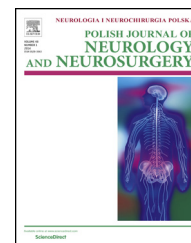


Available online at www.sciencedirect.com

ScienceDirect

journal homepage: <http://www.elsevier.com/locate/pjnns>

Case report

Yellow fever vaccine-associated neurotropic disease (YEL-AND) – A case report

Jolanta Florczak-Wyspiańska^{*}, Ewa Nawotczyńska, Wojciech Kozubski

Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland

ARTICLE INFO

Article history:

Received 6 March 2016

Accepted 14 September 2016

Available online 22 September 2016

Keywords:

Yellow fever vaccine

Adverse event

Neurological disease

ABSTRACT

Yellow fever (YF) is a mosquito-borne viral hemorrhagic fever, which is a serious and potentially fatal disease with no specific antiviral treatment that can be effectively prevented by an attenuated vaccine (YEL). Despite the long history of safe and efficacious YF vaccination, sporadic case reports of serious adverse events (SAEs) have been reported, including yellow fever vaccine-associated neurotropic disease (YEL-AND). YEL-AND usually appears within one month of YF vaccination, manifesting as meningoencephalitis, Guillain-Barré syndrome (GBS) or acute disseminated encephalomyelitis (ADEM). We report a case of YEL-AND with meningitis presentation in a 39-year-old Caucasian man without evidence of significant risk factors, which was confirmed by the presence of the YF virus and specific immunoglobulin G (IgG) antibodies in the cerebrospinal fluid (CSF). In conclusion, we should stress the importance of balancing the risk of SAEs associated with the vaccine and the benefits of YF vaccination for each patient individually.

© 2016 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

1. Introduction

Yellow fever (YF) is a viral hemorrhagic fever, which is a vector-borne disease resulting from transmission of the yellow fever virus (YFV) to a human from the bite of an infected mosquito, *Aedes* or *Haemagogus* species [1,2]. YFV is a single-stranded ribonucleic acid (RNA) virus that belongs to the genus *Flavivirus* [1,2]. YF is endemic to sub-Saharan Africa and tropical South America and is estimated to cause 200,000 cases of clinical disease and 30,000 deaths annually [1,2]. Clinically, the disease varies from a mild, undifferentiated febrile illness to a severe disease with jaundice, hemorrhagic

manifestation and hepatorenal failure marked by a case-fatality ratio of 20–50% [1–3]. Differences in viral strains and host immune factors are probably responsible for the range of clinical symptoms [1]. Because no specific antiviral treatment exists for YF, prevention is critical to lower disease morbidity and mortality. All residents and travelers to areas in which YF is endemic should be warned of the risk of contracting the disease and should be advised about available preventive measures [2]. Immunization, supplemented with prevention of mosquito bites, is now the most important method of YF prevention [1]. Vaccines against YF have been available since the 1940s and are responsible for a significant reduction of disease occurrence [1,4].

^{*} Corresponding author at: Department of Neurology, Poznan University of Medical Sciences, Przybyszewskiego 49 St., 60-355 Poznan, Poland. Tel.: +48 61 8691 454; fax: +48 61 8691 697.

E-mail address: jolaflorczak@op.pl (J. Florczak-Wyspiańska).

<http://dx.doi.org/10.1016/j.pjnns.2016.09.002>

0028-3843/© 2016 Polish Neurological Society. Published by Elsevier Sp. z o.o. All rights reserved.

