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YELLOW FEVER VACCINE-ASSOCIATED NEUROTROPIC DISEASE: A CASE REPORT OF A 9 –MONTH OLD INFANT AND REVIEW OF LITERATURE.

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ABSTRACT

INTRODUCTION

Yellow fever vaccine-associated neurotropic disease (YEL-AND) is a rare and serious complication following vaccination with the 17D live attenuated yellow fever vaccine. Cases of YEL-AND present as acute inflammatory demyelinating polyneuropathy, acute disseminated encephalomyelitis, and meningo-encephalitis and encephalitis. To date, only a few cases have been reported in the literature in children.

METHODS/SUBJECTS:

We present the case of a 9-month-old male who developed YEL-AND. He suffered "3 episodes of unprovoked generalized tonic-clonic seizure," the first occurring within 2 hours of receiving a dose of the Yellow Fever vaccine, Measles, and Meningococcal vaccines. He was lethargic for 28 hours and had intermittent inconsolable cries for 48 hours, low-grade fever, and loss of motor milestones (sitting and standing).

Available laboratory investigations and neuroimaging ruled out other possible causes. He was treated with anticonvulsants and IV Methylprednisolone and made a significant recovery and was discharged on the sixth day and has remained stable on follow-up. His clinical presentation, neuroimaging, and challenges in his management are discussed in this case report.

CONCLUSION

The licensed Yellow fever vaccines are safe, effective for the prevention of Yellow fever, and highly recommended, however, it is not completely devoid of serious adverse reactions. This case highlights a possibility of a very early onset of YEL-AND in children and should be suspected in individuals with a temporal relationship of symptom onset to vaccination.

KEY WORDS

Immunization; Yellow fever vaccine; neurotropic disease; Seizures, adverse drug reaction reactions, Encephalitis

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INTRODUCTION

Yellow fever (YF) is an acute viral hemorrhagic fever caused by a mosquito-borne arbovirus of the family flaviviridae with a significant global impact on public health. The WHO estimates there are 200 000 cases of clinical disease, resulting in 30 000 deaths each year.¹ The Nigeria Centre for Disease Control (NCDC) says 1,715 suspected cases of YF, were reported so far this year as at July 2023 in Nigeria.² Concerted efforts are being made by authorities to bring this epidemic under control in the midst of other simultaneous outbreaks of other infectious diseases in the country.³ Yellow Fever vaccines have been available since the 1930's and constitute the most successful, cost-effective and safe public health interventions to control the disease. A single dose of the vaccine provides effective immunity within 30 days of vaccination for 99% of the vaccine, conferring sustained immunity with life-long protection.⁴ Currently, YF vaccines recommended by the World Health Organization⁵ are from 17D ahypersensitive reactions, YF vaccine-associated neurotropic disease (YEL-AND), and YF vaccine-associated viscerotropic disease (YEL-AVD).⁸ A study in eight African countries put the incidence of serious adverse YFV reactions was 0.058 per 100,000 doses. and 17DD sub strains and they have similar safety and immunogenicity profiles.^{6,7} Although, the YF vaccines are safe and effective, rare serious adverse events (SAEs) including neurological complications have been reported over the years. They are classified as hypersensitive reactions, YF vaccine-associated neurotropic disease (YEL-AND), and YF vaccine-associated viscerotropic disease (YEL-AVD).⁸ A study in eight African countries put the incidence of serious adverse YFV reactions was 0.058 per 100,000 doses.⁹

Yellow Fever vaccine-associated neurologic disease (YEL-AND) is a rare but potentially severe adverse event following immunization (AEFI). The incidence of YEL-AND varies between studies; in the United States and Brazil, the estimated range is 0.2–0.94 cases/100,000 doses.⁶ A study done in 8 African countries found an incidence of 0.016 per 100,000 vaccine doses for YEL-AND.⁹ There is evidence that an overly robust or dysregulated immune response leading to neuroinflammation may contribute to the development of neurological complications, such as encephalitis or acute disseminated encephalomyelitis (ADEM).¹⁰ The risk factors for this event in children include age less than 9 months and congenital or acquired immunodeficiency. While in adults, age greater than 60 years and

immunosuppression are risk factors. However, several cases with unknown risk factors have been reported, suggesting the involvement of other host immunological features.¹¹ Almost all cases of reported YEL-AND have been in first-time vaccine recipients.¹²

