Journal of Clinical Virology 58 (2013) 737–740

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Case Report

Fulminant encephalitis associated with a vaccine strain of rubella virus

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ARTICLE INFO

Article history:
Received 13 August 2013
Received in revised form 8 October 2013
Accepted 12 October 2013

Keywords:
Rubella vaccine
Encephalitis
Vaccinal virus isolation
RA 27/3 strain

ABSTRACT

Involvement of the central nervous system is common in measles, but rare in rubella. However, rubella virus (RV) can cause a variety of central nervous system syndromes, including meningitis, encephalitis, Guillain–Barré syndrome and sub acute sclerosing panencephalitis. We report the occurrence of one fatal case of the encephalitis associated with measles-rubella (MR) vaccine during an immunization campaign in São Paulo, Brazil. A 31 year-old-man, previously in good health, was admitted at emergency room, with confusion, agitation, inability to stand and hold his head up. Ten days prior to admission, he was vaccinated with combined MR vaccine (Serum Institute of India) and three days later he developed 'flu-like' illness with fever, myalgia and headache. Results of clinical and laboratory exams were consistent with a pattern of viral encephalitis. During hospitalization, his condition deteriorated rapidly with tetraplegia and progression to coma. On the 3rd day of hospitalization he died. Histopathology confirmed encephalitis and immunohistochemistry was positive for RV on brain tissue. RV was also detected by qPCR and virus isolation in cerebrospinal fluid, brain and other clinical samples. The sequence obtained from the isolated virus was identical to that of the RA 27/3 vaccine strain.

1. Why this case is important?

Post-natal rubella infection is rarely implicated in central nervous system (CNS) syndromes as acute encephalitis or postinfectious encephalitis [1–6]. The mortality rate is between 20% and 50% and survivors usually have a good outcome with no sequelae [1,5,6]. After the introduction of measles, mumps and rubella (MMR) vaccine, the incidence of neurologic events associated with these viruses has markedly decreased [1,4,7,8]. Most reported cases occurred before the immunization campaigns or in places where the vaccine is not available.

Although unusual, some adverse effects–including neurologic ones [9] – have been associated with MMR vaccine since its introduction [8], but events concerning specifically the rubella component are even scarcer. In this report, it is described the occurrence of a fatal case of the encephalitis associated with vaccinal rubella virus (vRV) detection in the brain and cerebrospinal fluid (CSF), after measles/rubella (MR) vaccine during the 2008 immunization campaign on the state of São Paulo, Brazil.

2. Case report

A 31-year-old man, previously in good health, presented to the emergency room with confusion and agitation. He was not able to stand and hold his head up. There was no additional alteration in the physical examination. He did not have any skin rashes or oral lesions. The function of cranial nerves was normal. There was no history of recent travels, arthropods or animals' exposure, opportunistic or repeated infections. Ten days prior to admission, he received combined MR vaccine (Serum Institute of India). He had received one dose of MMR before, on a vaccination campaign in

Abbreviations: CNS, central nervous system; MMR, measles, mumps and rubella; RV, rubella virus; vRV, vaccinal rubella virus; CSF, cerebrospinal fluid; MR, measles-rubella; MRI, magnetic resonance imaging; EBV, Epstein–Barr virus; CMV, cytomegalovirus; HSV 1/2, herpes simplex virus 1/2; VZV, varicella zoster virus; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; qPCR, quantitative polymerase chain reaction.

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http://dx.doi.org/10.1016/j.jcv.2013.10.016

1992. There was no epidemiological evidence of rubella transmission where the patient lived. He had 'flu-like' illness with fever, myalgia and headaches tree days after immunization. Initial laboratory tests revealed Hb 16.2 g/dL; Hct 47%; 24,000 leukocytes/mm^3 (N 84%/L 8%/M 7%); platelets 326,000 mm^{-3}; erythrocyte sedimentation rate 65 mm/h. Liver and renal studies were normal. Brain magnetic resonance imaging (MRI) was normal and his CSF showed: 2 leukocytes/mm^3, 0 erythrocyte/mm^3; glucose 63 mg/dL, protein 51 mg/dL; direct staining for bacteria, fungi and cultures were negative in the CSF. Electroencephalography showed slow wave activity and no epileptogenic activity.

Serum IgM antibodies for measles virus, parvovirus B19 human, Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus 1/2 (HSV 1/2), varicella zoster virus (VZV), herpesvirus 6 and Dengue were negative. IgG antibodies were positive for EBV, CMV and VZV. Serum antibodies for HIV and syphilis were negative. IgG against rubella was positive (Siemens, Marburg, Germany) in serum and CSF, but IgM was negative in both samples. Rubella IgG avidity was determined using commercial enzyme immunoassay DIESSE Enzywell (Diagnostica Senese, Italy). IgG antibodies were positive with high titers in serum specimens and found to contain high rubella-specific IgG avidity (AI: 60–89%).

Initial therapy included acyclovir and immunoglobulin. During hospitalization, his condition deteriorated rapidly with tetraplegia, progression to coma, apnea and hypotension. On the 3rd day, he died after cardiorespiratory failure. An autopsy was made and histological findings of brain samples include neuronal lesion, lymphocytes and histiocytes infiltrating cerebral parenchyma forming groups amidst neurons, and mononuclear cells gathering in the Virchow–Robin space around blood vessels (Fig. 1). Demyelization was absent. Brain tissue was submitted to indirect immunoperoxidase-staining reaction with monoclonal rubella anti-E1 antibody (MAB925, Millipore Inc., Temecula, CA, USA) and it was positive (Fig. 1).