All current YF vaccines derive from the 17D strain: 17DD and 17D-204 [1,2]. The live attenuated YF vaccine (YEL) is one of the safest and most efficacious vaccines ever made [5]. Seroconversion occurs in >95% of recipients by 10 days after vaccination [2,5]. According to the World Health Organization's (WHO) International Health Regulations (IHRs), the certificate of immunization for travelers is valid for 10 years after the most recent YF vaccination [4]. Neutralizing antibodies (NAs) against YFV, estimated by means of a plaque reduction neutralization test (PRNT), are considered to be the best surrogate marker for protection against YF [4,6]. Despite a long history of safe and efficacious YF vaccination, sporadic cases of serious adverse events (SAEs) have been reported, including severe allergic reactions, neurotropic disease (yellow-fever vaccine-associated neurotropic disease, YEL-AND) and viscerotropic disease (yellow-fever vaccine-associated viscerotropic disease, YEL-AVD) [3,4]. The last one is especially notable for its lethality [7]. YEL-AVD is an acute multi-organ dysfunction resembling a fulminant infection by wild-type YFV, with manifestations that include fever, jaundice, hepatitis, renal failure, thrombocytopenia, bleeding dyscrasia and respiratory failure [8]. Incidence of YEL-AVD is approximately 0.4 per 100,000 doses of vaccine administered, and the case-fatality ratio is estimated at 65% [2,9,11]. YEL-AND appears typically within one month after YF vaccination, manifesting itself as meningoencephalitis, Guillain-Barré syndrome (GBS) or acute disseminated encephalomyelitis (ADEM) [2,10]. Its estimated incidence is 0.4–0.8 per 100,000 doses administered [2,9,11]. Although the majority of patients recover without sequelae [1–3], a few reports of fatal YEL-AND have been published [5,8,10]. The meningoencephalitis cases were considered to definitely have been caused by the YF vaccine if 17D-204 YFV was isolated from the cerebrospinal fluid (CSF) and/or 17D-204 YFV RNA was amplified from CSF by nucleic acid-amplification testing (for example RT-PCR, reverse-transcription polymerase chain reaction), or the YFV-specific immunoglobulin M (IgM) antibody was found in CSF by IgM-capture ELISA [2,5,10]. ADEM and GBS are thought to be associated with autoimmune mechanisms in which pathogenic autoantibodies are generated in response to an antecedent stimulus [2,10].

The YF vaccine is contraindicated in several situations, e.g. in allergy to YF vaccine components, age <6 months, symptomatic human immunodeficiency virus (HIV) infection or CD4 T-lymphocyte count <200 cells/mm³, thymus disorders associated with abnormal immune cell function, primary immunodeficiency, malignant neoplasm, organ transplantation, and immunosuppressive or immunomodulatory therapy [2,4]. Precautions for its use include an age of 6–8 months, an age over 60 years, asymptomatic HIV infection and a CD4 T-lymphocyte count of 200–499 cells/mm³, pregnancy and breast-feeding [2,3,12].

One of the vaccines available against YF is the live, attenuated, 17D-204 vaccine Stamaril® (Sanofi, Pasteur, France), which is available in more than 100 countries, including in Europe, with a licence since 1983 [3]. In the last 20 years of pharmacovigilance surveillance, only six cases of definite YEL-AND have been reported worldwide following Stamaril® vaccination for approximately 392 million doses distributed [3]. Since marketing authorization in 1996,

approximately 236,000 doses of the Stamaril® vaccine have been distributed in Poland, and a total of 3 cases of SAEs as per international recommendations [13], has been reported in Poland.

2. Case report

A 39-year-old Caucasian man was admitted to the neurological ward due to severe headache, malaise and increasing fever for a few days ranging from 37.5 to 39 °C. Two weeks before admission the patient had been vaccinated against YF with Stamaril® for the first time in his life due to a planned journey to Panama. The above-mentioned symptoms commenced five days after the vaccination. There was also a history of frequent sinusitis, and the last infection had taken place one month before the YF vaccination. Generally, the patient was in good health, without chronic illnesses, including thymus disorders and primary immunodeficiency, or any necessity of chronic treatment. On admission, the patient's neurological examination, basic laboratory tests of blood and urine, X-ray of the chest and paranasal sinuses, electroencephalography (EEG) as well as computerized tomography (CT) of the head showed no abnormalities. The CSF examination revealed lymphocytic cytositis, 448 cells per mm³, while the protein and glucose concentrations were within normal limits, and oligoclonal bands were absent. Based on the clinical picture and CSF examination, the diagnosis of meningitis was made and empiric therapy with acyclovir and ceftriaxone was started. On the second day of hospitalization, signs of a stiff neck, hyperreflexia and pain in the cervical and thoracic region of the vertebral column appeared. Magnetic resonance imaging (MRI) studies of the brain, cervical and thoracic spinal cord were ordered and, except for intensive meningeal contrast enhancement in the cervical localization, no abnormalities were found. Ultrasonography (USG) of the abdomen, CT of the chest and abdomen were all within normal limits. Subsequent extensive investigations from the blood, urine and CSF for infection (bacteria, fungi and viruses, including HIV) were all negative with the exception of YF. The analyses of serum and CSF samples performed on the 20th and 15th day post-vaccination for YFV by RT-PCR were negative in the serum and positive in CSF. Moreover, the results obtained on the 20th day post-vaccination were negative for the presence of specific IgM and IgG antibodies in CSF while positive for both classes of antibodies in the serum (see Table 1). On the 7th day after admission, due to a worsening of the patient's clinical status, with fever up to 39.9 °C and severe headache, intravenous immunoglobulin (IVIG, 0.4 g/kg/day) therapy was introduced for three days with good effect. Subsequently, empiric therapy was stopped and only supportive therapy was continued. The control lumbar puncture performed on the 19th day of hospitalization (32nd day post-vaccination) revealed a significant decrease in cytositis to 23 cells/mm³, with normal glucose and protein concentrations. Control analyses of serum, CSF and urine for YFV, and specific IgM and IgG antibodies in the serum and CSF were conducted, revealing the presence of IgG antibodies in the serum and in CSF (see Table 1). In the meantime, a transient yet significant increase of liver enzymes was observed. A number of diagnostic procedures as well as

