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Short Communication

Potential autoimmune encephalitis following yellow fever vaccination: A report of three cases

Bruno Fukelmann Guedes [a,*], Ana Freitas Ribeiro [b,h], Lecio Figueira Pinto [a], José Ernesto Vidal [c,d,i], Fernanda Gurgel de Oliveira [e], Jaques Sztajnbok [f,g], Augusto César Penalva de Oliveira [d], Mateus Mistieri Simabukuro [a]

[a] Departmento de Neurologia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[b] Departamento de Epidemiologia, Instituto de Infectologia Emilio Ribas, São Paulo, Brazil
[c] Departamento de Moléstias Infecciosas e Parasitárias, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[d] Departmento de Neurologia, Instituto de Infectologia Emilio Ribas, São Paulo, Brazil
[e] Departamento de Infectologia, Instituto de Infectologia Emilio Ribas, São Paulo, Brazil
[f] Unidade de Terapia Intensiva, Instituto de Infectologia Emilio Ribas, São Paulo, Brazil
[g] Instituto da Criança do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[h] Universidade Nove de Julho
[i] Laboratório de Investigação Médica em Protozoologia, Bacteriologia e Resistência Antimicrobiana (LIM 49), Instituto de Medicina Tropical, Universidade de São Paulo, São Paulo, Brazil

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ABSTRACT

Meningoencephalitis following yellow fever vaccination is considered a viral neuroinvasive disease. We describe three patients with typical autoimmune encephalitis syndromes that developed 1–27 days following yellow fever vaccination. Anti-*N*-methyl-D-aspartate-r antibodies were identified in the CSF and serum of two patients and the other case was associated with anti-neurexin-3 antibodies. One case was confirmed as vaccine-associated neurotropic disease due to reactive CSF yellow fever IgM, which suggested an infectious-autoimmune overlap mechanism. Two aditional cases of Anti-*N*-methyl-D-aspartate-r encephalitis were identified in the literature review. Antibody-positive autoimmune encephalitis should be included in the differential diagnosis of neurologic adverse events following yellow fever vaccination.

1. Introduction

The yellow fever (YF) vaccine may rarely cause serious adverse events which include viscerotropic disease and neurologic disease (YEL-AND). Viscerotropic disease mimics the typical disease associated with wild virus infection, while YEL-AND can manifest as neurotropic (meningoencephalitis) or autoimmune disease. Current guidelines for the diagnosis of YEL-AND, from the Yellow Fever Vaccine Working Group (YFVWG), and the Brighton Collaboration, recognize only Guillain-Barré and Miller-Fisher syndromes (Sejvar et al., 2011; Staples et al., 2010), acute disseminated encephalomyelitis (Sejvar et al., 2007; Staples et al., 2010), and myelitis (Sejvar et al., 2007) as potential autoimmune YEL-ANDs. Meningoencephalitis is considered a neuroinvasive disease, for which the diagnosis relies heavily on demonstration of CNS viral invasion by an YF-IgM assay or through detection of vaccine-strain RNA in the cerebrospinal fluid (CSF) (Sejvar et al., 2007; Staples et al., 2010; Tapiainen et al., 2007). Autoimmune encephalitis (AE) with antibodies against neuronal-cell-surface and synaptic proteins were first described by Josep Dalmau in 2007, so this important cause of encephalitis, which is associated with an increasing array of infectious causes, could be underrepresented in these routinely used case definitions that were issued between 2002 and 2007.

In the 2017–2018 summer (November through march), a serious outbreak of yellow fever (YF) took place in the greater São Paulo metropolitan area, Brazil (Kallas et al., 2019). Vaccination against yellow fever was not routine, and the population was largely unvaccinated. A massive vaccination program was carried out and over 10 million total doses were distributed throughout the region (Programa Nacional de Imunizações, unpublished communication). Several cases of YF vaccine neurological adverse reactions were reported.

* Corresponding author at: Av. Dr. Enéas de Carvalho Aguiar, 255, 5° andar, sala 5084, Cerqueira César, 05403-900 São Paulo, SP, Brazil.
E-mail address: bruno.guedes@hc.fm.usp.br (B.F. Guedes).

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In a recent retrospective, multi-center review of 50 suspect YEL-AND during the campaign, we found 8 patients with encephalitis (Ribeiro et al., 2021), including three patients with unique presentations associated with antibodies against cell surface and synaptic proteins. Compared to the other five encephalitis cases, these patients tended to have more psychosis (100% vs 0%) and seizures (100% vs 20%) and much longer lengths of hospital stay (range 21–286 days vs 0–29 days). These novel potentially vaccine-associated encephalitis cases are described extensively in this report. Antibodies against cell-surface or synaptic proteins were assessed by rat brain immunohistochemistry and cell-based-assays with HEK 293 cells in serum and CSF samples at dr. Josep Dalmau's laboratory (IDIBAPS, Barcelona, Spain), as described (Dalmau et al., 2008; Gresa-Arribas et al., 2016).