Case definitions for the diverse clinical manifestations has been proposed by the Centers for Disease Control and Prevention (CDC) "Yellow Fever Vaccine Safety Working Group" and the Brighton collaboration. These two bodies have proposed a surveillance case definition for YEL-AND including meningo-encephalitis, aseptic meningitis, encephalitis, Guillain-Barré syndrome (GBS), and acute disseminated encephalomyelitis (ADEM) 6, all distinct from each other. The criteria for definitive diagnosis requires one of the following: isolation of vaccine virus strain in serum or CSF, virus quantitation in serum, YF-specific IgM in CSF or amplification of vaccine virus strain in the CSF.¹³ Meeting this criteria could be challenging in resource constrained settings, however there are diagnostic criteria for suspected cases of YEL-AND (Table I).

There is dearth of data on YEL-AND especially in children especially from the sub-Saharan Africa, we report a case of YF vaccine associated neurotropic disease in a 9-month old, with a review of Literature.

CASE REPORT

A 9-month old male who was previously healthy, suffered "three episodes of unprovoked generalized tonic-clonic seizure," the first occurring within two hours of receiving a full dose of YF vaccine, Measles and Meningococcal vaccines. He was lethargic for about 28 hours and had intermittent inconsolable cries for 48 hours and loss of motor milestones (sitting and standing). The child had no prior history of seizure or developmental delay and his birth history was uneventful, he had no history of previous hospitalizations, no use of medications, allergies, there was no contact with ill individuals or any remarkable changes during the last months of life. He had previously received all immunizations appropriate for age.

The child was well nourished. There was no retinal abnormalities on fundoscopic examination, no bulging fontanelle, nuchal rigidity or other signs of meningeal irritation. There was no photophobia, sensory deficits on neurological examination. Tendon reflexes were normal. The vaccines were of good quality and there was no immunization errors. The Full

blood count, Electrolytes and Liver function tests were normal. He was HIV negative. Malaria parasite test was negative. Research for antibodies (IgM) against yellow fever was requested, but was not done due to unavailability of the test resource. A brain MRI scan done on the third day showed brain oedema with punctate haemorrhages within the deep white matter and mild cortical atrophy, an electroencephalographic examination revealed generalized low-amplitude slowing of background activity consistent with encephalopathy; no epileptiform activity or organized electroencephalographic seizures were seen and Cerebrospinal fluid analysis was also normal (done on the first day). A presumptive diagnosis of meningo-encephalitis was made. YEL-AND with encephalitis was also considered because of the patient's vaccination history. Specimens of blood were obtained for blood tests, sample was collected for CSF analysis, and Ceftriaxone and Aciclovir, IV Phenytoin and Phenobarbitone were administered. After negative cultures from the CSF sample, the antibiotics were suspended. He was treated with anticonvulsants and Intravenous Methyl prednisolone with a favourable progression and was discharged after 6 days. He was discharged on oral steroids and Phenobarbitone which were successfully weaned over 2 weeks. He has remained stable over a six months follow-up. Considering the history of immunization history and a combination of clinical, laboratory and radiological data, a diagnosis as suspected of YEL-AND with encephalitis was sustained. This case report highlights the need for high index of suspicion and the challenges of diagnosis in middle and low income countries.

DISCUSSION AND LITERATURE REVIEW

The YF vaccine is generally well tolerated and efficient with low rates of adverse effects. However, severe adverse reactions, such as neurotropic diseases estimated at eight individuals per one million vaccines administered can occur.¹⁴

The mechanisms underlying the occurrence of YEL-AND remain unknown. It is postulated that it is likely related to the manner in which 17D was attenuated to make the vaccine: serial passages through mouse and chick brains, leading to neuro-adaptive but otherwise attenuating mutations.¹⁴ Conversely, viral and host factors have been postulated to explain the basis of YEL-AND.¹¹ Neuro-invasion by the 17D virus resulting in neurologic manifestations have been implicated, antibody and T-cell triggered autoimmunity may also be