Table 1 – Results of serum, CSF and urine analyses estimating YFV presence and serological assay performed in the Robert Koch-Institute, Berlin, Germany.

Samples		RT-PCR	Serological assay		
Collected	Type	5'-NC assay	IIF IgM	IIF IgG	YF PRNT
18.02.2015	Serum	Negative	Positive	Positive	Positive (1:83)
02.03.2015	Serum	Negative	Negative	Positive	Positive (1:320)
13.02.2015	CSF	Positive	Negative	Negative	NP
02.03.2015	CSF	Negative	Negative	Positive	Negative
02.03.2015	Urine	Negative	NP	NP	NP

IIF – indirect immunofluorescence; RT-PCR – reverse-transcription polymerase chain reaction; PRNT – plaque reduction neutralization test.

gastroenterological and parasitological consultations were performed, confirming that the increase was associated with drug-induced damage of the liver. Based on the clinical picture, the temporal association with YF vaccination, course of the disease, parasitological consultation, laboratory tests and EEG and MRI studies, YEL-AND with meningitis manifestation was finally diagnosed. A gradual improvement of the patient's clinical status was observed and he was discharged from the hospital without sequelae except for a mild headache.

The case was reported to the manufacturer Sanofi Pasteur in Poland and in France via Vaccine Adverse Events Reporting/ Pharmacovigilance System and was classified as meeting the definite YEL-AND criteria, according to Centers for Disease Control and Prevention (CDC), 2010 [2, a letter from Global Pharmacovigilance Department of Sanofi Pasteur, Lyon, France].

3. Discussion

17D YF vaccines (17D-204 and 17DD) are well tolerated and the rate of post-vaccination SAEs is, generally, low [2,3,14,15]. In healthy persons the onset of viremia occurs within 2–7 days after primary YF vaccination, lasting an average of 2–5 days [2,5,12], while in patients with YEL-AEs this timing can be prolonged [5]. Cases of YEL-AND have been the most common SAEs associated with YF vaccination [16] and are estimated to occur in 0.4 per 100,000 vaccines [10]. However, fortunately most patients suffering from YEL-AND recover well [3,10]. Cases of YEL-AND are classified as neurotropic disease (meningoencephalitis) or neurological autoimmune disease [2,14]. Meningoencephalitis is diagnosed when the 17D YF virus (YF 17D virus isolation from CSF or, like in our patient, 17D YFV RNA presence in CSF detected by nucleic acid-amplification test, by means of RT-PCR) or positive IgM for YF on CSF are found, which suggests direct YF vaccine viral invasion of the CNS and intrathecal antibody production [2,12,14,17,18]. YFV IgM antibodies are not believed to cross the blood–brain barrier normally [2]. The sole detection of IgG would only confirm a previous contact with YFV or with another flavivirus as serological cross-reactivity [19]. In the case we reported there was coexistence of the typical clinical picture, the temporal association with YF vaccination, positive RT-PCR for YFV in CSF and presence of IgG in the second but not in the first CSF specimen, what confirmed the current production of specific IgG in CSF. Neurological autoimmune disease may present itself as GBS, ADEM, transverse myelitis