2. Case reports

2.1. Case 1

A 42-yr-old woman developed headache, fever and malaise one day after a first-dose of the yellow fever vaccine. On post-vaccination day four, she had two bilateral convulsive seizures followed by confusion and psychosis. She was unable to recognize relatives and had hallucinations, persecutory delusions and agitation, and was treated for psychosis and epilepsy with risperidone, diazepam, carbamazepine, and phenobarbital. On post-vaccination day 9, the patient was admitted to the emergency department with impaired consciousness and was intubated, then transferred to a tertiary referall center. On arrival, she was still febrile and tachycardic. An electroencephalogram showed generalized background slowing. CSF studies revealed 15 white blood cells (WBC)/mm^3 and 28 mg/dL of protein. CSF-yellow-fever IgM (CSF-YF-IgM) was non-reactive, and blood YF virus RNA was not detected with RT-PCR. Anti-neurexin3 IgG antibodies were detected in serum and CSF. This patient also had antinuclear antibodies (titer, 1:1280), positive serum anti-DNA and anti-SSA antibodies, and low complement levels. A detailed history revealed previous episodes of arthritis, and she was ultimately diagnosed with systemic lupus erythematous (SLE). The disease course was complicatated by refractory status epilepticus and difficult-to-treat psychosis. She was treated with high-dose methylprednisolone (5 g over five days) and intravenous immunoglobulins (2 g/Kg total dose) during the first month of hospitalization, followed by continuous oral azathiproine, with gradual recovery over the following months. Three months after discharge, she walked with unilateral support, had mild and occasional persecutory delusions, and was otherwise functional.

2.2. Case 2

Twenty-one days after receiving her first dose of yellow fever vaccine, a 14-yr-old girl developed headache followed within a few days by severe depressive symptoms, severe insomnia and finally psychosis. She was started on haloperidol and promethazine. Three days after the onset of psychosis, the patient developed partial seizures, neuroleptic malignant syndrome and rapidly progressive encephalopathy requiring intubation. Brain-MRI and CSF studies were normal. EEG showed increased, diffuse theta activity. NMDA-r IgG antibodies were identified in both serum and CSF. She recovered gradually with high-dose intravenous methylprednisolone and plasma exchange, and was back to school 1 month after discharge. A CSF sample collected three months after symptom-onset detected YF-IgM antibodies.

2.3. Case 3

A 39-yr-old women presented with fever, insomnia, vertigo, vomiting, malaise, weight loss, and generalized anxiety, 23 days after receiving a first dose of yellow fever vaccine. She was diagnosed with panic disorder and labirinthitis. The patient was first seen by a neurologist 45 days after symptom-onset. Neurological examination then showed restlessness, generalized myoclonus, ataxia and opsoclonus. CSF showed 50WBC/mm^3 and 50 mg/dL of protein. Brain-MRI was unremarkable and EEG revealed generalized background slowing. Molecular and immunological tests for yellow fever were not performed in serum or CSF. Anti-NMDA-r IgG antibodies were identified in both serum and CSF. She developed severe encephalopathy requiring intubation and high doses of anesthetics for control of agitation, and recovered partially over the first first month of hospitalization, after first-line treatment with methylprednisolone (5 g over five days) and intravenous immunoglobulins (2 g/Kg). Due to incomplete recovery, she was given second-line threapy with rituximab (two 1 g doses, two-weeks apart, at hosptial month 5) and intrevenous cyclophosphamide (750 mg, monthly, at hosptial months 3, 7, 8, 9), as suggested for patients with refractory disease (Titulaer et al., 2013). She was discharged home 9 months after admission with residual treatment-resistant epilepsy but good cognition.

Whole-body CT was performed in all patients at admission and on follow-up, showing no signs of cancer. All patients received yellow fever vaccination alone.

3. Discussion

We found two previous published cases of antibody-positive AE following YFV. First, a Brazilian 10-month old previously healthy child, who presented with seizures, chorea and encephalopathy four days after YFV and was diagnosed with anti-GABAaR encephalitis (Spatola et al., 2017). Second, a young woman that developed seizures, psychosis and EEG slowing 27 days after YFV. CSF and serum tested positive for anti-NMDA-r IgG. The patient improved completely over a few months with anticonvulsants, steroids and plasma exchange (Hozáková et al., 2018). Clinical and laboratory data from these two cases and the three patients in this report are summarized in Table 1.

Although encephalitis with antibodies against cell surface and synaptic proteins can be triggered by central nervous system infections (Armangue et al., 2015), it is usually considered a paraneoplastic or post-infectious autoimmune disease. Several case reports propose anti-NMDA-r encephalitis may be also associated with tetanus, diphtheria, pertussis, and polio (Tdap-IPV, Repevax®) (Endres et al., 2019; Hofmann et al., 2011), H1N1 (Dalmau et al., 2011), human papillomavirus (Blitshteyn and Brook, 2017), and Japanese encephalitis (Wang, 2017) vaccines.

