CASE REPORT

Yellow fever vaccine-associated neurological disease, a suspicious case

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SUMMARY

A 70-year-old man with known cardiovascular risk factors, presented with acute onset expression aphasia, agraphia, dyscalculia, right-left disorientation and finger agnosia, without fever or meningeal signs. Stroke was thought to be the cause, but cerebrovascular disease investigation was negative. Interviewing the family revealed he had undergone yellow fever vaccination 18 days before. Lumbar puncture revealed mild protein elevation. Cultural examinations, *Coxiella burnetti,* and neurotropic virus serologies were negative. Regarding the yellow fever virus, IgG was identified in serum and cerebrospinal fluid (CSF), with negative IgM and virus PCR in CSF. EEG showed an encephalopathic pattern. The patient improved gradually and a week after discharge was his usual self. Only criteria for suspect neurotropic disease were met, but it's possible the time spent between symptom onset and lumbar puncture prevented a definite diagnosis of yellow fever vaccine-associated neurological disease. This gap would have been smaller if the vaccination history had been collected earlier.

BACKGROUND

Yellow fever vaccine is quite frequently administered all over the word. It is important to be aware of its possible complications, namely this one, encephalitis, which might be mistaken for other conditions, as was the case with our patient. Since these occurrences are rare, this case report will help to keep in mind not only its existence but also the importance of having an updated vaccination history, even if a particular event seems to be straight forward.

CASE PRESENTATION

This case concerns a 70-year-old man who presented to the emergency room with expression aphasia, agraphia, dyscalculia, right-left disorientation and finger agnosia, with onset 12 hours before. There was no history of fever, and no meningeal signs were observed during the physical examination. Despite the initial CT scan being absent of acute lesions, he was admitted with the diagnosis of acute cerebrovascular accident (Aphasia+Gerstmann syndrome) and began the appropriate treatment in the emergency room. He had history of type 2 diabetes mellitus, arterial hypertension, hypercholesterolemia and was a heavy smoker. Two years before he had a myocardial infarction and a year after that a vertebrobasilar stroke from which he recovered without significant limitations. He had a known allergy to aspirin and was taking clopidogrel, oral nitrate, captopril and low-dose carvedilol. His diabetes was controlled with metformin, sitagliptin as well as insulin.

The patient underwent cerebrovascular disease investigation in which the echocardiogram revealed slight left ventricle dyskinesia with mild systolic dysfunction, and the holter had no relevant alterations. The carotid Doppler ultrasound showed atheromatous disease without haemodynamic relevance.

The patient was transferred to the ward on the fifth day of admittance, at which time he had only aphasia and periods of disorientation and agitation. An elevation in temperature (38°C) was detected, and he reported of a slight headache and muscle pain. On further interviewing the family we became aware that the patient was planning a trip to Angola and had undergone yellow fever vaccination 18 days before the beginning of the symptoms. There was no other relevant epidemiological history, namely recent trips, contact with animals or sick individuals. In fact, he had not left the city in over 6 months.

INVESTIGATIONS

The blood work showed no elevation of inflammatory markers (leucocytes 10,8 10^9/L—C reactive protein 0.1 mg/dL—erythrocyte sedimentation rate 30 s), despite a slight elevation of the α fraction on protein electrophoresis. Rapid plasma reagin and HIV 1–2 were negative. The MR with angiography (MRA) revealed mild microvascular leukoencephalopathy and chronic right parasagittal pontine lacunar infarct, without acute lesions.

As vascular cause became improbable, blood and urine samples were collected for culture and a lumbar puncture was performed without complications. The CSF was crystal clear with a cell count of 3 cells/μL, a slight elevation in protein content (75 mg/dL) and a mild hypoglycorrhachia (119 mg/dL) when compared to blood glucose (255 mg/dL). Cultural examinations were negative as were *Coxiella burnetti* and other neurotropic virus serologies in the CSF adequate for the seasonality and geographic area (*Herpesviridae* family (herpes simplex virus (HSV)-1, HSV-2, Varicella-zoster virus, Epstein-Barr virus and cytomegalovirus), enteroviruses and West Nile virus). Regarding yellow fever (YF) virus, the samples collected 25 days after vaccination were positive for IgG in serum and CSF, with negative IgM and virus PCR in CSF.

EEG revealed generalised slowing of the background activity, consistent with an encephalopathic pattern.

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OUTCOME AND FOLLOW-UP

The patient continued to improve spontaneously regarding thermal profile, speech and mental status. He was discharged after 12 days at the ward and achieved normalcy by the follow-up observation the next week. He went on his trip to Angola the following month without limitations.

DISCUSSION

Yellow fever virus is endemic to sub-Saharan Africa and tropical regions of South America.[1] Although most infections are asymptomatic, the WHO estimates there are 200 000 cases of clinical disease, resulting in 30 000 deaths each year.[1 2] These estimates have been questioned, and the continued occurrence of epidemics, particularly in Africa, indicate considerable disease burden. As no drug to date shown benefit, the treatment remains supportive in nature and prevention remains of the utmost importance.[1 2]

The vaccine, created in the 1930s, is a live attenuated virus. Currently, there are two equally effective substrains being manufactured (17DD in South America and 17D-204 everywhere else).[3 4] It is viewed as a safe and effective vaccine, conferring immunity 10 days after inoculation that's thought to be lifelong.[5] Despite this 10-year interval boosts are required for international travel to endemic regions and certain countries require evidence of vaccinations from entering travellers.[6]

