as ADEM⁵. Patients presented with focal neurological deficits at days 7, 15 and 20 following receipt of the vaccination. While no images were provided, MRI scans were reported as showing acute demyelinating disease in 2 patients and retrobulbar optic neuritis in 1 patient.
In conclusion, our case provides representative MRI images of acute disseminated encephalomyelitis following yellow fever vaccination and serves as a reminder of this rare but serious adverse event.

References:


Figure legend:

Figure 1: Initial MRI (September 2023), with Post-Gadolinium Axial FLAIR Sequence and Diffusion Weighted Sequence.

Figure 2: Follow up MRI (October 2023), with FLAIR Sequences.