The clinical presentation of YEL-AND includes a high grade fever, and headache, accompanied by focal neurological dysfunction, including, but not limited to, ataxia, aphasia, and paresis. More severe cases could show mental status changes, confusion, lethargy, personality changes, the new onset of seizures, or a recurrence of previously controlled seizures.¹¹ Our patient had fever, seizures, lethargy and irritability and loss of control of truncal and neck musculature. This is the first case where rapid onset encephalopathy was reported in children with following YF vaccine with associated neuroimaging findings. In this case report, a previously well infant developed signs and symptoms of neurotropic disease with encephalitis within 24 hours of YF vaccine administration. The clinical course in terms of onset time of the adverse events for the patient described here is unusual in comparison to the profiles of the cases reported so far. Previous reports in literature shows a mean time of AR after VAYF ranging between 3 and 27 days.¹⁵ Breugelmans et al 2013 in study on the adverse reactions from eight countries in Africa reported two cases of onset symptom less than 24 hours after immunization.⁹ These cases were adult patients.

Initially, although we had a suspicion of reaction to the vaccine, we opted to keep ceftriaxone and acyclovir until we got negative results of cultures for Meningitis. Study of antibodies against YF virus was not done due to logistical difficulties. However the brain MRI showed punctate haemorrhages in the subcortical white matter of the brain (figure 1). Reports of MRI imaging findings in YEL-AND have been limited to date. MRI findings in YEL-AND may not show any neurologic changes.^{15,18} Gandolfi et al⁸ reported focal pachymeningeal enhancement in the frontal brain area in a 10-month old infant who had symptoms of fever, increased somnolence, seizures 10 days after receiving the first shot of YF vaccine. Diffuse leptomeningeal enhancement have also been reported. Our patient had mild cortical atrophy, similar findings were reported by Lecomte et al.¹⁷ Our patient's EEG findings were consistent with encephalopathy with generalized slowing and similar to other report by Gandolfi et al⁸ which showed bilateral degree I slowing, without epileptiform disorder. In other reports, the EEG was either unremarkable or demonstrated disorganized background or revealed generalized low-amplitude slowing.¹⁴

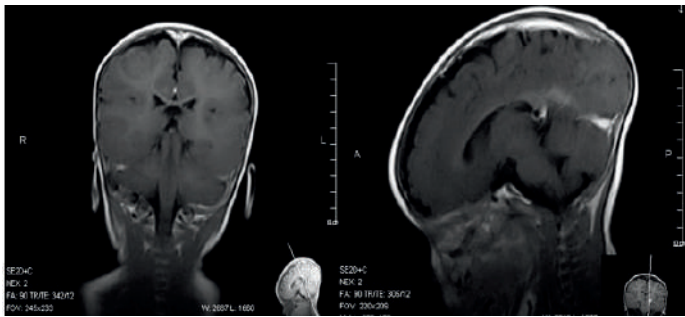


Fig 1. MRI showing cortical atrophy in the fronto-parietal area and punctate haemorrhages in the subcortical white matter

Treatment is symptomatic and also depends on the particular clinical syndrome. Treatment for encephalitis is supportive, and manifestations such as seizures or autonomic dysfunction should be managed according to acceptable medical standards for each disorder.^{15,18} Our patient received anticonvulsants and steroids. The clinical evolution of the patient was favorable, with recovery of neurologic deficits in a short period of time without any significant sequelae. Although the majority of children who develop YEL-AND do recover, there have been reports of fatal cases.⁹ The risk of developing YEL-AND is higher in infants under six months old, for whom the yellow fever vaccine is contraindicated.^{10,14}

According to the Centre for Disease Control and Prevention (CDC) the diagnostic criteria for YEL-AND, for a case to be considered 'probable' or 'definite' requires one of the following: isolation of vaccine virus strain in serum or CSF, virus quantitation in serum, YF-specific IgM in CSF or amplification of vaccine virus strain in the CSF.¹³ In the absence of isolation of YF vaccine virus in CSF or YF specific IgM in CSF, the definition of a suspected YEL-AND case according to the CDC criteria (Table I), requires the presence of fever, seizures, neurological impairment occurring within the first 30 days following yellow fever vaccination with evidence of acute brain lesions either by Electroencephalography or neuroimaging and laboratory investigations excluding other causes.^{6,8} These criteria render them poorly suited to diagnose YEL-AND in resource-limited settings or during massive vaccination campaigns, making the diagnosis challenging. Based on the CDC diagnostic criteria, the index case met the criteria for a suspected case, as he had clinical signs of encephalitis, neuroimaging consistent with inflammation and an EEG consistent with an encephalopathy