Blood, CSF, urine and frozen samples of brain, heart, lung, liver and kidney were also collected and processed for analyses. RV was amplified by qPCR in peripheral blood mononuclear cells (PBMCs), ultracentrifugated CSF, urine, liver, kidney and brain, as previously described [10]. Real time PCR with oligonucleotides specific for the following virus was negative on the same samples: measles, mumps, CMV, VZV, HSV 1/2, Dengue, EBV and erythrovirus B19.

RV was also isolated from CSF, PBMC and urine samples in a rabbit corneal epithelium cells and Vero cell line after 7 days of culture, during the first and second passage, respectively. The isolated virus showed a cytopathic effect characteristic of RV. The viruses isolated in cell cultures were identified by PCR. For phylogenetic studies, samples were amplified utilizing primers described in the literature [11]. Amplified DNA fragments were purified with PureLink PCR Purification Kit (Invitrogen) and submitted to the sequencing reactions with ABI Prism Big Dye Terminator v3.1 Cycle Sequencing Kits (Applied Biosystems), according to the manufacturer's protocol. The sequence obtained from the glycoprotein E1 gene PCR product from our patient was identical to that of the RA 27/3 vaccine strain (GenBank # JX047998).

3. Other similar and contrasting cases in the literature

Squadrini et al. [12] was the first author to describe RV isolation from CSF of a patient with the signs of encephalitis. Our group [2] recently described a case of rubella encephalitis in a young adult male, with wild type virus isolation on CSF and PBMCs. The patient recovered completely and was discharged 15 days after admission. Other authors have reported cases of rubella encephalitis [13–17], but they were confirmed only with detection of antibodies against rubella in serum and/or CSF.

Public concern has emerged since the introduction of MMR vaccination because of the temporal relationship of several disorders and the vaccination [1,8]. Reliable causality is difficult to prove and the association of neurological adverse effects with vaccine has remained controversial and inconclusive [8,9,18]. Recently, Shuper et al. [19] reported two cases of children with encephalitis in close temporal proximity to MMR vaccination. One patient recovered completely while the other remained severely neurologically handicapped. It was suggested that the vaccine was the probable cause. However, the author did not identify any specific virus or other organisms – by neither PCR nor culture – and could not rule out postinfectious encephalitis as the cause of symptoms. Only Bitnun et al. [20] described a case of measles inclusion-body encephalitis in a 21-month-old boy, 8.5 months after measles-mumps-rubella vaccination, associated with vaccinal measles virus detection in the brain tissue. Concerning rubella, there are no similar cases.

4. Discussion

This is a case report of a male patient with confusion and ataxia, with rapid progression to coma and death, 10 days after MMR vaccination. The clinical presentation was associated with histological findings of encephalitis, a positive immunohistochemistry for E1 rubella protein on brain tissue and rubella RA27/3 vaccine strain RNA detection in brain, CSF and blood, suggesting the diagnosis of acute encephalitis caused by vRV.

The patient history is similar to the ones described in encephalitis cases associated with wild strain of RV [12,13,14,15,16]. The neurological symptoms started 10 days after vaccination, temporally consistent [19] with the hypothesis that the encephalitis could be caused by a direct effect of vRV into the brain. The pathogenesis of rubella encephalitis have not been systematically elucidated, but some elements support the hypothesis of direct viral damage in our case: (i) RV is neurotropic [1], it has been previously isolated from mature brain and involved with neuronal damage [2,12]; (ii) brain histological findings were suggestive of encephalitis; (iii) immunohistochemistry staining of the brain tissue was positive for rubella E1 protein; (iv) RV was isolated from various samples, including brain and CSF; (v) RNA sequences obtained from brain and CSF were phylogenetically aligned with RA 27/3 vaccine virus, but not wild-type virus.

Other hypothesis that could explain the neurologic symptoms is postinfectious encephalitis (immune-mediated response to RV). It is postulated the occurrence of genetic variation during replication of the vaccine virus in the host and mimicking of the host brain proteins, with autoimmune mediated damage [21]. However, nucleotide sequence analysis of the PCR products in the glycoprotein E1 amplified of the patient's samples revealed no changes in the virus genome compared with other vaccine lots. Moreover, postinfectious encephalitis is less probable due to: (i) the short time interval between vaccination and symptom onset; (ii) there were no signs of demyelination lesions on the brain MRI; (iii) histological findings did not revealed diffuse or multifocal areas of demyelization; (iv) RV was isolated from the brain tissue, an excluding criteria for postinfectious encephalitis [21].

The effectiveness of the MMR vaccine is sometimes a subject of controversy because of its adverse effects, especially because it contains live attenuated virus. A recent review [22] addressed this issue and concluded that the vaccine is very effective against measles and mumps, and only in very rare occasions, these two vaccinal virus strains are associated with adverse events like aseptic meningitis. Rubella component effectiveness and safety was not evaluated by this study. Makella et al. [9] studied specifically the neurologic events occurring 3 months after MMR vaccination and found no evidence of an increased risk of encephalitis or aseptic