and bilateral optic neuritis [2,17], and a combination of all of the above-mentioned conditions can occur [2,17]. No specific test is available for the autoimmune-mediated syndromes. A diagnosis of these conditions should be made using appropriate studies (e.g. neuroimaging, EEG, electromyography and nerve conduction studies) [2,10]. An autoimmune manifestation of YEL-AND is associated with the production of specific antibodies and/or a T-cell response as a result of the molecular mimicry mechanism, when T-cells mistakenly recognize vaccine epitopes as neuronal ones, which leads to central or peripheral nerve damage [2]. The mechanisms underlying the development of these AEs remain unknown and probably include viral and host features [5,14,18]. It is generally considered that host factors, mainly host immune responses to the 17D YF vaccine, may represent the major causes of YEL-SAEs [5,14,18]. An immature blood–brain barrier, the degree of viremia and immaturity of the immune system are the most probable reasons for YEL-AND in infants [2,12]. Also, advanced age (60 years and older), a history of thymus disorder, immunosuppression, male gender and a first-time YF vaccination are vital risk factors for SAE after YF vaccination [2,5,12,16,20]. Likewise, naturally acquired YF is more likely to be severe among males [21]. A higher humoral immune response in men may be due to higher viremia, accompanied by a higher rate of AEs in men than in women [5]. On the contrary, patients who were previously vaccinated against YF are at lower risk of YEL-AND [16]. Roukens et al. postulated that older patients have a weaker immune response to the YF vaccine, which allows the attenuated virus to cause higher viremia levels and increases the risk of developing SAEs [22]. Yet not only the 17D YF vaccination virus may be responsible directly for YEL-AEs in vaccinated persons, as transmission of the vaccine strain of YF via breastfeeding [12] or blood products after vaccination of the donor were reported, showing the risk of contact with body fluids through the parenteral route [23]. However, several cases with unknown risk factors have been reported [14], and our case seems to be included in that number. The only risk factor identified in our patient could have been the preceding sinusitis one month before the YF vaccination which could have altered his immune system to some extent. Treatment for YEL-AND depends on the clinical syndrome [2]. For meningoencephalitis, the only treatment is, in fact, supportive therapy, while for GBS IVIG or plasma exchange, and for ADEM corticosteroids, IVIG or plasma exchange are recommended [2]. Healthcare providers need to balance the risk of SAEs associated with the vaccine and the benefits of YF vaccination for each patient individually [8]. A

new inactivated vaccine has been developed and awaits further clinical evaluation [4]. If the live-attenuated 17D vaccine could be replaced with the new one in the near future this would most likely decrease the difficulty in decision making before using YF vaccination, especially in immuno-compromised individuals [4].

4. Conclusions

Although the risk of SAE incidence after YF vaccination is low [24,25], it is necessary to limit it as much as possible due to the likely fatal sequelae. Further investigations and assessments of YEL-AE cases are necessary to improve our understanding and methods of prevention. The YF vaccine ought to be administered to a person at risk based on reports of epidemic activity, season, duration of travel and the overall likelihood of exposure to vector mosquitoes [2,16,26].

Conflict of interest

None declared.

Acknowledgement and financial support

The authors would like to thank the Robert Koch Institute in Berlin, Germany, and especially Dr Cristina Domingo-Carrasco for performing and interpreting the diagnostics tests associated with this case.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES

- [1] Barnett ED. Yellow fever: epidemiology and prevention. *Emerging Infections*. Clin Infect Dis 2007;44:850–6.
- [2] Staples JE, Gershman M, Fischer M. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2010;59(July (RR07)):1–27. Centers for Disease Control and Prevention.
- [3] Cottin P, Niedrig M, Domingo C. Safety profile of the yellow fever vaccine Stamaril®: a 17-year review. *Expert Rev Vaccines* 2013;12(11):1351–68.
- [4] Jonker EFF, Visser LG, Roukens AH. Advances and controversies in yellow fever vaccination. *Ther Adv Vaccines* 2013;1(4):144–52.
- [5] Bae H-G, Domingo C, Tenorio A, de Ory F, Muñoz J, Weber P, et al. Immune response during adverse events after 17D-derived yellow fever vaccination in Europe. *J Infect Dis* 2008;197(June (1)):1577–84.
- [6] Niedrig M, Kürsteiner O, Herzog C, Sonnenberg K. Evaluation of an indirect immunofluorescence assay for detection of immunoglobulin M (IgM) and IgG antibodies against yellow fever virus. *Clin Vaccine Immunol* 2008;15(2):177–81.
- [7] Monath TP. Review of the risks and benefits of yellow fever vaccination including some new analyses. *Expert Rev Vaccines* 2012;11(4):427–48.
- [8] Lown BA, Chen LH, Wilson ME, Sisson E, Gershman M, Yanni E, et al. Vaccine administration decision making: the case of yellow fever vaccine. *Clin Infect Dis* 2012;55(6):837–43.
- [9] Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, et al. Adverse event reports following yellow fever vaccination. *Vaccine* 2008;26(48):6077–82.
- [10] McMahon AW, Eidex RB, Marfin AA, Russell M, Sejvar JJ, Markoff L, et al. Neurologic disease associated with 17D-204 yellow fever vaccination: a report of 15 cases. *Vaccine* 2007;25:1727–34.
- [11] World Health Organization. Vaccines and vaccination against yellow fever WHO Position Paper, 88. 2013, June;p. 269–84. <http://www.who.int/wer>.
- [12] Kuhn S, Twele-Montecinos L, MacDonald J, Webster P, Law B. Case report: probable transmission of vaccine strain of yellow fever virus to an infant via breast milk. *Can Med Assoc J* 2011;183(4):E243–5. <http://dx.doi.org/10.1503/cmaj.100619>
- [13] WHO. Report of CIOMS Working Group V. Appendix 5. List of Adverse Event/Reaction Terms to be Considered Always “Serious”: Explanation. Geneva 2001; 2001.
- [14] Silva ML, Espírito-Santo LR, Martins MA, Silveira-Lemos D, Peruhype-Magalhães, Caminha RC, et al. Clinical and immunological insights on severe, adverse neurotropic and viscerotropic disease following 17D yellow fever vaccination. *Clin Vaccine Immunol* 2010;17(1):118–26.
- [15] Dąbrowska MM, Flisiak R. Efficacy and safety of vaccination against yellow fever of persons travelling to endemic areas. *Przegl Epidemiol* 2010;64:319–22.
- [16] Guimard T, Minjolle S, Polard E, Fily F, Zeller H, Michelet C, et al. Short report: incidence of yellow fever vaccine-associated neurotropic disease. *Am J Trop Med Hyg* 2009;81(6):1141–3.
- [17] De Menezes Martins R, Braz Pavão A, Nunes de Oliveira PM, Gomes dos Santos PR, Carvalho DSM, Mohrdieck R, et al. Adverse events following yellow fever immunization: report and analysis of 67 neurological cases in Brazil. *Vaccine* 2014;32(49):6676–82.
- [18] Khromava AY, Eidex RB, Weld LH, Kohl KS, Bradshaw RD, Chen RT, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. *Vaccine* 2005;23:326–3263.
- [19] Domingo C, Escadafal C, Rumer L, Méndez JA, García P, Sall AA, et al. First international external quality assessment study on molecular and serological methods for yellow fever diagnosis. *PLoS ONE* 2012;7(5):e36291.
- [20] Miyaji KT, Luiz AM, do Socorro Souza Chaves T, de Oliveira Pirelli R, Lopes MH, Christovam Sartori AM. Active assessment of adverse events following yellow fever vaccination of persons aged 60 years and more. *Hum Vaccines Immunother* 2013;9(2):277–82.
- [21] Tuboi SH, da Costa Vasconcelos PF, Hatch D. Clinical and epidemiological characteristics of yellow fever in Brazil: analysis of reported cases 1998–2002. *Trans R Soc Trop Med* 2007;101:169–75.
- [22] Roukens AH, Soonawala D, Joosten SA, de Visser AW, Jiang X, Dirksen K, et al. Elderly subjects have a delayed antibody response and prolonged viremia following yellow fever vaccination: a prospective controlled cohort study. *PLoS ONE* 2011;6(12):e27753.

-
- [23] Centers for Disease Control and Prevention. Transfusion – related transmission of yellow fever vaccine virus: California, 2009. *MMWR Morb Mortal Wkly Rep* 2010;59:34–7.
- [24] Thomas RE, Lorenzetti DL, Spragins W, Jackson D, Williamson T. Reporting rates of yellow fever vaccine 17D or 17DD-associated serious adverse events in pharmacovigilance data bases: systematic review. *Curr Drug Saf* 2011;6(30):145–54.
- [25] Thomas RE, Lorenzetti DL, Spragins W, Jackson D, Williamson T. Active and passive surveillance of yellow fever vaccine 17D or 17DD-associated serious adverse events: systematic review. *Vaccine* 2011;29(28):4544–55.
- [26] Gershman MD, Staples EJ. Yellow fever. *Infectious diseases related to travel*, Chapter 3 – Viral hemorrhagic fevers; 2010. <http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/yellow-fever>.