Table I. CDC's Yellow Fever Vaccine Safety Working Group case definition for yellow fever vaccine-associated neurological disease. (Box adapted from Staples et al; 2010)

'Suspect' neurotropic disease

1. Neurological disease presenting with one or more of the following:
 - Fever, focal neurological dysfunction, mental status change, seizures, cerebrospinal fluid (CSF) pleocytosis, elevated CSF protein.
2. One or more of the following:
 - Neuroimaging consistent with inflammation.
 - Electroencephalogram finding consistent with encephalopathy.
3. Symptoms occur within 1 and 30 days of vaccination with yellow fever (YF) vaccine, either given alone or in combination with other vaccinations.
4. No evidence of other diagnoses.

'Probable' neurotropic disease

1. Fulfils criteria for suspect neurotropic disease.
2. One or more of the following:
 - YF vaccine strain isolated from blood (>7 days postvaccination).
 - YF vaccine virus concentration in serum >1000 pfu/mL (on any day).

'Definite' neurotropic disease

1. Fulfils criteria for suspect neurotropic disease.
2. One or more of the following:
 - YF vaccine strain isolated from CSF.
 - YF-specific IgM detected in CSF.
 - Amplification of YF vaccine strain from CSF.

The WHO recommends a causality assessment in suspected cases of acute adverse reactions following immunization.¹⁹ Causality assessment is the systematic review of the case that aims to determine the likelihood of a causal association between the event and the vaccine(s) received. The lack of evidence of another cause, despite available investigation, the timeline causality and good outcome without directed treatment, all support this hypothesis that the index case meets the CDC criteria for diagnosis for "Suspected YEL-AND". We attempted a short review of published literature using the databases (PubMed, Medline) with the keywords "YELLOW FEVER AND "NEUROTROPIC" or "YELLOW FEVER VACCINE" AND "NEUROLOGICAL" AND "ADVERSE EVENT" AND "CHILDREN" AND "PAEDIATRICS". Five articles that reported cases of YEL-AND in children were identified and summarized in Table II.^{8,9,16,20,22} The data showed that few cases has been reported in children, with a Male to Female ratio of 1:1

and an age range of 9 months to 4 years. Both types of vaccines were implicated with the adverse effects and presented after administration of the first dose. This findings were consistent with our case report.

Table II. Cases of Yellow Fever vaccine-related neurological disease in Children reported in main databases

Cases of Yellow Fever vaccine-related neurological disease in Children reported in main databases

Ref	Age/gender	Clinical features	Clinical outcome	Imaging findings	Yellow fever Vaccine given	Year/ Country
De oliviera et al	M/9months	Meningitis	Recovered	Nil abnormality	Not reported	Brazil
Gandolfi et al	F/4years F/10 months F/9 months	Meningoencephalitis	Recovered	Diffuse or focal leptomenigeal enhancement, increased dimensions of the ventricular system	17DD	Brazil
Gerin et al	M/4years	Meningoencephalitis	Recovered	Multifocal white matter lesions	17D-204	France
Receveur et al	F/3 years	Encephalitis	Died	Not available	17D	USA
Breugelmans	M/4 years M/ 4years	Facial paralysis Lower extremity muscle spasm and incordination	recovered	Not reported	17D-204	Mali Senegal

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ABBREVIATIONS

ADEM Acute Disseminated Encephalomyelitis
CDC Centres for Disease Control

CSF Cerebrospinal fluid
EEG Electroencephalogram
GBS Guillain-Barré syndrome
IgM Immunoglobulin M
MRI Magnetic Resonance Imaging
NCDC Nigeria Centre for Disease Control
WHO World Health Organization
YF Yellow fever
YEL-AND Yellow Fever vaccine Associated Neurotropic Disease

SOURCE(S) OF SUPPORT

Nil

CONFLICTING INTEREST

Nil

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