Whether yellow fever vaccination caused AE in our cases is uncertain, specially in case#1. Anti-neurexin antibodies are strongly associated with systemic autoimmune disease, and this patient had several symptoms consistent with lupus that predate vaccination in about 6 months. Moreover, neurological symptoms developed shortly after vaccination.

However, exacerbation of underlying systemic autoimmune disease with central nervous system activity is a potential disease mechanism. In SLE, influenzae vaccination can temporarily increase anti-nuclear antibodies and anti-double-stranded DNA titers (Wiesik-Szewczyk et al., 2010), and polio vaccine can lead to an increased disease flare rate (Schattner et al., 1992). Patients with Sjogren's syndrome may also exhibit increasing autoantibody titers with other signs of in vitro activation following influenza vaccines (Brauner et al., 2017). Vaccines can also trigger or exacerbate central nervous system inflammation in immune-mediated neurological diseases. Clinicians must be cautious when prescribing YFV to multiple sclerosis patients, due to risk of increasing disease activity (Farez and Correale, 2011).

Endres et al. described the case of a young woman who developed psychosis three days after receiving a Tdap-IPV booster dose. Investigation revealed positive serum anti-NMDA-r IgG antibodies and altered regional brain metabolism. They proposed anti-NMDA-r antibodies were already present before vaccination. Preexisting specific T- and B-lymphocyte clones could have been re-stimulated, leading to excessive

Table 1.
Clinical and laboratory data on five patients with autoimmune encephalitis following yellow fever vaccination

Study	Age (yrs), sex	Clinical features	Timing of yellow fever vaccine	CSF findings	Serum YF IgM/PCR	CSF YF IgM/PCR	Antibodies	Aditional info
Case #1	42 F	Headache, fever, malaise -> seizures- > psychosis- > status epilepticus	One day before headache and fever. 4 days before first seizure	15 cells/mm^3 protein: 28 mg/dL	NP/NP	−/−	Neurexin-3	Positive anti-DNA and anti-SSA antibodies, low complemente. Probable lupus erythematous
Case #2	14 F	Psychosis - > encephalopathy with coma	21 days before psychosis	5 cells/mm^3 protein: 45 mg/dL	NP/NP	+/−	NMDA-R	CSF-YF-IgM and PCR not performed at presentation, only three months after presentation
Case #3	39 F	Fever, vertigo malaise and anxiety - > opsoclonus-myoclonus-ataxia syndrome plus encephalopathy	23 days before fever and vertigo. 45 days before admission	50 cells/mm^3 protein: 50 mg/dL	NP/NP	NP/NP	NMDA-R	Typical opsoclonus-myoclonus-ataxia plus encephalopathy
Hozáková et al., 2018	17 F	Fever, anorexia, seizure - > psychosis, catatonia ataxia, epilepsy, tachicardia	27 days before fever and anorexia. 30 days before first seizure	"standard"	Not reported	Not reported	NMDA-R	Biphasic disease. Initial recovery followed by dementia and worsening over several months
Spatola et al., 2017	10mo F	Focal motor seizures - > irritability, chorea, orofacial and limb dyskinesias, nystagmus- > refractory status epilepticus, autonomic failure	4 days before symptom-onset. 3 weeks before dyskinesias	"normal cell count and protein concentration"	Not reported	Not reported	GABAaR	Progressive but partial recovery at 8 months post-treatment

F, female; CSF, cerebrospinal fluid; YF, yellow fever; PCR, polymerase chain reaction; +, reactive/detected; −, non-reactive/not detected; NP, not performed.

antibody synthesis (Endres et al., 2019). It is possible that YFV led to exacerbation of LES activity or increased antibody production in a similar manner, which could be associated with the development of anti-neurexin encephalitis symptoms in case #1.

One patient from our series had reactive CSF-YF-IgM and met the diagnostic criteria for definite neurotropic disease (Staples et al., 2010; Sejvar et al., 2007), even though the clinical presentation was typical of anti-NMDA-r encephalitis. Whether this means CNS invasion with vaccine-strain yellow fever virus caused the AE is debatable. The other two cases met the YFVWG suspect neurotropic (Staples et al., 2010) and the Brighon Collaboration's encephalitis case definitons (Sejvar et al., 2007), but lack of reactive CSF-YF-IgM precludes causal associations with current criteria.

4. Conclusions

This study shows encephalitis following YFV may also have an autoimmune nosology, but the exact mechanism of disease is unknown. When vaccine-associated AE is suspected, serum and CSF testing for autoantibodies could be a valuable addition to YF-IgM.

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Declaration of Competing Interest

None.

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