Adverse reactions to the vaccine are divided into general mild events both local and systemic (38 per 100 000 vaccinees). Anaphylaxis is estimated to occur in 1.8 per 100 000 vaccinees, vaccine-associated neurological disease (YEL-AND) in 0.4–0.8 per 100 000 vaccinees and vaccine-associated viscerotropic disease (YEL-AVD) in 0.3–0.4 per 100 000 vaccinees. The overall rate for serious events is estimated to be 4.4–4.7 per 100 000 vaccinees.[7 8] Some studies suggest an even lower rate of adverse events.[9] However, viscerotropic disease incidence estimates vary widely and are associated with a mortality rate as high as 66%. Given the increased risk of fatal reactions in elderly males, many authorities would not vaccinate such men. In contrast, older women who do not have either an autoimmune disease or thymoma are not at increased risk of developing YEL-AVD.[10]

This case pertains to YEL-AND which is a rare event that, although serious, rarely results in death. Clinical manifestations occur as a result of direct invasion of the central nervous system (menningoencephalitis) or autoimmune manifestation to the vaccine (Guillain-Barré syndrome, acute disseminated encephalomyelitis and bulbar palsy).[2]

To improve the classification of events and its rating, the Yellow Fever Vaccine Safety (YFVS) Working Group of the Centers for Disease Control and Prevention devised case definition criteria (table 1).[6]

Our patient presented criteria for suspect neurotropic disease related to YFV: fever and headache lasting over 24 hours, focal neurological dysfunction, mental status change, elevated cerebrospinal fluid protein and EEG findings consistent with encephalopathy; onset of symptoms within 30 days of vaccination (17 days) and no evidence of an alternative diagnosis. Since we were unable to procure viral isolation on blood or ascertain its concentration, criteria for probable neurotropic disease could not be met.

The criteria for definite neurotropic disease is based on viral isolation (culture or PCR) or detection of specific IgM antibodies, which are not believed to cross the blood–brain barrier, in the cerebrospinal fluid.[2 11] We were once more unable to procure viral culture on the CSF sample, and both the virus amplification and IgM antibodies were negative.

A possible reason for this is the time interval between onset of symptoms and the performance of the lumbar puncture (9 days), particularly for the reverse transcription-PCR. At the time of CSF collection, the patient had already been improving steadily and we believe, past the acute phase of the encephalitis. Thus IgM and virus PCR were already undetectable.

Although we were unable to achieve definite criteria for YEL-AND, it's our belief that this was indeed the case. The lack of evidence of another cause, despite a thorough investigation, the timeline causality and good outcome without directed treatment, all support this hypothesis. Furthermore, neurological side effects to the vaccine are increased (1.8 vs 0.8 per 100 000 population) in the population aged >60 years, particularly in the first dose of the vaccine, which was the case with our patient.[7 8]

This case brings to light the importance of a thorough patient history (including vaccination). Considering the patient's prior medical history, the presenting symptoms had, in fact, a high probability of being caused by cerebrovascular disease. The fact that a stroke, particularly a minor one, might not be detected by CT until 12–24 hours after it's occurrence, prompted the request of an MRA which would increase the probability of detecting a recent lesion, even a minor one.[12] However, this examination took considerably more time to be performed than

Table 1 CDC's YFVS Working Group case definition for YEL-AND.[6]

Case ascertainment

Level 1: neurological disease

- Fever (≥100.5°F (>38.1°C) for >24 hours) and headache (>24 hours)
- Focal neurological dysfunction (including but not limited to ataxia, aphasia and paresis)
- Mental status change (confusion, lethargy, or personality change lasting >24 hours)
- New onset seizure or recurrence of previously controlled seizures
- Cerebrospinal fluid (CSF) pleocytosis (>5 WCC/mm)
- Elevated CSF protein (>1.5 times the normal limit)

Level 2: neurotropic disease

- Level 1 neurological disease, and one or more of the following:
- Neuroimaging consistent with inflammation (with or without demyelination)
- EEG finding consistent with encephalopathy

Case definitions

Suspect neurotropic disease

- Onset of symptoms and signs occurs within 1–30 days of vaccination with yellow fever vaccine, either given alone or in combination with other vaccinations;
- Level 2 neurotropic disease; and no evidence of other diagnoses

Probable neurotropic disease

- Suspect YEL-AND, and one or more of the following:
- Vaccine-type yellow fever viral isolation from blood (>7 days postvaccination)
- Yellow fever 17D§ virus concentration in serum on any day exceeds 3 $\log_{10}$ pfu/mL

Definite neurotropic disease

- Suspect YEL-AND, and one or more of the following:
- YF-specific CSF IgM
- Yellow fever 17D§ virus isolation from CSF
- Amplification of vaccine type virus§ from CSF

CDC, Centers for Disease Control and Prevention; YEL-AND, vaccine-associated neurological disease; YF, yellow fever; YFVS, Yellow Fever Vaccine Safety; WCC, white cell count.

the CT and further lengthened the delay before investigating other causes.

The time spent between admittance to the hospital and arrival in our ward, as well as the time it took to discover the inoculation status and exclude other causes, probably lost us the possibility of confirming the diagnosis.

Learning points

- Never neglect the importance of a patient's vaccination history.
- Vaccine-associated neurological disease definite diagnosis is based on IgM-specific antibody detection or viral isolation in cerebrospinal fluid (CSF).
- Suspicion and time sensitive CSF collection and analysis are of the utmost importance.

Contributors PB participated in bibliographic research, manuscript writing. PP was involved in admittance to the emergency room data collection and manuscript review. AN was involved in patients follow-up consult and manuscript review. PA was involved in the daily management of the patient during his stay at our ward, and contributed to manuscript review.

Competing interests None declared.

Patient consent Obtained.

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